Clarifying the Role of Insulin in Type 2 Diabetes Management

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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, ulcerations 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.

IN BRIEF

The prevalence of type 2 diabetes has been increasing rapidly and with it has been resultant morbidity and mortality. Strict glycemic control reduces the progression of diabetic microvascular disease; however, most patients treated with sulfonylureas require additional insulin therapy. This article addresses common clinician concerns about prescribing insulin early in type 2 diabetes. It presents strategies for incorporating basal insulin therapy with glargine (Lantus) into a regimen that promotes compliance.

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 hyperinsulinenic, 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 significa...
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. As a result of meal (glycemic load) was either absent or greatly diminished. As a result of meal (glycemic load) was either absent or greatly diminished. As a result of meal (glycemic load) was either absent or greatly diminished. As a result of meal (glycemic load) was either absent or greatly diminished.

**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 nonpregnant people with diabetes.

**Insulin: Misconceptions and Reality**

Contrary to some beliefs, there is no evidence that doses of insulin used in clinical practice exacerbate insulin resistance. It has long been recognized that the chronic hyperglycemia associated with type 2 diabetes (glucose toxicity) leads to impairment in insulin secretion and a possible defect in glycogen synthesis. In a study of intensive insulin therapy in patients with type 2 diabetes, the use of insulin partially reversed the postbinding defect in peripheral insulin action, produced near-normal basal hepatic glucose output, and enhanced insulin secretion, thereby maintaining lower glucose values. In addition, the mean daily insulin requirement fell by 23% after ~2 weeks of therapy, leveling off thereafter.

The use of insulin has been associated with weight gain, which in turn has been considered a major factor in insulin resistance. In the UKPDS, patients in intensive therapy gained more weight than those in conventional therapy groups; patients taking insulin gained ~4 kg compared to 2.6 kg for those on chlorpropamide (Diabinese) and 1.7 kg for those on glibenclamide (glyburide [Micronase]). Yet patients in the intensive therapy groups also had fewer microvascular complications, suggesting that tight glycemic control may be more important in therapeutic decision-making. The use of metformin (Glucophage) as an adjunct to insulin therapy provides effective glycemic control without significant weight gain.

The incidence of heart disease and ischemic heart mortality is up to four times higher in people with diabetes. Ischemic heart disease, other heart disease, and cerebrovascular disease account for 40, 15, and 10% of all deaths in this population, respectively (Figure 1). A population-based survey of almost 3,000 people identified high prevalence rates for a constellation of disorders known as syndrome X, metabolic syndrome, and insulin resistance syndrome interchangeably—abdominal obesity, type 2 diabetes, glucose intolerance, hypertension, hypertriglyceridemia, and hypercholesterolemia—that far exceeded the rates for each disorder alone or in pairs. For each of these conditions, fasting and post-glucose hyperinsulinemia was a common thread that suggested the presence of insulin resistance. When insulin-resistant subjects were compared to control subjects, significantly lower HDL cholesterol levels were also seen.

### 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><strong>Fasting</strong></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><strong>24-Hour Study</strong></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><strong>Hyperglycemic Clamp Study</strong></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{23} 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...
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.27

**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.28 Although prandial forms offer flexibility in that they can be injected just before a meal, most patients also require daily basal insulin injections.29

**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.30,31 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.29,32 Data on ultralente vary; in one study of type 1 diabetes,30 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.33 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,34 256 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
randomized to a glargine group than were patients previously on once-daily NPH. The longer duration of glargine also provided a statistically significant advantage in reducing the likelihood of the dawn phenomenon.

**Basal insulin in type 2 diabetes.** 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.35

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.36 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.25 The addition of NPH to glipizide (Glucotrol) was superior to high- and low-dose NPH alone in restoring glycemic control.37 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.18 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.38

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Recent clinical trials suggest that glargine provides basal insulin glycemic control equal to that of NPH with less risk of hypoglycemia. Glargine has been evaluated in patients with type 2 diabetes in a trial comprising 518 patients who had been receiving NPH with or without regular insulin for postprandial control.39 This 28-week, multicenter, open-label comparison of NPH once or twice daily and glargine once daily at bedtime reported similar decreases in A1C but a lower risk of nocturnal hypoglycemia with glargine compared with NPH (26.5 vs. 35.5%; \( P = 0.016 \)). There was significantly less weight gain with glargine than with NPH (0.4 vs. 1.4 kg; \( P = 0.0007 \)).

A 6-month, multicenter, randomized, open-label trial40 compared the addition of glargine or NPH to an oral therapy regimen to restore glycemic control to a target \( A1C \leq 7\% \) in 756 insulin-naive patients with type 2 diabetes. A1C results were lower in both treatment groups and \( \leq 7\% \) in 58% of patients. At the end of the study, the mean glargine dose was higher than that of NPH; however, symptomatic hypoglycemia rates, particularly nocturnal hypoglycemia, were significantly lower in the glargine group. Risk was reduced by 21% for any incidence of hypoglycemia and by 42% for nocturnal hypoglycemia (Table 3).

Other studies comparing glargine to NPH at bedtime reported that similar control was achieved with each agent; however, there were significantly less hypoglycemia41 and significantly lower postdinner glucose concentrations 42 with glargine than with NPH. Among insulin-naive patients and overweight patients who had been taking oral agents with or without insulin, significantly fewer receiving glargine experienced nocturnal hypoglycemia.43

**An Algorithm for Using Insulin**

There is no single best way to initiate insulin therapy in patients with type 2 diabetes in whom oral treatments no longer maintain adequate control. Clinicians should consider 10 units of basal insulin at bedtime, supper, or in the morning a safe, effective recommendation for beginning insulin therapy. This dose can then be titrated based on how well a patient has met individual glycemic goals as measured by fasting blood glucose, postmeal glucose levels, and self-monitoring of blood glucose. In obese, insulin-resistant patients, a higher starting dose may be safely used.

Figure 444 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>
<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 confirmed</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.
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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