

When and how to implement basal-bolus therapy: Treating to success

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Most patients with diabetes will require insulin therapy

The majority of patients with longstanding diabetes are candidates for insulin therapy,¹ as a substantial proportion of pancreatic β -cell function has been lost by the time the disease is diagnosed. Results from one recent study indicated that, at the time of diagnosis, most patients with type 2 diabetes had already lost 80% of their β -cell function.² It has further been shown that β -cell function begins to decline in patients with insulin resistance prior to the emergence of impaired glucose tolerance.³ During the early stages of type 2 diabetes, lifestyle interventions (including modifications to diet and exercise patterns) may be successful for improving glycemic control for some patients.⁴ However, as β -cell function continues to decline, pharmacologic treatment, consisting of combination therapy with 2 or 3 oral antihyperglycemic agents, in addition to lifestyle modifications, is often required.⁵ When oral agents are not effective in reaching A1C targets, addition of insulin therapy is required.⁶ Indeed, by 6 years after initiation of treatment with oral agents, about one-half of patients will require insulin treatment.¹ With the recent information by DeFronzo suggesting that 80% of a patient's β -cell function has been lost by the time of diagnosis,² insulin therapy may be indicated even earlier in the management of type 2 diabetes.

Because β -cell failure is progressive and most patients with type 2 diabetes will ultimately require insulin therapy, there is an emerging awareness that using insulin earlier in the course of the disease is physiologically sound and should be an integral part of adequate diabetes management.⁷ Therapy for patients with diabetes should be aimed at "treating to target," using information gained from careful patient monitoring.⁸ With this approach, treatment should be directed at a specific A1C goal and promptly adjusted as needed to reach the target. This approach is in contrast to a slower stepwise approach, which is likely to result in repeated failure and loss of glycemic control. Treating to target is particularly important because of the progressive nature of diabetes, with increasing insulin resistance and decreasing insulin secretion over time. As the disease progresses, so should therapy.

Treatment progression in patients with diabetes

The remainder of this article presents information about management of type 2 diabetes in the face of progressive loss of β -cell function and declining production of endogenous insulin.

CASE STUDY

A 41-year-old African American woman presents to her primary care physician for her annual physical examination. Her medical history includes two normal pregnancies with delivery of healthy children and hypertension with blood pressure controlled by a combination of valsartan and hydrochlorothiazide. The patient smokes cigarettes (one-half pack per day) but does not consume alcohol. Physical examination reveals an overweight woman with no other abnormalities. The patient's vital signs and laboratory values are summarized in **TABLE 1**.

The patient's A1C and fasting plasma glucose (FPG) levels are consistent with a diagnosis of diabetes. A repeat evaluation of FPG carried out 3 days after the initial evaluation resulted in an FPG of 131 mg/dL, confirming a diagnosis of diabetes.⁹ Initial treatment is consistent with the recommendations of the American Diabetes Association (ADA) and includes dietary and lifestyle changes and pharmacotherapy with metformin (1000 mg/day).^{6,9} Atorvastatin is also initiated at a dose of 10 mg/day in accordance with ADA recommendations for treatment of dyslipidemia.⁹ This regimen is continued for 2 years with titration of metformin to 2000 mg/day and continuation of atorvastatin at the initial dose. At the end of 1 year, A1C had declined to 7.1% and low-density lipoprotein cholesterol (LDL-C) was reduced to 97 mg/dL. The patient's body weight decreased to 157 lb. By 2 years, A1C had increased to 7.9%, LDL-C remained stable at 98 mg/dL, and body weight increased slightly to 161 lb. The increase in A1C prompted addition of glyburide (initial dose 5 mg/day, titrated to 20 mg/day) to the treatment regimen. Follow-up 6 months later demonstrated a decline in A1C to 7.3%, but further follow-up at 1 year showed that A1C had again increased to 8.0%. At this point, a decision is made to initiate insulin therapy. This change in treatment is consistent with ADA recommendations.⁶

Initiation of insulin therapy

There are multiple approaches to the initiation of insulin therapy in a patient with type 2 diabetes who

TABLE 1

Case study: Baseline vital signs and clinical laboratory values

Vital signs		Laboratory values	
Height	5 ft, 7 in	A1C	8.4%
Weight	159 lb	FPG	129 mg/dL
Temperature	98.7°F	Lipid panel: Total cholesterol	178 mg/dL
		LDL-C	134 mg/dL
		HDL-C	54 mg/dL
		Triglycerides	141 mg/dL
Blood pressure	139/91 mm Hg	Hematology	Normal
Pulse rate	74 bpm	Blood chemistry	Normal
Respiratory rate	19 breaths/min	Urinalysis	Normal

A1C, glycosylated hemoglobin; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

can no longer maintain glycemic control on oral agents. In this case, the decision is made to add basal insulin and continue treatment with oral drugs. This approach is consistent with results from clinical trials that have shown that adding basal insulin to ongoing oral therapy can improve glycemic control.¹⁰ The improvement in glycemic control achieved with the addition of basal insulin is believed to result from suppression of overnight hepatic glucose production, both through direct effects on the liver and indirect effects due to inhibition of free fatty acid release by adipose tissue.¹¹

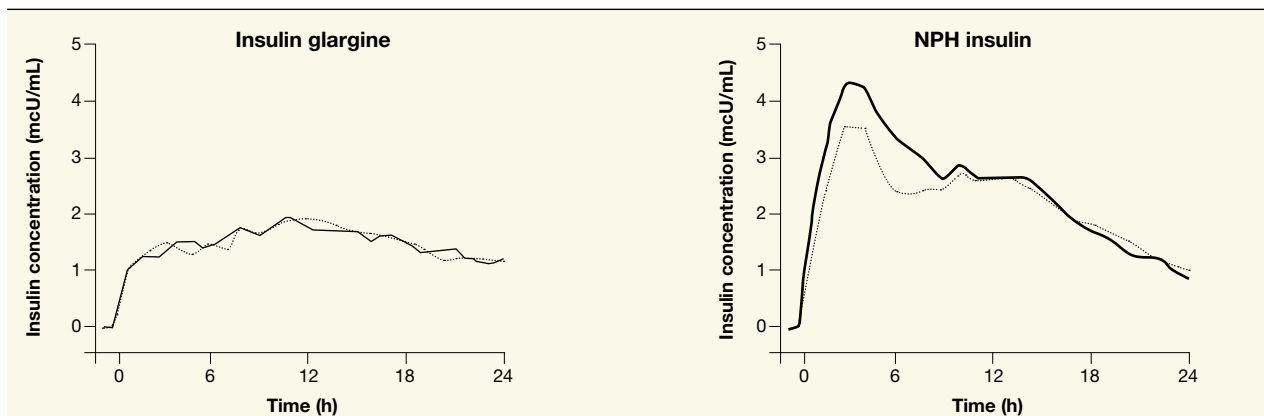
Basal insulin properties

The two main options for basal insulin therapy are neutral protamine Hagedorn (NPH) insulin or a long-acting insulin analog (insulin glargine or insulin detemir). The pharmacokinetic/pharmacodynamic profiles for NPH insulin and long-acting insulin analogs are substantially different (**FIGURE**). Those for the long-acting insulin analogs are relatively flat, while those for NPH insulin have a distinct peak at about 4 hours.¹²

These differences in time-action profiles affect both dosing requirements and clinical efficacy. Insulin with an intermediate duration of action (13 to 16 hours), such as NPH insulin, must be given in the evening or at bedtime and often requires twice-daily administration, with a second dose in

FIGURE

Pharmacokinetic profiles for insulin glargine and NPH insulin



NPH, neutral protamine Hagedorn. The solid and dashed lines represent 2 different study days.

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the morning. Long-acting insulin analogs can be administered at bedtime, before dinner, or in the morning, due to their longer durations of action and lower peak effects.¹¹

The pharmacokinetic effects of NPH insulin are also more variable than those of insulin glargine or insulin detemir. This is the case within patients even when the insulin is injected at the same site from one day to the next. This variability is a result of the manner in which NPH insulin is structured.¹³ Protamine is added to regular insulin to extend its duration of action. Protamine ionizes the insulin molecule, which forms a complex with itself to remain in a hexameric structure at the injection site, resulting in a longer duration of action and longer time to peak. However, the resulting poor solubility of this insulin preparation increases the variability in its pharmacokinetic profile. The requirement for resuspension of NPH insulin prior to injection may also contribute to inter- and inpatient variability in the action of this insulin because the actual amount of insulin administered may vary from one injection to the next.¹³ This high variability is not observed with long-acting insulin analogs,¹³ which may contribute to the lower risk for hypoglycemia with these agents versus NPH insulin.⁸ Results from multiple clinical studies have demonstrated the effectiveness of adding a long-acting basal insulin analog to oral therapy in patients with type 2 diabetes.^{8,14-16} Furthermore, a recent comparison of long-acting insulin analogs used in addition to oral agents indicated similar efficacy and safety; however,

insulin detemir was associated with less weight gain than insulin glargine.^{17,18}

Basal insulin dosing regimens

Dosing regimens for long-acting insulin analogs are straightforward. The initial dose for insulin detemir is usually 10 U.¹⁹ In the PREDICTIVE 303 study, patients self-adjusted their insulin detemir dose every 3 days based on the average of 3 self-monitored blood glucose (SMBG) values. Insulin detemir doses were adjusted as follows: if the mean FPG is <80 mg/dL, the dose is reduced by 3 U; if the mean FPG is 80 to 110 mg/dL, there is no change in dosing; and if the mean FPG is >110 mg/dL, the dose is increased by 3 U.²⁰ Another recent study demonstrated that patients can safely self-titrate insulin detemir to an FPG target of 70 to 90 mg/dL with low rates of hypoglycemia.²¹

The typical initial dose for insulin glargine is 10 U.²² In one study, doses for insulin glargine were adjusted as follows: no change is required if FPG remains between 70 and 94 mg/dL; if FPG is <70 mg/dL for 3 days, the dose should be decreased by up to 10% of the total dose; and if FPG is 95 to 119, 120 to 139, 140 to 180, or >180 mg/dL for 3 days, the dose should be increased by 2, 4, 6, or 8 U, respectively.²³

Intensifying treatment with basal-bolus administration of long- and rapid-acting insulin analogs

Although the addition of basal therapy is highly effective in many patients, the progressive nature of diabetes may require further intensification of treatment.

CASE STUDY

The patient had insulin glargine (initial dose 10 U) added to ongoing oral therapy, and follow-up at 6 months indicated that her A1C level had declined to 7.1%. However, after an additional year of treatment, her A1C increased to 7.8%. This increase prompted consideration of intensification of the treatment regimen with the addition of bolus insulin.

Rapid-acting insulin analogs are a suitable first choice for intensification of therapy. Rapid-acting insulin analogs have lower variability in absorption and more consistent pharmacodynamic profiles than regular human insulin.^{24,25} Rapid-acting insulin analogs provide higher 1- and 2-hour insulin values and reduced risk for late postprandial hypoglycemia due to a shorter duration of action, and may provide quality-of-life benefits due to greater flexibility in timing and dosing (eg, dosing with meals versus regular human insulin, which requires dosing 30 to 45 minutes prior to meals).²⁶ These insulin analogs provide a more physiologic action that coincides with meal patterns.

Stepwise initiation of basal-bolus therapy

Adding prandial insulin to basal insulin may be considered the best way to restore postprandial and overall glycemic control when the combination of basal insulin and oral therapies is no longer sufficient. However, making an immediate transition from a basal (or premixed) insulin regimen to a more complex basal-bolus regimen is challenging. Stepwise addition of prandial insulin to basal insulin may be considered a more practical alternative than using multiple daily injections.¹¹ In many cases, a single mealtime prandial injection of a rapid-acting insulin analog that controls the highest postprandial glucose (PPG)—often associated with the largest meal—might be sufficient to restore glycemic control.²⁷ The prandial insulin dose can then be titrated in accordance with SMBG values measured 2 hours after the start of the meal, before the next meal, or at bedtime if the injection is administered before the evening meal. The prandial insulin dose can be adjusted independently to limit postprandial hyperglycemia without affecting basal insulin action.^{11,27} A simple dose titration scheme for both basal

and prandial insulin analogs is provided in a tear-off sheet at the end of this article.

Initiation of basal-bolus therapy

A logical treatment progression for a patient who has had prandial insulin added to the treatment regimen is transition to basal-bolus therapy. The initial total daily insulin dose is 0.5 U/kg.²⁸ In these regimens, basal and bolus insulin requirements are each approximately half of the total daily insulin needed. The total dose of rapid-acting insulin analog is divided, with 38% delivered at breakfast, 28% at lunch, and 33% at dinner (White RD, et al. Unpublished data). The reason that the highest prandial dose is delivered at breakfast is based not only on the carbohydrate content of the meal but also on the “dawn phenomenon,” a morning surge in plasma glucose that occurs secondary to a physiologic morning rise in cortisol and growth hormone levels. Carroll et al found that this phenomenon occurs in 55% of patients with type 2 diabetes.²⁹ Patients who do not experience this morning glucose surge may have one-third of their prandial insulin dose administered at each meal.

A patient can begin insulin therapy with one evening dose of a long-acting insulin (approximately 10 U) with the dose adjusted as described above.^{20,23} Insulin levels should be titrated until the patient’s FPG is between 70 and 130 mg/dL. If a patient experiences hypoglycemia (FPG <70 mg/dL), bedtime insulin must be reduced by ≥ 4 U, or by 10% if the dose is >60 U, to minimize these events.³⁰

Rapid-acting insulin analogs have accelerated pharmacokinetics compared with long-acting insulins, and they require adjustments that can be made at shorter intervals. Many factors should be considered when titrating an insulin dose. For example, exercise improves insulin sensitivity, and it is often necessary to reduce the insulin dose in patients who engage in moderate or strenuous exercise.³¹

Carbohydrate counting is an alternative to dosage algorithms for determining prandial insulin dose and it provides for more flexibility in meal planning,²³ but this is not absolutely necessary. An example of a carbohydrate-counting method that has been used in combination with prandial insulin glulisine is shown in **TABLE 2**.²³

SMBG should be carried out 3 or more times daily for patients using multiple insulin injections.⁹ To achieve

TABLE 2

Example of carbohydrate counting and insulin glulisine dose adjustment^a

Mealtime dose	Pattern of mealtime glucose values below target ^b	Pattern of mealtime glucose values above target ^c
1 U/20 g CHO	Decrease to 1 U/25 g CHO	Increase to 1 U/15 g CHO
1 U/15 g	Decrease to 1 U/20 g	Increase to 1 U/10 g
1 U/10 g	Decrease to 1 U/15 g	Increase to 2 U/15 g
2 U/15 g	Decrease to 1 U/10 g	Increase to 3 U/15 g
3 U/15 g ^d	Decrease to 2 U/15 g	Increase to 4 U/15 g

CHO, carbohydrate.

^a Each patient in the carb count group was also given a schedule for a mealtime insulin glulisine correction dose to add a few units if high or subtract a few units if low.

^b If more than one-half of the mealtime blood glucose values for the week were below target.

^c If more than one-half of the mealtime blood glucose values for the week were above target.

^d Increase mealtime insulin as needed following this pattern.

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PPG targets, postprandial SMBG may be appropriate.⁹ Concern about hypoglycemia is a significant psychological barrier to intensive insulin therapy,³² but this risk is reduced by the use of modern long- and rapid-acting insulin analogs. For example, in one study, switching patients from the combination of regular human insulin and NPH insulin to insulin lispro and insulin glulisine resulted in a 44% reduction in the occurrence of hypoglycemia.³³ Results from a second comparison of these combinations for intensive insulin therapy indicated a 43% reduction in the occurrence of nighttime hypoglycemia with the insulin analogs.³⁴ The combination of insulin detemir and insulin aspart has also been associated with a 38% lower risk for nighttime hypoglycemia vs NPH insulin plus regular human insulin in patients receiving basal-bolus treatment.³⁵

Practical considerations for treating to target with basal-bolus therapy

A number of actions can increase the probability of reaching treatment targets in patients receiving basal-bolus therapy. Treatment regimens must be made as simple as possible to increase the possibility of adherence and therefore A1C goal attainment.²⁷ Advances in therapy may help in this process. Rapid-acting insulin analogs that can be administered shortly before or even after meals³⁶ have the potential to improve adherence.

Adherence to treatment in difficult-to-manage patients may also be improved with multisystemic therapy, an intensive home- and community-based psychological intervention originally used with youths presenting with serious mental health problems and their families. Multisystemic therapy has been shown to improve treatment adherence in patients with type 1 diabetes.³⁷

Patient referral to specialists for intensive diabetes care may be necessary to reach treatment targets in some patients. A study by Graber et al,³⁸ suggests that referral of patients with unsatisfactory glycemic control, frequent hypoglycemia, or inadequate self-management to a diabetologist-directed team of nurse and dietitian educators for intensive diabetes care may significantly improve adherence and glycemic control.³⁸

Additional practical steps that may increase the probability of reaching treatment goals include monitoring A1C levels every 3 months in addition to SMBG; aggressively managing hyperglycemia, dyslipidemia, and hypertension with the same intensity to obtain the best patient outcomes; addressing the underlying pathophysiology, including the treatment of insulin resistance; initiating combination therapy or insulin immediately for all patients with A1C $\geq 9\%$ at diagnosis; and implementing a multidisciplinary and interdisciplinary team approach to diabetes management, both to encourage patient education and self-care and to share responsibility with patients in achieving their glucose goals.³⁹

TEAR-OFF SHEET

Dosing titration for insulin analogs

BG levels for 3 consecutive days (fasting, prandial, or bedtime)	Adjust basal insulin dose (U)	Adjust rapidly acting insulin dose (U/injection)
≥180 mg/dL	+8	+3
160-180 mg/dL	+6	+2
140-160 mg/dL	+4	+2
120-140 mg/dL	+2	+1
100-120 mg/dL	+1	Maintain dose
80-100 mg/dL	Maintain dose	-1
60-80 mg/dL ^a	-2	-2
<60 mg/dL ^a	-4	-4

BG, blood glucose; FBG, fasting blood glucose.

^aIf any single blood glucose measurement is in this range, make the appropriate reduction in insulin dose.

For elevated FBG levels, adjust only the basal insulin dose.

For elevated preprandial BG at lunchtime, adjust breakfast rapid-acting insulin dose.

For elevated preprandial BG at dinnertime, adjust lunchtime rapid-acting insulin dose.

For elevated bedtime BG, adjust dinnertime rapid-acting insulin dose.

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