Type 2 diabetes mellitus is on the rise, yet glycemic control continues to elude patients—and their physicians. During the past decade, the use of insulin monotherapy has decreased while the use of oral antidiabetic agents (either alone or in combination with insulin injections) has increased. The continued prevalence of the disorder, changes in prescribing patterns, and recent data indicating that only one third of patients with type 2 diabetes mellitus achieve glycemic control underscore the need for physicians to reevaluate the clinical management of this now common disorder. Insulin analogs provide flexibility in the delivery of insulin therapy for this population. Although potential barriers and complications to initiation exist, patients should understand that achieving and maintaining glycemic control reduces the risk of long-term complications as a result of type 2 diabetes mellitus. Physicians are encouraged to actively identify and address patient concerns about this treatment modality.

Diabetes, which affects more than 20 million Americans, is linked to heart disease, stroke, and high blood pressure, among other health complications. Measurement of glycated hemoglobin A1c (HbA1c) continues to be the criterion standard for evaluating glycemic control, the ultimate goal of insulin therapy and a fundamental component of diabetes management. Reducing HbA1c levels has been shown to lower the incidence of microvascular complications of diabetes and is associated with decreased risk of myocardial infarction and fatal cardiovascular events. The American Diabetes Association and the American Association of Clinical Endocrinologists (AACE) in conjunction with the American College of Endocrinology (ACE) have recently published recommendations for glycemic control, including goals for HbA1c levels (Table 1). The American Diabetes Association recommends an HbA1c goal of less than 7.0% in general for adults with diabetes, but a goal of less than 6.0% for individual patients with diabetes (normal nondiabetic range 4.0%-6.0%). The AACE and the ACE as well as the International Diabetes Federation recommend an HbA1c goal of 6.5% or less in general for patients with diabetes. These target HbA1c values have been achieved in clinical trials and can be achieved and maintained by patients through careful adherence to a whole-person treatment plan.

- medical nutrition therapy (ie, nutrition-based treatment such as diet changes and diet counseling)
- physical activity
- self-management (eg, increased attention and dedication to achieving and maintaining glycemic control)
- pharmacologic intervention

Even with these guidelines and the expansion of therapeutic options, the majority of patients with diabetes do not reach target HbA1c levels. According to epidemiologic data from the National Health and Nutrition Examination Surveys (NHANES III and NHANES 1999-2000), the percentage of...
people with diabetes achieving glycemic control has decreased from 44.5% to 35.8%, and the distribution of different treatment methods being used has changed (Figure 1). In the NHANES III report,8 27.4% of patients used nutrition therapy (diet alone) compared with 20.2% in the NHANES 1999-2000 report.9 The percentage of patients using insulin injections alone dropped from 24.2% to 16.4%, and the use of insulin in conjunction with oral antidiabetic agents increased from 3.1% to 11.0%. The increasing use of insulin with oral agents could be interpreted as evidence of a trend toward more intensive treatment, but more than two thirds of adults with type 2 diabetes mellitus have not achieved glycemic control.7 The widespread decrease in glycemic control among this population, which may be a result of inadequate management of oral drug therapy and delayed initiation of insulin therapy,5 is of particular concern because it is inconsistent with reductions achieved for many indicators of long-term complications, such as blood pressure and cholesterol (Figure 2).10 The inability to achieve glycemic control in the majority of these patients, when combined with the disorder’s increasing prevalence, has implications for increasing morbidity and mortality among patients with diabetes.2,10 Clearly, diabetes care must be optimized to improve patient outcomes. Diagnostic and interventional efforts—including improved diet, pharmacologic therapy, and diabetes education—need to be more rigorous and comprehensive.2,10

**Benefits of Insulin**

Since its discovery in the 1920s, insulin has been a cornerstone of diabetes care.11 However, for insulin therapy to be effective in treating patients with type 2 diabetes, physicians need to convey to patients, especially those in whom diabetes has been recently diagnosed and those who are not achieving glycemic control with oral drug therapy, that insulin therapy is effective and well-tolerated. Physicians must also provide their patients with the rationale for pursuing glycemic control.12 Misperceptions about insulin therapy may delay therapeutic intervention and increase symptom severity and microvascular complications.13

**Psychological Resistance**

**Misperceptions About Insulin**

The unwillingness of physicians and their patients to initiate insulin therapy according to conventional recommendations has been referred to as “psychological insulin resistance.”14 Such reluctance may prolong the time that glycemia is not optimally controlled, therefore increasing the risk of neurologic, microvascular, and macrovascular complications. Physicians should discuss insulin therapy as an effective treatment option with their patients. Negatively portraying insulin therapy at any time during patient encounters can result in patient reluctance to initiate insulin therapy as well as reduced patient compliance—and reduced patient benefit.15 For example, some patients may perceive the initiation of insulin therapy as a sign that the disease has progressed to a serious stage.13,14 Other patients may interpret the need for insulin as an indication that they have not effectively self-managed diabetes through diet, physical activity, and prior use of oral antidiabetic drugs.13 These misperceptions may be inadvertently fostered and reinforced by physicians who position insulin use as a “threat” to control patient adherence to alternative treatment protocols, such as medical nutrition therapy, self-management, and oral antidiabetic agent therapy.14

Because perceived notions regarding insulin therapy can have detrimental effects, physicians’ attitudes, beliefs, and practices regarding intensive glycemic control are essential to successful clinical outcomes. A survey of 200 diabetologists, 99 general practitioners, and 3297 of their patients revealed a linear relationship between physicians’ stated goals for patients’ fasting plasma glucose (FPG) to meet new levels and the actual HbA1c levels that those patients achieved.16 Patients of physicians who set FPG goals of 110 mg/dL or less achieved mean HbA1c levels of 7.0%, whereas patients of physicians who set FPG goals greater than 140 mg/dL achieved mean HbA1c levels of 7.8%. This finding suggests that the patients of physicians who pursue intensive glycemic control have more suc-

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**Figure 1. Changes in treatment therapies for adults with type 2 diabetes mellitus based on National Health and Nutrition Examination Survey (NHANES) results.8,9 (Copyright 2004 American Diabetes Association from Diabetes Care, Vol. 27, 2004;17-20. Modified with permission from The American Diabetes Association.)**
successful outcomes than those whose physicians set more modest goals.16

To achieve glycemic control, the AACE and the ACE2 recommend the early use of insulin in the form of basal insulin (with or without oral antidiabetic agents) or basal bolus insulin therapy (premixed insulin preparations are recommended for those who require additional insulin during meals). The AACE and ACE guidelines2 recognize the effectiveness of insulin therapy, the decreased risk of hypoglycemia, and the simplified therapy with minimal daily injections associated with insulin analogs. To destigmatize insulin, physicians should present these considerations to patients recently diagnosed as having type 2 diabetes mellitus when discussing various treatment options, including oral antidiabetic agents and oral antidiabetic agents with insulin.

Because oral drug therapy alone will not reduce HbA1c levels by more than 2.0%, it is unlikely that patients with HbA1c levels greater than 10.0% will achieve glycemic control using oral agents alone (Table 2).17 However, oral agents still have a substantial role early in the type 2 diabetes mellitus treatment continuum. For example, in patients with impaired glucose tolerance or insulin resistance, recent studies18,19 have demonstrated that thiazolidinediones can substantially delay or prevent the progression of type 2 diabetes mellitus. A simple algorithm for meeting HbA1c targets is available on the Texas Diabetes Council Web site.20

Frequent Daily Injections

Intensive insulin regimens typically require complex daily injection schedules and demand a high level of motivation and commitment to frequent injections and glucose monitoring.11 Patients with type 1 diabetes mellitus generally recognize their need for insulin and accept that these injections support their health.13 In contrast, patients with type 2 diabetes mellitus, whose prior therapy may have consisted of alterations to diet or oral agent therapy exclusively, may have reservations about insulin therapy. These patients may display apprehension toward using needles and express concern regarding perceived pain from injections and the incon-

Table 2

<table>
<thead>
<tr>
<th>Type 2 Diabetes Mellitus: Typical Decreases in Fasting and Postprandial Plasma Glucose and Glycemic Levels in Response to Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication</td>
</tr>
<tr>
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</tr>
<tr>
<td>Metformin</td>
</tr>
<tr>
<td>Glucosidase inhibitors</td>
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<tr>
<td>Meglitinides†</td>
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<tr>
<td>Sulfonylureas</td>
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<td>Thiazolidinediones</td>
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<tr>
<td>Pioglitazone hydrochloride</td>
</tr>
<tr>
<td>Rosiglitazone maleate</td>
</tr>
<tr>
<td>Insulin</td>
</tr>
</tbody>
</table>

* Decrease in 1-hour postprandial plasma glucose and glycated hemoglobin A1c (HbA1c) levels is measured from baseline. † Includes nateglinide and repaglinide.

Abbreviation: NA, not applicable.
Source: Adapted with permission from American Association of Clinical Endocrinology as featured in Endocrine Practice, volume 8, 2002, page 52.11

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Figure 2. Percentage of adults with diabetes who have achieved target glycemic, blood pressure, and total cholesterol levels as reported in the National Health and Nutrition Examination Surveys (NHANES III and NHANES 1999-2000).7 Glycemic control is based on recommended glycated hemoglobin A1c (HbA1c) levels less than 7.0%; blood pressure control is defined as less than 130/80 mmHg; and total cholesterol control is described as less than 200 mg/dL. (JAMA10 reported slightly different values of glycemic control: 44.3% for NHANES III and 37.0% for NHANES 1999-2000.)
venience of including multiple injections in their daily routine. These concerns may cause nonadherence, which will compromise patients’ glycemic control and, subsequently, their long-term health status.

Overcoming concerns about frequent daily injections can be approached in three basic ways. First, physicians can introduce the concept of insulin therapy to patients with type 2 diabetes mellitus early in the course of diabetes, with an emphasis on its effectiveness, to help counter preconceptions that injection therapy is frightening, painful, or implemented as a “last resort.” Having patients practice self-injection with saline before they require insulin therapy and, if insulin therapy becomes necessary, encouraging patients to begin injecting insulin on a trial basis can help patients achieve this goal and enable them to discover the ease of implementing insulin therapy into individual treatment regimens.

A second approach is to address the frequency of injection. The key consideration is to balance the individual’s need for glycemic control with his or her tolerance for performing self-injection. For some patients, starting an insulin regimen with a single daily injection may be the best approach. Also, the use of basal insulin either alone or in combination with an oral antidiabetic agent such as metformin provides considerable flexibility. While usually taken at bedtime, the long-acting basal insulins can be administered at the same time, any time of the day, at 24-hour intervals. Regimens involving two daily injections of split-mixed insulin (regular human insulin [RHII] plus neutral protamine Hagedorn [NPH] insulin) are useful in patients who do not require as much flexibility and who take meals at consistent intervals. The type of regimen that most closely mimics physiologic insulin delivery involves basal insulin combined with bolus (or mealtime) rapid-acting insulin. Although this approach may require three or four daily injections, these can be advanced gradually (ie, by starting with a basal insulin and then adding a prandial insulin with the largest daily meal).

The third approach to overcoming patient concerns about frequent injections is to use insulin pen devices instead of conventional vial-and-syringe delivery. Insulin pens make self-injection simpler and more convenient and provide increased dosing accuracy. Clinical trials have shown that patients overwhelmingly prefer these devices compared with conventional insulin delivery and that this alternative delivery method may lead to improved adherence with daily insulin therapy and improved glycemic control. Insulin pens have been used extensively in Europe and Japan and are expected to gain broader acceptance in the United States.

In addition, the first inhaled insulin was approved in January 2006 by the US Food and Drug Administration and has been shown to be an effective tool to address postprandial glucose excursions in patients with type 2 diabetes mellitus. Such an insulin formulation may be an effective mode of initiating prandial insulin therapy in patients for whom insulin injections represent a substantial barrier to progressing insulin therapy to more physiologic regimens.

**Misperceptions About Cardiovascular Complications**

After learning that cardiovascular complications are sometimes associated with diabetes, some patients and physicians may make an incorrect causal connection between these complications and insulin use. For example, symptomatic cardiovascular disease may have developed in a patient’s relative who had diabetes shortly after starting insulin therapy. The patient may have inaccurately perceived a cause-and-effect relationship between insulin therapy and cardiovascular disease. Physicians may also have a similar misconception due to old data that associated hyperinsulinemia (actually a compensatory physiologic response to insulin resistance) with cardiovascular risk. However, it is important that physicians convey to their patients that the most clinically significant predictors of coronary heart disease and mortality are uncontrolled blood glucose levels (particularly postprandial), high blood pressure, and plasma triglyceride levels.

Patients should be informed that insulin use does not cause cardiovascular complications or mortality. To reassure patients about insulin, physicians can cite the evidence that glycemic control with insulin may actually reduce the risk of cardiovascular complications. The United Kingdom Prospective Diabetes Study (UKPDS) evaluated cardiovascular complications in 4585 patients with newly diagnosed type 2 diabetes mellitus. A risk analysis for myocardial infarction, stroke, and heart failure estimated that these complications significantly decreased by 14% (P < .001), 12% (P = .035), and 16% (P = .021), respectively, with every 1.0% reduction in HbA1c levels. In addition, long-term, intensive insulin therapy may reduce the risk of mortality, primarily fatal cardiovascular events, in patients with diabetes who have had a myocardial infarction. Intensive glycemic control with insulin, oral antidiabetic agents, or both as part of a multifactorial regimen can reduce the risk of microvascular and macrovascular complications in patients with diabetes. Thus, patients using insulin therapy may receive cardiovascular benefits from early glycemic control achieved through intensive regimens.

**Physical Resistance Hypoglycemia**

Patients’ risk of having hypoglycemia may be a substantial barrier to initiation of insulin therapy and ultimately will hinder their ability to achieve glycemic control and experience the long-term benefits of therapy. Although more common in patients with type 1 diabetes mellitus, hypoglycemia is a well-known, potential adverse effect of insulin therapy and has been reported with the use of most oral antidiabetic agents in the treatment of patients with type 2 diabetes mellitus. In a long-term study of patients with recently diagnosed type 2 diabetes mellitus, the annual incidence of hypoglycemia was
Evaluate the extent of the patient’s and family’s knowledge of hypoglycemia (eg, its causes and symptoms) and ask if the patient has experienced any of these symptoms. Respond to any concerns and convey that the symptoms of hypoglycemia often result from low blood sugar levels.

Ensure that the patient is following the “principles of aggressive therapy” to achieve optimal glycemic control. If symptoms of hypoglycemia occur, evaluate whether additional intervention (eg, patient education, ongoing professional guidance and support) would be beneficial for the patient and his or her family members.

Consider both aspects of glucose balance: insulin excess and compromised glucose counterregulation. Once the conventional risk factors for insulin excess (eg, insulin dose, type, and timing; patterns of food ingestion; and exercise) have been considered, determine the risk factors for compromised glucose counterregulation, which may impair the natural behavioral and physiologic defenses that protect against hypoglycemia. Related risk factors include being uninformed about hypoglycemia and having insulin deficiency, a history of severe hypoglycemia, or a diagnosis of hypoglycemia unawareness.

Figure 3. Recommended three-step approach for physicians to reduce patient risk of hypoglycemia. Physicians should discuss hypoglycemia with patients whenever treatment therapies and patients’ responses to treatment regimens are evaluated.

1. Evaluate the extent of the patient’s and family’s knowledge of hypoglycemia (eg, its causes and symptoms) and ask if the patient has experienced any of these symptoms. Respond to any concerns and convey that the symptoms of hypoglycemia often result from low blood sugar levels.

2. Ensure that the patient is following the “principles of aggressive therapy” to achieve optimal glycemic control. If symptoms of hypoglycemia occur, evaluate whether additional intervention (eg, patient education, ongoing professional guidance and support) would be beneficial for the patient and his or her family members.

3. Consider both aspects of glucose balance: insulin excess and compromised glucose counterregulation. Once the conventional risk factors for insulin excess (eg, insulin dose, type, and timing; patterns of food ingestion; and exercise) have been considered, determine the risk factors for compromised glucose counterregulation, which may impair the natural behavioral and physiologic defenses that protect against hypoglycemia. Related risk factors include being uninformed about hypoglycemia and having insulin deficiency, a history of severe hypoglycemia, or a diagnosis of hypoglycemia unawareness.

In a recent 24-week, multinational study of 4961 patients with type 2 diabetes mellitus who either adjusted their own insulin glargine dose every 3 days based on a titration schedule or whose physicians adjusted the patients’ doses during weekly visits or phone calls, there was a significant reduction in HbA1c levels for those patients who self-titrated compared with those patients who had their doses adjusted by their physicians (−1.22% vs −1.08%, respectively; P<.001).3 There was no statistically significant difference in hypoglycemia incidence rates between the two groups.4 Therefore, physicians should emphasize that simple titration schedules can help patients safely and effectively manage their diabetes with insulin therapy. The Texas Diabetes Council Web site provides a simple titration schedule for glycemic control in “treatment-naïve” patients as well as more detailed algorithms for various other diabetes-related prevention and therapy options.

Insulin detemir, another basal insulin analog, was approved in the United States in June 2005. Insulin detemir can be dosed once to twice daily for patients with type 2 diabetes mellitus, though the majority of patients require twice-daily injections to achieve glycemic goals.46

Many patients, depending on duration of type 2 diabetes mellitus and β-cell function, are able to achieve glycemic control with the addition of basal insulin to oral agents. Several clinical studies document substantial reductions in hypoglycemia with insulin glargine compared with NPH insulin (Table 3). Insulin glargine, which is associated with a lower risk of hypoglycemia than NPH insulin,5,37,40 has been reported to reduce the risk of hypoglycemic events from 21% to 56% when compared with NPH insulin.5,38,39

Split-mix insulin therapies administered on a twice-daily schedule may be appealing to patients when compared with basal bolus regimens that require multiple injections. However, split-mix insulin regimens restrict coverage in increments of 4- or 8-hours and greatly increase the probability of hypoglycemia if meals are late or missed.2 Janka et al38 reported that the overall rate of hypoglycemia, including the symptomatic and nocturnal forms, of patients with type 2 diabetes mellitus is approximately 50% lower in regimens consisting of insulin glargine once daily plus oral antidiabetic agents than with
human premixed insulin (30% RHI, 70% NPH insulin) administered twice daily.

**Weight Gain**
For overweight or obese patients with type 2 diabetes mellitus, any additional weight gain may become an obstacle to their adherence to intensive glucose-lowering therapy.47 Although insulin therapy is associated with weight gain, which is indirectly caused through calorie retention resulting from reduced glycosuria, it may not be directly linked with changes observed in body weight.21,47-49 For example, sulfonylureas have also been associated with weight gain.17,50 Metformin is not associated with weight gain,12,48,51,52 but this may be a result of the decreased dietary intake that is associated with the drug. Although thiazolidinediones have been associated with causing weight gain, the increased weight from thiazolidinediones tends to stabilize after initial reductions in HbA1c levels.53 A combination of glucose-lowering therapy, diabetes education, and medical nutrition therapy with a certified diabetes educator may help control weight gain from insulin therapy.53

Weight gain after initiation of insulin monotherapy or in combination with oral agents has been reported in controlled clinical trials of patients with type 2 diabetes mellitus (Table 4).5,22,37-39,48,52,54-62 As with hypoglycemia, the treatment therapy influences the degree of weight gain, which can result from a reduction in glycosuria and glucose retention rather than from a direct effect of the therapy.48 High baseline glycosuria and good responsiveness to insulin therapy are major predictors of weight gain.54 Although many patients will not be able to avoid insulin therapy–related weight gain, patients who start this therapy early in the course of diabetes (when FPG...
levels are <180 mg/dL and before glycosuria manifests) may prevent weight gain associated with insulin.54

Exenatide, approved by the US Food and Drug Administration in April 2005, is an injectable agent that mimics the effects of incretin peptides by increasing the secretion of insulin from the pancreas, slowing absorption of glucose from the gut, and reducing the action of the glucose secretory hormone, glucagon, in the liver. Notably, this twice daily injectable agent has been associated with weight loss in recent studies55,63 and may thus be a particularly important agent for addressing

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Table 4

<table>
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</table>

* Means in overall study population or range of means across treatment groups.
† Statistical significance among groups in weight changes from baseline.
‡ Auvé-Santa et al53 reported a weight change of 3.2 kg and Bergenstal et al52 reported a weight increase of 2.7 kg with a treatment regimen of RHI and placebo.
§ Change from 2-month run-in with insulin only.
∥ Treatment administered at bedtime.
¶ Treatment administered in the morning.
†† Premixed insulin (70% NPH insulin, 30% RHI).
** Compared with NPH insulin + metformin.
††† Treatment administered once in the morning and once at bedtime.

Abbreviations: BMI, body mass index; NA, not available; NPH, neutral protamine Hagedorn; NS, not statistically significant; RHI, regular human insulin.
hyperglycemia in overweight or obese patients.\textsuperscript{46} Heine et al\textsuperscript{55} conducted a survey in which approximately 550 patients with type 2 diabetes mellitus and with inadequate glycemic control were randomized to either exenatide twice daily or insulin glargine once daily with dose titration goals of maintaining FPG levels of less than 100 mg/dL. Although exenatide was more effective at reducing postprandial glucose excursions and insulin glargine was more effective at reducing FPG levels, both regimens lowered HbA\textsubscript{1c} levels by 1.11\%.\textsuperscript{55} After 26 weeks, patients treated with exenatide had a decrease in body weight of 2.3 kg, whereas patients treated with insulin glargine had an increase in body weight of 1.8 kg.\textsuperscript{35}

Although patients may also be concerned that increased body weight will affect body image and overall health, these concerns should not prevent patients from getting the full benefit of optimal diabetes care. When initiating insulin therapy in patients with poor glycemic control and documented glycosuria, the patients’ commitment to decrease caloric intake and increase physical activity is essential to keeping weight gain to a minimum. Patients need to know that these steps can help compensate for the reduction in glucose excretion that may contribute to weight gain.\textsuperscript{12-20,32-35,37-40,46,47} The use of a regimen that takes advantage of the relatively weight-neutral effects of metformin, such as the combination of this agent with a once-daily basal insulin, may help to improve glycemic control with acceptable weight gain.\textsuperscript{22} However, patients with diagnosed type 2 diabetes mellitus must understand that glucose control takes priority over weight loss because of its impact on long-term health and quality of life.\textsuperscript{21}

Comments

Patients’ attitudes toward insulin therapy and frequent daily injections; their misconceptions regarding cardiovascular disease; and their concerns about hypoglycemia and weight gain may all constitute real barriers to the consideration and initiation of appropriate insulin therapy. Physicians should address each of these barriers as early as possible with patients so that they are comfortable weighing their treatment options. Insulin analogs and basal-bolus regimens with or without oral antidiabetic agents provide a tremendous therapeutic advancement toward obtaining optimal glycemic control in patients with type 2 diabetes mellitus. Patients with diabetes must be educated that good glucose control is essential to the management of their condition. Uncontrolled blood glucose, along with uncontrolled blood pressure and plasma triglyceride levels, are key predictors of coronary heart disease and mortality. The achievement and maintenance of optimal glycemic control are critical steps in preventing serious long-term health complications associated with diabetes.

References


