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PRACTICAL INSULIN STRATEGIES

for **Family
Physicians**

The Role of the Family Physician
in the Diagnosis and Treatment of
Type 2 Diabetes Mellitus

■ Robert E. Rakel, MD

Insulin Regimens for Type 2
Diabetes Mellitus

■ Stephen Brunton, MD

Options for Insulin Delivery
and Overcoming Physician
and Patient Concerns

■ Russell D. White, MD

Practical Strategies for Achieving
Targeted Glycemic Control in Patients
With Type 2 Diabetes

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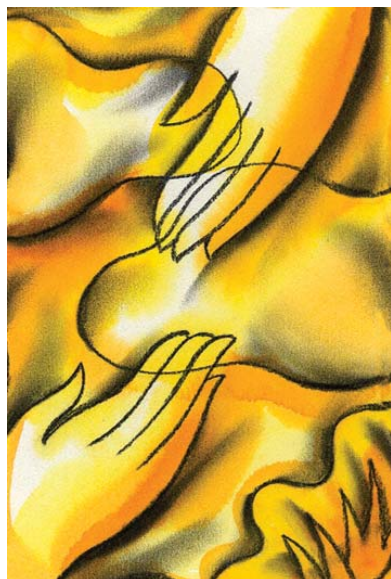
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Introduction

The burden of diabetes continues to increase. Nearly 21 million persons—7% of the US population—have diabetes, although nearly one third do not know it. Most persons with diabetes mellitus (DM) have type 2 DM (T2DM), while 1 in 500 children and adolescents has type 1 DM (T1DM).¹ An estimated 10% of patients with T2DM may actually have latent autoimmune diabetes mellitus, which is a slow-onset form of T1DM.² An additional 41 million persons have prediabetes. From 1997 through 2005, the number of new cases of DM in adults increased by 54% (FIGURE).¹ In 2005 alone, 1.5 million new cases of DM were diagnosed among adults.³

The consequences of DM are enormous. In 2003, DM was the sixth leading cause of death, accounting for nearly 75,000 deaths, with an age-adjusted mortality rate of 25 per 100,000 population. Both numbers have doubled since 1986.⁴⁻¹⁰ Estimated direct and indirect medical costs totaled \$132 billion in 2002. But the greatest cost of diabetes is its well-established contribution to other diseases and complications, such as heart disease and stroke, retinopathy, kidney disease, neuropathy, amputation, and periodontal disease.¹¹

Given the hazards of prolonged hyperglycemia and the benefits of achieving near-normal glycemia with treatment, where is the sense of urgency to treat patients with DM aggressively? Compared with a decade ago, fewer—not more—patients are achieving the American Diabetes Association's normal glycemic goal of a glycosylated hemoglobin (A1C) level less than 7%, let alone the more stringent American Association of Clinical Endocrinologists goal of 6.5% or lower. To be sure, the management of diabetes is complex and a long-term commitment. Sadly, the obesity epidemic places millions—if not tens of millions—of persons at risk for diabetes in years to come. Weight loss and other risk reduction interventions are clearly needed now. It is also urgent that diabetes be recognized as the killer it is.

The relative silence of T2DM until late in its course may make it easy to accept a “slightly” elevated A1C and avoid using more aggressive therapy, including insulin (TABLE). Insulin is the most effective agent available to lower glycemia and the most physiologically compatible.

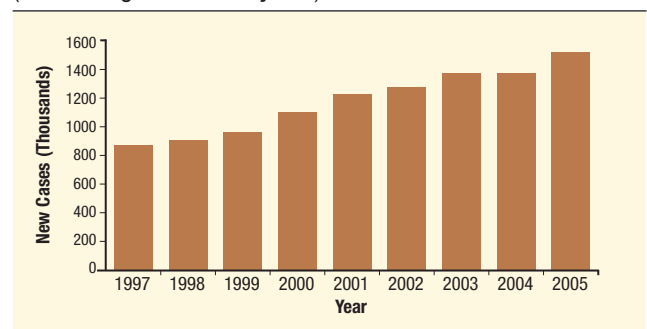
Because of the progressive nature of T2DM, insulin therapy is usually needed to achieve glycemic goals. Oral antidiabetic drugs (OADs) are effective early during the course of T2DM because they improve insulin sensitivity and stimulate insulin secretion. OADs, as well as glucagon-

like peptide-1 analogs and dipeptidyl peptidase-4 enzyme inhibitors, have a limited capacity to lower A1C. In contrast, the capacity of insulin to lower A1C levels is limited only by the potential to induce hypoglycemia. However, the risk of hypoglycemia can be minimized by educating patients about the use of insulin, including self-monitoring of blood glucose. Major hypoglycemia is uncommon among patients with T2DM, and death from hypoglycemia is rare.

This supplement includes 4 articles that focus on the importance of achieving currently accepted glycemic goals and the role of insulin in achieving these goals. In the first article, “The Role of the Family Physician in the Diagnosis and Treatment of Type 2 Diabetes Mellitus,” Dr Robert Rakel describes the currently accepted glycemic goals and the microvascular and macrovascular benefits of achieving those goals. The progressive nature of insulin resistance and pancreatic beta-cell exhaustion in T2DM are summarized, with a description of the implications for long-term limitations of oral agents. Although oral agents generally lose their ability to control hyperglycemia over time, and many persons with DM currently do not meet the accepted glycemic goals, the initiation of more aggressive therapy is often delayed. The article emphasizes the need for earlier intensification of therapy.

The benefits and limitations of currently available oral agents are summarized by Dr Stephen Brunton in “Insulin Regimens for Type 2 Diabetes Mellitus.” The insulin formulations currently available are reviewed in

FIGURE
 Number of new cases of diabetes mellitus'
 (Persons aged 18 to 79 years)



¹US Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/diabetes/statistics/incidence/fig1.htm>. Accessed September 15, 2006.

TABLE
Drugs approved to treat diabetes mellitus
in the United States

Class	Generic Name	Trade Name
Alpha-glucosidase inhibitors	Acarbose Miglitol	Precose Glyset
Biguanide	Metformin	Glucophage
Dipeptidyl peptidase-4 enzyme inhibitor	Sitagliptin	Januvia
Insulin		
Rapid-acting	Insulin glulisine Insulin lispro Insulin aspart	Apidra Humalog NovoLog
Regular	Regular human	Humulin R Novolin R
Intermediate-acting	NPH	Humulin N Novolin N
Long-acting	Insulin detemir Insulin glargine	Levemir Lantus
Premix	50% NPH/50% regular 70% NPH/30% regular 50% lispro protamine/ 50% lispro 75% lispro protamine/ 25% lispro 70% aspart protamine/ 30% aspart (BIAsp or biphasic insulin aspart)	Humulin 50/50 Humulin 70/30 Novolin 70/30 Humalog Mix 50/50 Humalog Mix 75/25 NovoLog Mix 70/30
Inhaled	Insulin human [rDNA origin]	Exubera
Meglitinides	Nateglinide Repaglinide	Starlix Prandin
Sulfonylureas	Acetohexamide Chlorpropamide Glimiperide Glipizide Glyburide Tolazamide Tolbutamide	Generic Diabinese Amaryl Glucotrol DiaBeta, Glynase, Micronase Generic Generic
Thiazolidinediones	Pioglitazone Rosiglitazone	Actos Avandia
Amylin analog	Pramlintide	Symlin
Incretin mimetic	Exenatide	Byetta

NPH = neutral protamine Hagedorn.

detail, with a comparison of their profiles with that of endogenous insulin secretion. The clinical efficacy and safety of different insulin formulations alone, as basal-bolus therapy, and in combination with oral agents are compared, with results of clinical trials generally demonstrating improved glycemic control when insulin therapy is utilized.

Additional strategies for utilizing insulin in patients with T2DM are offered by Dr Russell White in “Options for Insulin Delivery and Overcoming Physician and Patient Concerns.” Initiating insulin in patients with T2DM is often complicated by patient and clinician barriers. Many of these barriers are described, with suggestions for effectively addressing them in individual patients. One of the keys to individualizing insulin therapy is the selection of an appropriate insulin delivery system, many of which are described.

With clear evidence demonstrating DM as a growing public health problem—despite the benefits of intensive glycemic control and the availability of effective therapies, including insulin—Dr Jeff Unger provides “Practical Strategies for Achieving Targeted Glycemic Control in Patients With Type 2 Diabetes.” Using a case-based format, implementation of the “treat-to-target” and “all-to-target” approaches are described, with suggestions for initiating and titrating insulin therapy to achieve accepted glycemic goals, while minimizing the risk of hypoglycemia. Tips for managing patients with DM in the primary care setting are offered, with the physician as the leader of the health care team.

In summary, this supplement is intended to help the primary care physician understand the urgency of taking a more aggressive approach to the management of patients with DM, particularly type 2, and the important role of insulin in management, given the limitations of OADs in responding to the evolving pathophysiology. Practical strategies are offered for initiating and intensifying insulin therapy—while minimizing the risk of hypoglycemia—and for overcoming patient and physician barriers to insulin therapy.

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The Role of the Family Physician in the Diagnosis and Treatment of Type 2 Diabetes Mellitus

■ Robert E. Rakel, MD

KEY POINTS & RECOMMENDATIONS

- For both type 1 and type 2 diabetes mellitus, improved glycemic control is associated with reductions in microvascular complications, including retinopathy, nephropathy, and neuropathy. (SOR: A)
- The benefits of intensive therapy are sustained over many years. (SOR: C)
- During the course of several years of treatment with maximal doses of various oral agents as monotherapy or combination therapy, the proportion of patients who maintain an A1C level less than 7% declines sharply. (SOR: A)
- Further efforts aimed at earlier intensification of therapy are needed, yet changes in therapy are routinely delayed for many months, if not years. (SOR: C)

Goals of Treatment

Optimal management of patients with type 1 and type 2 diabetes mellitus (DM) includes aggressive and persistent efforts to achieve physiologic control of blood glucose concentrations, as well as other conditions associated with DM, including dyslipidemia, hypertension, and obesity.¹ Therapy should be individualized to achieve and maintain the desired goal, while reducing the frequency and consequences of adverse effects and treatment complications.

Although glycosylated hemoglobin (A1C) levels are the primary measure of overall glycemic control, preprandial (fasting) and postprandial glucose (PPG) levels are useful measures for daily monitoring as well. Postprandial hyperglycemia has been established as an independent risk factor for cardiovascular disease and death. The DECODE Study, which followed more than 25,000 subjects for a

mean of 7.3 years, showed that increased mortality risk was much more closely associated with 2-hour post-glucose-load plasma levels than with fasting plasma glucose (FPG) levels.² Postprandial glucose concentrations may, in fact, be targeted if A1C goals are not met despite reaching preprandial glucose goals. As the A1C levels approach the 7% target (ie, <8.5%), the postprandial glucose level contributes more to hyperglycemia; therefore, improving postprandial hyperglycemia will more effectively lower the patient's A1C.³

The recommended treatment goals vary slightly between those of the American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) (TABLE 1).^{1,4} The ADA recommendations acknowledge that less stringent treatment goals may be appropriate for patients with a history of severe hypoglycemia or with limited life expectancies, for very young children or older adults, and for individuals with comorbidities. Hence, the ADA's recommendation that an A1C level less than 7.0% applies to patients in general. For individual patients, the ADA recommends an A1C level as close to normal (<6%) as possible without significant hypoglycemia.⁴

Importance of Reaching Goals

The goals of DM treatment have evolved, and have become progressively more aggressive, based on more than a decade of intensive investigation. The incidence of microvascular and macrovascular complications clearly increases with rising A1C levels in both type 1 DM (T1DM) and type 2 DM (T2DM).⁵ However, the Diabetes Control and Complications Trial (DCCT), Kumamoto trial, United Kingdom Prospective Diabetes Study (UKPDS), and others have clearly demonstrated that improved glycemic control is associated with reductions in microvascular complications, including retinopathy, nephropathy, and neuropathy associated with T1DM⁶⁻⁸ and T2DM (TABLE 2).⁹⁻¹¹ The benefits of reducing the risk of cardiovascular disease by attaining lower A1C

TABLE 1
Current recommended treatment goals for adults with type 1 and type 2 diabetes mellitus^{1,4}

	AACE	ADA
Glycemia		
A1C, %	≤6.5	<7.0
Preprandial glucose,* mg/dL	<110	90-130
Peak postprandial glucose,* mg/dL	<140	<180
Blood pressure, mmHg	—	<130/80
Lipids, mg/dL		
LDL cholesterol	—	<100
Triglycerides	—	<150
HDL cholesterol	—	>40

*Blood glucose (AACE) and capillary plasma glucose (ADA).
AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association; HDL = high-density lipoprotein; LDL = low-density lipoprotein.
¹AACE/AACE Diabetes Road Map Task Force. Available at: <http://www.aace.com/meetings/consensus/odimplementation/roadmap.pdf>. Accessed September 12, 2006.
⁴American Diabetes Association. *Diabetes Care*. 2006;29(suppl 1):S4-S42.

TABLE 2
Reduction of A1C lowers incidence of complications

	DCCT ^a	Kumamoto trial ¹¹	UKPDS ⁹
A1C reduction	9 → 7	9 → 7	8 → 7
Retinopathy	63	69	17-21
Nephropathy	54	70	24-33
Neuropathy	60	—	—
Macrovascular disease	41*	—	16*

Values provided as percent (%).
*Not statistically significant.
DCCT = Diabetes Control and Complications Trial; UKPDS = United Kingdom Prospective Diabetes Study.
^aDCCT Research Group. *N Engl J Med*. 1993;329:977-986; ⁹UKPDS Group. *Lancet*. 1998;352:837-853; ¹¹Ohkubo Y, et al. *Diabetes Res Clin Pract*. 1995;28:103-117.

levels have been shown in T1DM^{12,13} and T2DM.⁵ Furthermore, citing epidemiological analyses, the ADA has stated that there is no threshold below which complications do not occur, although they acknowledge that the absolute risks and benefits of attaining lower A1C levels are unknown.⁴

Long-Term Benefits of Glycemic Control

The DCCT studied 1441 patients with T1DM; 726 had no retinopathy and 715 had mild retinopathy. Patients were randomized to 2 groups: conventional group patients were treated with once-daily or twice-daily injections of intermediate- and rapid-acting insulin without daily adjustment of dose; intensive group patients received insulin through an external pump or 3 or more injections daily with dose adjustment.⁶ After completion of the DCCT, with a mean of 6.5 years of treatment, patients in the conventional treatment group were urged and helped to adopt intensive treatment, at which time they entered the Epidemiology of Diabetes Interventions and Complications (EDIC) trial. By year 5 of the EDIC trial, the A1C levels of the intensive and the conventional groups were not significantly different (8.0% vs 8.2%).¹⁴

The further progression of retinopathy from the end of the DCCT through the eighth year of EDIC was reduced by 63% for the group that received prior intensive treatment compared with the initially conventional treatment group.¹⁴ Similarly, the need for retinal photocoagulation was also significantly reduced for the prior intensive treatment group. In this same group, similar reductions in risk were observed for nephropathy,¹⁵ neuropathy,¹⁶ and cardiovascular events,¹² compared with the conventional group.

These sustained benefits of intensive therapy are thought to result from a phenomenon called “metabolic memory.”¹⁴ Preliminary evidence indicates that hyperglycemia induces abnormalities in the structure and/or function of glycated long-lived molecules, such as collagen, in proportion to the level of glycemia. Because of the longevity of these molecules, damage done to them has long-lasting consequences. Conversely, improved glycemic control (ie, lower A1C level) causes less damage—a benefit that is observed over a long time. With the case of the EDIC trial, this benefit was observed for 8 years.

Subsequent to the DCCT, the UKPDS confirmed that intensive blood glucose control decreased the risk of microvascular disease for patients with T2DM.⁹ Patients in the intensive group of the UKPDS were treated to achieve an FPG concentration less than 110 mg/dL. Patients were treated with chlorpropamide, glyburide, glipizide, or metformin alone or in combination, or insulin. Treatment changes were made based on glucose concentrations above the target. After 10 years, the mean A1C in the intensive group was 7.0%, compared with 7.9% in the conventional group (FPG maintained <270 mg/dL). Compared with the conventional group, the risk for any diabetes-related end point was 12% lower in the intensive group, with most of the risk reduction due to a 25% risk reduction in microvascular end points.

An added benefit of long-term glycemic control is a reduction in diabetes-related costs. A retrospective analysis of 6780 patients with T2DM calculated the costs of diabetes-related care for a 12-month period.¹⁷ The average cost for patients whose A1C levels remained above 7% was 32% higher than for patients who maintained an A1C level below 7% (\$1540 vs \$1171, respectively).

Trends in Management

Despite the demonstrated benefits of intensive treatment, 57.7% of patients with T2DM continue to have A1C levels above the target goal of less than 7%, as recommended by the ADA.¹⁸ Although the percentage of patients with T2DM who achieved the ADA target goal has not changed appreciably from the 1990s to the 2000s (41.3% vs 42.3%, respectively), an upward shift in A1C levels has occurred.¹⁸⁻²⁰ For example, compared with patients with T2DM in the 1990s, fewer patients with T2DM in the 2000s achieved an A1C level below 6.0% (23.4% vs 16.4%, respectively), and more patients had an A1C level between 6.0% and 7.9% (34.2% vs 47.0%, respectively).¹⁸ This finding has impor-

tant implications because the UKPDS showed that each 1% reduction in a patient's A1C level (eg, from 8% to 7%) was associated with a 37% decrease in risk of microvascular complications and a 21% decrease in risk of any diabetes-related end point (FIGURE 1).⁵

Disease Progression

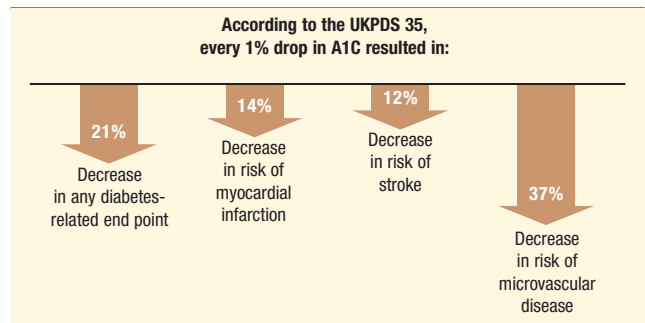
The pancreatic beta cell plays a central role in the pathogenesis of diabetes mellitus. With T1DM, beta-cell destruction occurs as a result of an interaction between genetic and environmental factors. Inadequate insulin production results and usually occurs at an early age.⁴ These patients require exogenous insulin to sustain life. Persons with latent autoimmune diabetes of the adult (LADA) have an attenuated autoimmune response that leads to slowed beta-cell destruction, with insulin dependency intermediate between T1DM and T2DM. Persons with LADA are often incorrectly categorized as having T2DM based on their adult age, lack of ketoacidosis, and initial response to oral agents.²¹ The diagnosis of LADA is based on the presence of glutamic acid decarboxylase-65 (glutamic acid decarboxylase) autoantibodies, which indicate the presence of autoantigens that cause autoimmune destruction of islet cells.²²

With T2DM, progressive pancreatic beta-cell dysfunction is 1 of the 2 hallmarks of the disease.²³ The other hallmark of T2DM is insulin resistance, which results in increased hepatic glucose production and decreased glucose disposal by peripheral tissues. Obesity is a common cause of insulin resistance, and the increasing incidence of obesity is fueling the diabetes epidemic.²⁴ Insulin resistance occurs earlier and plateaus when beta-cell damage is progressive.

Available evidence suggests that the progression of diabetes occurs in 5 stages, each of which is characterized by different changes in beta-cell mass, phenotype, and function.²⁵ Stage 1 is characterized by compensation, in which insulin secretion increases to maintain normal glucose levels in the face of insulin resistance resulting from obesity, physical inactivity, and genetic predisposition. Glucose levels rising to 89-116 mg/dL mark stage 2, which consists of a stable state of beta-cell adaptation. Stage 3 is an unstable period of early decompensation, in which glucose levels rise quickly, leading to stage 4, which is characterized by stable decompensation. Stage 5 represents severe decompensation, consisting of profound beta-cell failure with progression to ketosis.

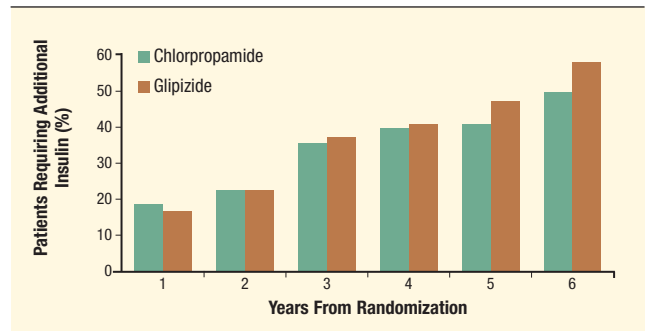
Although research has suggested that prior to stage 5, the disease can move back to a lower stage with effective therapy,²⁵⁻²⁸ T2DM is characterized by a progressive decline in beta-cell function over time despite treatment. The UKPDS investigators observed a progressive increase over 6 years in the proportion of patients requiring additional insulin to achieve an FPG level of 108 mg/dL, despite maximal doses of sulfonylurea monotherapy (FIGURE 2).²⁹ The UKPDS investigators also found that during 9 years of

FIGURE 1
Effect on vascular complications of reducing A1C by 1%⁵



UKPDS = United Kingdom Prospective Diabetes Study.
⁵Stratton IM, et al. *BMJ*. 2000; 321:405-412

FIGURE 2
Increasing need for insulin therapy in type 2 diabetes mellitus²⁹



Percentage of patients requiring early addition of insulin each year because fasting plasma glucose increased to >108 mg/dL despite maximal sulfonylurea doses. Includes patients who agreed to take insulin and patients who refused.

Reprinted with permission from Wright A, Burden AC, Paisey RB, Cull CA, Holman RR. Sulfonylurea inadequacy: efficacy of addition of insulin over 6 years in patients with type 2 diabetes in the U.K. Prospective Diabetes Study (UKPDS 57). *Diabetes Care*. 2002;25:330-336.²⁹

treatment with maximal doses of various agents as monotherapy, the proportion of normal weight and overweight patients who attained the goal of an A1C level below 7% declined sharply.³⁰ At year 3, an A1C level below 7% was maintained by only half of the patients treated with insulin, chlorpropamide, or glyburide. By years 6 and 9, only one third and one quarter of patients, respectively, maintained an A1C level below 7%. Among overweight patients only, an A1C level below 7% was achieved at 9 years by only 13% of patients treated with metformin. The effect of pharmacologic therapy on FPG was even less beneficial. At 6 years, only 5% of patients treated with a sulfonylurea were able to maintain an FPG level of 108 mg/dL or less. However, more patients treated with insulin were able to maintain the FPG goal with only a slight decline over the study (52%, 48%, and 42% at 3, 6, and 9 years, respectively).

These findings are not surprising given that, on average, patients with T2DM have lost approximately half of

their beta-cell function by the time their diabetes is diagnosed.²⁶ Surprisingly, by year 3 of treatment only half of the patients were able to maintain an A1C level below 7%. This finding indicates that for many patients, combination treatment must be implemented soon after diagnosis.^{1,31} Given the benefits of insulin for decreasing FPG concentrations, its use earlier during the course of the disease may be warranted. (See “Insulin Regimens for Type 2 Diabetes Mellitus” on page 10 of this supplement.)

Role of the Family Physician

The prevalence of diabetes places the primary care physician (PCP) at the center of diabetes management. In fact, more than 90% of patients with diabetes are managed in the primary care setting.³² This central role requires the PCP to coordinate the activities of the health care team to optimize patient care. (See “Options for Insulin Delivery and Overcoming Physician and Patient Concerns” on page 18 of this supplement.)

To serve this central role effectively, it is vital that the PCP evolve her or his practice in keeping with new evidence and recommendations. This task, although challenging, has an important bearing on the ability of patients with diabetes to achieve the evidence-based goals for glycemic control and the associated health benefits. Although not the subject of this supplement, early identification of patients at risk for diabetes—ideally in the prediabetes stage—is critical. One step toward early identification is to obtain an FPG level from persons who have comorbidities such as obesity, hypertension, hyperlipidemia, albuminuria, and periodontal disease.

For patients diagnosed with diabetes, vigilant screening for complications is necessary. Recent evidence from the US Centers for Disease Control and Prevention indicates that only 40% of patients with diabetes receive annual foot and dilated eye examinations and have an A1C determination twice yearly.³³

More timely intensification of pharmacologic treatment also is needed when glycemic goals are not attained. Evidence presented at the 2006 Scientific Session of the ADA showed that changes in therapy are routinely delayed. One study assessed the prescribing of oral antidiabetic drugs (OADs) and examined the pharmacy and laboratory claims by a commercial, preferred-provider organization model of a national managed care group.³⁴ Data were collected on 9416 patients who had received a first prescription for an OAD between January 2001 and April 2004. Although 67% of the patients had an A1C level higher than the ADA goal, with a mean of 8.5%, an average of 240 days passed before a second antidiabetic drug was added. Similar findings have been observed with antihypertensive medications for patients with diabetes.^{35,36} These data are consistent with earlier data on more than 7200 completed courses of treatment for patients with T2DM between 1994 and 2002.³⁷ In this study, the average

patient accumulated nearly 5 years of excess glycemic burden with A1C levels higher than 8.0% or 10 years with A1C levels higher than the ADA goal of 7.0%. Results such as these show that treatment should be intensified more rapidly than is the current practice. These issues are covered in more detail in other sections of this supplement.

The Diabetes Health Care Team

The comprehensive management of diabetes often requires a multidisciplinary diabetes health care team. With the patient at the center of this team, the family physician is in the best position to coordinate team activities. The composition of the team may vary, depending on the needs of the patient, but might include a certified diabetes educator, dietician, nurse, pharmacist, and social worker. A key role of the family physician is to create the sense of urgency necessary and to ensure that the treatment plan evolves to meet the specific needs and preferences of each patient, with the aim of achieving accepted glycemic goals with minimal adverse consequences. (See “Practical Strategies for Achieving Targeted Glycemic Control in Patients With Type 2 Diabetes” on page 25 of this supplement.)

Summary

The benefits of intensive glycemic control for reducing microvascular and macrovascular complications have been demonstrated in landmark clinical trials such as the DCCT/EDIC and UKPDS. Unfortunately, the ability of oral agents—even in combination—to control glycemia declines over time due in part to the generally progressive nature of T2DM. Nonetheless, the initiation of more aggressive therapy to reestablish glycemic control is often delayed for many months or years, placing the patient at increased risk for diabetes-related complications. As the leader of comprehensive diabetes care, the PCP must demonstrate on a daily basis a greater sense of urgency to the patient and members of the health care team. This urgency must start with an intolerance to accepting an A1C level above goal and the establishment of a more aggressive, intensified approach to diabetes management that involves the patient and minimizes the risk of adverse effects such as hypoglycemia and weight gain.

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Insulin Regimens for Type 2 Diabetes Mellitus

■ Stephen Brunton, MD

KEY POINTS & RECOMMENDATIONS

- Most patients with type 2 diabetes mellitus eventually require insulin to achieve glycemic control. **(SOR: B)**
- The addition of basal and/or bolus insulin to existing oral therapy is effective in achieving glycemic control. **(SOR: A)**
- The combined use of rapid-acting and long-acting insulin analogs more closely mimics endogenous insulin secretion than combined use of short-acting and long- or intermediate-acting human insulins. **(SOR: B)**
- Rapid-acting insulin analogs effectively control postprandial hyperglycemia, while reducing the risk of hypoglycemia compared with short-acting human insulin. **(SOR: A)**
- Long-acting insulin analogs decrease the risk of hypoglycemia seen with intermediate- and long-acting human insulins. **(SOR: A)**

Overview of Available Treatments for Diabetes Mellitus

Many options are available to treat both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), including lifestyle modification and pharmacologic management. For most patients, several options will be utilized during the course of their disease to achieve A1C (glycosylated hemoglobin) goals, minimize adverse effects, and meet patient needs.

Lifestyle modification remains an important component of diabetes treatment because of its demonstrated benefits, few adverse consequences, and relatively low cost. Effectively addressing overweight and obesity is the pri-

mary focus of lifestyle modification; therefore, treatment involves weight loss, increased physical activity, and balanced nutrition.¹ Weight loss for overweight and obese patients (body mass index 25-29 kg/m² and ≥30 kg/m², respectively) with DM provides numerous health benefits, including decreases in plasma glucose levels and insulin resistance.² For obese persons with T2DM, consumption of a low-carbohydrate diet for 2 weeks (days 8-21) has been shown to reduce energy intake to a level appropriate to height and to improve 24-hour blood glucose profiles, A1C levels, and insulin sensitivity compared with a standard diet (days 1-7).³ A pooled analysis of 14 aerobic/resistance training studies showed that increased aerobic physical activity significantly decreased A1C levels, with a benefit that was only partly attributable to weight loss.⁴ Long-term adherence to the lifestyle modifications necessary for sustained weight loss is, however, difficult. A permanent approach to weight loss involving bariatric surgery is another option. Substantial weight loss (ie, >20 kg), with essentially complete resolution of diabetes, has been reported.^{5,6}

For all patients with T1DM, insulin treatment is life-saving. For most patients with T2DM, several classes of pharmacologic agents are available to provide effective treatment, at least for the initial stages of the disease. Such agents include the alpha-glucosidase inhibitors, biguanides, meglitinides, sulfonylureas, thiazolidinediones, amylin analog, incretin mimetic, and dipeptidyl peptidase-4 enzyme inhibitors. These agents lower plasma glucose by various mechanisms, principally by stimulating the secretion of insulin by pancreatic beta-cells or decreasing insulin resistance by muscle cells (**TABLE 1**). Both the amylin analog and incretin mimetic suppress glucagon secretion and slow gastric emptying. The amylin analog also promotes satiety; incretin mimetic also stimulates pancreatic insulin secretion. Pramlintide is approved as adjunctive therapy with insulin. The dipeptidyl peptidase-4-enzyme (DPP-4) inhibitor sitagliptin inhibits the DPP-4 enzyme, which degrades incretins in vivo.

TABLE 1
Characteristics of antidiabetic interventions as monotherapy^{7,57-60}

Intervention	Mechanism of Glucose Lowering	Examples	Expected Decrease in A1C (%)	Advantages	Disadvantages	Daily Cost†
Lifestyle to decrease weight and increase activity	• Decrease insulin resistance	—	1-2	Low cost, many benefits	Fails for most patients in first year, long-term adherence difficult	—
Alpha-glucosidase inhibitors	• Slow digestion of some carbohydrates	Acarbose Miglitol	0.5-0.8	Weight neutral, do not cause hypoglycemia	Frequent GI side effects, dosing 3 times/d	\$ \$
Amylin analog	• Slow gastric emptying • Prevent postprandial rise of glucagon • Satiety	Pramlintide	0.5-1.0	Weight loss	Injections, dosing 3 times/d, frequent GI side effects, limited experience	\$
Biguanide	• Decrease hepatic glucose production	Metformin	1.5	Weight neutral, may improve lipid profile	GI side effects, lactic acidosis (rare)	\$
Dipeptidyl peptidase-4 enzyme inhibitor	• Inhibit degradation of incretins	Sitagliptin	0.5-0.7	Weight neutral	Limited experience	—
Incretin mimetic	• Stimulate pancreatic insulin • Suppress inappropriate glucagon secretion • Slow gastric emptying	Exenatide	0.5-1.0	Weight loss	Injections, frequent GI side effects, limited experience	\$\$\$
Insulin	• Replace insulin	See Table on page 4	1.5-2.5	No dose limit, improved lipid profile	Injections, self-monitoring of blood glucose twice daily or more often, hypoglycemia, weight gain	\$
Meglitinides	• Stimulate pancreatic insulin secretion	Nateglinide Repaglinide	1-1.5*	Short duration	Weight gain, dosing 3 times/d	\$\$ \$\$
Sulfonylureas	• Stimulate pancreatic insulin secretion	Acetohexamide Chlorpropamide Glimepiride Glipizide Glyburide Tolazamide Tolbutamide	1.5	—	Weight gain, hypoglycemia†	— \$ — \$ \$ \$ —
Thiazolidinediones	• Decrease insulin resistance • Decrease hepatic glucose production	Pioglitazone Rosiglitazone	0.5-1.4	Improved lipid profile	Fluid retention, weight gain	\$\$\$ \$\$

*Repaglinide is more effective for lowering A1C than is nateglinide.

†Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (eg, chlorpropamide, glyburide, and sustained-release glipizide) are more likely to cause hypoglycemia than are glipizide (immediate release), glimepiride, and gliclazide.

‡Based on an average daily maintenance dose of available products. \$ = <\$3.00/day; \$\$ = \$3.01-5.00/day; \$\$\$ = \$5.01-10.00/day. Source: www.drugstore.com.

Accessed November 4, 2006.

GI = gastrointestinal.

⁷Nathan DM, et al. Diabetes Care. 2006;29:1963-1972; ⁵⁷McCarren M. Diabetes Forecast. Available at: http://www.diabetes.org/uedocuments/rg06_type2.pdf. Accessed November 1, 2006. ⁵⁸Symlin [prescribing information]. San Diego, Calif: Amylin Pharmaceuticals Inc; 2005; ⁵⁹Januvia [prescribing information]. Whitehouse Station, NJ: Merck & Co Inc; 2006; ⁶⁰Byetta [prescribing information]. San Diego, Calif: Amylin Pharmaceuticals Inc; 2006.

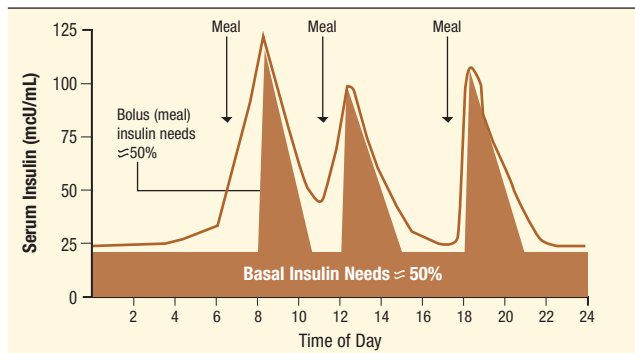
Several factors should be considered when selecting the specific agent(s) to be used for individual patients, including the magnitude of the glycemia-lowering effect, extraglycemic effects that may reduce long-term complications, safety, and tolerability (TABLE 1).⁷ Clearly the most important factor is the effectiveness of an agent for lowering glycemia. In this regard, exogenous insulin is the most effective agent for T1DM and T2DM when dosed appropriately. When used in adequate doses, insulin can decrease glycemia and A1C levels to essentially any level desired.⁷ Of the oral agents, metformin and the sulfonylurea agents are the most effective for reducing the A1C level, typically on the order of 1.5%. The alpha-glucosidase inhibitors and dipeptidyl peptidase-4 enzyme inhibitors are generally the

least effective for reducing A1C levels (TABLE 1).

Other factors might be considered in developing the treatment plan. Alpha-glucosidase inhibitors, insulin, metformin, pramlintide, and sulfonylureas are relatively inexpensive. The thiazolidinediones, particularly pioglitazone,^{8,9} and insulin have a positive effect on lipid profiles.

Weight gain is a disadvantage of the sulfonylurea, thiazolidinedione, meglitinide, and most insulin preparations, whereas alpha-glucosidase inhibitors, metformin, insulin detemir, and sitagliptin are weight neutral, and exenatide and pramlintide promote weight loss. Hypoglycemia is a concern with insulin and sulfonylurea agents, although severe hypoglycemia is relatively rare with the newer sulfonylurea agents (glimepiride, glipizide).^{10,11} Patients with

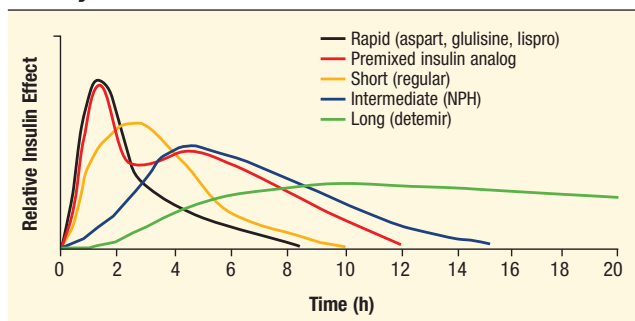
FIGURE 1
Time course of physiologic insulin secretion and its ideal replacement¹⁶⁻¹⁸



¹⁶Tillel H et al. *Am J Physiol.* 1998;254:E349-E357; ¹⁷Polonsky KS et al. *N Engl J Med.* 1988;318:1231-1239.

Adapted with permission from Brunton S, Carmichael B, Funnell M, Lorber D, Rakel R, Rubin R. Type 2 diabetes: the role of insulin. *J Fam Pract.* 2005;54(5):445-452.¹⁸

FIGURE 2
Activity curves of selected insulins¹⁶⁻¹⁸



¹⁶Tillel H et al. *Am J Physiol.* 1998;254:E349-E357; ¹⁷Polonsky KS et al. *N Engl J Med.* 1988;318:1231-1239.

Adapted with permission from Brunton S, Carmichael B, Funnell M, Lorber D, Rakel R, Rubin R. Type 2 diabetes: the role of insulin. *J Fam Pract.* 2005;54(5):445-452.¹⁸

T2DM are much less likely to experience hypoglycemia than are patients with T1DM, with reported rates of 1 to 3 per patient-year¹²⁻¹⁴ and 61 per patient-year,¹⁵ respectively. Alpha-glucosidase inhibitors, exenatide, metformin, and pramlintide can cause gastrointestinal side effects. Nausea, vomiting, or diarrhea occur in 30% to 45% of patients treated with exenatide.⁷ Exenatide, insulin, and pramlintide are administered parenterally; insulin can also be administered by oral inhalation.

Insulin Overview

The insulin preparations now available are dramatically different from those first introduced when insulin was discovered in the early 1900s. Insulin preparations are now highly purified, with recombinant human insulin having virtually eliminated insulin allergy and immune-mediated lipoatrophy. During the last decade, development of insulin preparations has focused on duplicating the basal and mealtime components of endogenous insulin secretion to

more effectively manage glycemia and reduce the risk of hypoglycemia.

The ideal insulin preparation should produce the same biphasic physiologic pattern as that of endogenous insulin in a healthy person. After food intake, serum insulin levels should rise rapidly from a baseline of 5-20 mcU/mL, reaching a peak concentration of 80-120 mcU/mL within 30 to 60 minutes after the meal, followed by a rapid return to baseline before the next meal (FIGURE 1).¹⁶⁻¹⁸ This physiologic serum insulin profile reflects both the basal (baseline) and prandial (mealtime) secretion of insulin after a meal. Approximately half of the total daily insulin dose should cover glycemia associated with the basal need, reserving the remaining half for prandial needs. The rapid initial rise in the insulin level affords postprandial glycemic control, and the rapid decline reduces the potential for hypoglycemia between meals and secondary weight gain. Low basal concentrations of insulin reduce hepatic glucose production yet allow sufficient glucose levels for brain energy production.¹⁷ Additionally, the maintenance of near-normal basal insulin levels improves long-term metabolic control and reduces the risk of late complications of diabetes.

None of the insulin preparations currently available exactly mimic the endogenous biphasic insulin pattern (FIGURE 2).¹⁸ The rapid- and short-acting insulins are best suited for coverage of mealtime glycemia, whereas the intermediate- and long-acting insulins serve to control basal levels of plasma glucose. Regular human insulin has a relatively slow onset of action and must be administered 30 minutes before meals, whereas the rapid-acting insulin analogs (insulin aspart, insulin glulisine, and insulin lispro) have a faster onset and can be taken 15 minutes prior to meals.¹⁹⁻²¹ Furthermore, the peak effect is greater and the duration of action is shorter for insulin aspart, insulin glulisine, and insulin lispro compared with that for regular human insulin.²²⁻²⁴ Insulin detemir and insulin glargine have an onset similar to that of neutral protamine Hagedorn (NPH) insulin, but exhibit a relatively flat time-action profile and a longer duration of action that generally permits once-daily dosing.²⁵⁻²⁷ For many patients, various insulin combinations are used—typically a rapid- or short-acting insulin with an intermediate- or long-acting insulin—to more closely simulate the physiologic insulin profile. Many of these combinations are available as premixed formulations.

Bolus Insulin Analogs

In recent years, analogs of human insulin have been designed to better reflect the physiologic insulin secretion profile. As stated, rapid-acting insulin analogs currently available are insulin aspart, insulin glulisine, and insulin lispro. The ideal rapid-acting insulin analog should have an onset of action of less than 1 hour, a duration of action of less than 4 hours, and minimal, if any, inpatient variability.

ity. Reduced variability in absorption within individuals has been documented for insulin aspart and insulin lispro compared with regular human insulin.^{28,29} Rapid-acting insulin analogs are associated with a more rapid onset than is associated with regular human insulin. The mean peak insulin action has been shown to be 99 minutes for insulin lispro compared with 179 minutes for regular human insulin²⁹ and 94 minutes for insulin aspart compared with 173 minutes for regular human insulin.²³ Thus, patients do not have to administer their insulin analog 30 minutes before the meal as with regular human insulin, but can take insulin aspart, glulisine, or lispro within 15 minutes of the meal, which tends to be more convenient.

The rapid-acting insulin analogs also have a shorter duration of action compared with regular human insulin, thereby providing a short, rapid burst of insulin to respond to meal-stimulated glucose, which lowers postprandial blood glucose levels more effectively than does regular human insulin, while reducing the risk of hypoglycemia between meals. Because of the more rapid onset of action associated with rapid-acting insulin analogs, glucose-lowering effects occur sooner with these agents than with regular human insulin.^{30,31} The frequency of severe hypoglycemia has been reported to be reduced by 25% for patients using insulin lispro compared with regular human insulin.³² When administered at dinnertime, rapid-acting insulin analogs do not require a bedtime snack because their duration of action does not overlap with the action of bedtime basal insulin. Patients who exercise within 1 to 3 hours of a meal require a decrease in the insulin dose each time they exercise, whereas individuals who exercise 3 to 5 hours after a meal require a smaller change in dose or none at all.³³

Basal Insulin Analogs

Intermediate-acting insulin (NPH) has been used for many years (as was the long-acting insulin ultralente until its removal from the market), but has been associated with the risk of hypoglycemia, variable response, and other issues.³⁴

To overcome these limitations, the insulin molecule has been altered structurally such that the basal insulin analogs (insulin detemir and insulin glargine) are slowly taken up into the systemic circulation. Insulin detemir self-associates into hexamers and dimeric hexamers at the injection site and binds to albumin at the injection site and in the systemic circulation, further delaying its distribution to target tissues.³⁵ Insulin glargine has limited solubility at the injection site, precipitating in the subcutaneous tissue to form a depot from which insulin is slowly released.³⁶ As a result, both of these insulin analogs exhibit a long, relatively flat pharmacokinetic profile with a duration of action of up to 24 hours,²⁵ which is longer than that of NPH and comparable to that of the now unavailable ultralente insulin.³⁷

The rate of absorption of insulin glargine at different sites does not differ,³⁷ and no evidence suggests that insulin

glargine accumulates after multiple injections.³⁸ The pharmacokinetic profile of insulin detemir is consistent across age groups³⁹ and exhibits less within-subject pharmacodynamic variability than either NPH insulin or insulin glargine.⁴⁰

Hypoglycemia occurs less frequently in patients treated with basal insulin analogs compared with other intermediate- and long-acting insulins. Riddle and colleagues observed 13.9 hypoglycemic events per patient-year in patients with T2DM treated with insulin glargine at bedtime compared with 17.7 events per patient-year in patients treated with NPH insulin once daily ($P < .02$).⁴¹ The mean A1C levels were the same for both groups at baseline (8.6%) and study end (7.0%). Other studies have yielded similar results.^{42,43} In combination with oral agents, the risk of all hypoglycemic events was reduced 47% and the risk of nocturnal hypoglycemia was reduced by 55% with insulin detemir, compared with NPH insulin at comparable levels of glycemic improvement in patients with T2DM.⁴⁴ Among patients with T1DM, the incidence of minor and nocturnal hypoglycemia was significantly lower for patients treated with twice-daily insulin detemir compared with patients treated with twice-daily NPH insulin.⁴⁵

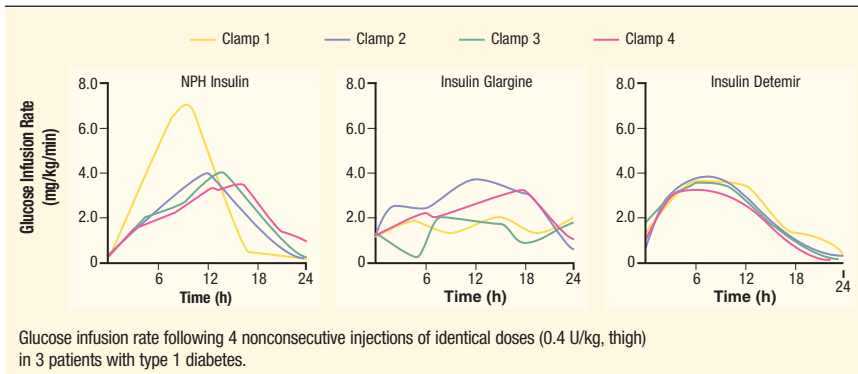
A possible explanation for the lower incidence of hypoglycemia with insulin detemir is less variability of the glucose-lowering effect compared with insulin glargine and NPH.⁴⁰ In a randomized, double-blind study of patients with T1DM, each participant received 4 single subcutaneous doses of 0.4 U/kg of insulin detemir ($n=18$), insulin glargine ($n=16$), or human NPH insulin ($n=17$) under euglycemic glucose clamp conditions (target blood glucose concentration, 100 mg/dL), 1 dose on each of 4 identical, nonconsecutive study days. The pharmacodynamic (glucose infusion rates [GIRs]) and pharmacokinetic (serum concentrations of insulin detemir, human insulin, and insulin glargine) properties of the basal insulin preparations were recorded for 24 hours after each dosing. Insulin detemir was associated with significantly less within-subject variability than both NPH insulin and insulin glargine, as assessed by the coefficient of variation (CV) for the pharmacodynamic end points studied (**FIGURE 3**). The results suggest that insulin detemir has a significantly more predictable glucose-lowering effect than both NPH insulin and insulin glargine.

Premixed Insulin Analogs

To attain the goal levels of A1C, fasting plasma glucose (FPG), and postprandial glucose (PPG), basal and bolus insulin analogs are usually used in combination. To simplify administration, premixed insulin preparations are available that combine basal and bolus insulin analogs:

Insulin lispro premix 75/25 contains insulin lispro protamine suspension as the long-acting component, mixed at a 75/25 ratio with rapid-acting insulin lispro. A 50/50 mix also is available.

FIGURE 3
Within-subject variability of the glucose-lowering effect of intermediate and long-acting insulins⁴⁰



Glucose infusion rate following 4 nonconsecutive injections of identical doses (0.4 U/kg, thigh) in 3 patients with type 1 diabetes.

NPH = neutral protamine Hagedorn.

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Insulin aspart premix 70/30 (BIAsp 70/30) contains insulin aspart protamine suspension as the long-acting component, mixed at a 70/30 ratio with rapid-acting insulin aspart.

BIAsp 70/30 has been shown to lower elevated PPG excursions compared with both human insulin premix 70/30 and insulin lispro premix 75/25.^{46,47} In patients with T2DM, BIAsp 70/30 significantly improved postprandial glycemic control without increasing the risk of hypoglycemia when compared with human insulin premix 70/30.⁴⁸ In a study of 100 patients with T2DM that was poorly controlled by oral antidiabetic drug (OAD) regimens with or without basal insulin, the addition of BIAsp 70/30 was shown to be effective for reaching glycemic goals.⁴⁹ With 1 daily injection of BIAsp 70/30 before dinner, an A1C level of 6.5% or lower was achieved in 21% of patients, and an A1C level lower than 7% was achieved in 41%. With 2 daily injections, 52% and 70% of patients achieved these two A1C goals, respectively, and with 3 daily injections, 60% and 77% of patients, respectively, reached these target A1C levels. Major hypoglycemia was reported by 3 patients during both once-daily and twice-daily dosing and by 1 patient who received thrice-daily dosing. Thus, patients can start with once-daily administration of BIAsp 70/30 and intensify as necessary without changing their insulin preparation. Interestingly, in patients with T2DM, twice-daily doses of BIAsp 70/30, when taken at breakfast and dinner, were shown to be nearly as effective as basal-bolus therapy using insulin detemir once daily plus insulin aspart 3 times daily.⁵⁰

Although basal-bolus therapy requires 4 or more injections per day, or use of an insulin pump, carbohydrate counting, and self-monitoring of blood glucose levels several times daily, premixed insulin analogs may not be suitable for all patients with DM. For example, premixed insulin analogs may not provide enough exogenous insulin for

lunchtime needs when administered twice daily—before breakfast and dinner. They may, therefore, be better suited for persons who eat relatively small lunches,²⁴ as well as those who have fairly regular eating habits and schedules.

Insulin in Combination with Oral Agents

Most patients with T2DM begin their treatment management with lifestyle modifications and, if target A1C levels are not met, progress to oral agents. Therefore, insulin is most frequently added to oral antidiabetic regimens. Only 42.3% of patients diagnosed with T2DM are at the A1C goal, according to the latest

NHANES data. (See “The Role of the Family Physician in the Diagnosis and Treatment of Type 2 Diabetes Mellitus” on page 5 of this supplement.) One reason for this unacceptably low level of success may be an overreliance on oral agents by primary care providers. OADs will reduce A1C levels by only 1% to 2% when used as monotherapy and perhaps 2% to 4% when used in combination with other OADs. Yet 52% of patients are treated with OAD therapy without any insulin use. Ten percent of patients use a combination of OADs plus insulin. The following section provides clinical data related to combination therapy with insulin and various oral agents.

After the positive benefits of adding insulin to sulfonylurea therapy were observed in the United Kingdom Prospective Diabetes Study (UKPDS) and the finding that glycemic control declined over time despite maximal doses of OADs alone, several clinical trials investigated the efficacy of insulin for patients whose T2DM was not maximally controlled with the use of 1 or more OADs.

OADs Plus Basal Insulin

The addition of basal insulin to OADs has been investigated in several trials. Yki-Jarvinen and colleagues compared bedtime NPH regimens of 96 patients with T2DM that was poorly controlled with sulfonylurea therapy (mean A1C level, 9.9%).⁵¹ All patients received NPH insulin at bedtime and were randomized in double-blind fashion to also receive glyburide, metformin, glyburide plus metformin, or a second injection of NPH in the morning. The insulin dose was adjusted based on self-monitoring of blood glucose levels.

At 3 months, patients in the bedtime NPH plus glyburide and metformin group had significantly lower A1C levels than did patients in the other groups. Patients in the bedtime NPH plus metformin group showed a progressive decline in A1C level over time. At 1 year, the mean A1C

level in this group was 7.2%, whereas the mean A1C level for the other 3 groups ranged from 7.6% to 7.9% ($P < .05$). The bedtime NPH and metformin group also experienced significantly fewer symptomatic and biochemical cases of hypoglycemia than the other groups.

For patients who have T2DM with inadequate glycemic control (mean baseline A1C level, 8.6%) while taking 1 or 2 oral agents, the addition of a basal insulin analog has demonstrated similar benefits in two “treat-to-target” studies. In the first study, 756 overweight patients were randomized to receive bedtime insulin glargine or NPH insulin once daily for 24 weeks in addition to their prestudy oral agents.⁴¹ Insulin therapy was monitored and titrated weekly using a forced titration algorithm to achieve an FPG level of 100 mg/dL or less. At study end, the mean A1C level was 7.0% for both groups. About 60% of patients in each group achieved an A1C value of 7% or less, but more patients in the glargine group than in the NPH group did so without documented nocturnal hypoglycemia (33% vs 27%, respectively). In the second study, 475 persons were randomized to treatment with insulin detemir or NPH insulin, both administered twice daily using an open-label protocol.⁴⁴ Patients continued treatment with OAD therapy (consisting of metformin plus secretagogue in ~65%). Insulin doses were titrated using an algorithm to achieve a prebreakfast and predinner plasma glucose of 108 mg/dL or less. After 24 weeks, A1C levels decreased from 8.6% to 6.8% and 8.5% to 6.6% in the detemir and NPH groups, respectively. Seventy percent of patients in both groups achieved an A1C level of 7% or less, but more patients in the insulin detemir group achieved an A1C level of 7% or less without hypoglycemia during the last 12 weeks of treatment compared with the NPH group (26% vs 16%, respectively [$P = .008$]).

OAD Plus OAD or Basal Insulin or Bolus Insulin Analog

The efficacy of bolus insulin, basal insulin, or the addition of another OAD has been evaluated among patients with T2DM that was not adequately controlled with oral sulfonylurea agents alone.⁵² In one trial, 135 patients were randomized to receive 3 months of treatment with glyburide in combination with insulin lispro before meals, metformin, or bedtime NPH insulin. At study end, the mean A1C level was significantly lower in the insulin lispro group compared with either the metformin or the NPH group (7.7%, 8.3%, and 8.5%, respectively). An end point A1C level less than 7% was attained in 23%, 8%, and 10% of patients, respectively (FIGURE 4). The superiority of insulin lispro (with glyburide) for improving A1C levels was determined by statistical analysis to largely result from the effectiveness of insulin lispro for lowering 2-hour PPG and elevated glucose levels compared with metformin or bedtime NPH insulin. Patient self-monitoring of blood glucose concentrations showed that the levels were generally lower in the glyburide plus insulin lispro group compared

with the other 2 groups during much of a 24-hour period.

Another study compared the efficacy and safety of insulin glulisine with regular human insulin, both given twice daily, in combination with twice-daily NPH for 876 patients with T2DM (mean A1C level, 7.6%).⁵³ All patients continued their prestudy OAD therapy. After 26 weeks of treatment, the A1C level decreased by a mean of 0.5% for the glulisine group compared with 0.3% for the regular human insulin group ($P = .0029$). Also at the end of the study, lower postbreakfast (156 vs 162 mg/dL; $P < .05$) and postdinner (154 vs 163 mg/dL; $P < .05$) blood glucose levels were found in the glulisine group compared with the regular human insulin group, respectively. Symptomatic hypoglycemia and weight gain were comparable between the 2 groups.

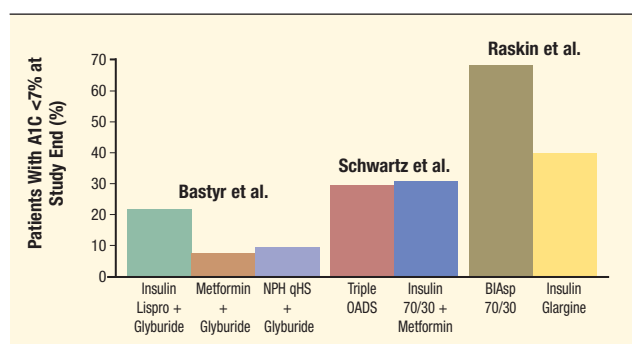
Premixed Human Insulin

The use of premixed human insulin has been compared with triple oral therapy, showing comparable lowering of A1C and FPG levels in 188 patients with T2DM who had an inadequate response to 2 oral agents (mean A1C level, 9.6% at baseline).⁵⁴ Patients were randomized to treatment with a third oral agent (in a different pharmacologic category from the other 2) or premixed human insulin (70% NPH/30% regular human insulin) in combination with metformin. Although a reduction in A1C level occurred more quickly for the insulin plus metformin group, no significant difference in mean A1C level was observed between groups at weeks 12 and 24. The mean A1C level at 24 weeks was 7.6% for both groups, with an equivalent percentage in both groups achieving an A1C level less than 7% (FIGURE 4).

Premixed Insulin Analog vs Basal Insulin Analog

One recent study compared the use of twice-daily insulin aspart premix 70/30 with a single injection of long-acting insulin glargine.⁵⁵ Each insulin was used with a simple titra-

FIGURE 4
 Effectiveness of various agents for lowering A1C values below 7%—Results from 3 trials^{52,54,55}



NPH = neutral protamine Hagedorn; OADs = oral antidiabetic drugs; qHS = every night.
⁵²Bastyr EJ III, et al. *Diabetes Care*. 2000;23:1236-1241; ⁵⁴Schwartz S, et al. *Diabetes Care*. 2003;26:2238-2243; ⁵⁵Raskin P, et al. *Diabetes Care*. 2005;28:260-265.

tion schedule for 233 patients with T2DM in whom glycemic targets could not be achieved with OADs alone (mean A1C value, $\geq 8.0\%$). Secretagogues and alpha-glucosidase inhibitors were discontinued during the run-in period, metformin was optimized to 1500 mg/day or more, and patients receiving pioglitazone were switched to rosiglitazone. Patients were then randomized to receive either insulin glargine (10-12 U) at bedtime, or BIAsp 70/30 before breakfast and dinner (5 or 6 U per dose). At 28 weeks, a significantly greater percentage of patients had an A1C value below 7.0% and 6.5% with twice-daily BIAsp 70/30 versus bedtime glargine (66% vs 40% and 42% vs 28%, respectively) (FIGURE 4).

Furthermore, these data are supported by another study that demonstrated that more patients who received insulin lispro premix twice daily plus metformin had an A1C level of 7% or less compared with glargine once daily plus metformin (41% vs 22%, respectively).⁵⁶ Additionally, the rise in 2-hour blood glucose concentrations after breakfast and dinner was lower in the premix group (18 vs 47 mg/dL, respectively), demonstrating the importance of addressing PPG concentrations in insulin treatment strategies.

The results of these trials clearly demonstrate the benefits of combining insulin with oral agents for patients with T2DM. These benefits include significant reduction with near normalization of A1C, FPG, and PPG levels for many patients. Moreover, results of these trials support the use of basal and bolus insulin analogs as reasonable and effective choices when initiating insulin therapy for patients with T2DM.

Summary

The effective management of diabetes requires nonpharmacologic and pharmacologic therapy. Nonpharmacologic therapy—consisting primarily of weight reduction and increased physical activity—is generally singularly effective for only a short period of time. The mainstay of pharmacologic therapy has been the use of 1 or more OADs, although the long-term ability of maximal OAD therapy to achieve glycemic control generally declines. Insulin formulations have evolved over time and now provide more physiologic levels while minimizing hypoglycemic episodes and weight gain. The newer insulin analogs more closely parallel the basal or mealtime components of endogenous insulin secretion. The use of insulin analogs for basal-bolus therapy, often in combination with an OAD such as metformin, frequently provide near normalization of A1C, FPG, and PPG levels for many patients.

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Options for Insulin Delivery and Overcoming Physician and Patient Concerns

■ Russell D. White, MD

KEY POINTS & RECOMMENDATIONS

- Negative attitudes on the part of the patient with diabetes—as well as the physician—can create important barriers that prevent the intensification of treatment for patients who require it. (SOR: B)
- Many patient fears and concerns about insulin relate to the perceived complexity of insulin delivery, anticipated complications, and disease severity. (SOR: A)
- To help overcome barriers to insulin therapy, it may be helpful to quantify the A1C goal and the time period in which to achieve it and to conspicuously track the patient's progress toward achieving that goal. (SOR: C)
- The availability of several different systems for delivering insulin provides the opportunity to individualize treatment to better meet patient needs. (SOR: C)

Barriers to Insulin Therapy

While treatment decisions are ultimately made by the patient with diabetes, negative attitudes held by the patient—as well as the physician—create important barriers that may prevent the intensification of treatment despite the established benefits.¹⁻⁵ An overarching factor that contributes to resistance to intensifying therapy is the relatively silent nature of type 2 diabetes mellitus (T2DM) until late in the course of the disease.⁶ Until that time, diabetes is often marked by abnormal laboratory values with few symptoms. Consequently, the use of drugs, with their attendant side effects, costs, and administration difficulties, may be viewed by some as more problematic than diabetes

itself. Because of existing resistance to intensifying therapy, it is not surprising that adding insulin can be a major challenge.⁵

Patient Barriers

The mere mention of insulin therapy is likely to produce considerable fear or concern among some patients with T2DM. This reaction may often be influenced by experiences of family and friends who have used insulin. No matter what may be the basis of the fear or concern, addressing these issues is essential for the successful initiation and long-term use of insulin. Possible questions to ask patients that may be helpful toward uncovering and thoroughly understanding their perspective are shown in **TABLE 1**.⁷

Surveys have been conducted to identify the patient's fears or concerns that serve as barriers to initiating insulin therapy.^{5,8,9} Many of these fears or concerns about insulin relate to the complexity involved in insulin delivery, fear of injections, fear of hypoglycemia and weight gain, anticipated complications, and disease severity. (See "Practical Strategies for Achieving Targeted Glycemic Control in Patients With Type 2 Diabetes" on page 25 of this supplement.)

Education. Because many of the barriers to initiating insulin therapy stem from misperceptions, the best way for family physicians to overcome these barriers is to provide patient education, beginning at the time of diagnosis. For example, a patient who believes insulin is only for individuals with type 1 diabetes mellitus (T1DM) should be educated about the progressive decline in insulin production associated with T2DM. A patient who believes insulin injections are painful should be shown the different devices for administering insulin. If possible, injecting the patient with a comparable volume of saline will demonstrate the minimal discomfort involved.

The patient's concerns about the complexity of insulin administration and monitoring also should be addressed at the time of diagnosis. Helping patients to be self-sufficient and to feel more in control of their diabetes is likely to provide them with a "can do" attitude, not only regarding insulin therapy but about diabetes in general. Also helpful is communicating to the patient that a variety of insulin therapies are available that can be selected based on the patient's preferences. (A description of these therapies appears below.) Fears that insulin will worsen the disease should also be addressed by explaining the progressive nature of T2DM and complications caused by uncontrolled hyperglycemia, and how these developments can be delayed or prevented by tight glycemic control with insulin.

Adherence. Once insulin therapy has been initiated, patient education should focus on identifying and addressing barriers to long-term adherence and self-management. This step is critically important yet often difficult, given the necessary modifications to lifestyle and nutrition, the drug treatments typically involved, and the need for self-monitoring of blood glucose levels. Adherence rates to oral blood-glucose-lowering therapy from 65% to 85% are common, although rates of only 36% to 54% have been reported for Medicaid recipients and patients taking medications requiring frequent dosing.¹⁰ Adherence to insulin-containing regimens has been reported to be lower than that with oral antidiabetic drugs (OADs),^{10,11} although this finding is uncertain.¹²

Many factors may contribute to patients' nonadherence (TABLE 2).¹⁰ Although many of these factors may in fact be the same barriers to initiating therapy, other factors may also emerge. The Diabetes Distress Scale, which asks patients to rate their level of concern for 17 issues, may be a helpful tool in this regard (TABLE 3).¹³ All of these factors should be explored on a regular basis, especially if the response to treatment is less than expected. Again, it is important for physicians to communicate that they and the rest of the health care team will work with the patient to prevent anticipated concerns and to resolve additional concerns as they arise.

Clinician Barriers

Patients are not alone in resisting insulin therapy—many clinicians also resist its implementation despite ample evidence demonstrating the benefits of tight glycemic control and the relatively small percentage of patients with T2DM who maintain excellent glycemic control with OADs. For patients with T2DM, the use of insulin—with or without an OAD—remained unchanged at 27%, from the period of the National Health and Nutrition Examination Survey (NHANES) III study in 1988-1994 to the NHANES 1999-2000 study. Between these time periods, the percentage of individuals receiving insulin alone decreased from 24% to 16%, while patients treated with insulin and an OAD increased from 3% to 11%.¹⁴

TABLE 1
Assessment questions for decision making about insulin therapy⁷

<ul style="list-style-type: none"> • What is your greatest concern about your diabetes? • What is the hardest thing for you in taking care of your diabetes? • How satisfied are you with your current therapy for diabetes? • How satisfied are you with your current level of glucose control? • How interested are you in making a change in therapy? • What do you need to know to consider insulin therapy? • What is your biggest fear about insulin? • What problems do you think that you will encounter? • What do you see as the biggest negative aspect for you? • What do you see as the most positive aspect for you? • What supports do you have to overcome barriers? • How faithful do you think you would be in taking your insulin? • Are you willing to try insulin? If not, what would cause you to start taking insulin?

Funnell MM, Kruger DF, Spencer M. *Diabetes Educator*, volume 30, pages 274-280,⁷ copyright © 2004 by Sage Publications, Inc. Reprinted by permission of Sage Publications, Inc.

TABLE 2
Interventions to facilitate treatment adherence¹⁰

Barrier	Goal/Target	Intervention
Poor comprehension of the treatment regimen	Enhance regimen recall/comprehension	<ul style="list-style-type: none"> • Verify patient's understanding while in the office • Use visual aids • Involve other members of the diabetes health care team
Inappropriate perception of treatment benefits	Enhance perceived benefits of regimen	<ul style="list-style-type: none"> • Clarify limited symptom relief and importance of optimal glycemic control • Find meaningful long-term benefits
Overestimation of incidence and severity of adverse effects	Minimize adverse effects	<ul style="list-style-type: none"> • Discuss and monitor • Make adjustments
Fear of hypoglycemia and weight gain	Minimize hypoglycemic episodes and weight gain	<ul style="list-style-type: none"> • Educate about prevention of hypoglycemia and weight gain, and treatment for hypoglycemia
Cost of treatment higher than ability/willingness to pay	Minimize costs	<ul style="list-style-type: none"> • Discuss and monitor • Change regimen when appropriate • Check health insurance • Check for patient assistance programs
Complex treatment regimen	Minimize regimen complexity without compromising glycemic goals	<ul style="list-style-type: none"> • Monitor • Change regimen when appropriate
Impaired emotional well-being	Facilitate emotional well-being	<ul style="list-style-type: none"> • Screen for depression • Treat or refer depressed patients • Screen for diabetes-related distress • Facilitate problem solving • Refer for diabetes education

Adapted with permission from Rubin RR. Adherence to pharmacologic therapy in patients with type 2 diabetes mellitus. *Am J Med*. 2005;118(suppl 5A):27S-34S.¹⁰

TABLE 3
The Diabetes Distress Scale¹³

Each item is rated on a 6-point scale from 1 (no problem) to 6 (serious problem)
1. Feeling that diabetes is taking up too much of my mental and physical energy every day.
2. Feeling that my doctor doesn't know enough about diabetes and diabetes care.
3. Feeling angry, scared, and/or depressed when I think about living with diabetes.
4. Feeling that my doctor doesn't give me clear enough directions on how to manage my diabetes.
5. Feeling that I am not testing my blood sugar levels frequently enough.
6. Feeling that I am often failing with my diabetes regimen.
7. Feeling that friends or family are not supportive enough of my self-care efforts (eg, planning activities that conflict with my schedule, encouraging me to eat the "wrong" foods).
8. Feeling that diabetes controls my life.
9. Feeling that my doctor doesn't take my concerns seriously enough.
10. Not feeling confident in my day-to-day ability to manage diabetes.
11. Feeling that I will end up with serious long-term complications, no matter what I do.
12. Feeling that I am not sticking closely enough to a good meal plan.
13. Feeling that friends or family don't appreciate how difficult living with diabetes can be.
14. Feeling overwhelmed by the demands of living with diabetes.
15. Feeling that I don't have a doctor I can see regularly about my diabetes.
16. Not feeling motivated to keep up my diabetes self-management.
17. Feeling that friends or family don't give me the emotional support that I would like.

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TABLE 4
Steps for overcoming clinician barriers to insulin therapy⁶

1. Establish an "actionable" A1C goal for each patient with diabetes <ul style="list-style-type: none"> a. ADA goal <ul style="list-style-type: none"> i. General: <7.0% ii. Individual: As close to normal (<6%) as possible without significant hypoglycemia b. AACE goal ≤6.5%
2. Establish time frame for achievement of A1C goal
3. Publicly display progress toward achieving the A1C goal for the patient <ul style="list-style-type: none"> a. Keep A1C results prominently displayed in the patient's medical record b. Make the patient aware in advance of the A1C goal
AACE = American Association of Clinical Endocrinologists; ADA = American Diabetes Association.

Adapted from *Insulin*, volume 1, Shaefer CF; Clinical inertia: Overcoming a major barrier to diabetes management; pages 61-64; Copyright © 2006, with permission from Excerpta Medica, Inc.

Several of the barriers to insulin therapy that patients experience are also experienced by clinicians.^{5,6,15,16} This observation is not entirely surprising since clinicians may inadvertently communicate their biases to their patients.¹⁷ Whatever the clinician's barriers to initiating insulin therapy may be, it is important that she or he examine the cause(s) of these barriers in full recognition of the evidence and available treatment options. At the same time, a greater sense of urgency in achieving the evidence-based goals of the American Association of Clinical Endocrinologists (AACE) or the American Diabetes Association (ADA) is critical.

Overcoming Barriers. To overcome these barriers, Shaefer suggests the implementation of 3 simple strategies in the primary care setting (TABLE 4).⁶ These strategies can help to consistently and accurately assess each patient's care and to avoid "being pulled off task by soft reasons for not acting."⁶

The first 2 strategies relate to clearly identifying the goal of treatment in terms of both the A1C goal and the time frame for achieving that goal. Together, both help to focus the clinician and the patient on a specific, quantifiable goal instead of an abstract goal such as a "low A1C over the next year or so." Depending on the baseline A1C level and the treatment used, the time frame to reach the A1C goal will vary. (See "Practical Strategies for Achieving Targeted Glycemic Control in Patients With Type 2 Diabetes" on page 25 of this supplement.) In clinical trials, mean reductions in A1C of 0.5% to 3.1% have been observed over 12 to 28 weeks.¹⁸⁻²²

The third strategy is to display the progress toward achieving the treatment goal on a chart in the patient's medical record. This serves to keep diabetes and its ongoing management in the forefront of both the clinician's and patient's minds, thereby avoiding the potential to file the A1C result away and "forget about it."

In response to the numerous barriers to initiating insulin treatment—some of which stem from myths and misperceptions, while others may concern lifestyle and personal preferences—many different options have been developed and are now available to patients to meet their individual needs for insulin delivery.

Insulin Delivery Options

In the outpatient setting, the delivery of insulin has routinely been performed using a vial and syringe, mainly because this method was the first to be developed, is widely available, and can accommodate all insulin types. However, there are several drawbacks to the use of a vial and syringe to deliver insulin, many of which may present themselves as barriers to use.

Some of the difficulties encountered with the use of a vial and syringe can be overcome or lessened with various injection aids or alternatives. Injection aids for syringes include those that accelerate needle insertion into the skin or aid in pushing down the plunger. Most injection aids are spring-loaded and hide the needle from view. For people who are visually impaired, several products are available to make injecting insulin easier. Needle guides and vial stabilizers help patients insert the needle into the correct insulin vial. Syringe magnifiers attach to the barrel of the syringe and make it easier to read the marks on the syringe.²³

Insulin Pens

Insulin pens are prefilled or reusable insulin-containing cartridges with disposable needles. They are convenient, accurate, inconspicuous, and often used by people who require

multiple daily injections of insulin. Insulin pens are especially useful to improve injection accuracy for patients with poor dexterity or neurologic impairment and for patients requiring small doses, or for individuals whose schedules make multiple daily injections difficult (TABLE 5).²⁴ Although insulin pen use is still low in the United States, insulin pens are the main delivery system throughout most other Western countries.²⁵

Several studies have reported patient preference for insulin pens compared with vials and syringes.²⁶⁻²⁹ Insulin pens can improve the accuracy of insulin administration because low-dose insulin pens can deliver insulin in half-unit increments, which is attractive for patients using small doses (ie, <5 units) of insulin. In addition, when the dial of the insulin pen is turned to select the dose, the patient can feel and/or hear clicks corresponding to each dosing unit. This feature, along with a dose scale that is easy to read,²⁸ may make the insulin pen particularly helpful for patients with poor dexterity or cognitive impairment. Eighty-two percent of patients have reported increased confidence in setting the dose with an insulin pen compared with 11% of patients using a vial and syringe, with 73% and 19%, respectively, reporting more confidence with the accuracy of the dose delivered.²⁸

Other reasons contributing to patients' preference for pens over vials and syringes include overall ease of use^{26,28,29} and faster and easier administration,²⁶ thereby providing patients with a more discreet method for administering insulin outside the home.²⁸ Adherence to insulin therapy has been observed to be greater among patients using a pen device compared with the vial and syringe. Eighty-five percent of patients reported missing no injections while using the pen device compared with 72% using the vial and syringe.²⁷ Improved adherence is likely to result in improved glycemic control, although this assumption has not been proven.

Insulin pens may also cause less discomfort than conventional needles, which can lose their lubrication when inserted through the rubber stopper of the insulin vial.³⁰ In fact, pain perception has been found to be reduced significantly with an insulin pen compared with a conventional vial and syringe.²⁹ This benefit may be especially attractive to individuals with needle phobia or individuals who experience unacceptable discomfort with the traditional syringe.

Various studies have directly compared different pen devices. One study (N=48) that compared 5 insulin devices (FlexPen, HumaPen Ergo, Humulin Pen, InnoLet, and NovoPen 3) found that FlexPen and NovoPen gave patients the most confidence in setting the correct dose due to auditory and/or physical sensory confirmation.³¹ Another study (N=137) found that compared with the Humalog Pen, the FlexPen was rated higher with respect to aspects of ease of use, utility, and convenience, and the patient's confidence in setting and injecting the correct

TABLE 5
Considerations for the use of insulin pens²⁴

Benefits	
•	Portability, speed, and ease of use in delivering basal or bolus insulin
•	May improve accuracy for patients with poor dexterity or neurologic impairment and for patients requiring small doses
•	Well suited for administering insulin outside the home
•	May be associated with less discomfort
•	Studies show patient preference for insulin pens over the vial and syringe method of insulin delivery
•	May improve patient adherence
Drawbacks/cautions	
•	Not available for all insulin types
•	Cannot mix insulin types
•	Air bubbles can reduce insulin flow rate
•	Per-unit cost higher than for 10-mL vials
•	Follow state laws for disposing of used syringes and needles

Adapted from *Insulin*, volume 1, Flood T; Advances in insulin delivery systems and devices: Beyond the vial and syringe; pages 99-108²⁴; Copyright © 2006, with permission from Excerpta Medica, Inc.

dose.¹⁹ Furthermore, 9% of patients experienced problems with the FlexPen compared with 32% with the Humalog Pen. Another insulin pen that has been shown to accurately deliver the required dose of insulin over the 3-year life of the pen is the OptiClik pen device, which uses a novel cartridge system with an integrated plunger.³²

Limitations with insulin pens do exist, however. Not all insulin formulations are available for all of the different pens, and the insulin formulas in reservoirs that are pre-filled cannot be altered. Thus, the selection of a pen device may depend on the insulin formulation used and vice versa. Second, although shown to be generally accurate,^{30,33,34} the pens can leak insulin. A recent study found that leakage from OptiClik may have contributed to underdosing of 17% of doses at 10 units and 29% of doses at 30 units.³⁵ Available since 1987, insulin pens have generally proven to be sturdy and reliable. The possibility of malfunction exists with any device, so patients should have a back-up pen or alternative delivery method readily available, should a mechanical problem occur.^{23,24}

Air bubbles may enter the insulin during manufacture or filling; bubbles may reduce the insulin flow rate, resulting in underdelivery of insulin even if the needle remains under the skin for as long as 10 seconds after depressing the plunger. This error can be avoided by not leaving the needle on the pen between injections and by priming the needle with 2 units of insulin before injection.³⁰

Finally, the higher per-unit cost of insulin for the insulin pen (about 10%-30% higher than the vial and syringe) may be a limitation for individuals not covered by health insurance, although the benefits described above may justify the added expense. Nearly one third of the approximately 21 million Americans with diabetes have some degree of vision loss, and diabetes is the leading cause of blindness among working-age adults. The

TABLE 6
Considerations for the use of insulin pumps²⁴

<p>Benefits</p> <ul style="list-style-type: none"> • Most closely mimics the body's normal release of insulin • American Diabetes Association has recommended continuous subcutaneous insulin infusion as acceptable for intensive insulin management • Demonstrated efficacy equivalent to that of multiple daily insulin injections in achieving glycemic control when recommended procedures are followed • May provide greater lifestyle flexibility regarding meal and travel schedules
<p>Drawbacks/cautions</p> <ul style="list-style-type: none"> • Discomfort of wearing pump around-the-clock • Insertion site must be changed every 3 days to prevent site infections and lipohypertrophy • Need for frequent blood glucose monitoring to detect any interruptions in pump function, which can lead to ketotic episodes
<p>Special considerations</p> <ul style="list-style-type: none"> • Requires a motivated patient committed to improving glucose control and willing to accept responsibility for self-care • May be especially beneficial for hospitalized patients with high pretreatment A1C levels and individuals with a history of long-term poor glycemic control

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accessibility and usability of insulin pens is important because 27% of Americans with T2DM use insulin.¹⁴ Since not all persons with diabetes can or want to use an insulin pump to deliver their insulin, an insulin pen is an attractive alternative to a regular syringe.

A 1998 study in the United Kingdom found that insulin pens delivered more accurate doses of insulin than did syringes.³⁶ In a 2002 study conducted at the University of Pittsburgh, 87% of the participants described the insulin pen as easier to use than a syringe, and 85% found the pen to be more discreet than a syringe.³⁷ Greater accuracy of insulin delivery is essential for successfully managing diabetes, and a person may be more likely to do what is necessary to manage diabetes properly if his or her device is less painful, easier to use, and more discreet. In a public place, such as a restaurant, a person would almost certainly be more comfortable using a device that looks like a regular writing pen than using a syringe.

Continuous Subcutaneous Insulin Infusion

Continuous subcutaneous insulin infusion (CSII), or insulin pump therapy, has been in use for more than 4 decades.²⁴ The number of people using an insulin pump increased almost 10-fold from 1990 to 2001, to approximately 160,000 users in 1998.³⁸ Today's insulin pumps are small (pager-size), computerized devices that deliver insulin as a steady, continuous dose (basal insulin) and as a surge (bolus) dose to cover mealtime. Pumps can be programmed to deliver insulin at varying rates to meet changing physiologic needs during the 24-hour day, such as occurs during the hours before and after waking.^{24,34} Self-monitoring of

blood glucose is important while using the pump, and must be done frequently (TABLE 6).^{23,34}

Only regular human insulin or a rapid-acting insulin analog are used for CSII. The 3 rapid-acting insulin analogs—aspart, glulisine, and lispro—have been approved by the US Food and Drug Administration (FDA) for administration as a continuous subcutaneous insulin infusion. Because of their rapid onset and short duration of action, rapid-acting insulin analogs are the insulin formulations that best meet mealtime needs. Rapid-acting insulin analogs are preferred for CSII because of less variability in onset, peak, and duration of action compared with regular human insulin.

Candidates for CSII therapy include patients with T1DM or T2DM whose hyperglycemia is not adequately controlled despite multiple daily injections of insulin, including individuals with a marked increase in blood glucose level at dawn (dawn phenomenon). Other candidates for CSII therapy include patients with unpredictable hypoglycemia and motivated patients whose schedules make multiple daily injections of insulin difficult or less effective.^{24,34} CSII therapy may provide greater lifestyle flexibility, particularly with regard to meal schedules and travel,³⁴ but may be too demanding for some individuals. Consequently, CSII therapy should be limited to individuals who are strongly motivated to improve glycemic control and are willing to assume that level of responsibility for their own daily care.³⁹

CSII therapy has been used successfully in adults, adolescents, and children, and is deemed by the ADA to be an effective means of implementing intensive diabetes management.³⁴ For adults⁴⁰⁻⁴⁴ and for adolescents and children⁴⁵⁻⁴⁸ with T1DM or T2DM, CSII therapy has shown equivalent or better glycemic control than multiple daily injections of insulin. In a pooled analysis of 3 studies involving adults who used rapid-acting insulin analogs for which CSII provided better glycemic control, the relative benefit of CSII over multiple daily injections of insulin was found to increase with a higher baseline A1C level.⁴² Most clinical trials of CSII therapy have used regular human insulin or other older insulin formulations. A meta-analysis of 6 clinical trials—each lasting at least 10 weeks—that compared insulin analogs with regular human insulin found that, compared with baseline A1C level, the mean A1C level decreased 0.26% in patients treated with an insulin analog.⁴⁹

Regarding complications, the risk of hypoglycemia (including severe hypoglycemia) often appears to be reduced with CSII therapy,^{40,43,44,46,47,50} although the use of different metrics among clinical trials precludes drawing a firm conclusion.

Inhaled Insulin

The first inhaled insulin (regular human insulin) was recently approved by the FDA for the treatment of adults with T1DM and T2DM. Insulin human [rDNA origin] inhala-

tion powder has many unique attributes²⁴ and may be used as an alternative to rapid-acting insulin or OADs, or in combination with an OAD or longer-acting (injected) insulin for T2DM. For T1DM, insulin human [rDNA origin] inhalation powder should be used in combination with longer-acting (injected) insulin. Used as a bolus insulin administered 10 minutes before a meal, the powder is inhaled into the lungs via the mouth using a hand-held inhaler.^{51,52}

Clinical trials involving insulin human [rDNA origin] inhalation powder have demonstrated efficacy comparable to that of conventional insulin regimens for reducing A1C levels over 24 weeks^{53,54} and better efficacy compared with that of 3 months of rosiglitazone for patients whose glycemia is poorly controlled by diet and exercise.³⁹ After 24 weeks of premeal inhaled insulin plus bedtime ultralente insulin (no longer available in the United States) or conventional subcutaneous insulin with mixed NPH/regular insulin before breakfast and supper, the mean A1C levels declined from 8.1% to 7.4% and 8.2% to 7.6%, respectively.⁵³

The safety of insulin human [rDNA origin] inhalation powder is comparable to that of conventional subcutaneous insulin regimens, with the exception of short-term cough. In one study, approximately 21% of patients who used inhaled insulin experienced mild to moderate cough, compared with 2% of patients using subcutaneous insulin.^{53,54}

Lung function must be assessed using spirometry prior to initiating inhaled insulin therapy and periodically thereafter because declines in the forced expiratory volume in 1 second (FEV₁) and carbon monoxide-diffusing capacity (DL_{CO}) have been observed.⁵²

Matching Insulin Delivery to the Patient

The availability of several systems for delivering insulin provides an unprecedented opportunity to meet the needs and preferences of patients with T1DM and T2DM. By doing so, many of the barriers to insulin therapy may be overcome, thereby allowing insulin to be initiated with the goal of improving glycemic control. The promise of easy-to-use delivery systems may be sufficiently persuasive to attract patients who had previously avoided insulin therapy.

The needs and preferences of each patient should be identified well in advance of starting insulin therapy. The patient should be assured that the best delivery option to meet his or her needs and preferences will be used whenever possible, and that this method will be reassessed periodically, with changes made as needed.

The patient's needs and preferences may result from physical or cognitive limitations, as well as constraints due to lifestyle and affordability. Patient preferences are important to consider because they may have a substantial bearing on adherence to insulin therapy. Recommendations for insulin therapy based on patient needs are provided in **TABLE 7**. For example, a patient who has poor dexterity, needle phobia, or requires multiple daily injections outside the

TABLE 7
Insulin delivery options based on individual patient needs^{23,24,34}

Patient Need or Difficulty	Delivery Option(s)
Poor dexterity	Insulin pen, inhaled insulin
Cognitive impairment	Insulin pen
Poor eyesight	Insulin pen
Self-mixing of insulins	Vial/syringe
Poor adherence	Insulin pen
Needle phobia	Insulin pen
Busy lifestyle/considerable time spent outside the home	Insulin pen, continuous subcutaneous insulin infusion, inhaled insulin

²³Drab S, et al, eds. *Diabetes Forecast*. January 2006. Available at: http://www.diabetes.org/uedocuments/rg06_delivery.pdf. Accessed November 4, 2006; ²⁴Flood T. *Insulin*. 2006;1:99-108; ³⁴American Diabetes Association. *Diabetes Care*. 2004;27(suppl 1):S110.

home may benefit from insulin delivery using a pen device or inhaled insulin. A person who needs further intensification of therapy or experiences severe hypoglycemic episodes with multiple daily injections of insulin may, if appropriately motivated, be a good candidate for CSII.

The importance of matching the insulin delivery system to the needs and preferences of the individual patient cannot be overemphasized. Although this process may take time—and can often be accomplished by a qualified member of the diabetes health care team other than the primary care physician—the likelihood of patient acceptance and successful adherence to insulin therapy, leading to improved glycemic control, may be greatly increased.

Summary

Patients and physicians often exhibit beliefs that serve as barriers to the intensification of diabetes therapy when insulin is indicated. For the patient, many beliefs about insulin relate to the complexity involved, anticipated complications, and disease severity. Needle phobia is also a common concern. For the clinician, the expected need for more patient education is an important consideration. Fortunately, much of the patient education can be accomplished by other members of the diabetes health care team. Customizing the insulin regimen using 1 or more of the available insulin delivery devices such as vials and syringes, pens, pumps, and inhalation systems to meet the patient's needs and preferences can be critically important to promoting long-term adherence and achievement of established glycemic goals.

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Practical Strategies for Achieving Targeted Glycemic Control in Patients With Type 2 Diabetes

■ Jeff Unger, MD

CASE STUDY

Mrs Smith is not happy with her physician's suggestion that she begin insulin replacement therapy. This is only her second visit with her new primary care physician (PCP), as she recently moved from a different part of the country. Diagnosed as having type 2 diabetes (T2DM) 5 years ago, Mrs Smith is a 55-year-old African American woman whose father died of diabetes complicated by a stroke when he was 56 years old. Mrs Smith has repeatedly stated that she "feels just fine" and cannot understand why her physician has taken such an aggressive approach toward her diabetes self-management. Despite receiving maximum doses of a sulfonylurea, metformin, and pioglitazone, Mrs Smith's A1C level is 8.4%. She is also taking a statin (to improve her LDL cholesterol [LDL-C]), an angiotensin-receptor blocker (ARB) in combination with a diuretic (to manage her marginally controlled hypertension), and low-dose aspirin daily.

"Doctor, as soon as they put my father on insulin, he had a stroke. I believe insulin contributed to his stroke. Before they started the insulin, the only problem he really had was with his kidneys. Sure, he never ate right or exercised. I'm scared that insulin will have the same effect on me."

Improving Inertia Toward Intensification of Diabetes Care

Mrs Smith's concerns regarding initiating insulin therapy are not unique. And, the tendency among many PCPs is to continue oral agents for an indefinite period of time. (See "Options for Insulin Delivery and Overcoming Physician and Patient Concerns" on page 18 of this supplement.) The current standards of diabetes care warrant improving the inertia toward normalization of glycemia as soon as a patient is diagnosed with hyperglycemia.¹

KEY POINTS & RECOMMENDATIONS

- An important function of the primary care physician is to serve as the leader of the multidisciplinary diabetes health care team. **(SOR: C)**
- Various approaches have been used to initiate insulin therapy; the choice depends on the A1C level as well as the fasting plasma glucose and postprandial glucose levels. **(SOR: A)**
- When initiating insulin, continuation of oral antidiabetic drugs must be reassessed for side effects, impact on the action of exogenous insulin, adherence, and cost. **(SOR: B)**
- Several approaches exist for selecting the insulin dose upon initiation. **(SOR: A)**
- Patient education that includes discussion of diet and physical activity, timing of insulin doses, self-monitoring of blood glucose, and identification and management of hypoglycemia is important. **(SOR: A)**

CASE STUDY ...Continued

Having thoroughly reviewed Mrs Smith's medical record, her new PCP found that her A1C level decreased only 0.4% because of the addition of the pioglitazone 5 months ago. The addition of metformin 2 years ago also caused a smaller decrease in her A1C level than expected. Overweight but not obese, Mrs Smith's body mass index (BMI) was noted by her physician to be 28 kg/m². He decides to check her fasting plasma glucose (FPG) and 2-hour postprandial glucose (PPG) levels to determine their contribution to her elevated A1C level. He also orders an islet cell antibody panel to rule out latent autoimmune diabetes of adulthood (LADA).

Latent Autoimmune Diabetes of Adulthood

LADA is a common form of autoimmune diabetes, with several identifying clinical features (TABLE 1).²⁻⁶ The diagnosis of LADA is based on the presence of GAD-65 (glutamic acid decarboxylase) autoantibodies. These antibodies signify the presence of autoantigens that provoke autoimmune destruction of islet cells. Persons with LADA are often incorrectly categorized as having T2DM based on their adult age at onset, lack of ketoacidosis, and initial response to oral agents.⁷

The prevalence of LADA can be inferred from the UK Prospective Diabetes Study (UKPDS),⁸ which found that GAD antibodies and islet cell antibodies were positive in 10% and 6%, respectively, of the entire cohort. In patients aged 25 to 34 years, tests for GAD antibodies and islet cell antibodies were positive in 34% and 21%, respectively.

CASE STUDY ...Continued

The results of Mrs Smith's tests were as follows:

GAD-65 autoantibodies	Negative
FPG	138 mg/dL (goal, 90-130 mg/dL)
PPG	196 mg/dL (goal, <180 mg/dL)

The negative result of the GAD-65 autoantibody test indicated that Mrs Smith does not have LADA. Based on her FPG and PPG levels and the recent A1C level of 8.4%, Mrs Smith's diabetes was poorly controlled despite triple oral antidiabetic drug (OAD) therapy. Nonetheless, Mrs Smith continued to resist intensification of her diabetes treatment with insulin. Understanding the benefits of intensifying therapy, but doubtful that Mrs Smith would adhere to

insulin therapy, the PCP schedules Mrs Smith to meet with the certified diabetes educator (CDE), who is also a dietician.

The Diabetes Health Care Team

Diabetes is a chronic, progressive, and complex disease capable of affecting one's quality of life and longevity; therefore, a multidisciplinary approach to education may improve patient adherence and outcomes. Diabetes self-management provides the foundation from which all aspects of reaching metabolic targets may be successfully achieved. Patients must understand their responsibilities regarding self-monitoring of blood glucose (SMBG), medical nutrition therapy, physical activity, proper timing and use of medications, adherence to medical follow-up appointments, and participation in diabetes continuing education programs. As the leader of the diabetes health care team, the PCP may choose to engage the special skills of a CDE, dietician, pharmacist, nurse, social worker, and specialty physicians to optimize patient self-management.

CDEs are well trained in the "art of communication," especially with patients who have special needs. Not all patients learn diabetes self-management skills at the same speed or using the same techniques. For example, some individuals may have developed cognitive dysfunction secondary to hypoglycemic unawareness. Others may face cultural or economic barriers, which tend to delay diabetes intensification. Physicians often do not have the time, training, or personnel to manage these patients within the office setting. Partnering with a strong diabetes support team would certainly be beneficial to many patients with diabetes, especially those who are newly diagnosed or those who have multiple medical comorbidities.

CASE STUDY ...Continued

At follow-up, Mrs Smith stated that she understood the nature of the rapid progression of T2DM and the long-term inability of OADs to achieve glycemic control. Mrs Smith also indicated that after talking with the CDE, she now understood how diabetes can increase the risk of other health problems, such as the stroke that her father experienced. Although remaining anxious about starting insulin therapy, upon receiving the training and reassurance she needed, Mrs Smith agreed to intensify her diabetes management by adding insulin to her treatment regimen.

Prior to making a therapeutic decision regarding this patient's treatment regimen, the PCP addresses the following questions:

1. What treatment targets should be established for this patient?
2. Should treatment focus on improving the fasting or the postprandial hyperglycemia?
3. In attempting to achieve the targeted A1C level, what insulin regimen would be the most likely to achieve success?
4. Should the patient's current OADs be continued?
5. At what dose should insulin be initiated?
6. Is the patient well educated with respect to diet and physical

TABLE 1
Clinical characteristics associated with latent autoimmune diabetes of adulthood (LADA)²⁻⁶

- Slowly progressive form of autoimmune diabetes
- Occurs in approximately 10%-30% of patients with T2DM
- Reported in children and as well as in adults
- 90% of patients with LADA will require insulin within 1-2 y of being diagnosed
- Patients with LADA are most often positive for GAD65-Ab or ICA, but not IA-2Ab or IAA
- Patients with LADA may have lower BMIs than individuals with T2DM
- Patients with LADA are more likely to be symptomatic (polyuria, polyphagia, polydipsia, weight loss, and fatigue) than are individuals with T2DM
- Patients with LADA should be treated with insulin to maintain better glycemic control during a period of rapid pancreatic beta-cell deterioration
- Stabilization of glycemia may reduce long-term diabetes-associated complications

BMI = body mass index; GAD65-Ab = glutamic acid decarboxylase antibodies; IA-2Ab = insulin antibody; IAA = insulin autoantibody; ICA = islet cell antibodies; T2DM = type 2 diabetes mellitus.

²Gilliam LK, et al. *Insulin*. 2006;1:122-127; ³Juneja R, et al. *Autoimmunity*. 1999;29:65-83; ⁴Kobayashi T, et al. *Diabetes Care*. 1993;16:780-788;

⁵Lohmann T, et al. *Diabetes Care*. 2000;23:1707-1708; ⁶Gilliam LK, et al. *J Autoimmun*. 2005;25:244-250.

activity, timing of doses, self-monitoring of blood glucose, and identification and management of hypoglycemia?

7. If further intensification of insulin therapy is needed, which option should be selected?

1. What treatment targets should be established for this patient?

The AACE recommends an A1C goal of 6.5% or less, whereas the ADA recommends an A1C below 7%, which is often the treatment goal selected. Although reasonable, an A1C below 7% is the *general* treatment goal recommended by the ADA. Consideration should be given to determining whether Mrs Smith might actually qualify for the individual ADA A1C treatment goal of 6%. This individual treatment goal is appropriate for most patients, except for those with a history of severe hypoglycemia or limited life expectancy, very young children or older adults, and individuals with comorbidities.⁹ Because Mrs Smith suffers from hyperlipidemia and hypertension, initially targeting an A1C of less than 7% should reduce her risk of developing microvascular and macrovascular complications considerably. Once this target is safely achieved, further intensification of her regimen should be attempted unless she begins to experience episodes of hypoglycemia. According to the ADA, Mrs Smith's FPG levels should range between 90 and 130 mg/dL, and her peak PPG levels should be lower than 180 mg/dL. AACE recommendations strive to attain glycemic targets that are more in line with "normal" glucose levels. Thus, a patient's FPG levels should be lower than 110 mg/dL, whereas the 2-hour PPG levels should not exceed 140 mg/dL.¹⁰

2. Should treatment focus on fasting or postprandial hyperglycemia?

Although the A1C level is the primary target for glycemic control, fasting and postprandial glucose levels are useful targets as well. Postprandial hyperglycemia has been established as an independent risk factor for cardiovascular disease and death.¹¹ Postprandial glucose may, in fact, be targeted if A1C goals are not met despite reaching FPG goals. As the A1C level drops below 8.5% and more closely approaches the 7% target, the postprandial glucose level contributes more to hyperglycemia. Thus, improving postprandial hyperglycemia will more effectively lower Mrs Smith's A1C level.¹²

3. What insulin regimen would be the most likely to achieve glycemic control?

Various approaches have been used to initiate insulin therapy, and the choice depends on the A1C as well as the FPG and PPG levels (**TABLE 2**).¹³ (See "Insulin Regimens for Type 2 Diabetes Mellitus" on page 10 of this supplement.) These include: (1) the addition of basal insulin with continuation of 1 or more OADs, (2) the addition of mealtime (bolus) insulin with continuation of 1 or more OADs, or (3) discontinuation of OADs and initiation of intermediate- or

TABLE 2
AACE road map for treatment of type 2 diabetes mellitus in previously treated patients¹³

Current A1C (%)	Current Therapy	Intervention
6.5-8.5	Monotherapy: Meglitinide, SU, AGI, metformin, TZD, premixed insulin analogs, or basal insulin	Initiate combination therapy* <ul style="list-style-type: none"> • Metformin + SU or meglitinide • Metformin + TZD or AGI • TZD + SU • Exenatide+metformin and/or SU • Basal or premixed insulin analogs • Other approved combinations
6.5-8.5	Combination therapy: Meglitinide, SU, AGI, metformin, TZD, exenatide, premixed insulin analogs, rapid-acting insulin analogs, basal insulin	Maximize combination therapy Maximize insulin therapy <ul style="list-style-type: none"> • If elevated FPG, add basal • If elevated PPG, add bolus • If elevated FPG and PPG add <ul style="list-style-type: none"> –Basal-bolus therapy, or –Premixed insulin analogs Add exenatide to patients on SU and/or metformin
>8.5	Monotherapy or combination therapy	Initiate insulin therapy (basal-bolus) <ul style="list-style-type: none"> • Long-acting plus rapid-acting insulin • Premixed insulin analogs

*Rapid-acting insulin analogs can be added at any time to address persistent postprandial hyperglycemia.

AACE = American Association of Clinical Endocrinologists; AGI = alpha-glucosidase inhibitor; FPG = fasting plasma glucose; PPG = postprandial glucose; SU = sulfonylurea; TZD = thiazolidinedione.

Used with permission from: Road map for the prevention and treatment of type 2 diabetes mellitus.¹³ Available at: <http://www.aace.com/meetings/consensus/odimplementation/roadmap.pdf>. Copyright © 2006 American Association of Clinical Endocrinologists.

long-acting insulin with rapid-acting or regular insulin (ie, basal-bolus therapy). Although basal-bolus therapy typically involves the use of multiple daily injections of basal and prandial insulins (4-5 shots per day) or use of an insulin pump, premixed insulin taken twice daily can be used as an alternative to cover basal and prandial needs in 1 injection for patients with T2DM. Traditional "basal-bolus" therapy is also more demanding to teach and implement because it requires comprehensive patient education, carbohydrate counting, and intensive blood glucose monitoring. (See "Insulin Regimens for Type 2 Diabetes Mellitus" on page 10 of this supplement.) Physicians should understand that many insulin regimens, when used properly and aggressively, will successfully lower a patient's A1C level to the desired target. Therefore, individualizing the initial choice of insulin regimen is just as important as individualizing diabetes self-management and treatment follow-up.

When a patient's A1C level is over 8.5%, the use of a basal-bolus strategy in combination with 1 or more OADs is appropriate. (See "Insulin Regimens for Type 2 Diabetes Mellitus" on page 10 of this supplement.) Premixed insulin analogs may also be useful for these patients. BIAsp (biphasic insulin aspart) 70/30 has been shown to more effectively lower PPG excursions compared with both human insulin premix 70/30 and insulin lispro premix 75/25, with a similar but low risk of hypoglycemia.¹⁴⁻¹⁶

For patients with T2DM and an A1C level between 6.5% and 8.5% who receive maximized combination therapy, the approach to insulin therapy is dependent on both the FPG and the PPG levels.¹³ Basal insulin should be used when the FPG is consistently above 130 mg/dL, whereas bolus insulin should be used if the PPG is 140 mg/dL or higher. When both the FPG and PPG are elevated, the combination as basal-bolus therapy is appropriate.

4. Should the patient's current oral hypoglycemic agents be continued?

The continuation of OAD therapy is an important consideration when insulin therapy is initiated. Issues such as side effects (weight gain, increased risk of hypoglycemia, peripheral edema, or treatment-emergent congestive heart failure), effect on the action of exogenous insulin, patient adherence, and cost must be considered. A significant concern of insulin therapy is weight gain. Thus, strategies to maintain current weight or at the very least minimize the magnitude of weight gain should be employed. Patients should be encouraged to reduce their caloric intake by 150 calories per day—the equivalent of eating 1 cookie. This can be accomplished by switching from whole or 2% milk to skim milk; reducing consumption of fast foods; “brown bagging” food for lunch rather than eating at restaurants or purchasing take-out meals; limiting consumption of sugary drinks, including flavored coffees; and eating 3 balanced meals per day while avoiding between-meal snacks.¹⁷ Exercising 30 minutes per day, 5 days a week should be strongly encouraged. OADs that have a neutral effect on weight or cause weight loss should be employed.

An additional consideration is to enhance the activity of the insulin by decreasing insulin resistance or by enhancing the activity of insulin. Although metformin also increases hepatic insulin sensitivity, a thiazolidinedione may be used to decrease insulin resistance in skeletal muscle and adipose tissue, whereas pramlintide may be used to enhance the activity of insulin.

Finally, when a basal-bolus or twice-daily premixed insulin regimen is initiated, an insulin secretagogue such as a sulfonylurea (eg, glimepiride, glipizide, or glyburide) or a meglitinide (nateglinide or repaglinide) should be discontinued, or tapered and then discontinued, because they provide no added benefit.¹⁸

CASE STUDY ...Continued

Mrs Smith and her physician decide to begin basal insulin analog while continuing her current OAD therapy using a “treat-to-target” protocol. A study by Riddle and colleagues evaluated the efficacy of using either insulin glargine or neutral protamine Hagedorn (NPH) insulin added to OADs in 756 patients with poorly controlled T2DM (A1C >7.5%).¹⁹ Insulin adjustments were made by patients on a weekly basis according to a fixed-dosing protocol until the FPG levels

were lower than 100 mg/dL or the patient developed hypoglycemia. In both groups, FPG levels decreased from 194 to 117 mg/dL or 198 to 120 mg/dL, respectively, by study end, and A1C levels decreased from 8.6% to 6.9% by 18 weeks. Although both insulins successfully reduced A1C levels to the ADA target of less than 7% in 60% of patients, those using NPH experienced significantly more nocturnal hypoglycemia than did patients randomized to glargine. The basal insulin analogs (glargine and detemir) have more predictable absorption, relatively flat time-action profiles, and a longer duration of action, produce less weight gain (detemir), and result in less hypoglycemia than does NPH.²⁰⁻²³ Additionally, the basal analogs are available as pen injector delivery devices, which offer more convenient and accurate dosing of insulin when compared with vials and syringes.^{24,25}

Treatment Plan for Mrs Smith:

On the basis of these considerations, Mrs Smith's PCP developed the following treatment plan to better manage her T2DM:

- Continue metformin 1 gram twice daily.
- Begin basal insulin analog therapy once daily at bedtime.
- Place on a treat-to-target protocol, advising Mrs Smith to increase the dose of her basal insulin by 5 units weekly until her FPG levels are below 100 mg/dL for 7 consecutive days. Mrs Smith is advised to check her blood glucose levels before breakfast (fasting) and at bedtime. She will also notify the physician if her blood glucose levels fall below 60 mg/dL.
- Schedule a follow-up appointment for 6 weeks from today's appointment.
- Perform a point-of-service A1C test at the time of the follow-up appointment.

5. At what dose should insulin be initiated?

Several dosing strategies for initiating basal insulin therapy are available. Assuming Mrs Smith weighs 70 kg, the following approaches to insulin initiation may be considered:

- a. In the “treat-to-target” approach, the initial dose of basal insulin is 10 units either once daily¹⁹ or twice daily.²³ If the initial prebreakfast or predinner plasma glucose level was below 126 mg/dL, or if the BMI was below 26 kg/m², the starting dose was reduced to 6 units twice daily.²³

$$\text{Dose} = 10\text{-}20 \text{ units/day}$$

- b. A second approach is to begin with a dose of 0.15-0.20 units/kg/day.

$$\text{Dose} = (0.15\text{-}0.20 \text{ units/kg/day}) \times 70 \text{ kg} = 11\text{-}14 \text{ units/day}$$

- c. A third approach is to begin with 50% of the calculated total daily dose (TDD) of insulin requirement, since the daily basal insulin requirement is approximately 50% of the TDD.²⁰ The TDD = 0.7 units/kg/day × weight (kg). This dose should be divided by the num-

ber of injections of basal insulin administered per day (1 or 2).

$$\text{Basal dose} = [(0.7 \text{ units/kg/day}) \times 70 \text{ kg} \times 50\%] \div 1 \text{ injection/day} = 24.5 \text{ units/day} = 25 \text{ units/day}$$

Thus, Mrs Smith could be started with a dose of basal insulin once daily before bedtime that ranges from 10 to 25 units. Because Mrs Smith is anxious about starting insulin, her physician decides to “start low and go slow.” Consequently, a dose of 10 units of a basal insulin analog once daily before bedtime was chosen for Mrs Smith to begin therapy. The initial dose of 10 units will not improve FPG levels in most patients with T2DM. Therefore, physicians should reassure patients that the starting dose is simply a point from which dose titration may begin. Weekly—or more frequent—dose titrations will allow rapid dose intensification. However, at the time of Mrs Smith’s 6-week follow-up appointment, it is expected that she will be using approximately 45 to 50 units of basal insulin at bedtime.

6. Is the patient well educated with respect to diet and physical activity, timing of doses, self-blood glucose monitoring, and identification and management of hypoglycemia?

The successful management of T2DM depends to a large extent on the patient’s ability and willingness to take control of the disease. An important aspect of patient education is addressing patient barriers to the use of insulin therapy. (See “Options for Insulin Delivery: Overcoming Physician and Patient Concerns” on page 18 of this supplement.) As Mrs Smith’s hyperglycemia improves, she is likely to begin feeling more energetic. Other symptoms of chronic hyperglycemia, such as thirst, blurred vision, paresthesias, and abdominal bloating, are also likely to improve as the patient’s inertia toward intensification progresses toward euglycemia. When the patient’s hard work at diabetes self-management is reinforced by her physician, she will very likely be more willing to add additional injections of insulin if that becomes necessary. The overall treatment goal for this patient is to safely reduce her A1C level to as near normal (6%) as possible.

Patients with T2DM must receive diabetes education in concert with the ongoing collaboration and support necessary to sustain the level of self-care needed for a lifetime of managing diabetes. Patients need self-management support and collaborative care that links patients with ongoing provider support.²⁶ Along with the benefits of strict glycemic control, diabetes education must include information about the patient’s role in treatment; the benefits, risks, and costs of various therapeutic options as well as self-management decisions; behavioral change strategies; and psychosocial issues. Effective strategies for self-management support include peer support programs,²⁷ multidisciplinary diabetes team management,²⁸ and scheduled telephone follow-up systems.²⁹ Patient education in a group setting has been found to be usually more effective than

individual education^{27,30,31} and the costs are often paid by insurers. Patient education that incorporates the behavioral and affective components of diabetes care and is culturally specific has been shown to be more effective than strictly knowledge-based programs.^{27,30,31}

Physical Activity

Based on each patient’s health status, ability, and willingness, initial physical activities should be modest. Ideally, physical activity remains an important part of treatment (including weight management) for most patients with T2DM. Exceptions include patients with retinopathy and possibly autonomic neuropathy. All patients should undergo a general medical examination before increasing usual patterns of physical activity, whereas patients with autonomic neuropathy or cardiovascular disease should undergo cardiac evaluation prior to intensifying their physical activity.⁹ As an alternative to aerobic activities such as walking and swimming, resistance activities such as weight training and calisthenics are also effective³²⁻³⁵ and may be preferred for some patients with long-term complications of diabetes, such as peripheral neuropathy. Although physical activity can acutely increase urinary protein excretion, there is no evidence that vigorous physical activity increases the rate of progression of diabetic nephropathy.⁹

Physical activity should consist of at least 150 minutes per week of moderate-intensity aerobic activity and/or at least 90 minutes per week of vigorous aerobic physical activity. The physical activity should occur over at least 3 days per week with no more than 2 consecutive days without physical activity. Unless contraindicated, resistance activity should be performed 3 times per week, targeting all major muscle groups.⁹ Involvement of a physical therapist or trainer familiar with the special needs and limitations of patients with diabetes may be helpful.

Timing of Insulin Doses

The timing of insulin doses is an important consideration and must be matched to individual patient needs. Basal insulins are typically administered once daily before dinner, bedtime, or breakfast, or twice daily before dinner/bedtime and breakfast. The timing of bolus insulins varies according to the onset of action. Insulin analogs and inhaled insulin can be administered immediately prior to a meal, whereas regular human insulin must be administered at least 30 minutes before a meal. (See “Insulin Regimens for Type 2 Diabetes Mellitus” on page 10 of this supplement.) The importance of administering the dose(s) of insulin at the prescribed time(s) and of eating regularly should be clearly understood by the patient.

Self-Monitoring of Blood Glucose

Definitive guidelines for SMBG have not been developed. Nonetheless, SMBG should be accomplished as frequently as needed to ensure that glycemic goals are being achieved

TABLE 3
Minimizing risks of hypoglycemia³⁸⁻⁴²

- Frequently review the aspects of diabetes self-management that may minimize the frequency and consequences of iatrogenic hypoglycemia: carbohydrate counting, proper timing of oral agents in relation to insulin or exenatide dosing, home blood glucose monitoring prior to driving, and adjustment of insulin dosages prior to exercise or increased physical activity.
- The use of alcohol may limit the counterregulatory response of the liver to hypoglycemia. Insulin also minimizes hepatic glucose production. Therefore, patients using exogenous insulin should always eat if they consume alcohol to avoid inducing severe and prolonged hypoglycemia.
- Elderly patients at risk for developing hypoglycemia include patients taking multiple oral agents in conjunction with exogenous insulin and patients with impaired renal or hepatic metabolism, dementia, depression, history of stroke, or suboptimal nutritional intake. The AGS has recommended an A1C level <7% for healthy older adults and an A1C of <8% for frail elderly patients.³⁸
- Substitution of preprandial regular insulin with rapid-acting insulin (eg, glulisine, lispro, or aspart) reduces the frequency of daytime hypoglycemia. Similarly, substitution of a long-acting insulin analog (eg, glargine or detemir) for intermediate-acting insulins such as NPH or human premix 70/30 or 50/50 also reduces the frequency of nocturnal and daytime hypoglycemia.^{39,40}
- If a diagnosis of hypoglycemic unawareness is made, the solution will involve the acceptance of somewhat higher glucose levels in the short term. At least a 3-week period of meticulous avoidance of hypoglycemia could be attempted with the goal of encouraging a return to awareness of hypoglycemia. With the return of symptomatic hypoglycemia, patients can once more work toward achieving better glycemic control.^{41,42}

AGS = American Geriatric Society; NPH = neutral protamine Hagedorn insulin.
³⁸American Diabetes Association. Available at: <http://docnews.diabetesjournals.org/cgi/search?fulltext=target&sendit=Enter&volume=3&issue=4&journalcode=docnews>. Accessed November 7, 2006; ³⁹Ratner RE, et al. *Diabetes Care*. 2000;23:639-643; ⁴⁰Heller SR, et al. *Diabetes Care*. 1999;22:1607-1611; ⁴¹Cryer PE. *N Engl J Med*. 2004;350:2272-2279; ⁴²Unger J, et al. *Emergency Medicine*. 2002;9:24.

and to identify episodes of asymptomatic hypoglycemia or hyperglycemia. SMBG should be performed more frequently by patients with T2DM who use insulin than by patients with T2DM who do not use insulin.

Mrs Smith was asked to monitor her fasting plasma glucose level and her postprandial level (at bedtime) daily. Patients using premixed insulin analogs should monitor blood glucose levels fasting (which represents the efficacy of the predinner dose of insulin) and before dinner (which represents the efficacy of the prebreakfast insulin dose). Patients taking a third injection of a mixed insulin at lunchtime should also check their glucose levels 2 hours after lunch. Blood glucose levels consistently higher than 140 mg/dL will require an increase in pre-lunch insulin dosing.³⁶

Identification and Management of Hypoglycemia

Patients who take insulin (and/or insulin secretagogues) are prone to hypoglycemia if the insulin dose and/or carbohydrate consumption is not altered in relation to physical activity. Persons with certain comorbidities can be at greater risk of hypoglycemia. Patients who have suffered a stroke, for example, may find it more difficult to recognize the symptoms of hypoglycemia.

The level of glucose that causes symptoms of hypoglycemia varies from person to person and for the same person under different circumstances. Hypoglycemia generally occurs gradually and is preceded by warning signs. These warning signs may include tachycardia, diaphoresis, shakiness, anxiety, and hunger. Hypoglycemia is not normally associated with loss of consciousness or a seizure, provided that the warning signs are recognized by the patient and the blood glucose level is maintained.³⁷

For situations in which a patient engages in planned physical activity, SMBG should be done in advance. If the pre-physical activity glucose level is below 100 mg/dL, carbohydrate (15-20 g glucose) should be administered. The acute glycemic response correlates more closely with the glucose content than with the carbohydrate content. Because the rise in glycemia may only be temporary, SMBG should be repeated in 15 minutes.⁹

TABLE 3 lists ways patients may be educated to reduce their likelihood of developing hypoglycemia.³⁸⁻⁴²

CASE STUDY ...Continued

At the 6-week follow-up office visit, Mrs Smith reports that she initially had some difficulty adjusting to the basal insulin. On occasion she would feel as though her blood glucose level was low when in fact—for the first time in years—her levels have been near normal. The physician explains that these symptoms, which resemble hypoglycemia, are common among patients in their initial stages of insulin therapy. However, within 2 weeks, the symptoms should subside and her treatment can be intensified once again.

Mrs Smith's basal insulin dose before bedtime has ranged from 10 to 22 units. Her FPG level this morning was 130 mg/dL. Her A1C level, measured 2 days ago, was 8.0%.

Her physician congratulates her on making progress. He reiterates the benefits of better glycemic control, especially because she also has hypertension and hyperlipidemia. Due to her family history of premature death from heart disease and stroke, Mrs Smith agrees to press forward in an attempt to achieve her individualized A1C glycemic target of less than 7%.

7. If further intensification of insulin therapy is needed, which option should be selected?

Mrs Smith's FPG is within the ADA's normal range, yet her 8% A1C level suggests that the primary contributor to her hyperglycemic state is her elevated PPG levels. Mealtime prandial insulin is needed to improve her overall glycemic control.

Mrs Smith's physician has several choices for introducing prandial insulin in her care. The "all-to-target" regimen encourages the use of a rapid-acting insulin analog prior to the consumption of the patient's largest meal of the day. The initial dose of the prandial insulin should be 0.1 U/kg. Because Mrs Smith weighs 70 kg, she should administer 7 units of either insulin aspart, glulisine, or lispro at the time of the meal. Simple instructions

may be given for dosing adjustments. For example, a “large meal” should require an additional 2 units of insulin, whereas a medium meal might require 1 additional unit. An unusually small meal might require the patient to reduce his or her insulin dosing by 1 to 2 units. Alternatively, the dose of bolus insulin can be initiated by adding 4 units of a rapid-acting insulin analog (aspart, glulisine, or lispro) and adjusting the dose, as shown in **TABLE 4**.⁴³ Alternatively, inhaled regular insulin, 1 mg, could be initiated prior to dinner.

The addition of insulin glulisine to basal insulin therapy has been shown to further reduce A1C levels in patients with T2DM who had a normal FPG but elevated PPG.⁴⁴ Patients were previously treated with once-daily insulin glargine plus OAD therapy. A single daily dose (average 11 units/day at end point) of insulin glulisine was administered at breakfast or the predominant meal of the day. At 26 weeks, there was a reduction in the mean A1C level (from 7.4% to 7.0%) and the PPG level but not the FPG level.

Had Mrs Smith been treated initially with a premixed insulin analog once daily, a second dose prior to breakfast would have been appropriate. (See “Insulin Regimens for Type 2 Diabetes Mellitus” on page 10 of this supplement.) Switching Mrs Smith to a premixed insulin analog also is an option. The addition of BIAsp 70/30 in 100 patients with T2DM poorly controlled on various OAD regimens with or without basal insulin also was shown to be effective for reaching glycemic goals.³⁶ With 1 daily injection before dinner, 21% of patients achieved an A1C level of 6.5% or less, while 41% achieved an A1C below 7%. With 2 daily injections, the glycemic goals were achieved by 52% and 70%, respectively, and in 60% and 77%, respectively, with 3 daily injections. Major hypoglycemia was reported by 3 patients during both once-daily and twice-daily dosing and by 1 patient with thrice-daily dosing. Thus, patients can start with once-daily administration and intensify as needed without changing insulin preparations. Interestingly, BIAsp 70/30 taken twice daily—at breakfast and dinner—has been shown to be nearly as effective as basal-bolus therapy using insulin detemir once daily plus insulin aspart 3 times daily in patients with T2DM.⁴⁵

Basal-bolus insulin regimens may also incorporate the use of adjunctive therapies, such as pramlintide, to limit glycemic variability, reduce postprandial glucagon production, limit weight gain, and lower A1C levels.⁴⁶

Patients who are reluctant to use injectable insulin might be candidates for inhaled insulin. Inhaled insulin may be used with oral agents or with a basal insulin. Because the inhaled insulin is in a powdered formulation, the drug is expressed in terms of milligrams rather than units. Inhaled insulin cannot be used by smokers or patients younger than age 18. The learning time for inhaled insulin is considerably longer than that required to use a pen injector.

TABLE 4
Adjustment of preprandial insulin doses⁴³

Insulin Formulation	Initial Premeal Starting Dose	Suggestions for Premeal Dose Adjustments
Rapid-acting insulin analog (aspart, glulisine, lispro)	<ul style="list-style-type: none"> •4-10 U •0.1 U/kg •Based on carbohydrate counting 	<ul style="list-style-type: none"> • Target postprandial glucose \leq140 mg/dL. • For carbohydrate counting, 1 U insulin generally covers 10 g of carbohydrate. • Can use fixed-dose adjustment based on the premeal glucose level; for every 20 mg/dL $>$150 mg/dL, add 1 U. If blood glucose is $<$70 mg/dL, subtract 1 U.
Inhaled insulin	1-3 mg	Increase by increments of 1 mg as below.

If 2 of the last 3 measures for the same meal are not at goal

	Recommended Goal (mg/dL)	Action
Prelunch test	90-130	Adjust prebreakfast dose
Predinner test	90-130	Adjust prelunch dose
Prebedtime test	$<$ 180	Adjust predinner dose

(a) Due to the physics of crystallized insulin inhalation, consecutive inhalation of three 1-mg dose blisters results in significantly greater insulin exposure than inhaling one 3-mg dose blister. Thus, 1 mg + 1 mg + 1 mg \neq 3 mg. (b) If a 3-mg blister is unavailable, patients should temporarily substitute two 1-mg blisters for a single 3-mg blister and carefully monitor their postprandial glucose levels. (c) The fewest number of blister packs should be used per dose. Thus, instead of using four single 1-mg blisters, patients should inhale 1 mg + 3 mg = 4 mg (= 12 U subcutaneous insulin).

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Summary

Insulin therapy should be initiated in anyone who is unable to achieve an A1C level of 7% or less while taking a combination of OADs. Patients should be treated with the goal to achieve the lowest and safest A1C level possible. The rate-limiting steps in intensification of diabetes management are hypoglycemia and weight gain. Several viable and successful options with which to treat patients who have chronic hyperglycemia are available. Using treat-to-target regimens, patients may be transitioned to a basal insulin regimen while continuing oral agents. The continuation of OADs for patients with an A1C level of 8.5% or higher appears to improve their success at achieving a lower A1C target while minimizing injection frequency. Premixed insulin analogs provide patients with convenient dosing and delivery options while controlling elevations in both basal and prandial glycemia in a single, painless injection. For patients who achieve the targeted A1C level using the premixed insulin analogs but experience either unacceptable weight gain or hypoglycemia, the “all-to-target” protocol may be effective. With this approach, patients receive a basal insulin plus additional prandial injections of a rapid-acting analog or inhaled insulin, beginning with the

largest meal of the day. Injections may be added if the patient does not progress toward the A1C target.

The road toward glycemic intensification is littered with debilitated and painful bodies suffering from the haunting effects of chronic exposure to hyperglycemia. As primary care physicians, we must always remember that achieving “some control” is not equivalent to successfully attaining one’s “targeted goal.”

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