Diabetes is a highly prevalent chronic disease. The Third National Health and Nutrition Examination Survey, conducted between 1988 and 1994, estimated the prevalence of diagnosed and undiagnosed diabetes in people aged 20 years and older at 15.6 million. Of these people, ~90–95% have type 2 diabetes, with a higher prevalence seen among Native Americans and Americans of African, Mexican, and Japanese descent. The prevalence of diabetes rose from 4.9% in 1990 to 6.9% in 1999, primarily because of an increase in the prevalence of obesity. It has been postulated that, with the growing obesity problem, diabetes will become an even more pervasive threat.

Type 2 diabetes produces or is a contributor to considerable morbidity in the form of metabolic complications, vision disorders, neuropathy, kidney disease, peripheral vascular disease, ulcers and amputations, heart disease, stroke, digestive diseases, infection, oral complications, and depression. The associated mortality rate has been estimated at 5.5% annually. Moreover, the disease reduces life expectancy by 5–10 years.

Although there is no cure for diabetes, two large controlled studies, the Diabetes Control and Complications Trial (DCCT) and the U.K. Prospective Diabetes Study (UKPDS) have pointed to the importance of intensive blood glucose control in reducing its associated morbidity. In fact, the UKPDS, the largest and longest trial ever conducted in patients with type 2 diabetes, found that for each 1% reduction in hemoglobin A1c (A1C), there was a 21% decrease in any endpoint related to diabetes and in diabetes-related death, a 14% decrease in all-cause mortality and myocardial infarction, a 43% decrease in amputation or death from peripheral vascular disease, and a 37% decreased risk for microvascular complications, each of which was statistically significant. The Japanese Kumamoto study also found that intensive glycemic control reduced the risk for retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes.

Although sulfonylurea therapy has been the mainstay of treatment for type 2 diabetes for >40 years, the UKPDS reported that over a 6-year period, ~53% of patients who were randomized to receive treatment with sulfonylureas needed additional insulin therapy, reinforcing the concept that hyperglycemia in type 2 diabetes is progressive. Clinicians should consider this when establishing a therapeutic regimen for patients with type 2 diabetes.

This article addresses the pathophysiology of type 2 diabetes, goals of therapy, misconceptions about insulin, restoration of natural insulin patterns, and ways to incorporate basal insulin into a strategy that promotes compliance.

Pathophysiology of Type 2 Diabetes
Type 2 diabetes is characterized by hyperglycemia caused by defects in insulin secretion (impaired β-cell function) and insulin action (insulin resistance by the liver and muscle tissue). These defects occur early in the course of the disease and are often present before diagnosis.

In a prospective study of Pima Indians, a group at high risk for developing diabetes, body composition, insulin action, insulin secretion, and endogenous glucose output were measured over several years in subjects whose glucose tolerance went from normal to impaired to diabetic. A two-step hyperinsulimemic, euglycemic glucose clamp test assessed insulin action. During the transition from normal to impaired glucose tolerance, there was a 27% decrease in the acute insulin secretory response (AIR), the average incremental plasma insulin concentration from the third to the fifth minute after the glucose bolus. Furthermore, during the transition from impaired glucose tolerance to diabetes, there was an additional 57% decrease in AIR.

Another controlled study in patients with type 2 diabetes who were either untreated or attempting to achieve control using diet or oral hypoglycemic agents found that basal and mean 24-hour glucose concentrations were significant.
icantly higher in the diabetic patients, pointing to potentially impaired insulin secretion. During the hyperglycemic clamp portion of this study, patients secreted ~70% less insulin than control subjects (Table 1). In nondiabetic individuals, a biphasic insulin response begins upon glucose stimulation, starting with a rapid rise in insulin 1–3 minutes after the glucose level is raised (first phase), returning toward baseline 6–10 minutes after glucose stimulation, and rising gradually once again (second phase). Among patients in this study, however, the first-phase response after meals (glycemic load) was either absent or greatly diminished. As a result of meal (glycemic load) was either absent or greatly diminished.9 As a result of meals (glycemic load) was either absent or greatly diminished.9

Therapeutic Objective

The American Diabetes Association (ADA) recommends that patients with diabetes receive care from a medical team. Working with patients and their families, these teams develop self-management and problem-solving plans that consider each patient’s cultural, social, physical, and medical needs. ADA supports the findings of the DCCT and the UKPDS for intensive glycemic control; Table 2 lists its recommendations for nondiabetic individuals, a biphasic insulin response begins upon glucose stimulation, starting with a rapid rise in insulin 1–3 minutes after the glucose level is raised (first phase), returning toward baseline 6–10 minutes after glucose stimulation, and rising gradually once again (second phase). Among patients in this study, however, the first-phase response after meals (glycemic load) was either absent or greatly diminished. As a result of meals (glycemic load) was either absent or greatly diminished.9 As a result of meals (glycemic load) was either absent or greatly diminished.9

Table 1. Glucose Concentrations and Insulin Secretion in Control and Diabetic Subjects Under Three Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Control Subjects</th>
<th>Patients With Diabetes</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>95.2 ± 2.1</td>
<td>221.4 ± 19.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin secretion (nmol/m²/24 hours)</td>
<td>71.7 ± 9.5</td>
<td>82.7 ± 11.5</td>
<td>NS</td>
</tr>
<tr>
<td>24-Hour Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>109.7 ± 1.9</td>
<td>282.3 ± 25.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Insulin secretion (nmol/m²/24 hours)</td>
<td>220.5 ± 30.4</td>
<td>201.7 ± 19.7</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperglycemic Clamp Study</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>303.6 ± 4.5</td>
<td>299.8 ± 1.0</td>
<td>NS</td>
</tr>
<tr>
<td>Insulin secretion (nmol/m²/24 hours)</td>
<td>80.6 ± 11.7</td>
<td>24.1 ± 4.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Adapted with permission from Ref. 9.
Because of the connection among hyperinsulinemia, insulin resistance, and cardiovascular risk factors, the UKPDS\textsuperscript{17} compared cardiovascular events among patients randomized to conventional lifestyle and dietary management and those on a tight glycemic control regimen with sulfonylureas, metformin (in overweight patients), or insulin. No adverse effects on cardiovascular outcomes were seen with any of the treatments, including insulin.

The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study\textsuperscript{22,23} assessed the effect of acute insulin-glucose infusion followed by long-term intensive (multidose) insulin treatment in diabetic patients who have had an acute myocardial infarction. Among patients who had received an acute infusion, there was a significant decrease in glucose. After 1 year, there was a significant reduction in mortality in the group who received intensive insulin treatment, particularly in patients who had a low cardiovascular risk profile and were insulin naive.\textsuperscript{22} These effects persisted after a mean follow-up of 3.4 years; the absolute reduction in mortality was 11\%.\textsuperscript{23}

Other studies\textsuperscript{24–26} have reported improvement or neutral effects on other cardiovascular risk factors—total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, or hypertension—with insulin, even among obese patients.

Considering the comorbidity of diabetes and several cardiovascular risk factors, ADA\textsuperscript{14} recommends the following in addition to lifestyle alterations: blood pressure measurement at routine medical visits; the use of antihypertensive agents in patients with hypertension; testing for lipid disorders at least annually; lowering LDL and triglycerides; increasing HDL and using statins as first-line lipid therapy; using fibrates in patients with low HDL; and using aspirin therapy to prevent cardiovascular events.

Clinicians often cite hypoglycemia as an adverse effect that might preclude the use of insulin. Indeed, in the DCCT study of type 1 diabetes,\textsuperscript{4} tighter control produced a risk of severe hypoglycemia three times higher than that of conventional therapy (Figure 2). This must be viewed, however, in the context of substantially reduced microvascular and neurological complications. Furthermore, the rates of severe hypoglycemia are quite low in type 2 diabetes. In the Kumamoto study of type 2 diabetes,\textsuperscript{6} average A1C results were 7.1 and 9.4\% for tight and conventional groups, respectively. However, only mild hypoglycemic reactions occurred and at similar rates in both groups.

The UKPDS\textsuperscript{17} found that the rate of major hypoglycemic episodes (defined as an episode in which help from another person was needed) was 1.3% for conventional therapy and 4.4% for tight glycemic control. The overall rate of hypoglycemic episodes in the tight group was 13%, compared with 5% in the conventional group. Despite the higher rate of episodes, the overall rate of severe hypoglycemic episodes was 0.4% in the tight group and 0.1% in the conventional group.

Figure 1. Cardiovascular and cerebrovascular diseases account for 65\% of all deaths in patients with diabetes. Adapted from Ref. 20.
concentration that result from the ingestion of food. In people with diabetes, however, bolus and basal glucose levels are increased; thus, strategies for insulin replacement must focus on mimicking the phases of insulin secretion. Figure 3 shows available insulins by onset, peak, and usual effective duration.

**Prandial (Bolus) Insulin**

Prandial forms of insulin mimic the normal first-phase response. These regular insulin or rapid-acting insulin analogs are administered 30–60 minutes (regular) or 10–15 minutes (lispro [Humalog] or aspart [Novolog]) before food consumption. They must also mimic the second-phase response, requiring a more prolonged duration of action to control prolonged glucose elevation after the meal. Although prandial forms offer flexibility in that they can be injected just before a meal, most patients also require daily basal insulin injections.

**Basal Insulin**

Both intermediate (NPH and lente) and long-acting (ultralente and glargine [Lantus]) insulins have been used to mimic physiological basal insulin secretion, with varying results. An insulin that mimics basal secretion should be slowly and evenly absorbed with no peak, have consistent bioavailability, and have a long half-life that permits once-daily administration. This has not been the case with most basal insulin products. NPH and lente have early peaks with rapid waning of action; this may contribute to both nighttime hypoglycemia and the “dawn phenomenon,” a pre-breakfast rise in plasma glucose. There is also variability in the absorption of NPH and lente. Data on ultralente vary; in one study of type 1 diabetes, the onset of action of human ultralente was 2–4 hours, and there was a broad, variable peak 6–12 hours after injection. The authors concluded that this product did not provide a constant basal insulin concentration.

**Basal insulin in type 1 diabetes.** The pharmacokinetics and pharmacodynamics of the insulin analog glargine were compared to those of NPH, ultralente, and continuous subcutaneous insulin infusion (CSII) of lispro in 20 type 1 diabetic patients using an isoglycemic 24-hour clamp. Glargine was absorbed slowly and produced no pronounced peaks over a 24-hour period. Its onset of action was ~1.5 hours, compared with 0.8 hours for NPH, 1 hour for ultralente, and 0.5 hours for CSII. Its concentration/action profile was similar to CSII, with lower intersubject variability than with NPH and ultralente. These factors make glargine an excellent choice for basal insulin replacement.

In another study of type 1 diabetes, 256 patients were randomized to receive NPH (once daily at bedtime or twice daily before breakfast and at bedtime) or glargine once daily at bedtime. After 1 week and sustained throughout the 4-week study, fasting plasma glucose was significantly lower in the pooled glargine groups than in the NPH group (165.6 vs. 203.4 mg/dl, respectively; \( P = 0.0001 \)). Patients who had been taking NPH twice daily before the study were more likely to demonstrate greater improvement if...
The management of type 2 diabetes has traditionally followed a stepped approach of lifestyle changes, to oral agents, to combinations of oral agents, to insulin. Along the way, however, complications resulting from poor glycemic control may occur, some of which might have been reduced or possibly avoided with the early introduction of insulin.

Many studies have evaluated how to use insulin effectively for the treatment of type 2 diabetes. Two- and four-dose regimens of NPH improved glycemic control but caused basal hyperinsulinemia. The addition of 70/30 insulin (a premixed formulation with 30% fast-acting insulin and 70% intermediate-acting insulin) before supper to glimepiride (Amaryl) restored glycemic control more quickly than did 70/30 insulin alone, without producing severe hypoglycemia. The addition of NPH to glipizide (Glucotrol) was superior to high- and low-dose NPH alone in restoring glycemic control. Combination therapy with an intermediate-acting insulin at bedtime plus metformin was superior to bedtime insulin plus glyburide and metformin, bedtime insulin plus glyburide, and insulin twice daily and produced no weight gain. The addition of evening NPH to existing oral agents was similar in efficacy to morning NPH plus an existing antidiabetic agent, a two-injection regimen of 70/30 insulin, multiple injections, and oral hypoglycemic agents alone; however, this regimen did not induce as much weight gain and hyperinsulinemia.

Figure 3. The action of human insulins. Onset, peak, and usual effective durations vary among available insulins. In some reports, ultralente has demonstrated a peak concentration after several hours, followed by waning. Values shown are the mean in each range. Adapted with permission from Ref. 27.

Glargine
Ultralente
Lente
NPH
Regular
Lispro
Aspart

<table>
<thead>
<tr>
<th></th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ultralente</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lente</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspart</td>
<td></td>
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</tbody>
</table>

Figure 4 provides an algorithm that includes recommendations for the use of insulin therapy in type 2 diabetes.
Compliance

Patients with diabetes play an integral role in any treatment strategy. Lifestyle modification; goal setting; self monitoring; preventing, detecting, and treating acute complications; and using medications correctly are all important components in achieving glycemic control. This makes patient education crucial, particularly when it comes to dispelling myths about insulin therapy. The content areas that must be clearly established for patients are listed in Table 4.

The relationship between health care provider and patient is crucial to compliance. In the management of diabetes, this is more than a relationship between the patient and a single provider—it includes an entire health care team. Other factors also influence compliance. On the patient’s side, the belief that the benefits of therapy are worth the consequences, a readiness to change, memory, communication skills, literacy level, knowledge, competence, confidence, skills, and a good support system work together to influence the patient’s acceptance of therapy. On the team’s side, communication skills, the quality of information and instructions, and a willingness to identify and address barriers affect compliance. The regimen itself is also a factor; if it is difficult, costly, or has many side effects, compliance may diminish.

In the treatment of type 2 diabetes with insulin, reluctance to inject oneself and fear of weight gain or hypoglycemia may hinder compliance. Clinicians need to explain to their patients that type 2 diabetes is progressive and that insulin will probably have to be used at some point; therefore, clinicians may need to dispel myths associated with insulin use, allay patient fears, and assure patients that insulin will likely improve symptoms, enhance quality of life, and provide a sense of well-being.

“Resistance to insulin” on the part of clinicians may also be a significant provider-driven factor in compliance. Concerns regarding hypoglycemia, patients’ fear of needles, cultural health beliefs, and the time necessary to teach self-injection can all emerge as barriers to insulin use.

Table 3. Relative Risk of Hypoglycemic Episodes per Patient-Year

<table>
<thead>
<tr>
<th>Hypoglycemia</th>
<th>Glargine (%)</th>
<th>NPH (%)</th>
<th>P</th>
<th>Relative Risk With Glargine (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All confirmed</td>
<td>13.9</td>
<td>17.7</td>
<td>&lt;0.02</td>
<td>21</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>4.0</td>
<td>6.9</td>
<td>&lt;0.001</td>
<td>42</td>
</tr>
</tbody>
</table>

Adapted with permission from Ref. 40.

Figure 4. An algorithm of treatment for patients with type 2 diabetes. Reprinted with permission from Ref. 44.
Table 4. Content Areas for Diabetes Self-Management Education

- The disease process and its treatment
- Nutrition and exercise goals
- Appropriate use of medications
- Monitoring of blood glucose and urine and blood ketones to improve control
- Prevention, recognition, and treatment of acute and chronic complications
- Goal-setting and problem-solving
- Psychosocial adjustment
- Counseling about pregnancy and diabetes, if appropriate

Adapted with permission from Ref. 45.

Conclusions

With the prevalence of type 2 diabetes on the rise and with the recognized need for strict glycemic control in the prevention of complications, strategies for aggressive treatment must be put into effect. Such strategies might include the early use of insulin, alone or in combination with other antidiabetic agents. Clinicians must weigh the risks associated with the use of insulin against the benefits. Several studies have clearly shown that basal insulin therapy, particularly using the insulin analog glargine, closely mimics the body’s physiological secretion of basal insulin and may be added to an existing oral regimen, used alone, or used with preprandial insulin.

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