Use of Insulin in Type 2 Diabetes: When Maximal Oral Therapy Fails

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INTRODUCTION

Evidence suggests that type 2 diabetes is diagnosed 4 to 7 years after the onset of glycemic changes capable of causing microvascular complications.  
Unfortunately, most patients do not achieve or maintain recommended target levels of glycemia on usual care. Furthermore, the traditional management approach is to wait until one treatment regimen is failing before adding another agent or intensifying therapy. This holds true for the use of insulin, which is often seen as the treatment of last resort.

Among the many lessons revealed by the United Kingdom Prospective Diabetes Study (UKPDS) is a dark aspect of the natural history of type 2 diabetes: gradual failure of therapy over time correlating with a decline in insulin secretion and an increase in plasma glucose concentration. UKPDS participants required progressively more intensive therapy, including insulin in many cases, to attain or approximate the treatment goal. After 6 years of antihyperglycemic monotherapy, approximately 55% of patients were able to attain glycosylated hemoglobin (HbA\(_1c\)) levels below 7%, but by 9 years only 24% were able to do so. Most practitioners with sufficient longitudinal experience treating patients with type 2 diabetes can relate to this problem of progressively treatment-resistant hyperglycemia and can be comforted that their experience is affirmed by the UKPDS.

PATHOGENETIC MECHANISMS IN TYPE 2 DIABETES

A brief review of the pathogenetic mechanisms of type 2 diabetes may shed light on why progressive therapeutic failure is so often encountered. The pathogenesis of type 2 diabetes is characterized by variable expression of 2 major defects: impaired insulin secretion and impaired response to the action of insulin (insulin resistance). Complex genetic factors involving the function of muscle, adipose, and islet cells dictate susceptibility to type 2 diabetes, but lifestyle and other factors that promote obesity appear to influence disease expression. Clearly, all obese individuals are not destined to become diabetic; however, obesity is associated with insulin resistance, and the presence of obesity appears to increase the degree of expression of diabetogenic genetic factors. Studies in lean children of patients with type 2 diabetes have identified abnormalities in muscle mitochondrial function, excessive myocyte fatty acid accumulation, and reduced glucose phosphorylation, underscoring the genetic aspect of insulin resistance.

One distinction between the insulin resistance of simple obesity and that of obesity associated with type 2 diabetes is that in simple obesity, hypersecretion of insulin provides full metabolic compensation for insulin resistance. In type 2 diabetes, insulin hypersecretion gradually falters, and in the continued presence of impaired insulin action the net result is hyperglycemia. In longitudinal studies of groups at high risk for type 2 diabetes (eg, Pima Indians), sequential oral glucose tolerance tests have demonstrated fasting and postprandial hyperinsulinemia prior to any abnormality in fasting or postprandial glycemia. In these studies, impaired glucose tolerance was accompanied by a declining response of insulin secretion to feeding, and overt diabetes was heralded by further blunting of meal-induced insulin response and the appearance of fasting hyperglycemia. When Pima Indians with declining glucose tolerance were compared with weight-matched subjects with normal glucose tolerance, insulin-stimulated glucose disposal declined in both groups over time; however, absolute insulin secretory capacity declined in those who developed diabetes but increased (to compensate for insulin resistance) in the nondiabetic controls.

The concepts of glucotoxicity and lipotoxicity have evolved in recent years as explanations for the progressive decline in insulin secretion and insulin action. Glucotoxicity relative to the pancreatic beta cell may be attributable to impaired proinsulin cleavage into C peptide and bioactive insulin. Alternatively, beta cell dysfunction may be reflected by impaired secretion and resultant accumulation of amylin in pancreatic islets. Lipotoxicity may involve a shift in adipocyte gene products from a cytokine that amplifies insulin secretion and insulin responsiveness (adiponectin) to one that impairs insulin secretion (eg, tumor necrosis factor-\(\alpha\)). Also,
high intracellular levels of free fatty acids are associated with impaired glucose-stimulated insulin secretion by beta cells, and the beta cells themselves have been shown to undergo accelerated apoptosis.14

There is hope that early use of insulin-sensitizing agents may ameliorate glucoeotoxicity and lipotoxicity and thus prevent the metabolic progression to type 2 diabetes. However, until proven preventive interventions are available and widely employed, clinicians will encounter patients who present with extreme and often symptomatic hyperglycemia despite intensive oral therapy. Such patients will require some form of insulin therapy.

RATIONAL AND OPTIONS FOR USING INSULIN

CASE PRESENTATION

A 52-year-old woman comes to your office for a new patient diabetes evaluation. She admits being remiss in having her diabetes checked since changing health plans, and she is concerned that her blood glucose levels have been high. The patient’s medical records were transferred to your office, and results of recent diabetes-specific screening tests are available.

History

The patient was diagnosed with type 2 diabetes 10 years ago and is currently on sustained-release glipizide (20 mg/day), metformin (2550 mg/day), and pioglitazone (45 mg/day). Review of her records reveals no change in weight in the past year but a steady deterioration in HbA1c levels, from 7.1% 2 years ago to 9.2% 1 week ago. The patient reports that she checks her blood glucose every morning and, to her knowledge, has never experienced an episode of hypoglycemia. Her home blood glucose test records show an average fasting level of 210 mg/dL for the recent 2-week period.

Results on screening tests from 1 week prior are: high-density lipoprotein cholesterol, 51 mg/dL; low-density lipoprotein cholesterol, 136 mg/dL; triglycerides, 189 mg/dL; alanine aminotransferase, 28 U/L; and urine albumin-to-creatinine ratio, 25 mg/g.

The patient is a single mother of 2 teenagers and teaches art at a local private school. She recently adopted a vegetarian diet, which she hopes will help her lose weight. She says she used to be more physically active, and now that her children are older she is trying to find time for such activities.

Physical Examination

Physical examination reveals a blood pressure of 134/80 mm Hg and a pulse of 72 bpm. The patient is 163 cm (5’4”) in height and weighs 79.8 kg (176 lb), with a body mass index of 30 kg/m². Otherwise, the physical examination is normal. A recent dilated-pupil retinal examination by an ophthalmologist revealed no background or proliferative retinopathy.

During the examination, the patient says she fears “losing the battle” with diabetes and ending up like her father, who has had significant loss of eyesight due to the disease. She asks, “How can I get my blood sugar down?”

• What therapeutic options remain for improving this patient’s glycemic status?

RATIONAL FOR INITIATING INSULIN

Progressive resistance to type 2 diabetes treatment can be partly overcome by employing rational therapy targeting specific underlying contributory defects. In the case patient, sulfonylurea therapy serves to augment meal-related insulin secretion, metformin attenuates excessive hepatic gluconeogenesis, and pioglitazone improves insulin-mediated glucose uptake by muscle tissue. Yet, despite this aggressive oral regimen, the patient’s meal-related and fasting hyperglycemia suggests that the time is right to add exogenous insulin. The extent to which insulin should replace existing oral therapy is largely a matter of personal taste, taking into account cost and compliance factors.

This scenario reflects the UKPDS experience, in which patients with newly diagnosed type 2 diabetes required progressively more intensive therapy, from diet and exercise alone through multiple drug combinations.1–3 For such patients, insulin becomes essential if glycemic control is to be reestablished. Importantly, insulin should be considered earlier in the course of therapy for patients who are not achieving glycemic targets on 1 or 2 oral agents and who cannot afford the cost of an additional medication. Although typically saved for last, insulin therapy is the most powerful and effective hypoglycemic intervention available and, thus, is an option at any point in the course of treatment for type 2 diabetes.

OPTIONS FOR INITIATING INSULIN

The question of whether late addition of insulin to complex oral regimens is superior to insulin therapy alone, with regard to glycemic control and frequency of hypoglycemia, is unanswered and important. Likewise, many insulin regimens have been shown effective by clinical trials, without any inherent superiority of one over another. Until these questions are answered by well-designed randomized controlled trials (RCTs), logic and
pragmatism must suffice in making day-to-day individual decisions regarding therapy.

Considerations in whether to add supplemental insulin or to replace oral therapy with an all-insulin regimen include the likelihood of adverse effects, patient acceptance, and cost. For example, an edema-prone patient who is treated with a thiazolidinedione (TZD) may develop cosmetically unacceptable edema if insulin is used concurrently, and a patient with congestive heart failure (CHF) can develop a severe exacerbation if this combination is used. Some patients may be unwilling or unable to accommodate a therapeutic regimen that requires medications be taken more often than twice daily. For the case patient, the monthly financial cost of her oral regimen is already high; before a decision is made to add insulin, it would be important to determine whether the patient can afford all the medications.

Currently available insulins include basal preparations used to suppress hepatic glucose production overnight and between meals (ie, intermediate-acting and long-acting insulins) and bolus preparations used to control blood glucose surge following meals (ie, rapid-acting and short-acting insulins); premixed, fixed-ratio formulations of intermediate-acting and rapid- or short-acting insulins also are available (Table 1). Commonly prescribed once-daily, twice-daily, and multiple-daily (basal-bolus) insulin regimens are shown in Table 2.

Faced with a patient who is failing a maximal oral regimen, many experienced diabetologists would institute a simple basal insulin regimen in addition to continued oral therapy. Most often, the regimen is a once-daily injection of an intermediate-acting or a long-acting insulin preparation, given at bedtime (currently the most popular option) or at breakfast. In large part, the patient can decide on the timing of insulin administration.

The case patient is an appropriate candidate for a once-daily regimen of supplemental insulin. If she were very obese, with significant postsupper hyperglycemia, an alternative would be once-daily injection of a premixed preparation given before supper. Some patients with HbA1c levels greater than 9% may require a twice-daily regimen to achieve glycemic targets (ie, HbA1c < 7%), the simplest of which would be a premixed preparation before breakfast and before supper. For patients who are unable to control glycemia on twice-daily insulin therapy, the next step in treatment may be an intensive, multiple-injection insulin regimen.

• What evidence supports adding basal insulin to an existing oral regimen?

ORAL AGENT/BASAL INSULIN REGIMENS

Several clinical trials, reviews, and meta-analyses

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**Table 1. Currently Available Insulin Preparations**

<table>
<thead>
<tr>
<th>Type/Name</th>
<th>Onset of Action</th>
<th>Peak Effect</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lispro</td>
<td>5–15 min</td>
<td>60–120 min</td>
<td>4–5 hr</td>
</tr>
<tr>
<td>Aspart</td>
<td>5–15 min</td>
<td>40–90 min</td>
<td>4–5 hr</td>
</tr>
<tr>
<td>Glulisine</td>
<td>5–15 min</td>
<td>30–90 min</td>
<td>3–5 hr</td>
</tr>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular</td>
<td>30–60 min</td>
<td>2–4 hr</td>
<td>5–8 hr</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPH</td>
<td>2–4 hr</td>
<td>4–8 hr</td>
<td>10–16 hr</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td>1–2 hr</td>
<td>None</td>
<td>22–26 hr</td>
</tr>
<tr>
<td>Detemir</td>
<td>1–2 hr</td>
<td>6–8 hr</td>
<td>12–23 hr</td>
</tr>
<tr>
<td>Premixed</td>
<td>70% neutral protamine Hagedorn/30% regular</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75% insulin lispro protamine/25% lispro</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70% insulin aspart protamine/30% aspart</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Commonly Prescribed Insulin Regimens**

**Once-daily basal insulin delivery schemes**
- Neutral protamine Hagedorn (NPH) insulin at bedtime
- Insulin glargine at any time, the same time each day (most often at bedtime or before breakfast)
- Insulin detemir at bedtime

**Once-daily combination insulin delivery schemes**
- NPH insulin + regular insulin (commonly, 70%/30% or 50%/50% premixed combination) at supper
- Insulin lispro protamine + insulin lispro (75%/25%) at supper
- Insulin aspart protamine + insulin aspart (70%/30%) at supper

**Twice-daily combination insulin delivery schemes**
- NPH insulin + regular insulin (commonly, 70%/30% premixed combination) before* breakfast and supper
- Insulin lispro protamine + insulin lispro (75%/25%) with† before breakfast and supper
- Insulin aspart protamine + insulin aspart (70%/30%) with† before breakfast and supper

**Intensive basal-bolus insulin delivery scheme**
- NPH insulin or insulin glargine or insulin detemir at bedtime + regular insulin, insulin lispro, insulin aspart, or insulin glulisine with each meal

*30 minutes before the meal.
†Within 5 minutes of the meal.
support the general approach of combining oral antihyperglycemic agents with basal insulin supplementation. In 1992, Yki-Jarvinen et al\textsuperscript{15} reported a study comparing the efficacy of various insulin regimens in 153 patients failing oral therapy (baseline HbA\textsubscript{c} averaged 10%), which included glyburide, glipizide, or metformin or a combination of either sulfonylurea plus metformin. Patients were randomized to one of the following: (1) continued oral therapy plus once-daily NPH insulin before breakfast; (2) continued oral therapy before breakfast plus once-daily NPH insulin at 9 PM; (3) twice-daily 70% NPH insulin/30% regular insulin before breakfast and before supper; and (4) multiple daily insulin injections consisting of regular insulin before each meal and NPH insulin at 9 PM. At the study end point 3 months after randomization, HbA\textsubscript{c} levels had decreased similarly in the 4 groups (–1.7%, –1.9%, –1.8%, and –1.6%, respectively). The least weight gain (+1.2 kg) was seen in the group receiving daytime oral therapy and once-daily NPH insulin at 9 PM, and the greatest weight gain was seen in the multiple insulin injection group (+2.9 kg).

In 1995, Chow et al\textsuperscript{16} published a study involving 53 Chinese patients, which compared bedtime NPH insulin plus continued oral therapy (sulfonylurea, metformin, or both) with twice-daily insulin (70% NPH insulin/30% regular insulin) given before breakfast and supper. At 6 months, reduction in HbA\textsubscript{c} levels was greater in the insulin monotherapy than in the combined therapy group (–2.3% versus –1.5%), but weight gain also was greater (5.2 kg versus 2.1 kg). Hypoglycemic episodes were infrequent in both groups (1.4 episodes per patient on combined therapy compared with 1.0 episode per patient on insulin monotherapy) and were not significantly different in either group.

The Treat-to-Target Trial\textsuperscript{17} addressed the impact of adding a once-daily basal insulin injection to a failing oral regimen, which included a combination of agents (eg, sulfonylurea plus metformin, sulfonylurea plus TZD) in two thirds of study subjects. Using bedtime NPH insulin or insulin glargine, HbA\textsubscript{c} levels fell from a mean of 8.6% to the target of less than 7% in nearly 60% of participants. In this study, the insulin dose was adjusted weekly to attain target fasting glucose levels below 100 mg/dL, and by study’s completion the average dose was 47 U/day for the insulin glargine group and 42 U/day for the bedtime NPH insulin group. Nighttime hypoglycemia was significantly less frequent in the insulin glargine group.

In a meta-analysis of clinical trials totaling 1142 users of insulin glargine and 1162 users of NPH insulin, Rosenstock et al\textsuperscript{18} noted an 11% reduction in symptomatic hypoglycemia, a 26% reduction in nocturnal hypoglycemia, and a 46% reduction in severe hypoglycemia (hypoglycemia requiring emergency assistance from another person or medical personnel).

Insulin detemir is comparable to insulin glargine in efficacy and hypoglycemic frequency. When compared with twice-daily NPH insulin, twice-daily administration of insulin detemir has demonstrated comparable efficacy in lowering HbA\textsubscript{c} (–1.8% versus –1.9%) but has been shown to reduce hypoglycemic episodes by 47%.

Specific oral agent/basal insulin combinations that have been validated by prospective clinical trials are summarized below.

**Sulfonylurea/Insulin Combinations**

In 1992, Pugh et al\textsuperscript{20} published a meta-analysis of 17 RCTs comparing the combination of insulin and a sulfonylurea with insulin alone. A total of 354 patients were studied from 17 trials—14 using glyburide, 2 using tolazamide, and 1 using chlorpropamide or glipizide. In the pooled combined therapy groups, HbA\textsubscript{c} decreased from 11% to 10.2%, compared with an increase in HbA\textsubscript{c} from 11% to 11.2% in the insulin monotherapy groups. A 1996 meta-analysis by Johnson et al\textsuperscript{21} reached similar conclusions. A total of 351 patients were studied from 16 trials comparing insulin alone with insulin plus glyburide or glipizide. HbA\textsubscript{c} was marginally lower in the pooled combined therapy groups compared with the insulin monotherapy groups (10.1% versus 10.9%). Studies specifically evaluating a sulfonylurea plus once-daily insulin are highlighted below.

**Daytime sulfonylurea plus bedtime NPH insulin.**

The addition of bedtime NPH insulin at a starting dose of 15 to 20 U (or 0.2 U/kg) has been shown to reduce HbA\textsubscript{c} levels by at least 0.8% to 1.3% when added to failing oral regimens of glyburide or glipizide.\textsuperscript{22,23} Shank et al\textsuperscript{24} reported that respondents to this combination regimen have shown sustained improvement in HbA\textsubscript{c} for at least 1 year after initiation of the therapy.

**Sulfonylurea plus supprentime 70/30 insulin.** Riddle et al\textsuperscript{25} compared once-daily (before breakfast) glyburide plus once-daily (before supper) 70% NPH insulin/30% regular insulin with insulin alone in a 16-week study involving 21 obese patients who had failed monotherapy with glyburide 20 mg/day (average baseline HbA\textsubscript{c}, 11%). Patients were randomized to insulin before supper and placebo before breakfast or to insulin before supper and glyburide 10 mg before breakfast. HbA\textsubscript{c} levels decreased 1.3% in the combined therapy group compared with 0.8% in the insulin monotherapy group. In a separate 24-week study, Riddle et al\textsuperscript{26} employed incrementally adjusted once-daily (before supper) 70/30 insulin plus twice-daily glimepiride and demonstrated...
a 2.3% reduction in HbA1c levels (from 9.9% to 7.6%). The efficacy of the combined therapy was comparable to insulin monotherapy, but the required insulin dose was 35% lower than that needed for monotherapy.

**Sulfonylurea plus insulin glargine.** In an RCT, Fritsche et al. compared the efficacy and hypoglycemic frequency of glimepiride/insulin glargine therapy to that of glimepiride/bedtime NPH insulin therapy. The glimepiride/insulin glargine combination was further studied by comparing morning versus bedtime insulin administration. In this 28-week study, HbA1c levels improved by 1.24% in the morning insulin glargine group, by 0.96% in the bedtime insulin glargine group, and by 0.84% in the bedtime NPH insulin group. Frequency of nocturnal hypoglycemia was significantly less in the morning (17%) and bedtime (23%) insulin glargine groups than in the evening NPH insulin group (38%).

Because the degree of metabolic improvement effected by sulfonylurea/insulin combination therapy can be marginal, many experts prefer an insulin regimen titrated toward goal. In their review of clinical trials comparing insulin plus sulfonylurea versus insulin plus placebo, Peters and Davidson examined HbA1c, fasting glucose, and fasting serum insulin concentrations and found that fasting insulin was not significantly different. The authors concluded that sulfonylurea plus insulin therapy was effective only to the extent that endogenous insulin production was enhanced, and they argued that increased insulin-only dosing could achieve the same degree of glycemic control.

**Insulin Sensitizer/Insulin Combinations**

Clinical trials have mainly examined the effects of adding an insulin sensitizer to a failing insulin regimen rather than the effects of adding insulin to a failing oral regimen that includes metformin and/or a TZD, despite the latter situation being more common in practice. Nonetheless, the intuitive logic of combining drugs that promote insulin responsiveness with supplemental insulin is appealing, and this approach is widely employed.

**Metformin plus insulin.** Several RCTs comparing insulin monotherapy with insulin plus metformin suggest a synergistic effect of combined therapy. In a study by Yki-Jarvinen et al. patients failing sulfonylurea-only therapy (mean baseline HbA1c, 9.9%) were randomized to bedtime NPH insulin plus: (1) glyburide, (2) metformin, (3) glyburide and metformin, or (4) a second injection of NPH insulin in the morning. At 1-year follow-up, patients receiving metformin plus bedtime NPH insulin had the lowest attained mean HbA1c (7.2%) as well as the least weight gain and lowest incidence of hypoglycemia (both at P < 0.05). The results of this study favor insulin plus metformin over insulin plus metformin and a sulfonylurea, which clinicians should take into account when planning additive therapy for patients.

In a study by Wulffele et al., 990 patients whose diabetes was controlled on insulin (mean baseline HbA1c < 8%) were randomized to metformin or placebo in addition to insulin. At 16 weeks, mean HbA1c was 6.9% in the combined therapy group versus 7.6% in the insulin-only group. Also, the insulin dose requirement was reduced by about 8 U/day, and there was a net weight loss of 0.4 kg compared with a mean weight gain of 1.2 kg in the insulin-only group. Similarly, Giugliano et al. compared ongoing insulin monotherapy with metformin plus insulin in a 6-month placebo-controlled trial involving 50 patients. Compared with insulin monotherapy, combined therapy was associated with a 1.84% improvement in HbA1c (from 11.7% to 9.8%) and a 25% reduction in the daily insulin dose. Also, in a small crossover study comparing insulin and metformin with insulin and placebo, Ponsen et al. demonstrated a reduced insulin requirement (by about 8 U/day) and reduced HbA1c (–0.74%) favoring metformin plus insulin, after 5 months of therapy. Finally, Relimpio et al. compared a 20% increase in insulin dose with the addition of metformin and no increase in insulin dose in 47 poorly controlled patients (mean baseline HbA1c, 9.6%). Patients in the combined therapy group had a 1.9% decrease in mean HbA1c compared with a 0.03% decrease in mean HbA1c in the insulin-only group.

**TZD plus insulin.** Since the withdrawal of troglitazone from world markets, the remaining available TZDs have been studied in combination with insulin in RCTs. Raskin et al. conducted an 8-week trial comparing twice-daily insulin plus placebo with twice-daily insulin plus rosiglitazone in 319 patients (mean baseline HbA1c, 8.9%). In the insulin plus rosiglitazone group, HbA1c dropped by 1.2% and daily insulin dose was reduced by 12% compared with no changes in the insulin plus placebo group. Rosenstock et al. conducted a similar trial over a 16-week period in 566 patients initially on insulin monotherapy (mean baseline HbA1c > 8%). Patients were randomized to insulin plus placebo or insulin plus pioglitazone 30 mg/day. HbA1c fell by 1.3% in the combined therapy group. Additional benefits included a 9.3% increase in HDL cholesterol and a 23.7% reduction in serum triglycerides in patients receiving pioglitazone 30 mg/day.

Although the combination of a TZD and insulin can be effective in improving glycemic control, this combination carries an increased risk for severe edema and possibly CHF. Edema may be anticipated in 15% or more.
INSULIN DOSE CALCULATION AND TITRATION

For patients starting insulin therapy as a supplement to existing oral therapy, the most common approach is to use a single daily injection of NPH insulin or insulin glargine at a starting dose calculated as 0.1 to 0.2 U/kg body weight. As a practical guide, the lower dose range is more appropriate for thinner patients with fasting glucose levels closer to normal (eg, < 200 mg/dL), whereas the upper dose range is more appropriate for obese patients with higher fasting glucose levels. The dose may be adjusted in increments of 2 to 5 U once or twice weekly as needed to titrate the fasting glucose level toward the desired therapeutic target (usually 90 to 130 mg/dL).

For patients who are to discontinue their oral medications and undertake an insulin-only treatment regimen, calculation of total daily dose (TDD) and assignment of component basal and mealtime bolus fractions are detailed in Table 3.

INTRODUCING PATIENTS TO INSULIN THERAPY

Clinicians may lack the necessary in-office resources to provide patients with essential instruction in the use of insulin. However, many hospitals offer comprehensive diabetes education led by one or more ADA-recognized certified diabetes educators. If available, such programs provide critical patient education regarding: (1) how to measure insulin doses and perform insulin injections; (2) when and how to self-monitor blood glucose; (3) how to recognize, manage, and prevent hypoglycemia; and (4) how to manage febrile illness or nausea/anorexia. In the absence of such programs, clinicians may wish to develop patient education materials based on the ADA’s annual position statement on insulin administration. This useful document addresses several important issues for patients being introduced to insulin therapy, including proper storage and mixing of insulin, use and disposal of syringes, dose preparation, proper sites and procedures for injection, timing and dosing of injections, blood glucose self-monitoring, and hypoglycemia management.

Blood Glucose Self-Monitoring

It has been difficult to demonstrate efficacy of blood glucose self-monitoring in patients although the need for self-monitoring is intuitively acknowledged as integral to self-adjustment of the treatment regimen. The superiority of multiple daily blood glucose tests over a single daily test—or even testing several times per week—has never been established. In the absence of overwhelming evidence, recommendations must be empiric and/or based on expert opinion.

Measurement of fasting blood glucose allows assessment of the adequacy of basal insulin therapy, whereas
tests before lunch, supper, and at bedtime allow assessment of the adequacy of bolus therapy administered with breakfast, lunch, and supper, respectively. If any component of the insulin regimen is found to be inadequate, the dose can be adjusted on a weekly basis. Increasing the individual dose by 2 U or by 10% to 20% of the TDD is generally accepted as safe and can be done in the context of brief office visits or by telephone, fax, or e-mail. The method used for dose titration should be determined by patient and practitioner preference.

### Injection Devices

Apart from the nature of the insulin components, physicians and patients must consider an appropriate injection device. Disposable syringes with ultrafine needles remain the least costly option and are available in very low dose (1/3 mL), low dose (1/2 mL), and high dose (1 mL) sizes. Some manufacturers offer prefilled cartridges or disposable injection pens for their insulin products. Pen devices are particularly popular, albeit expensive, options to syringes. Pen devices allow patients to select the dose to be administered by clicking a dial on the device handle, potentially minimizing the chance of dosing errors and saving steps of drawing up insulin from a vial. Some patients perceive easier compliance and fewer dosing errors with insulin pens than with syringe-and-vial systems. Issues of convenience, preference, and cost should be discussed openly with patients.

### CASE CONTINUED

The patient undergoes comprehensive diabetes education and successfully begins insulin therapy. At her first 3-month follow-up visit, her fasting blood glucose values average 110 mg/dL, her HbA₁c level has dropped to 6.9%, and she is symptomatically doing well, with no reported episodes of hypoglycemia or other complaints. Her weight is unchanged. Over the next 6 months, the patient’s quarterly HbA₁c levels are 6.5% and 6.7%. At 1-year, her HbA₁c has increased to 7% and her fasting blood glucose values average 130 to 150 mg/dL. During this visit, you increase the insulin glargine dose and schedule a follow-up visit for 1 month later.

At the follow-up visit, the patient’s average fasting blood glucose values have improved (90 to 120 mg/dL), but she is disturbed by a 5-lb weight gain. She also reports that on 5 occasions she was awakened during the night by intense anxiety, sweating, and pounding palpitations. You advise her to reduce her insulin glargine dose by 2 U/day and to perform home blood glucose tests at the time of any recurring symptoms. Over the 2 weeks following the visit, the patient reports no further symptoms.

- What are the major adverse effects of insulin therapy, and how are they best managed?

### ADVERSE EFFECTS OF INSULIN THERAPY

#### Hypoglycemia

Hypoglycemia is defined clinically as an abnormally low blood glucose concentration in the presence of neurologic symptoms, the latter being rapidly reversed following glucose administration. Hypoglycemia is the most common side effect of insulin therapy, although it also may occur with the use of certain insulin secretagogues. Because insulin promotes cellular uptake of glucose and inhibits hepatic gluconeogenesis, therapy with exogenous insulin or long-acting insulin secretagogues

#### Table 3. Calculating and Titrating Insulin Dose

<table>
<thead>
<tr>
<th>Total daily dose calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculate total daily dose (TDD) of insulin based on patient body weight (kg).</td>
</tr>
<tr>
<td>Option 1: Insulin as supplement to continued oral agent therapy</td>
</tr>
<tr>
<td>TDD = body weight (kg) × 0.2 U/kg</td>
</tr>
<tr>
<td>Option 2: Insulin monotherapy (no oral antihyperglycemic agents)</td>
</tr>
<tr>
<td>TDD = body weight (kg) × 0.5 (range, 0.4–1.0 U/kg)</td>
</tr>
</tbody>
</table>

#### Administration

For once-daily regimens, give TDD all at once.

For twice-daily regimens (typically, premixed insulin preparations), give 50% of TDD at breakfast and 50% of TDD at supper.

For multiple-daily regimens, split TDD into basal (continuous) and bolus (mealtime) components. For example:

1. **Basal component**: Adjust TDD by 10% to 20% increments or decrements every 2 to 3 days based on 2-hour postprandial or immediate pre-lunch, pre-supper, and bedtime CBG.

2. **Mealtime agents**: Adjust TDD by 10% to 20% increments or decrements every 3 to 7 days, based on fasting CBG.

#### Usual glycemic targets

- **Preprandial blood glucose** (includes fasting), 90–130 mg/dL
- **Postprandial (2 hours) blood glucose**, < 180 mg/dL

<table>
<thead>
<tr>
<th>CBG = capillary blood glucose; NPH = neutral protamine Hagedorn.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 3. Calculating and Titrating Insulin Dose</strong></td>
</tr>
<tr>
<td><strong>Total daily dose calculation</strong></td>
</tr>
<tr>
<td>Calculate total daily dose (TDD) of insulin based on patient body weight (kg).</td>
</tr>
<tr>
<td>Option 1: Insulin as supplement to continued oral agent therapy</td>
</tr>
<tr>
<td>TDD = body weight (kg) × 0.2 U/kg</td>
</tr>
<tr>
<td>Option 2: Insulin monotherapy (no oral antihyperglycemic agents)</td>
</tr>
<tr>
<td>TDD = body weight (kg) × 0.5 (range, 0.4–1.0 U/kg)</td>
</tr>
</tbody>
</table>

#### Dose titration

- **Basal component**: Adjust TDD by 10% to 20% increments or decrements every 3 to 7 days, based on fasting CBG.
- **Mealtime component**: Adjust TDD by 10% to 20% increments or decrements every 2 to 3 days based on 2-hour postprandial or immediate pre-lunch, pre-supper, and bedtime CBG.

#### Issues of convenience, preference, and cost should be discussed openly with patients.

#### ADVERSE EFFECTS OF INSULIN THERAPY

#### Hypoglycemia

Hypoglycemia is defined clinically as an abnormally low blood glucose concentration in the presence of neurologic symptoms, the latter being rapidly reversed following glucose administration. Hypoglycemia is the most common side effect of insulin therapy, although it also may occur with the use of certain insulin secretagogues. Because insulin promotes cellular uptake of glucose and inhibits hepatic gluconeogenesis, therapy with exogenous insulin or long-acting insulin secretagogues

#### Use of Insulin in Type 2 Diabetes

The patient undergoes comprehensive diabetes education and successfully begins insulin therapy. At her first 3-month follow-up visit, her fasting blood glucose values average 110 mg/dL, her HbA₁c level has dropped to 6.9%, and she is symptomatically doing well, with no reported episodes of hypoglycemia or other complaints. Her weight is unchanged. Over the next 6 months, the patient’s quarterly HbA₁c levels are 6.5% and 6.7%. At 1-year, her HbA₁c has increased to 7% and her fasting blood glucose values average 130 to 150 mg/dL. During this visit, you increase the insulin glargine dose and schedule a follow-up visit for 1 month later.

At the follow-up visit, the patient’s average fasting blood glucose values have improved (90 to 120 mg/dL), but she is disturbed by a 5-lb weight gain. She also reports that on 5 occasions she was awakened during the night by intense anxiety, sweating, and pounding palpitations. You advise her to reduce her insulin glargine dose by 2 U/day and to perform home blood glucose tests at the time of any recurring symptoms. Over the 2 weeks following the visit, the patient reports no further symptoms.

- What are the major adverse effects of insulin therapy, and how are they best managed?

#### ADVERSE EFFECTS OF INSULIN THERAPY

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predisposes a patient to hypoglycemia, and the lower the glycemic target the more likely the occurrence of hypoglycemia. In the UKPDS, the incidence of hypoglycemia was 1.8% in patients treated with insulin and 1.4% in patients treated with sulfonylureas.3

Precipitating causes of hypoglycemia include missed meals, strenuous unanticipated exercise, alcohol consumption in the absence of food, and insulin overdosing errors. A common cause of dosing error is the use of a rapid- or short-acting insulin by mistake in lieu of an intermediate- or long-acting insulin. Advanced patient age, presence of intercurrent illness, and recent or frequent changes to an accustomed regimen may also contribute to dosing errors.

Most hypoglycemia is recognized and treatable by the patient via ingestion of quickly absorbed carbohydrate; this form of self-recognized, self-treated hypoglycemia is considered mild. Mild hypoglycemia is characterized primarily by adrenergic symptoms (eg, sudden diaphoresis, nervousness, tremulousness) accompanied by urgent hunger. The appearance of such symptoms warns the patient that the blood glucose level is dropping, prompting appropriate action on the part of the patient. By contrast, severe hypoglycemia has been defined as the inability to self-treat symptoms, requiring assistance from another person or from emergency medical personnel.41 Symptoms of severe hypoglycemia impair the patient’s ability to take corrective action and include cognitive dysfunction such as confusion, amnesia, bizarre behavior, seizures, or coma. Severe hypoglycemia, by the usual definition, occurred at a rate of 0.0156 episodes per patient per year during treatment with multiple insulin injections in a large study involving 7 Veterans Affairs medical centers.42 It is likely, although unproven, that patient education regarding dosing errors, the need to eat and exercise according to schedule, and the need to test blood glucose and take corrective action can minimize the likelihood of severe hypoglycemic episodes.

Weight Gain

Patients undergoing insulin therapy also are at risk for weight gain. Over 10 years, obese patients in the UKPDS who were treated with insulin gained an average of 4 kg more than patients assigned to diet-only therapy and 1.8 kg more than patients assigned to sulfonylurea treatment.2 Other studies of insulin therapy in type 2 diabetes have documented an average weight increase of 3% to 9% of pretreatment baseline weight.16,43–45 Body composition studies suggest that approximately two thirds of weight gained is adipose tissue, and the remaining third is lean body mass.46 Strategies for avoiding weight gain include 45 to 60 minutes of aerobic exercise at least 4 to 5 times weekly, bedtime insulin dosing, and concurrent use of metformin. Despite precautions, weight gain is regularly observed in patients treated to target glycemic levels.

A pharmacologic approach to the problem of treatment-associated weight gain is the addition of pramlintide (an analogue of human amylin, which is co-secreted with insulin) to prandial insulin regimens. Pramlintide is only available as a subcutaneous injection and cannot be mixed in the same syringe with insulin. The prandial insulin requirement is typically reduced by 50% when pramlintide is started, initially at a dose of 0.15 mcg, titrating to effect to a maximum recommended dose of 60 mcg thrice daily or 120 mcg twice daily. In a 1-year trial of pramlintide added to twice- or thrice-daily insulin regimens, HbA1c improved by -0.62% versus placebo injections and was associated with a 1.4-kg weight loss at 52 weeks.47

INTENSIFYING INSULIN THERAPY

CASE CONTINUED

Over the next 2 years, despite frequent changes in insulin dose, the patient experiences gradually increasing glycemia. At an interim visit roughly 3 years after beginning insulin therapy, her HbA1c is 8.3%, her fasting blood glucose values average 150 mg/dL, and her random blood glucose values average 180 mg/dL. Her weight has increased by 10 lb, but her physical examination and ophthalmologic examination remain normal. The patient continues to be on maximal doses of glipizide, metformin, and pioglitazone and now is receiving 100 U of insulin glargine each morning.

• What treatment options remain for this patient?

INTENSIVE INSULIN THERAPY

With rising HbA1c and daytime random blood glucose values in the setting of maximum-dose glipizide, it can be inferred that the patient is functionally unable to secrete endogenous insulin to meet mealtime demands for insulin.3 At this point, the best available treatment options for this patient involve intensive insulin therapy. Also called basal-bolus regimens, intensive insulin therapy attempts to simulate normal insulin homeostasis by providing continuous low-dose (basal) insulin delivery augmented by a short- or rapid-acting (bolus) insulin to control blood glucose surge following meals. In the Kumamoto study of 165 Japanese patients with type 2 diabetes, patients randomized to intensive
insulin therapy (3 to 4 daily injections) versus conventional insulin therapy (1 or 2 daily injections) attained lower average HbA\textsubscript{1c} levels (7.2% versus 9.4%) and had reduced incidence and progression of retinopathy, nephropathy, and peripheral neuropathy.\textsuperscript{48}

**Simplified Insulin Regimens**

The simplest effective basal-bolus regimen would be a twice-daily injection of a premixed fast-acting insulin component and an intermediate-acting component. Generally speaking, empiric calculation of a TDD of insulin of 0.4 to 0.8 U/kg body weight divided into 2 equal doses administered before breakfast and before supper is a reasonable and effective plan. The daily dose can be adjusted by adding or subtracting 10% of the TDD at 3- to 7-day intervals based on results of home blood glucose testing (see Table 3).

The mixture of 70% NPH insulin/30% regular insulin remains popular and relatively inexpensive. Due to the peak effect of regular insulin, however, such a mixture is most effective in attenuating postprandial hyperglycemia when given 30 minutes prior to the meal. As an alternative, the mixture of 70% insulin aspart protamine/30% insulin aspart or 75% insulin lispro protamine/25% insulin lispro can be given with the meal; these premixed insulins have been shown to produce lower peak postprandial glycemia and lower HbA\textsubscript{1c} levels at study end point.\textsuperscript{49,50} However, these insulin mixtures are more expensive than 70% NPH insulin/30% regular insulin.

**Multiple-Daily Injection Regimens**

Commonly prescribed multiple-daily injection regimens are summarized in Table 3 and briefly described below. For each, an effective TDD will usually be in the range of 0.4 to 0.8 U/kg body weight, with a usual empiric starting dose of 0.5 U/kg. Cost factors and individual preference should dictate the bolus insulin component to be used, as there are little data to objectively favor one over the other.

**Bedtime NPH or lente insulin plus mealtime regular insulin or a rapid-acting insulin analogue.** With this type of regimen, 40% of the TDD typically is given as NPH or lente insulin at 10 or 11 pm, and the remaining 60% of the TDD is split equally among 3 mealtime injections. Regular insulin is administered 30 minutes before meals, whereas the rapid-acting analogues (insulin lispro, insulin aspart, insulin glulisine) must be administered exactly at mealtime, owing to their quicker peak action. The delayed peak action of regular insulin compared with the rapid-acting insulin analogues may thwart attaining desirable postprandial glycemic targets, but this may have little effect on HbA\textsubscript{1c} in most patients with type 2 diabetes. Insulin lispro and insulin aspart have been shown to be pharmacologically interchangeable.\textsuperscript{51}

**Once-daily insulin glargine plus mealtime regular insulin or a rapid-acting insulin analogue.** With this type of regimen, approximately 40% to 50% of the TDD is given as insulin glargine. Insulin glargine has no pronounced peak action over approximately 24 hours\textsuperscript{32} and has been shown to produce less nocturnal hypoglycemia than NPH insulin.\textsuperscript{53} Originally approved for bedtime dosing, insulin glargine has been shown to have similar efficacy when given at any time of day, provided it is given at the same time each day.

For the case patient, many experienced diabetologists would discontinue use of glipizide and substitute a bolus insulin preparation at mealtimes. Metformin and pioglitazone could be discontinued (on the rationale of loss of efficacy) or continued (on the rationale of promoting insulin response), based on physician and patient preference. Thus, the regimen would consist of 1 injection of insulin glargine at the same time each day and a bolus injection of short-acting (regular) insulin or a rapid-acting analogue 3 times daily with meals. Because the bolus component typically represents 40% to 50% of the TDD in such a regimen, one would expect that in the case patient, an eventual dose of 30 U of a bolus preparation at each of 3 meals would be required. A starting dose of 10 U per meal would be safe in a patient receiving 100 U of basal insulin daily. A recommendation to measure blood glucose 2 hours after the meal would allow for titration of bolus therapy by increments of 10% to 20% of the TDD every 3 to 7 days.\textsuperscript{54} Nurse case management by telephone has been shown to be effective in helping patients adjust insulin doses incrementally toward target glycemic goals.\textsuperscript{55} Perhaps the most important concept for the patient and physician to understand is that there is no ceiling dose of exogenous insulin; the dose must be individually titrated to requirement.\textsuperscript{56} The usual goals of therapy apply (ie, HbA\textsubscript{1c} < 7% and fasting blood glucose between 90 and 130 mg/dL).

A newly available (June 2006) alternative to prandial insulin injections is inhaled human insulin, which is administered via a special inhalation device. Pellets containing 1 mg (equivalent to 3 U regular insulin) or 3 mg (equivalent to 8 U regular insulin) are inserted into a port on the hand-held inhaler, crushed by a triggering device, and subsequently aerosolized for inhalation. Similar to insulin aspart, insulin lispro, and insulin glulisine, inhaled insulin is administered immediately prior to eating due to its rapid onset of action. In a 12-week randomized trial, inhaled insulin, tested as a stand-alone insulin therapy without a basal insulin preparation, was
shown to be superior to monotherapy with rosiglitazone, with HbA1c levels of 7.2% achieved with inhaled insulin versus 8% with rosiglitazone (from baseline HbA1c levels of 9.5% and 9.4%, respectively). A 24-week trial comparing inhaled insulin versus metformin added to a failing regimen of sulfonylurea monotherapy resulted in slightly improved HbA1c values when the baseline HbA1c level was greater than 9.5% (−2.17% for inhaled insulin versus −1.79% for metformin), with a twofold increased risk of hypoglycemia. Current manufacturer guidelines for the use of inhaled insulin oblige baseline spirometry examination followed by repeat spirometry every 6 months to establish normal lung function. Cigarette smoking and virtually all forms of lung disease, including asthma and chronic obstructive lung disease, are contraindications to this form of insulin therapy.

Continuous Subcutaneous Insulin Infusion

When all other attempts at glycemic control have proven unsatisfactory, a final option for basal-bolus insulin delivery is a continuous subcutaneous insulin infusion (CSII, or an insulin pump). The paucity of evidence in support of CSII pump efficacy in type 2 diabetes must be carefully weighed against the substantial economic cost of this therapy on an individual basis. CSII pumps should be considered only as a last resort for patients who have failed other available, tolerated therapy.

Studies of the efficacy of CSII therapy in type 2 diabetes are small. Garvey et al. reported a 38% reduction in HbA1c after 3 weeks of CSII therapy in 14 patients previously receiving insulin injections. Concurrently, endogenous insulin function was shown to improve, as evidenced by a 74% increase in insulin-stimulated glucose disposal rate and a 45% reduction in hepatic glucose production, suggesting amelioration of glucoxicity. Jennings et al. conducted a trial of 20 insulin-naive patients with type 2 diabetes (median age, 60 years) who were randomized to twice-daily NPH plus regular insulin or to CSII. HbA1c decreased by 30% in the CSII group as compared with 17% in the insulin injection group.

With CSII therapy, half the TDD is delivered as a continuous basal infusion and the other half is provided by manual activation of the pump’s bolus delivery feature at mealtimes. To calculate the basal infusion rate, half the TDD is divided by 24 (hours). Thus, if the case patient were to switch from insulin glargine to CSII, her current 100 U dose of basal insulin would translate into a basal infusion rate of 4.2 U/hr.

Pumps have an hourly limit to the number of insulin units that can be infused (average ceiling is approximately 6 U/hr). For patients who exceed this requirement, an innovative approach was reported by Knee et al. who switched 4 patients failing high-dose subcutaneous insulin therapy to CSII therapy using U-500 insulin (5 times standard potency of U-100 insulin; available on special request from the manufacturer). The mean reduction in HbA1c was from 10.8% prior to CSII to 7.3% after several months of CSII therapy.

CASE CONCLUSION

The patient agrees to discontinue glipizide and to start a basal-bolus insulin regimen consisting of insulin glargine once daily and insulin aspart with each meal. You maintain her insulin glargine dose at 100 U/day, to be taken at bedtime, and start insulin aspart at a dose of 20 U with each meal. The patient continues to take pioglitazone and metformin.

On follow-up evaluation 1 month later, the patient’s fasting blood glucose values average 110 mg/dL, and her random glucose values average 140 mg/dL. Her weight is unchanged. Based on the improvement in her glycemia, the patient agrees to continue the prescribed regimen. Three months later, her HbA1c is 7.2%.

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