Trends in the Management of Type 2 Diabetes: An Emerging Role for Insulin

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Continuing Education Program
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1. Disclose the principal sources of funding in a manner that permits easy recognition by the reader.
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3. Describe all drugs by generic name unless the use of the brand name is necessary to reduce the opportunity for confusion among readers.
4. Strive to report subjects of current interest to managed care pharmacists and other managed care professionals.
5. Seek and publish content that does not duplicate content in the Journal of Managed Care Pharmacy.
6. Subject all supplements to expert peer review.
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Trends in the Management of Type 2 Diabetes:
An Emerging Role for Insulin

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S12 Continuing Education*:
CE Submission Instructions and Posttest Worksheet

Target Audience
Managed care pharmacists who are involved in the clinical management of diabetes

Learning Objectives
Upon completion of this program, participants will be able to
1. cite the relationship between the structural features of rapid-acting insulin and its function in glucose regulation;
2. explain the rationale behind the development of rapid-acting insulin; list available rapid-acting insulins; and compare the safety, efficacy, and pharmacologic properties of these agents;
3. describe the role of rapid-acting insulin in the aggressive management of diabetes and its importance to the prevention of comorbid conditions;
4. examine the scientific evidence and the appropriate clinical use of rapid-acting insulin and its analogues in patients with various stages of diabetes; and
5. explain the importance of basal insulins in maintaining euglucemia.

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*A total of .20 CEUs (2.0 contact hours) will be awarded for successful completion of this continuing education program (ACPE Universal Program No. 233-000-05-001-H04).

The article published in this supplement represents the opinions of the authors and does not reflect the official policy or views of the Academy of Managed Care Pharmacy, the authors' institutions, or Aventis Pharmaceuticals unless so specified.
OBJECTIVE: This review is intended to explore the pathophysiology of type 2 diabetes, examine the role of insulin as a means of achieving glycemic control in people with type 2 diabetes, and provide a practical approach for insulin use in type 2 diabetes in the managed care setting.

DATA SOURCES: This manuscript is based on the results of a MEDLINE literature search and presentations by the authors at a symposium titled, “Emerging Changes in Diabetes Management,” that took place on October 14, 2004, at the Academy of Managed Care Pharmacy’s 2004 Educational Conference in Baltimore, Maryland.

CONCLUSIONS: Despite advances in oral treatment, type 2 diabetes remains a substantial source of microvascular and macrovascular complications that cause unacceptable levels of morbidity, mortality, and cost. Accumulating clinical evidence suggests that insulin treatment, both basal and prandial, can advance the treatment of type 2 diabetes and reduce the risks for serious sequelae by providing consistent and optimal glycemic control. By more closely mimicking the actions of endogenous insulin, in terms of onset and duration of action, insulin analogues offer clear advantages over their regular insulin counterparts.

KEYWORDS: Type 2 diabetes, Basal insulin, Prandial insulin, Regular insulin, Insulin analogues, Glargine, Aspart, Lispro, Glulisine

ABSTRACT

A growing public health problem, diabetes mellitus results in serious long-term complications that increase morbidity and mortality as well as health care costs. With a striking increase in prevalence of about 30% over the last decade, diabetes now affects 18.2 million people in the United States, or 6.3% of the population. More than 90% of these cases are type 2 diabetes.

The treatment of diabetes has made notable strides over the last century. In the 1920s, the advent of insulin injections revolutionized the management of diabetes. The initial insulin preparations, however, were crude and short acting, requiring multiple injections throughout the day and night. In the 1930s, long-acting protamine zinc insulin was introduced, which was thought to represent an advantage. The 1940s saw the introduction of neutral protamine Hagedorn (NPH), an intermediate-acting insulin formulation.

Advances in chromatography during the 1960s and 1970s spurred the development of highly purified insulin, such as the Lente insulin series. Oral antihyperglycemic agents—sulfonylureas and the biguanide phenformin—also became available. Because of its link to lactic acidosis, phenformin was removed from the market United States during the 1970s. Currently, metformin is the only biguanide available in the United States.

Advances in recombinant DNA technology during the 1970s provided an opportunity for the development of synthetic human insulin. These research efforts culminated in the first U.S. Food and Drug Administration (FDA)-approved recombinant DNA-produced drug: human insulin. The 1990s also saw the introduction of a new class of oral insulin sensitizers—the thiazolidinediones—such as rosiglitazone and pioglitazone.

Yet, despite these notable advances in treatment, diabetes still results in substantial mortality and morbidity in the United States. Diabetes remains the leading cause of blindness in working age adults, contributes to half the nontraumatic lower extremity amputations, accounts for 35% of all new cases of end-stage renal disease, and causes a 2-fold to 4-fold elevation in the risk for cardiovascular disease. Indeed, ischemic heart disease accounts for 40% of all deaths in individuals with diabetes. In the United States, total diabetes costs have been estimated at $132 billion yearly. Three quarters of these costs, $92 billion, are direct costs associated with diabetes, including disease-related complications or comorbidities, with the remaining 25% ($40 billion) associated with lost productivity.

To dampen diabetes-related morbidity, mortality, and costs, consistent glycemic control remains an indispensable, but all too often elusive goal. Interestingly, several studies document that the majority of patients with treated diabetes achieve less than optimal glucose control. This manuscript will examine the pathophysiology of type 2 diabetes mellitus, as well as treatment
strategies for achieving optimal glycemic control, most notably with the use of early insulin treatment, an important but often underutilized step, in achieving consistent glycemic control.

II. Pathophysiology of Type 2 Diabetes

A chronic metabolic disorder, type 2 diabetes is associated with impaired pancreatic β-cell function, usually in the presence of insulin resistance in target tissues, including the liver, adipose, and muscle (Figure 1). Triggered by a genetic proclivity and the presence of modifiable risk factors, chiefly obesity, insulin resistance signals impending diabetes, often preceding its onset by 1 or 2 decades.7 In individuals with insulin resistance, the pancreas is required to produce more insulin to compensate for the diminution in insulin-mediated glucose metabolism.10 As a result, hyperinsulinemia is usually present in people with insulin resistance (Figure 1).

Over time, compensatory β-cell activity in the pancreas diminishes and insulin concentrations become insufficient to overcome blunted glucose metabolism secondary to insulin resistance. Eventually, β-cell failure occurs, further attenuating insulin secretion. Clinical studies suggest that, at the time of initial diagnosis of type 2 diabetes, about 50% of β-cell function is present.11,12 Despite subsequent treatment with diet, metformin, or sulfonylureas, a progressive 4% to 6% yearly loss occurs in β-cell function. Importantly from a therapeutic standpoint, once β-cell function diminishes to a certain point, oral agents are rendered ineffective and insulin replacement becomes the only alternative. Much research in the treatment of diabetes is now devoted to identifying the cause of β-cell failure and its prevention.

Normally, the insulin response to an intravenous glucose bolus is biphasic. In the first phase, a glycemic bolus triggers a burst of insulin production lasting about 10 minutes that does not stimulate glucose metabolism but signals the liver to reduce glucose output in the postprandial state. Postprandially, in nondiabetic individuals, the liver switches from an organ of glucose production to an organ of glucose uptake; yet, in individuals with diabetes or glucose intolerance, the liver continues to produce glucose. The second-phase response is characterized by a more sustained release of insulin lasting several hours or until glucose levels return to baseline or fasting values.13

Disruptions in both of these phases have been detected in individuals with glucose intolerance destined to develop type 2 diabetes. Indeed, the acute phase response has been shown to be absent in individuals with fasting glucose levels of ≥115 mg/dL.14 Further, the presence of glucose intolerance delays peak postprandial insulin secretions from the normal 60 minutes to 90 minutes in those with impaired glucose tolerance to 120 minutes for those with type 2 diabetes.15,16 Moreover, the presence of impaired glucose tolerance attenuates the magnitude (28% reduction) of the normal second-phase response.13 Loss of the first-phase response, a delay in peak postprandial insulin levels, and a dampened second-phase response are physiologic markers that act in concert to elevate glucose levels after meals in individuals with impaired glucose tolerance or type 2 diabetes.

Postprandial glucose elevations contribute to elevations in glycated hemoglobin A1c (HbA1c) levels, the best measure of diurnal hyperglycemia, and are typically the first detectable glycemic abnormality in glucose intolerance. Yet, the relative importance of postprandial hyperglycemia and fasting hyperglycemia to overall diurnal hyperglycemia, as measured by HbA1c, remains controversial. Some investigators have proposed that the contribution varies depending on prevailing glucose level as measured by HbA1c level, with postprandial glucose contributing about 70% when HbA1c is <7.3% and fasting plasma glucose contributing about 70% when HbA1c exceeds 10.2%.17

Metabolic Syndrome, Diabetes, and Cardiovascular Disease

Insulin resistance is often accompanied by a constellation of metabolic abnormalities including hypertension, dyslipidemia, obesity, glucose intolerance, procoagulant state, and endothelial inflammation that promote cardiovascular disease as well as diabetes. Collectively, these associated conditions have been called the Metabolic Syndrome or the Insulin Resistance Syndrome. An older designation is Syndrome X. This syndrome is associated with increased risk for cardiovascular disease (CVD), in part through the effects on the vascular endothelium.18

Endothelial Dysfunction

The endothelium is not just a dormant single layer of cells lining the surface of vessels. Instead, normally functioning endothelium teams with cellular activity involved in a variety of processes that maintain vascular health. Optimally, endothelial cells mediate vascular dilation, inhibit the growth and proliferation of cells that could narrow the arterial lumen, and prevent thrombus formation. The normally functioning endothelium resists inflammation and

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**Figure 1** Etiology of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Normal β-cell Function</th>
<th>Abnormal β-cell Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Euglycemia</td>
<td>Hyperglycemia</td>
</tr>
<tr>
<td>Compensatory Hyperinsulinemia</td>
<td>Relative Insulin Deficiency</td>
</tr>
<tr>
<td>Lifestyle, Diet, Genes</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Lifestyle, Diet, Genes</th>
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<tr>
<td>Normal β-cell Function</td>
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</tr>
<tr>
<td>Relative Insulin Deficiency</td>
</tr>
<tr>
<td>Type 2 Diabetes</td>
</tr>
</tbody>
</table>
**Optimizing Glucose Control**

In patients with type 2 diabetes, clinical evidence clearly demonstrates an important link between glucose control and a reduction in subsequent complications. Data from the large UK Prospective Diabetes Study (UKPDS) reveals that a 1% decline in HbA1c levels (from 8% to 7%) yields a substantial reduction in the risks for complications in individuals with type 2 diabetes (Figure 2). In fact, each percentage point decline in HbA1c resulted in a 35% reduction in microvascular complications.

These findings were buttressed by the results of the prospective Diabetes Control and Complications Trial (DCCT), which found that a 2% drop in HbA1c levels in patients with type 1 diabetes receiving intensive therapy can reduce the risk for diabetes-related retinopathy, nephropathy, and neuropathy by 50% to 60%. Based on these key clinical findings, the major guidelines for the management of diabetes now advocate stringent goals for glycemic control (Table 1).22,23

Unfortunately, many clinical studies indicate that the majority of the individuals with type 2 diabetes have not reached the glycemic goals recommended by these national organizations’ guidelines. The National Health and Nutrition Examination Survey (NHANES) III, a national survey of 1,026 individuals with either diagnosed or undiagnosed diabetes conducted from 1988 to 1994, found that despite treatment with either insulin or oral agents, fewer than half (45%) of the individuals with type 2 diabetes met the American Diabetes Association HbA1c goal of <7%.24

In the early stage, postprandial hyperglycemia characterizes type 2 diabetes. More established diabetes, however, is characterized by both postprandial and fasting hyperglycemia. Since postprandial and fasting hyperglycemia develop from somewhat different pathogenic mechanisms, specific treatments exist for each.25 In type 2 diabetes, postprandial glucose elevations stem from loss of normal first-phase insulin secretion, failure to reduce hepatic glucose production, and reduced glucose uptake by muscle as well as the absence of glucagon suppression.25

**Postprandial Hyperglycemia: An Independent Risk Factor for Macrovascular Complications?**

Determinants of postprandial hyperglycemia include the carbohydrate content of a meal, the endogenous insulin response to the glucose load imposed by the meal, and, in individuals with type 2 diabetes, an absent first-phase response and an overall delayed and reduced postprandial insulin response. Studies suggest that postprandial hyperglycemia alone contributes to CVD risk. For example in the Diagnostic Criteria in Europe (DECODE) study, 2-hour post-glucose-load concentrations in diabetic and nondiabetic individuals correlated better with subsequent risk of CV events and total mortality than did fasting glucose.26 These findings are consistent with emerging data that implicate postprandial hyperglycemia as an independent risk factor for macrovascular complications in individuals with type 2 diabetes.27,28

**Postprandial Hyperglycemia and Cardiovascular Risks**

The Honolulu Heart Study also demonstrated that, in more than 6,000 nondiabetic men followed for 12 years, a glucose value one hour after a 50 gram oral glucose challenge correlated with CV mortality.29 Men in the fourth quintile with glucose levels 157 to

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**TABLE 1** Guidelines for Glycemic Control

<table>
<thead>
<tr>
<th>Measure</th>
<th>ADA</th>
<th>ACE/AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>7%</td>
<td>≤6.5%</td>
</tr>
<tr>
<td>Preprandial glucose</td>
<td>90-130 mg/dL</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>Postprandial glucose</td>
<td>&lt;180 mg/dL</td>
<td>&lt;140 mg/dL</td>
</tr>
</tbody>
</table>

*ADA = American Diabetes Association; ACE/AACE = American Association of Clinical Endocrinologists/American College of Endocrinology.*

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prevents the oxidation of lipids that can cause atherosclerosis. In individuals with diabetes and insulin resistance, severe endothelial dysfunction occurs, increasing the risks for CVD.19

On the endothelial cell surface, insulin and acetylcholine receptors lie in close proximity to each other. They are both involved in stimulating the synthesis of nitric oxide, an important smooth muscle relaxant and vasodilator produced by endothelial cells. If neither of these receptors function properly, nitric oxide synthesis declines, resulting in vasoconstriction, hypertension, and an increased risk for cardiovascular (CV) complications secondary to diabetes.26 This disruption of normal endothelial cell function appears to be an important step leading to CVD in individuals with type 2 diabetes. In addition, insulin resistance has been linked to increased platelet aggregation and decreased thrombolysis, in part related to increases in plasminogen activator inhibitor-1 (PAI-1).19

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**III. Treatment Considerations**

**Optimizing Glucose Control**

The Honolulu Heart Study also demonstrated that, in more than 6,000 nondiabetic men followed for 12 years, a glucose value one hour after a 50 gram oral glucose challenge correlated with CV mortality.29 Men in the fourth quintile with glucose levels 157 to
The results of these studies have direct implications for the management of type 2 diabetes in the clinical setting. Specifically, the use of fasting plasma glucose levels alone may fail to identify adults at risk for CHD. In addition, impaired glucose tolerance in nondiabetic individuals and postprandial hyperglycemia in patients with type 2 diabetes places them at an increased risk for CVD. Clearly, correcting abnormalities in postprandial glucose levels, as well as fasting plasma glucose levels, should be considered an indispensable component of optimal diabetes management, as well as a critical step in the prevention of macrovascular complications. Postprandial hyperglycemia can be managed by a variety of agents that act via different mechanisms (Table 2).

### IV. Early Insulin in Type 2 Diabetes: An Underused but Effective Option

Proper nutrition, exercise, and education remain the cornerstone for the initial management of type 2 diabetes. The pharmacologic management of type 2 diabetes has become a challenging landscape requiring the clinician to exercise considerable clinical judgment to discern the optimal treatment for individual patients. Nonetheless, the pharmacologic tools are now available to achieve consistent glycemic control in those patients in need of drug therapy.

Findings from the UKPDS study imply that traditional therapies for type 2 diabetes—sulfonylureas, metformin, and insulin—effectively reduce HbA1c levels and are appropriate first-line treatments; but, over time, combination therapy is typically required to achieve glycemic target levels. In UKPDS, a greater percentage of patients receiving insulin therapy, when compared with diet modifications or sulfonylurea therapy, were able to maintain glycemic control, as measured by fasting plasma glucose or HbA1c levels, underscoring the importance of early insulin therapy in these patients.

When diet and exercise fail to achieve glycemic control in patients with type 2 diabetes, oral agents are typically added in a stepwise fashion to control hyperglycemia. Nonetheless, even with this strategy, the management of type 2 diabetes remains suboptimal; thus, more aggressive treatment appears medically reasonable.

Because of the progressive nature of the disease, most patients with type 2 diabetes will inevitably require insulin therapy. Yet, because of exaggerated concerns related to weight gain, hypoglycemia, or CV effects, many clinicians are reluctant to prescribe insulin in patients with type 2 diabetes. Moreover, patients often fear the use of needles and are concerned about the inconvenience and embarrassment of self-injecting insulin on a regular basis. The use of new, simple-to-use insulin pens and pumps, instead of the traditional needle and syringe, may lessen discomfort and embarrassment. Patient education about the important role of optimal insulin levels in averting serious complications also may improve patient acceptance of insulin therapy.

As a result of these barriers, insulin therapy for the treatment of type 2 diabetes remains a last resort for many physicians and patients. Yet, accumulating evidence now suggests that early initiation of insulin therapy is actually a positive step that can blunt the development of the key underlying pathophysiological abnormalities in type 2 diabetes—inulin resistance and impaired insulin secretions, for instance. Based on results from several clinical studies, some endocrinologists advocate initiating insulin therapy in combination with oral agents early in the course of type 2 diabetes, or immediately after nonpharmacologic therapy fails, in an effort to preserve β-cell function and improve long-term glycemic control.

In type 2 diabetes, both postprandial and fasting glucose levels contribute to overall diurnal hyperglycemia; as the disease worsens, the contribution of fasting glucose levels increase. This phenomenon may increase the difficulty of controlling blood glucose levels with oral agents alone. In type 2 diabetes,
**TABLE 3** Human Insulin and Analogues

<table>
<thead>
<tr>
<th>Insulin Preparations</th>
<th>Onset/Action</th>
<th>Peak/Action</th>
<th>Duration/Action</th>
<th>Costs (Selected Products)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular human insulin</td>
<td>30-60 minutes</td>
<td>2-4 hours</td>
<td>6-8 hours</td>
<td>Humulin R (regular insulin): 10 mL vial: $29.85</td>
</tr>
<tr>
<td>Lispro/aspart/glulisine</td>
<td>5-20 minutes</td>
<td>0.8-1.5 hours</td>
<td>1.75-4 hours</td>
<td>Humalog (lispro): 10 mL vial: $38.99</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NovoLog Fexpen (aspart): five 3 mL syringes: $125.29</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Apidra (glulisine): NA</td>
</tr>
<tr>
<td><strong>Intermediate-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>1-3 hours</td>
<td>5-7 hours</td>
<td>13-16 hours</td>
<td>Novolin N and Humulin N (NPH): 10 mL vial: $29.85</td>
</tr>
<tr>
<td>Lente</td>
<td>1-3 hours</td>
<td>4-8 hours</td>
<td>13-20 hours</td>
<td>Humulin L (lente): 10 mL vial: $29.85</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>1-2 hours</td>
<td>Peakless</td>
<td>&gt;24 hours</td>
<td>Lantus (insulin glargine): 10 mL vial: $57.76</td>
</tr>
<tr>
<td>Ultralente</td>
<td>2-4 hours</td>
<td>8-14 hours</td>
<td>&lt;20 hours</td>
<td>Humulin U (ultralente): 10 mL vial: $29.85</td>
</tr>
<tr>
<td><strong>Premix</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro 75/25</td>
<td>15 minutes</td>
<td>0.5-1.2 hours</td>
<td>24 hours</td>
<td>Humalog mix 75/25: 10 mL vial: $64.62</td>
</tr>
<tr>
<td>Insulin aspart 70/30</td>
<td>10-20 minutes</td>
<td>1-4 hours</td>
<td>24 hours</td>
<td>NovoLog mix 70/30 Flexpen: five 3 mL syringes: $134.08</td>
</tr>
</tbody>
</table>


exogenous insulin, at the appropriate dose, dampens glucose production by the liver and accelerates glucose uptake by muscle.\(^3^8\) A variety of human insulin products that mimic natural islet cell function are available and can be incorporated into a basal-bolus regimen (Table 3).\(^3^9,^4^0\)

**Basal Insulin**

The most effective means of achieving diurnal euglycemia in type 2 diabetes with insulin therapy may be to administer a basal dose of insulin—insulin that is active for 24 hours and mimics, as closely as possible, the activity of endogenous basal insulin. Generally, basal insulin requires once-daily administration and no mixing. Titration is slow, safe, and simple, and the dosage required is relatively low. The long-acting insulin analogue, insulin glargine, has emerged as a primary form of basal insulin. Insulin glargine is solubilized and released into the bloodstream within 2 to 3 hours of administration.\(^4^1\) In addition, levels in the serum remain relatively constant and reproducible over 24 hours and with multiple dosing, resulting in a desirable flat profile. In contrast, NPH insulin has discernible peaking at about 10 hours after administration and then gradually declines (Figure 3).

Overall, when insulin glargine and NPH treatments are compared in patients with type 2 diabetes, no between-treatment differences have been detected in the percentage of patients with symptomatic hypoglycemia—confirmed by a measurement of glucose ≤72 mg/dL—through the day and early evening, and the two forms of insulin were equally effective in achieving levels of glycemic control (HbA1c ≤7%).\(^4^2\) However, significantly more patients experienced nocturnal hypoglycemia with NPH than with glargine. Based on clinical studies of insulin glargine in type 2 diabetes, a protocol for initiating basal insulin therapy can be proposed (Table 4).\(^3^8,^4^2\)

While maintaining their oral agents, patients start with 10 U of either NPH or glargine. The insulin dose can be adjusted upward until reaching the target fasting blood glucose level (≤100 mg/dL). Although insulin doses can be adjusted weekly, twice-weekly adjustments can be made if faster titration is desired. Once the target fasting glucose is achieved, HbA1c level should be measured 2 to 3 months later to confirm that these levels are within the target range.

**Prandial Insulin**

In some individuals with type 2 diabetes, an oral agent in combination with basal insulin can effectively control postprandial hyperglycemia. In other individuals with type 2 diabetes and definitely in type 1 diabetes, the addition of an oral agent is insufficient to achieve glycemic control; consequently, short-acting insulin is required to control postprandial glucose excursions. When compared with regular solubilized insulin, rapid-acting insulin analogues provide many advantages over their regular insulin counterparts because their physiologic actions more closely resemble the characteristics of meal-stimulated endogenous insulin. These insulins include lispro (Humalog) and aspart (NovoLog) as well as soon-to-be-introduced glulisine (Apidra). Absorption and dissipation are faster and peak levels are higher with insulin analogues when compared with regular solubilized insulin (Figure 4).\(^4^3,^4^4\)

For these reasons, they can be taken immediately before meals and be very effective. Regular solubilized insulin should be taken 30 to 45 minutes before a meal for effectiveness, which is something patients rarely can manage.\(^4^5\) The rapid-acting insulins also allow more flexibility, in that the timing of the insulin...
Trends in the Management of Type 2 Diabetes: An Emerging Role for Insulin injection in relation to the meal is less rigid. Regular insulin, because of its slower absorption and longer activity, has the potential for “insulin stacking,” or the accumulation of insulin in the plasma with repeated dosing, a phenomenon that increases the risk for hypoglycemia. This is less likely with the rapid-acting insulin analogues. Indeed, the mean residence time for aspart (149 minutes), lispro (117 minutes), and glulisine (105 minutes) are all substantially less than that for regular insulin (182 minutes).45,46 Because they are absorbed and dissipate more quickly, short-acting insulin analogs usually require a larger basal insulin dose.

**Insulin Aspart and Lispro**

In type 2 diabetes, insulin aspart and insulin lispro display not only similar pharmacokinetic profiles but also levels of glycemic control and tolerability.47,48 Some investigators have shown that insulin aspart may induce a greater reduction in diurnal glycemic levels than regular insulin. In a 4-month, double-blind, randomized trial that included 403 subjects with type 2 diabetes, subjects who switched from twice-daily NPH insulin to twice-daily biphasic insulin aspart experienced a significantly greater reduction in HbA1c levels (0.78%) than those who continued to receive twice-daily NPH insulin.49 Further, insulin aspart diminishes mean post-prandial glycemic exposure to a greater extent than NPH insulin.

In a 6-month randomized, open-label study that compared a mixture of insulin lispro (25%) and intermediate-acting neutral protamine lispro (75%) (Humalog 75/25) with a product containing a combination of regular insulin (30%) and intermediate-acting NPH insulin (70%) (Humulin 70/30), the insulin lispro product resulted in significantly improved postprandial glycemic control after morning and evening meals with twice-daily dosing.50

**TABLE 4** Sample Protocol for Basal Insulin Therapy in Type 2 Diabetes50,62

| Maintain oral antidiabetic agents |
| Start 10 U of glargine or NPH (at bedtime) and adjust weekly |
| Obtain daily fasting glucose values |
| Mean of self-monitored fasting blood glucose (FBG) values from preceding 2 days (mg/dL) |
| ≥180—add 8 U |
| 140 to 180—add 6 U |
| 120 to 140—add 4 U |
| ≥100 to 120—add 2 U |
| Treat to target FBG ≤100 mg/dL |
| Measure A1c 2 to 3 months after target levels are reached |

NPH=neutral protamine Hagedorn.
Insulin Glulisine

Insulin glulisine, a new insulin analogue, differs from human insulin—the amino acid asparagine replaces lysine at position B3 and glutamic acid replaces lysine at position B29. A phase I, randomized, double-blind study compared the pharmacokinetics and pharmacodynamics of glulisine with regular insulin in 24 subjects with type 2 diabetes. The results revealed that the maximum concentration (Cmax) for glulisine (92 μU/mL) was significantly greater than that for regular human insulin (46 μU/mL), and the time for maximum concentration (Tmax) was significantly shorter for glulisine (83 minutes versus 92 minutes) (Figure 5).

Also assessed was the glucose infusion rate, an indirect measure of insulin activity that reflects the amount of glucose needed over time to maintain a normal blood glucose level in the presence of a specific insulin dose. Based on the glucose infusion rate results, glulisine demonstrated a more rapid onset of action and shorter duration of action when compared with regular human insulin. However, the total glucose disposal rate (total area under the curve) was similar in both groups. Other investigators have shown that glulisine, whether given before or immediately after meals, provides faster and greater insulin availability and, thus, enhanced bioavailability compared with regular human insulin.

A pivotal, randomized, double-blind, 26-week study compared the efficacy and safety of insulin glulisine with regular insulin, each given in combination with NPH twice daily, in 876 subjects with relatively well-controlled type 2 diabetes (mean HbA1c 7.55%). The results revealed that insulin glulisine treatment significantly reduced HbA1c levels versus regular insulin at the week-12 and week-26 evaluations, although the absolute differences in HbA1c levels were slight (0.16%). Further, at the study’s end, significantly lower postbreakfast (156 versus 162 mg/dL) and postdinner (154 versus 163 mg/dL) blood glucose levels were achieved with insulin glulisine when compared with regular insulin treatment. In the 26-week extension of this study, no noteworthy differences were discerned in treatment-related side effects, including injection site reactions, diabetic ketoacidosis, or potential systemic hypersensitivity reactions. Once in the syringe, glulisine can be mixed with NPH insulin and, once mixed, some attenuation occurs in Cmax (27%), but the Tmax remains unaffected.

Together, these data imply that not only are short-acting insulin analogues at least as effective as regular insulin in managing glycemic excursions in type 2 diabetes, but they also provide a more favorable pharmacokinetic profile that results in rapid absorption and a shorter duration of action that reduces the risk for “insulin stacking.”
Practical Approach to Improving the Management of Type 2 Diabetes

In type 2 diabetes, a new, more aggressive approach is needed to achieve the main goals of therapy (Table 5). Accumulating evidence underscores the importance of early treatment with insulin to avert downstream complications. In addition, elevations in postprandial glucose levels remain a particular concern because of their link to complications.

Postprandial glucose excursions should be identified early and managed with a combination of diet, exercise, and insulin analogues, if necessary. As a progressive disease, type 2 diabetes usually requires combination therapy to achieve glycemic goals. Successful management relies on the recognition that achieving optimal HbA1c levels requires treatment of both the β-cell defect and insulin resistance as well as controlling postprandial and fasting glucose levels. Therefore, an effective therapeutic approach is often the combination of oral agents like metformin and thiazolidinediones with insulin.

A critical step in effectively managing type 2 diabetes in patients with persistent hyperglycemia despite combination oral therapy is to use a simple, straightforward strategy that facilitates the initiation of insulin therapy (Table 6).

When initiating insulin therapy, patients should continue oral therapy at the same dosage, eventually reducing the dose when appropriate. Conservatively, a single insulin dose of about 10 U of NPH or glargine given at bedtime or 70/30 insulin given at the evening meal is a reasonable initial approach to treatment. The insulin dose should be adjusted according to the fasting self-monitored blood glucose level, with the insulin dose increased on a weekly basis, as needed. Typically, the insulin dose is increased by 4 U if the fasting blood glucose is greater than 140 mg/dL, and by 2 U if the fasting blood glucose is 120 to 140 mg/dL. The treat-to-target level is usually a fasting blood glucose level of <120 mg/dL. Clinical judgment should prevail when determining whether to advance to a basal/bolus insulin regimen, but this approach should be considered when the HbA1c levels are persistently elevated above 7% and/or the self-monitored blood glucose before dinner exceeds 180 mg/dL.

Summary and Conclusions

Diabetes is a common, serious, and vastly underdiagnosed and suboptimally treated disease that leads to progressive alterations in certain tissues that increase morbidity and mortality. Optimal glucose control, a chief goal and challenge of diabetes treatment, is a pivotal step in reducing disease-related complications and can be advanced with the use of insulin regimens that most closely mimic endogenous insulin patterns.

Conventional, rapidly acting insulin products, with onset of action up to an hour and peak concentration reached after about 4 hours after injection, are absorbed too slowly to mimic physiologic insulin. Further, long-acting conventional insulin products—NPH, for instance—are absorbed too quickly to mimic basal insulin secretions, and their short duration of action necessitates multiple daily injections.

Because of their favorable pharmacokinetics and pharmacodynamics, rapidly acting and long-acting insulin analogues may provide the best opportunity to achieve consistent glycemic control.
control in type 2 diabetes. Rapidly acting insulin analogues make it possible to compensate for post-prandial elevations in blood glucose without exceeding healthy insulin levels in the blood between meals and at night. Once an appropriate basal insulin regimen has been established, the fine-tuning required to achieve tight glycemic control usually involves adjustments in the timing and dosage of rapid-acting prandial insulin. Such fine-tuning requires the clinician to educate the patient about the importance of regularly self-monitoring glucose levels and the need for tight glycemic control as the central means for averting downstream morbidity and mortality.

DISCLOSURES
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REFERENCES


Continuing Education for this program is processed solely through the AMCP.org CE Learning Center site at www.amcp.org (CE Center/Online CE). No mailed forms will be accepted.

The posttest worksheet (below) is provided to assist you in marking your answers prior to entering the online CE center for submission; these pages cannot be submitted for CE credits.

In order to receive CE credit for this program, you must complete the following forms online:
1. Posttest form for this program, “Trends in the Management of Type 2 Diabetes: An Emerging Role for Insulin,” on the AMCP.org CE Learning Center site—to receive CE credit, you must receive a score of at least 70%.
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Posttest Worksheet: Trends in the Management of Type 2 Diabetes: An Emerging Role for Insulin

1. What percentage of adults with diabetes mellitus has been reported to receive optimal care for their disease?
   a. 10%
   b. 7%
   c. 5%
   d. 3%

2. In patients with type 2 diabetes, β-cell function is lost at a rate of about
   a. 10% to 12% yearly.
   b. 4% to 6% yearly.
   c. 1% to 2% monthly.
   d. 2% to 3% yearly.

3. The insulin response to glucose load is normally
   a. uniphasic.
   b. biphasic.
   c. triphasic.
   d. continuous.

4. Postprandially, type 2 diabetes is often characterized by disruptions in
   a. phase 1 insulin response.
   b. phase 2 insulin response.
   c. both the phase 1 and phase 2 response.
   d. neither the phase 1 or 2 insulin response.

5. In individuals with type 2 diabetes, peak postprandial insulin secretions are often delayed from the normal 60 minutes to
   a. 90 minutes.
   b. 100 minutes.
   c. 120 minutes.
   d. 150 minutes.

6. When HbA1c levels are less than 7.3%, the contribution of postprandial glucose levels to diurnal hyperglycemia in type 2 diabetes may approach
   a. 70%.
   b. 50%.
   c. 30%.
   d. 10%.
7. Metabolic syndrome, a constellation of conditions reflecting abnormal endothelial cell function, includes
   a. obesity.
   b. glucose intolerance.
   c. hypertension.
   d. All of the above

8. In the UK Prospective Diabetes Study, a 1% decline in HbA1c levels resulted in
   a. 60% reduction in macrovascular complications.
   b. 35% reduction in microvascular complications.
   c. significant reduction in cardiovascular complications.
   d. significant reduction in end-stage renal disease.

9. In the treatment of type 2 diabetes, both the ADA and the ACE/AACE guidelines agree that HbA1c levels should be
   stringently controlled and maintain at a level of
   a. <9%.
   b. <8%.
   c. <7%.
   d. <5%.

10. Despite treatment, fewer than half the patients with type 2 diabetes meet the ADA and ACE/AACE recommended
    goals for HbA1c control.
    a. True
    b. False

11. In the DECODE study, all-cause mortality in type 2 diabetes was best predicted by measures of
    a. diurnal hyperglycemia.
    b. fasting glucose levels.
    c. postprandial glucose load.
    d. comorbid hypertension.

12. In the Honolulu Heart Study, postprandial glucose excursions were linked to an elevated risk for
    a. coronary heart disease.
    b. type 2 diabetes.
    c. ineffective diabetes treatment.
    d. fasting glucose levels.

13. Which of the following are determinants of postprandial hyperglycemia?
    a. Carbohydrate content of a meal
    b. Endogenous insulin response to glucose load imposed by a meal
    c. Absence of first-phase insulin response and delayed second-phase response
    d. All of the above

14. To maintain glycemic control, most individuals with type 2 diabetes will eventually require which form of therapy?
    a. Insulin
    b. Thiazolidinediones
    c. Acarbose
    d. Tolazamide

15. Appropriate insulin therapy in type 2 diabetes can
    a. slow insulin resistance.
    b. preserve β-cell function.
    c. dampen glucose production by the liver.
    d. All of the above

16. Basal insulin preparations can best be described as
    a. short-acting insulin.
    b. insulin that is active for 24 hours and closely mimics endogenous basal insulin.
    c. insulins that require multiple daily injects to achieve their desired effects.
    d. inhaled insulin.

17. Insulin glargine, a long-acting insulin analogue, has emerged as a primary basal insulin therapy.
    a. True
    b. False

18. In studies of basal insulin, nocturnal hypoglycemia has been detected significantly more frequently with
    a. aspart versus lispro.
    b. NPH versus glargine.
    c. glargine versus NPH.
    d. aspart versus NPH.

19. When compared with regular insulin, prandial analogue insulins, such as lispro, aspart, and glulisine, provide
    a. faster absorption.
    b. more rapid peak plasma levels.
    c. reduced residence times.
    d. All of the above

20. When glulisine is mixed with NPH insulin in syringe, a 27% reduction has been noted in the
    a. Tmax for glulisine.
    b. Cmax for glulisine.
    c. AUC for NPH.
    d. half-life of glulisine.