INITIATING BEDTIME INSULIN

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Patients and practitioners alike may be reluctant to begin a regimen of injectable insulin—even when oral agents fail to control blood glucose. But such therapy can be highly effective if combined with carefully timed administration and patient education.

In the year 2000, the World Health Organization estimated that over 176 million people worldwide had type 2 diabetes mellitus (DM)—and predicted that by 2030, that number would more than double.[1] In the United States, DM is the sixth leading cause of death among people aged 25 years and older,[2] and its associated health care costs exceed $130 billion per year.[3]

The 1995 United Kingdom Prospective Diabetes Study (UKPDS), one of the most important studies on DM to date, demonstrated conclusively what many clinicians had known from clinical observation: that DM is a progressive disease and that intensive management can delay the onset of its devastating complications.[4] In light of these findings, which have been supported by a number of subsequent studies, the American Diabetes Association (ADA) now recommends that patients with type 2 DM maintain levels of glycosylated hemoglobin (HbA_{1C}) below 7%.[5]

To assist patients in meeting this ADA goal, we must consider all facets of glycemic control, focusing not only on pharmacologic treatment but also on patient education regarding diet, exercise, and disease self-management as well. And when a patient's DM fails to be controlled by oral agents alone, we must be willing to initiate insulin treatment—a vital step frequently resisted by practitioners and patients alike.

In this article, we guide primary care providers in the timely and efficient initiation of bedtime insulin. We review existing data on this treatment modality, explain the rationale behind its timing, and discuss the importance of patient education in promoting tight glycemic control.

SUPPORTING EVIDENCE

In 1992, Yki-Jarvinen and colleagues conducted a short but important trial to determine the optimal mode of insulin administration for diabetic patients in whom oral therapy with sulfonylureas and metformin no longer controlled blood glucose effectively.[6] The 153 study participants were divided randomly into five groups, each given one of the following treatment regimens: an oral hypoglycemic agent plus neutral protamine Hagedorn (NPH) insulin given at 7:00 AM; an oral hypoglycemic agent plus NPH insulin given at 9:00 PM; NPH insulin and regular insulin given at a 70:30 dose ratio before breakfast and dinner; NPH insulin given at 9:00 PM and regular insulin given before meals; or continued oral hypoglycemic therapy (the control group).

For patients with type 2 DM, the addition of bedtime NPH insulin is the optimal treatment to reduce blood glucose with the least amount of weight gain.

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At the end of three months, the mean HbA_{1C} level decreased similarly and significantly in the four insulin groups (1.7%, 1.9%, 1.8%, and 1.6%, respectively) compared with the control group (0.5%, $P < .001$). Weight gain was significantly less in the group receiving NPH insulin at 9:00 PM (1.2 kg) than in the other insulin treatment groups (2.2 kg in the 7:00 AM NPH group, 1.8 kg in the 70:30 NPH/regular insulin before breakfast and dinner group, and 2.9 kg in the NPH at 9:00 PM and regular insulin before meals group; $P < .05$). The authors concluded that, for patients with type 2 DM, the addition of bedtime NPH insulin is the optimal treatment to reduce blood glucose with the least amount of weight gain.

Yki-Jarvinen and colleagues followed up this study in 1999 with a one-year, randomized clinical trial designed to help determine which agents, when used in conjunction with bedtime insulin, resulted in the least weight gain by patients whose type 2 DM was controlled insufficiently with sulfonylurea monotherapy.[7] The 96 patients included in the study had a mean HbA_{1C} value of 9.9% and a fasting plasma glucose level of 11.9 mmol/L. All patients received intermediate-acting bedtime NPH insulin. The cohort was divided further into four groups that would receive either glyburide and placebo, metformin and placebo, glyburide and metformin, or a second morning injection of intermediate-acting insulin.

At one year, body weight remained essentially unchanged in patients receiving bedtime insulin plus metformin (mean change, 0.9 kg) but increased by 3.9 kg, 3.6 kg, and 4.6 kg in patients receiving bedtime insulin plus glyburide, bedtime insulin plus glyburide and metformin, and bedtime plus morning insulin, respectively ($P < .001$ compared with all other groups). Furthermore, the group receiving bedtime insulin plus metformin had the greatest reduction in HbA_{1C}—from 9.7% to 7.2% at one year ($P < .001$ compared with baseline and $P < .05$ compared with the other groups)—and significantly fewer symptomatic and biochemical episodes of hypoglycemia than the other groups ($P < .05$). The authors concluded that bedtime insulin with metformin was superior to other regimens in helping patients achieve glycemic control with less weight gain and fewer hypoglycemic events.

The data suggested that a regimen based on bedtime insulin targeted to fasting glucose levels could be maintained for more than two years.

Meanwhile, in 1995, VA researchers conducted the VA Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Mellitus (VA CSDM). The primary objective was to evaluate whether intensive glucose lowering therapy could be sustained over a two-year period, and the study yielded convincing scientific evidence for using long-acting NPH insulin at bedtime to maintain a lower HbA_{1C} level in patients with type 2 DM for whom oral therapy is no longer effective.[8]

In this prospective trial, 153 participants were assigned randomly to receive either standard insulin treatment (one morning injection per day) or one of four types of intensive therapy: an evening insulin injection, an evening insulin injection plus daytime glipizide, two injections of insulin daily, or multiple insulin injections daily. The mean HbA_{1C} differed significantly between the standard and intensive groups ($P < .001$): After six months, it was at or below 7.3% in the intensive therapy group, compared with 9% to 9.6% in the standard treatment group, and it remained 2% lower than the standard group for the duration of the trial. The authors noted that most of the decrease in HbA_{1C} in the intensive therapy group was obtained with a single evening injection of intermediate insulin ($P < .05$), alone or with daytime glipizide. The data suggested that a regimen based on bedtime insulin targeted to fasting glucose levels could be maintained for more than two years.

CONSIDERING GLITAZONES

It's important to note that the previous studies were initiated prior to the FDA approval of the thiazolidinediones and, therefore, didn't include this class of medications. There remains a paucity of scientific medical research comparing the effectiveness of insulin versus a third oral insulin sensitizing agent. It seems that for some patients, however, an insulin sensitizer can add benefit to the overall glycemic picture.

Fonseca and colleagues conducted a randomized, double-blind, placebo-controlled trial of 348 patients to determine whether met-

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Table 1. Advantages of bedtime NPH* insulin administration

- Potentially less weight gain than 24-hour NPH insulin coverage or addition of thiazolidinediones
- Morning euglycemia
- Ease of transition to insulin therapy
- No difficulty with renal, liver, or heart dysfunction or any other illness
- Less expensive
- Ability to lower HbA_{1C}† more than 1% to 2%

*NPH = neutral protamine Hagedorn. †HbA_{1C} = glycosylated hemoglobin.

formin or metformin plus rosiglitazone was more efficacious in reducing blood glucose indexes.[9] None of the patients in this study were receiving insulin and oral hypoglycemic medications concurrently. Over 26 weeks, the group that received the rosiglitazone plus metformin showed a statistically significant ($P < .001$) decrease in mean HbA_{1C} levels but an increase in body mass (from 0.7 kg to 1.9 kg).

While the authors concluded that the combination of metformin and rosiglitazone treatment is effective and safe in reducing blood glucose in type 2 DM, weight gain isn't uncommon with the thiazolidinediones, especially in patients who are already overweight or obese. This class of medications also can precipitate edema and congestive heart failure in patients with fluid overload. The thiazolidinediones also are contraindicated for patients with liver disease, and when they are used, require frequent liver function testing.

THE CASE FOR BEDTIME INSULIN

In most cases, sulfonylurea and metformin fail to control glucose levels adequately over the long term. After such treatment failure, clinicians often prescribe either a triple oral regimen of sulfonylurea, metformin, and a thiazolidinedione or bedtime insulin, but the optimal DM management strategy remains unknown. There are, however, clear advantages to initiating bedtime NPH insulin (Table 1). And while NPH remains the best initial bedtime insulin therapy, such recent pharmacologic breakthroughs as the 24-hour insulin analog glargine also are appropriate for bedtime use.

NPH insulin was compared to insulin glargine in a 2000 trial. Yki-Jarvinen and colleagues randomly assigned 426 patients with type 2 DM who had poor glycemic control while taking oral agents to receive either NPH insulin or insulin glargine at bedtime for one year.[10] Average improvement in HbA_{1C} levels was about the same for both groups, but there was less nocturnal hypoglycemia in the glargine group: 9.9% versus 24% in those patients treated with NPH ($P < .001$). Furthermore, there was the additional benefit of lower postdinner glucose concentrations in those patients treated with insulin glargine ($P < .02$). As practitioners gain more experience with insulin glargine, it may well become a first-line insulin treatment for certain patients—especially those predisposed to hypoglycemia.

Despite the advantages of insulin glargine, it's costly. And since it's a 24-hour insulin, it can be difficult to titrate the dose (compared to NPH insulin, for which the morning fasting levels determine adequate dosing). Also, patients who remain relatively active during the day may not need a 24-hour supplemental insulin, since glucose levels dip with activity. For patients who need primarily morning (not afternoon) blood glucose control, traditional NPH insulin is appropriate.

Bedtime NPH insulin is inappropriate for patients with relatively normal fasting blood glucose levels (less than 126 mg/dL) and elevated daytime glucose levels.

USING BEDTIME INSULIN PROPERLY

Practitioners must be aware that bedtime insulin isn't suitable for all patients who experience elevated HbA_{1C} levels while taking oral agents. Although fasting blood glucose levels tend to worsen with the duration of DM, bedtime NPH insulin is inappropriate for patients with relatively normal fasting blood glucose levels (less than 126 mg/dL) and elevated daytime glucose levels. In such cases, rather than tak-

Table 2. Suggested initial bedtime NPH* insulin dosage

BMI† (kg/m²)	Fasting glucose level (mg/dL)	NPH insulin (units)
> 30	> 300	15–20
	< 300	12–15
< 30	> 300	10–12
	< 300	5–8
Lean patient		5

*NPH = neutral protamine Hagedorn. †BMI = body mass index.

ing bedtime insulin, patients may consider walking after their main meal, changing their diet, or taking meglitinides to lower glucose levels.

Patients who experience the Somogyi effect, which is more common in type 1 than type 2 DM, comprise another group for whom bedtime insulin is inappropriate. The high morning blood glucose levels that characterize this phenomenon are a response to stress hormones activated by a low nighttime blood glucose level, brought on by either too much sulfonylurea, additional exercise, or too little food. Practitioners need to rule out the occurrence of the Somogyi effect by carefully checking the patient's history for night sweats and nightmares and recording several 3:00 AM blood glucose levels.

DETERMINING THE DOSE

Of course, all decisions regarding DM medical therapy must take into consideration the patient's lifestyle, age, mental status, and level of adherence. When the patient and practitioner agree that oral therapy is no longer adequate and bedtime insulin should be initiated, however, certain physiologic parameters may be used to determine initial insulin doses. At the Louis Stokes Cleveland VA Medical Center (LSCVAMC) in Cleveland, OH, we provide practitioners with general dosing guidelines based on body mass index (BMI) and fasting blood glucose values. Following these guidelines both expedites the lowering of HbA_{1C} values and minimizes the patient's risk for hypoglycemia (Table 2).

Generally, overweight or obese patients require more insulin to counteract the insulin resistance inherent in bodies with more fat cells. For this reason, if the BMI is greater than 30 kg/m² and fasting blood glucose levels are less than 300 mg/dL, our team recommends starting with 12 to 15 units of NPH insulin at bedtime. If the patient's BMI is greater than 30 kg/m² and fasting blood glucose levels are even higher than 300 mg/dL, larger amounts (up to 20 units) of bedtime insulin can be given. When the BMI is lower than 30 kg/m² or if the patient is especially lean, the more traditional dose of 5 to 10 units of NPH insulin at bedtime may be appropriate.

After insulin is started and the patient responds safely to the initial dose, the dose can be titrated up 2 units every two to four days until fasting levels are around 120 to 150 mg/dL—depending on the patient's age and ability to handle the insulin. There's no limit to the amount of NPH insulin that can be taken at bedtime. In the VA CSDM, for example, the mean final dose of bedtime NPH insulin was 61.3 ± 38.1 units.[8]

THE IMPORTANCE OF EDUCATION

Patient education regarding insulin administration is imperative. At the time of insulin initiation, it's important for a trained DM educator to discuss hypoglycemia precautions with the patient and provide instruction on administering the insulin, so that the patient is more likely to adhere successfully to the treatment program. It also can be helpful to explain to the patient that insulin is a normal substance within the body, has minimal adverse effects, and frequently is just what's needed to bring a high HbA_{1C} level into normal range.[11] At the LSCVAMC, we provide our patients with written instructions reiterating that insulin is to be administered at bedtime—not dinnertime. Be sure to ask patients when they usually go to bed because many older people have very early bedtimes, and this should be considered in determining the starting dose.

To lessen patients' risk of falling during the night, caution them to keep a glucose source (containing 15 g of carbohydrates) and meter at bedside in case they develop hypoglycemic shaking, nightmares, or night sweats. We instruct patients that the effects of NPH insulin generally peak eight hours after administration, and that they should avoid skipping breakfast, wear a bracelet that identifies them as having DM, and check blood glucose levels before driving—particularly in the morning.

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A PROGRESSIVE DISEASE, A CONTINUUM OF CARE

DM is a disease that's progressive in nature. When double or triple oral therapy is no longer effective or is contraindicated, insulin shouldn't be looked on as the last resort but rather as an effective, relatively inexpensive, and—provided that the patient is well educated on proper administration—safe choice for glycemic management. Initiating bedtime insulin with oral agents can have a tremendous impact on high fasting glucose levels, making it easier to achieve target daytime blood glucose levels and HbA_{1C} values with less weight gain. Insulin doses can be determined initially by considering the patient's BMI and fasting blood glucose levels and then titrated by the patient to achieve timely control. With more practitioners taking the initiative to move patients to this next level of DM management, we can hope to see better control of this devastating disease and its costly complications in the near future.

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