Context: Among the growing population of individuals with type 2 diabetes mellitus, many patients are failing to meet glycemic targets and are therefore at increased risk of complications.

Data Overview: Rapid-acting insulin analogs (ie, aspart, lispro, glulisine) have a pharmacokinetic profile that mirrors endogenous insulin more closely than regular human insulin. These insulin analogs can also be given closer to mealtimes and are less likely to cause hypoglycemia. Long-acting insulin analogs (ie, detemir, glargine) have relatively flat time-action profiles and last up to 24 hours, thus simulating endogenous basal insulin more precisely than neutral protamine Hagedorn insulin and producing less nocturnal hypoglycemia. The simplicity and efficacy of insulin analogs should help facilitate a patient’s transition to insulin therapy. Current guidelines advocate starting insulin therapy in patients who have not achieved glycemic targets or those with glycated hemoglobin greater than 8.5% and adjusting doses as necessary. Two case studies illustrate the benefits of insulin analog therapy.

Conclusions: Insulin analogs offer many benefits over human insulins, including improved physiologic profile, greater convenience, reduced risk of hypoglycemia, and, in some instances, less weight gain. Combined, these elements may increase a patient’s adherence to treatment, potentially increasing the level of glycemic control and improving the prognosis in patients with type 2 diabetes mellitus.

Type 2 diabetes mellitus is becoming a pandemic in the developed world. According to 2007 data,1 23.6 million people in the United States are estimated to have diabetes, with type 2 diabetes mellitus accounting for up to 95% of all diagnoses. The disease’s prevalence in US children and adolescents is also increasing, as illustrated by the fact that 30% of all patients aged between 10 and 19 years with newly diagnosed diabetes have type 2 diabetes mellitus.2 According to 2002-2003 data, 15,000 individuals younger than 20 years are newly diagnosed as having type 1 diabetes mellitus annually, and 3700 are newly diagnosed as having type 2 diabetes mellitus.1

Current guidelines3-6 from the American Diabetes Association (ADA) and other organizations stress the importance of intensive treatment to achieve glycated hemoglobin (HbA1c) levels less than 7% (lower than 6% in individuals who don’t have hypoglycemic episodes) because patients with inadequately controlled diabetes are at increased risk of micro- and macrovascular complications. Several landmark studies7-10 have shown that good glycemic control can limit complications, highlighting the importance of more physiologic insulin profiles in achieving this goal after other therapies have proven to be insufficient.

The UK Prospective Diabetes Study8,11 showed that each 1% reduction in mean HbA1c was associated with a 21% risk reduction for any diabetes-related end point, the lowest risk being in those with HbA1c values in the normal range. Early intervention with insulin therapy may help improve outcomes12-15—a viewpoint reflected in current US treatment guidelines.3-6 This rationale is based on the progressive decline in β-cell secretion, which limits the efficacy of insulin secretagogues and insulin sensitizers.

Of particular concern, 43% of patients with type 1 or type 2 diabetes mellitus fail to achieve HbA1c targets.16 In fact, recent survey data showed that 89% of adults with diabetes in New York City did not know their HbA1c levels, prompting the New York Board of Health to introduce mandatory electronic reporting.17 These test results will be used to create a statewide registry so that the diabetes epidemic can be better monitored and patients who need more support can be identified.17

Control of fasting plasma glucose (FPG) and postprandial glucose (PPG) levels is essential to reduce the risk of complications.3,5,7,8 For example, elevated 2-hour PPG values...
have been associated with increased cardiovascular risk independent of FPG.3 The Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe study18 demonstrated that patients with higher than recommended levels of fasting and 2-hour plasma glucose levels require more intensive treatment because they are at higher risk of premature death than patients with abnormal FPG alone.

The ideal goal of insulin therapy is to mimic the pattern of physiologic insulin secretion to control both FPG and PPG—in other words, combine a long-acting basal component that suppresses endogenous hepatic glucose production to control FPG and a shorter-acting component to address PPG.20,21 Such regimens should help optimize glycemic control to minimize the risk of diabetes-related complications.19 In addition, patients can be taught to self-monitor blood glucose and adjust their therapy—crucial steps in insulin therapy—on the basis of fasting and postprandial readings. Patients should keep a blood glucose diary and work with the physician and office staff to set up a monitoring schedule that has minimal impact on patient lifestyle.

Newer insulin analogs mimic the profile of endogenous insulin more closely than recombinant human formulations and are therefore a step closer to this ideal. The present review discusses how insulin analogs can contribute to the effective management of type 2 diabetes mellitus and describes the limitations of other medications once β-cell dysfunction reaches a critical threshold. Case studies are also provided to further illustrate the benefits of insulin analogs.

The Match: Injected vs Secreted Insulin

In a person with a healthy pancreas, basal insulin is continuously released at low levels in response to hepatic glucose output, while prandial (bolus) insulin is released intermittently in response to elevated glucose levels following a meal (Figure 1).20 Within seconds of food ingestion, there is an initial release of insulin, which peaks in 1 to 2 minutes and lasts about 10 minutes.21,22 This first phase is responsible for suppressing hepatic glucose output, limiting PPG elevations, and stimulating phase 2 insulin release of newly manufactured insulin. This second phase lasts 1 to 2 hours until normoglycemia is restored.20,21 However, in patients with type 2 diabetes mellitus, phase 1 insulin secretion is markedly decreased or absent. As the disease progresses, phase 2 insulin release is also reduced, often by more than 50%.20,21

Patients with type 2 diabetes mellitus can be treated initially with oral medications that increase insulin secretion throughout the day (secretagogues or incretins), enhance insulin action (sensitizers), or reversibly inhibit carbohydrate breakdown (α-glucosidase inhibitors). However, the latter agents are used infrequently in the United States because of low efficacy and adverse gastrointestinal effects. Also, oral agents may slowly lose durability and therefore fail to control glucose levels in the majority of patients, even when given in combination, making exogenous insulin necessary. Although joint guidelines from the ADA and European Association for the Study of Diabetes13 and the American College of Endocrinology and American Association of Clinical Endocrinologists24 recognize this problem with oral antidiabetic medications, they provide somewhat different algorithms for initiating pharmacotherapy. Four dosing algorithms are described later in greater detail.

Human insulin analogs, which may improve glycemic control, have been modified by altering the amino acid sequence. For example, this change can take place by transposing two amino acids, replacing one amino acid with another, or adding a fatty-acid side chain to a specific amino acid.20 As a result of these genetic modifications, human insulin analogs have enabled insulin therapy to more closely mimic normal physiologic insulin secretion, as shown in Figure 2.25,26 A comparison of the time courses of various human insulins and insulin analogs is shown in Table 1.27,28

Basal insulin is commonly administered to patients starting insulin therapy. Detemir and glargine, the two long-acting insulin analogs available in the United States, have relatively flat time-action profiles and more closely mirror the physiologic action of basal insulin than NPH insulin, which peaks at 6 to 14 hours. As the therapeutic effect of detemir and glargine can last for up to 24 hours,29,30 the recommended dose is once or twice daily for insulin detemir29 and once daily for insulin glargine.30 However, the duration of action of detemir increases with doses.

In two large observational studies31,32 of patients with type 2 diabetes mellitus, once daily dosing was used in the majority of cases (77% to 79%). Clinical data33-38 suggest that long-acting analogs control glucose levels as effectively as NPH but with less nocturnal hypoglycemia and intrasubject
variability and a more predictable time-action profile. Also, detemir and glargine have been shown to cause less weight gain than NPH. In fact, this difference was shown to be statistically significant in clinical trials.34-36,39,40 Compared with regular human insulin, rapid-acting analogs (ie, aspart, lispro, glulisine) have a time-action profile that is more similar to endogenous postprandial insulin release.41 They can be injected within 15 minutes of a meal, unlike regular human insulin, which must be administered 30 to 45 minutes before a meal. Rapid-acting analogs also provide better control of postprandial glucose excursions. A combination of rapid-acting insulin with each meal and basal insulin (ie, basal-bolus therapy) is required by most patients with type 1 diabetes mellitus as well as those with type 2 diabetes mellitus that cannot be controlled with other insulin regimens. An alternative to these multiple daily injections is an insulin pump, which continually infuses a rapid-acting insulin to supply basal needs and delivers bolus doses at mealtimes, as selected by the patient.42 Premixed insulin analogs contain a rapid-acting analog for prandial coverage and a protaminated analog for basal needs. Currently, biphasic insulin aspart 70/30 (70% insulin aspart protamine suspension, 30% insulin aspart injection), insulin lispro 75/25 (75% insulin lispro protamine suspension, 25% insulin lispro injection), and insulin lispro 50/50 (50% insulin lispro protamine suspension, 50% insulin lispro injection) are available in the United States. Premixed insulins eliminate self-mixing and minimize the number of injections. These formulations are also used to initiate insulin therapy, particularly in patients with regular eating habits, after oral antidiabetic agents such as secretagogues provide insufficient prandial insulin. Patients with unpredictable eating habits should be encouraged to use basal-bolus therapy.

**Initiating Insulin Analog Therapy**

Some evidence suggests that early introduction of insulin can help lower insulin resistance, reverse glucose toxicity, and preserve β-cell function for longer than is possible with oral medications alone. It could also help reduce the incidence of cardiovascular complications, as insulin has been shown to reduce the level of proinflammatory cytokines, a group of substances involved in obesity-linked insulin resistance and implicated in the occurrence of atherosclerosis.44-46 These findings have been supported by results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study in patients with type 1 diabetes mellitus. As that study suggests, intensive, early intervention before complications manifest produces the best outcomes.

**Figure 2.** Pharmacokinetic profiles of human insulins compared with insulin analogs and endogenous insulin. Abbreviation: NPH, neutral protamine Hagedorn. Sources: Data for graph were extracted from US Pharmacist.26 Data for the endogenous curve were adapted from Edelman SV and Morello CM.25

<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Onset of Action, min</th>
<th>Peak, h</th>
<th>Duration, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analog</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– detemir</td>
<td>48-120</td>
<td>NA</td>
<td>&lt;24</td>
</tr>
<tr>
<td>– glargine</td>
<td>66</td>
<td>NA</td>
<td>&lt;24</td>
</tr>
<tr>
<td>Rapid-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– aspart</td>
<td>10-20</td>
<td>1-3</td>
<td>3-5</td>
</tr>
<tr>
<td>– lispro</td>
<td>15-30</td>
<td>0.5-2.5</td>
<td>3-6.5</td>
</tr>
<tr>
<td>– glulisine</td>
<td>10-15</td>
<td>1-1.5</td>
<td>3-5</td>
</tr>
<tr>
<td>Premixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 70% aspart protamine suspension/30% aspart</td>
<td>10-20</td>
<td>1-4 (2.4)*</td>
<td>&lt;24</td>
</tr>
<tr>
<td>– 75% lispro protamine suspension/25% lispro</td>
<td>10-30</td>
<td>1-6.5 (2.6)*</td>
<td>&lt;24</td>
</tr>
<tr>
<td>Human</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– NPH</td>
<td>60-120</td>
<td>6-14</td>
<td>16-24</td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– regular</td>
<td>30-60</td>
<td>1.5</td>
<td>6-10</td>
</tr>
<tr>
<td>Premixed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>– 70% NPH/30% regular</td>
<td>30-60</td>
<td>1.5-16 (4.4)*</td>
<td>18-24</td>
</tr>
</tbody>
</table>

* Data reported as range (mean).

**Abbreviations:** NA, not applicable (ie, no pronounced peak); NPH, neutral protamine Hagedorn.

Sources: Mooradian AD et al27 and Allen J.28
Traditionally, insulin is introduced to patients only after combinations of two or even three oral antidiabetic medications have failed to provide adequate glycemic control. In fact, only 11% of patients with type 2 diabetes who are taking medication are given insulin therapy, which reflects the general trend of using insulin as a last resort in managing type 2 diabetes mellitus.

However, the established superior efficacy of insulin over oral agents in reducing HbA1c levels, augmented by the beneficial profile of the new insulin analogs versus human insulins, may be changing this view. Furthermore, trials such as the Glycemia Optimization Treatment study are addressing the concern that causes many physicians to delay or inadequately dose insulin—namely, that tight glycemic control can lead to hypoglycemia. This particular trial involves 4823 insulin-naive patients with type 2 diabetes mellitus and was initiated to ascertain the optimum dose of insulin glargine (in combination with oral agents) to achieve glycemic targets without increasing the risk of severe hypoglycemia.

While the capacity of insulin to reduce HbA1c is unlimited, it is restricted by the potential for hypoglycemia. Most noninsulin diabetes medications have limited efficacy, whether alone or in combination (Table 2). However, key trials have shown that because of their simplicity and efficacy, insulin analogs may help facilitate the transition between oral agents and insulin therapy more successfully than human insulins.

While current treatment guidelines differ, they all recommend that insulin therapy be instituted earlier than usual in patients not achieving HbA1c targets. The ADA and European Association for the Study of Diabetes adopted a stepwise approach: (1) start with metformin and lifestyle modification; (2) add either basal insulin, a sulfonylurea, or a thiazolidinedione if HbA1c is still higher than 7%; and (3) add or intensify insulin therapy if targets remain unmet. The guidelines also recommend early initiation of insulin for individuals presenting with weight loss, more severe symptoms, FPG levels greater than 250 mg/dL, or random glucose levels consistently higher than 300 mg/dL.

While pramlintide and exenatide have been approved for use in the United States as adjunctive therapy, they are not included in the ADA treatment algorithm because of their relatively low glucose-lowering effectiveness, limited clinical data, and relative expense. However, they are acknowledged as appropriate choices for “selected patients.”

The American College of Endocrinology and American Association of Clinical Endocrinologists recommend various treatment options depending on HbA1c levels at diagnosis. For treatment-naive patients with an HbA1c level between 6% and 7%, monotherapy with metformin, a thiazolidinedione, a dipeptidyl-peptidase 4 (DPP-4) inhibitor, or an α-glucosidase inhibitor is preferred, while prandial insulin, a glinide, or a sulfonylurea are alternative options. For those with an HbA1c level between 7% and 8%, a combination of oral agents (eg, a sulfonylurea plus metformin, a thiazolidinedione, or an α-glucosidase inhibitor; a DPP-4 inhibitor plus metformin or a thiazolidinedione) is recommended, while prandial, basal, or premixed insulin are offered as alternatives. For patients with an HbA1c level between 8% and 10%, basal, prandial, premixed, or NPH insulin can be combined with oral agents to achieve appropriate FPG and PPG levels, though glinides and DPP-4 inhibitors are not suitable for HbA1c levels between 9% to 10%. Finally, for those with HbA1c levels greater than 10%, a basal-bolus or premixed insulin regimen is required. If glycemic goals are not met after 2 to 3 months of therapy, a more intensive regimen should be initiated. For example, exenatide or pramlintide may be added, though pramlintide should only be used as an adjunct to prandial insulin.

For patients already receiving pharmacologic treatment, the therapeutic options for combination therapy are appropriate, though exenatide and pramlintide may be introduced at an earlier stage in this patient group. Insulin should be added if the HbA1c levels of patients on maximum combination therapy (ie, multiple oral agents or oral agents plus exenatide) are between 6.5% and 8.5%. Also, basal-bolus insulin should be considered for patients with HbA1c levels greater than 8.5%.

Table 2: Effect of Hypoglycemic Agents on Glycated Hemoglobin (HbA1c) Levels in Patients With Diabetes Mellitus

<table>
<thead>
<tr>
<th>Drug Therapy</th>
<th>HbA1c Reduction, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonylurea + metformin</td>
<td>1.7</td>
</tr>
<tr>
<td>Rosiglitazone + metformin</td>
<td>0.7</td>
</tr>
<tr>
<td>Pioglitazone + metformin</td>
<td>0.8</td>
</tr>
<tr>
<td>Biguanides (ie, metformin)</td>
<td>1.1-3.0</td>
</tr>
<tr>
<td>Sulfonylureas</td>
<td>0.9-2.5</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>1.5-1.6</td>
</tr>
<tr>
<td>α-glucosidase inhibitors</td>
<td>0.6-1.3</td>
</tr>
<tr>
<td>Dipeptidyl-peptidase 4 inhibitors</td>
<td>0.8</td>
</tr>
<tr>
<td>Noninsulin Injections</td>
<td></td>
</tr>
<tr>
<td>Pramlintide</td>
<td>0.43-0.56</td>
</tr>
<tr>
<td>Exenatide</td>
<td>0.8-0.9</td>
</tr>
</tbody>
</table>

Source: Copyright 2007 by the American Association of Clinical Endocrinologists as featured in Endocrine Practice. 2007;13(suppl):1-68. Reproduced with permission.
Although the timing of patient introduction to insulin varies, if HbA1c levels continue to exceed stated targets, insulin should be introduced. While there is no best way to initiate insulin therapy in patients with type 2 diabetes mellitus, a long-acting basal insulin such as detemir or glargine, either at bedtime or in the morning, combined with oral antidiabetic therapy is a common starting regimen.5,6

Unfortunately, if insulin treatment is initiated late in the disease process, patients with type 2 diabetes may have little β-cell function left, making once-daily injection of basal insulin insufficient to achieve glycemic targets.56 At this point, agents that stimulate insulin release—such as sulfonylureas, exenatide, or DPP-4 inhibitors—should be discontinued and prandial insulin should added to the basal insulin, thus providing the physiologic basal-bolus regimen. Adjunctive treatment with pramlintide has been shown to improve postprandial and overall glycemic control when given with prandial insulin.57

After basal insulin alone has become insufficient, prandial insulin is typically initiated with one injection at the largest meal of the day and additional injections as necessary to achieve glycemic control.55 Patients may prefer to use premixed analog formulations, which combine rapid- and long-acting insulins in one preparation. However, strict adherence to mealtimes and exercise schedules is necessary to maintain glycemic control.55 A summary of the key insulin options is given in Figure 3 with an indication of patient profiles.14,58

The first phase of the Treating to Target in Type 2 Diabetes study59 suggests that most patients are likely to need more than one type of insulin. This study59 investigated the relative benefits of adding a premixed insulin analog twice daily, a rapid-acting analog three times daily, or a basal insulin analog once or twice daily to patients with suboptimal glycemic control on maximally tolerated doses of metformin and a sulfonylurea. At 1 year, the proportions of patients with HbA1c values at 6.5% or lower were 17%, 23.9%, and 8.1%, respectively. The final 2 years of the trial will investigate the more complex insulin regimens required as the disease progresses.

### Benefits of Insulin Analog Therapy

Whether insulin is given as a basal, basal-bolus, or premixed regimen or is used in a continuous subcutaneous insulin infusion pump, insulin analogs offer several advantages over conventional human formulations.

#### Time-Action Profile

A basal-bolus regimen with long- and rapid-acting insulin analogs more closely mimics physiologic insulin secretion while providing glycemic control that is at least as effective as regular human insulin and NPH (Figure 4).14,25,33-35,37,52,60,61

#### Convenience

Unlike short-acting and premixed human insulins, rapid-acting analogs and premixed analog formulations can be injected immediately before or just after a meal. This option gives patients more flexibility, which is particularly welcome for those with irregular lifestyles, such as individuals with variable work hours. Long-acting analogs are slowly absorbed and distributed, with relatively flat and predictable time-action profiles that last up to 24 hours.62 As a result, they usually need to be given only once daily, which can be at bedtime for minimum disruption.

In patients who had not achieved glycemic control on one or two oral hypoglycemic agents, treat-to-target trials33,35 demonstrated that initiating basal insulin therapy with either insulin glargine or insulin detemir—rather than NPH—is a simple and standardized way to achieve glycemic control with a substantially reduced risk of hypoglycemia. In gen-

## Patient Profile

<table>
<thead>
<tr>
<th>Patient Profile</th>
<th>Recommended Insulin Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>Basal only</td>
</tr>
<tr>
<td>Continuing use of oral agents</td>
<td>Basal only</td>
</tr>
<tr>
<td>Overweight</td>
<td>Basal-bolus</td>
</tr>
<tr>
<td>Insulin resistant</td>
<td>Premixed (once, twice, or three times daily)</td>
</tr>
<tr>
<td>Optimal control not vital (eg, elderly with no complications)</td>
<td>Continuous subcutaneous insulin infusion</td>
</tr>
<tr>
<td>Reluctant to administer multiple injections</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 3

**Recommended insulin regimen according to patient’s profile.** Patiens should meet all characteristics listed in the profile before following the recommended insulin regimen. **Sources:** Hirsch IB et al14 and Gallichan M et al.58
infusion to multiple daily injection regimens. Rapid-acting insulin analogs are currently considered the insulins of choice for insulin pumps.72,73

Hypoglycemia
Human insulins have variable peaks in activity and unpredictable action durations, which can make patients vulnerable to episodes of hypoglycemia.62 Long-acting insulin analogs were specifically developed to address these problems and have less within-subject variability and a lower incidence of hypoglycemia than NPH (Figure 5).5,6,33,35,37,74-81 This is particularly true of insulin detemir, which has a statistically significant lower variation coefficient than insulin glargine and NPH: 27% versus 46% and 59%, respectively (P<.001 for both comparisons).82

Hypoglycemia can occur if regular human insulin is administered more than 30 minutes before eating. By contrast, rapid-acting insulin analogs decrease the potential for hypoglycemic episodes. Although severe hypoglycemia is uncommon in patients with type 2 diabetes mellitus,8 fear of hypoglycemia is a major concern for patients receiving insulin therapy and can be a barrier to the practice of strict glycemic control.75 Educating patients about the time-action profiles of different insulin preparations and prevention of hypoglycemia increases patients’ confidence in their treatment and makes them more willing to accept dose adjustments.49

Weight Gain
Clinical trials suggest that long-acting analogs cause less weight gain than NPH insulin.34-36,38-40,83 This difference may be associated with a decreased need for additional snacks because patients are less worried about the risk of hypoglycemia.34 Addressing the problem of weight gain should help reduce the potential for obesity-related complications and improve patient self-esteem.

Implications for Patient Adherence
It is generally accepted that restoring normal or near-normal glucose homeostasis can substantially reduce the risk of diabetes-related complications. Therefore, the more physiologic time-action profiles and convenient dosing of insulin analogs may help improve the long-term prognosis for patients with type 2 diabetes.12 However, the advantages identified in clinical trials need to be documented in clinical practice.

Two studies31,84 in a “real-world” setting have shown that long-acting insulin analogs provide good glycemic control with low levels of hypoglycemia. The Predictable Results and Experience in Diabetes through Intensification and Control to Target trial31 was a 3-month observational study in which patients were transferred from NPH plus oral agents, insulin glargine plus oral agents, or oral agents only to detemir plus oral agents. Once started on detemir, changes in insulin dose or oral agents during the study period were made as needed by the patient’s physician. All three detemir groups had sta-

![Figure 4. Comparison of human (A) and analog (B) basal-bolus insulin regimens. The shaded areas depict normal insulin secretion, thus showing the relationship of each insulin therapy to normal physiologic conditions. Abbreviations: B, breakfast; HS, bedtime; L, lunch; NPH, neutral protamine Hagedorn; S, supper. Source: Edelman SV, Morello CM. Strategies for insulin therapy in type 2 diabetes. South Med J. 2005;98:363-371. Copyright Southern Medical Association. Modified with permission of Lippincott Williams & Wilkins.]
produced statistically significant HbA1c reductions over care setting, insulin glargine plus oral antidiabetic agents at Point of Care trial, which was based in a predominantly pri-
titration and the benefits of insulin analog therapy. Further, they illustrate insulin or glycemic control. The two case studies presented below rep-
variety of delivery systems available, help patients adhere to
dosing and reduced risk of hypoglycemia, combined with the
Because the patient did not want to initiate a basal-bolus pro-
program, premixed insulin aspart 70/30 administered at dinner

Case Study 1
A 54-year-old male dockworker with a history of hypertension was diagnosed as having type 2 diabetes mellitus 12 years ago. He had no his
t of retinopathy or periph-
er neuropathy. His current med-
ones: metformin, 500 mg twice daily, and morning
doses of glipizide, 20 mg, and

On physical examination, his
weight was 216 lbs; body mass
index, 32; and blood pressure, 130/82 mm Hg. Cardiac and res-
piratory examinations were normal, and there was no evidence of reduced peripheral pain sense or peripheral edema. His most recent
HbA1c value was 9.4%, and his urine microalbumin/creatinine
ratio was 38 μg/μg/mL.
The patient typically ate very
little breakfast and lunch and had a
large, mixed meal dinner after 8 PM. He regularly checked his blood glucose levels before breakfast and at bedtime (11 PM), and he reported that his most recent glucose levels were 156 mg/dL (before breakfast) and 246 mg/dL (3 hours after dinner). The patient’s postprandial
dinner hyperglycemia was of
greatest concern. Although the
patient reported attempting lifestyle changes, he continued this food consumption pattern.

To improve glycemic control, three treatment options were available:

- addition of another insulin sensitizer
- addition of a DPP-4 inhibitor and discontinuation of glipizide
- initiation of basal-bolus insulin or premixed insulin analog formulation

Because the patient did not want to initiate a basal-bolus pro-
gram, premixed insulin aspart 70/30 administered at dinner
was determined to be the preferred option. This therapy option
would provide his dinner insulin requirements and improve
his overnight glycemic control without the risk of fasting hypoglycemia. (Insulin lispro 75/25 would also have been an
appropriate option.)

Premixed insulin analog aspart 70/30 was initiated at
10 units with dinner and titrated up to 20 units. The patient

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Starting Dose, IU/day</th>
<th>Increase Interval</th>
<th>Mean FPG or PPG Values, mg/dL</th>
<th>Change in Insulin, IU/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td>Riddle MC et al33</td>
<td>10 Weekly</td>
<td>100-120 120-140 140-180</td>
<td>+2 +4 +6</td>
</tr>
<tr>
<td></td>
<td>Davies M et al64</td>
<td>10 Weekly</td>
<td>≥100 &lt;120</td>
<td>+0-2</td>
</tr>
<tr>
<td></td>
<td>Selam JL et al63</td>
<td>NA Every 3 days</td>
<td>&lt;80 80-110</td>
<td>−3‡</td>
</tr>
<tr>
<td></td>
<td>Philis-Tsimikas A et al66</td>
<td>10 At least once every 4 weeks</td>
<td>≤108 109-126 127-144 145-162 163-180</td>
<td>0 2 4 6</td>
</tr>
</tbody>
</table>

*The titration regimen used by Riddle MC et al33 was based on mean fasting plasma glucose (FPG) values of the previous 2 days. Davies M et al64 also used mean FPG values, but they were based on measurements of the previous 3 days. The titration regimen set by Philis-Tsimikas A et al66 was based on mean postprandial glucose (PPG) values for the previous 3 days.
† A “+” denotes an increase in insulin dose; a “−” denotes a decrease in insulin dose.
‡ According to the 3-0-3 algorithm used in the PREDICTIVE study, insulin is increased or decreased by 3 units or left unchanged depending on the patient’s mean FPG values from three measurements.
§ Mean plasma glucose values were based on three consecutive measurements. If one or more of the three plasma glucose measurements were within the range of less than 56 mg/dL or between 56 to 72 mg/dL, for no obvious reason, the insulin dose was decreased by the amounts shown in the next column of this table.

Abbreviation: NA, not available.
to manage glucose levels. A few years later, he was placed on glyburide but was later taken off glyburide and switched to glimepiride (4 mg per day). However, his blood glucose levels continued to rise. Metformin was added as a cotherapy with a slow titration up to 2 g per day. Despite using these oral agents, his HbA1c was 8.6%.

To better control HbA1c levels, insulin detemir was added to the patient’s regimen at a starting dose of 10 units at bedtime followed by self-titration based on his FPG level—an average of the previous 3 days. He was instructed to titrate detemir as follows:

- If FPG is less than 80 mg/dL, reduce insulin by 3 IU.
- If FPG is 80–110 mg/dL, continue current dose.
- If FPG is greater than 110 mg/dL, increase insulin by 3 IU.

This treatment algorithm was similar to that used in the US PREDICTIVE 303 trial.65

The patient noted that FPG levels declined to the 120 mg/dL range. Glimepiride was stopped and metformin maintained at the dosage of 2 g per day. His HbA1c was 8.6%.

To better control HbA1c levels, insulin detemir was added to the patient’s regimen at a starting dose of 10 units at bedtime followed by self-titration based on his FPG level—an average of the previous 3 days. He was instructed to titrate detemir as follows:

- If FPG is less than 80 mg/dL, reduce insulin by 3 IU.
- If FPG is 80–110 mg/dL, continue current dose.
- If FPG is greater than 110 mg/dL, increase insulin by 3 IU.

Discussion

Groundbreaking studies7-10 have proven that maintaining HbA1c levels less than or equal to 7%, in accordance with professional guidelines,3-6 can limit the progression of complications in type 2 diabetes mellitus. In order to achieve optimum glycemic control, insulin analogs have proven to mimic physiologic insulin secretion better than other therapy options. For example, compared with short-acting human insulins, rapid-acting insulin analogs have a time-action profile closer to that of endogenous insulin and can be given immediately before or after meals.

Long-acting insulin analogs are relatively peakless, providing insulin for up to 24 hours in a way similar to endogenous basal insulin. In addition, premixed insulin analog formulations have proven effective in reducing both FPG and PPG in patients inadequately controlled on oral agents, as demonstrated in both the 1-2-3 study67 and the INITIATE study.85 In the 1-2-3 study,85 the majority of patients were con-

As a result of this regimen, the postprandial dinner and FPG levels were reduced and, 3 months later, his HbA1c level had fallen to 8.0%. Although this value was above the target level, continued titration should continue to decrease and improve the patient’s glycemic control.

Case Study 2

A 48-year-old man was diagnosed as having type 2 diabetes mellitus 18 years ago. He had a history of hypertension, hyperlipidemia, proteinuria, and diabetic peripheral neuropathy, and he had suffered a recent thrombotic stroke.

His medications included carvedilol, 3 mg twice a day; ezetimibe, 10 mg daily; furosemide, 40 mg daily; gabapentin, 100 mg daily; glimepiride, 4 mg daily; hydrochlorothiazide, 12.5 mg daily; losartan potassium, 100 mg daily; and simvastatin, 40 mg daily.

On physical examination his blood pressure was 110/74 mm Hg; pulse rate, 76 beats per minute; and respirations, 18 breaths per minute. Cardiac examination revealed an audible S4. Pulmonary and abdominal examinations were normal. He had an FPG of 263 mg/dL and an HbA1c level of 8.6%. Kidney function tests revealed a 24-hour urine protein level of 2.8 g, blood urea nitrogen of 37 mg/dL, and serum creatinine of 1.5 mg/dL. Subsequent laboratory tests revealed total cholesterol to be 114 mg/dL, low-density lipoprotein cholesterol, 52 mg/dL, high-density lipoprotein cholesterol, 32 mg/dL, and triglycerides, 216 mg/dL.

The patient reported that when he was first diagnosed as having type 2 diabetes mellitus, he used diet and exercise to control his blood glucose levels. He had a history of hypertension, hyperlipidemia, proteinuria, and diabetic peripheral neuropathy, and he had suffered a recent thrombotic stroke.

His medications included carvedilol, 3 mg twice a day; ezetimibe, 10 mg daily; furosemide, 40 mg daily; gabapentin, 100 mg daily; glimepiride, 4 mg daily; hydrochlorothiazide, 12.5 mg daily; losartan potassium, 100 mg daily; and simvastatin, 40 mg daily.

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trolled on two injections of biphasic insulin aspart 70/30 per day, an important consideration for patients reluctant to start basal-bolus insulin, such as the patient in the first case study.

Premixed insulins are a very attractive option for the initial introduction of insulin therapy in type 2 diabetes mellitus: they reduce the injection load, making insulin treatment easier to accept; provide prandial coverage from the beginning; avoid the possibility of mixing errors; and have proven more effective than basal insulin plus oral agents in lowering HbA1c.85-87 However, premixed insulins are less suitable as the disease progresses because of the substantially increased incidence of weight gain and hypoglycemia compared with basal analog therapy.85,86

The longer patients have type 2 diabetes mellitus, the more vulnerable they become to low blood glucose levels as a result of failure of endogenous counter-regulatory mechanisms that help protect against hypoglycemia.74 The body normally produces various hormones in response to hypoglycemia, including glucagon, epinephrine, cortisol, and growth hormone. The primary effect of these hormones is to suppress insulin release and stimulate glucagon- and epinephrine-mediated glucose production. Epinephrine is also key to the initiation of glucose-sparing lipolysis.74 In patients with type 2 diabetes mellitus, the glucagon response is virtually absent.88

Given that insulin analogs are associated with a lower incidence of hypoglycemia and a higher level of convenience than human insulins, patient adherence is more likely.

Conclusion

The goals of insulin therapy are to achieve glycemic control and to minimize the risks of hypoglycemia and weight gain. Regardless of the insulin regimen given, insulin analogs should help improve glycemic control and the health outlook for patients with type 2 diabetes mellitus.

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