American Diabetes Association®

PRACTICAL INSULIN

3rd Edition

A Handbook for Prescribing Providers

Starting Patients on Insulin

Choosing the Right Regimen

Correcting Doses

Avoiding Common Problems

Improving Glucose Control

PRACTICAL INSULIN 3rd Edition

A Handbook for Prescribing Providers

American Diabetes Association®

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Introduction

Your medical practice is handling ever-increasing numbers of patients with diabetes. Insulin therapy is a medical necessity for all patients with type 1 diabetes and the many patients with type 2 diabetes who cannot reach their glycemic goals without insulin therapy. Understanding proper use of insulin is vital to you and your patients.

Insulin's ability to lower glucose is unparalleled. It both increases glucose uptake by adipose and muscle tissues and suppresses hepatic glucose release. The primary limitation to its usefulness as a diabetes drug is hypoglycemia. In addition, insulin use often leads to weight gain, a negative effect for the commonly overweight or obese type 2 diabetes patient. Insulin has proven to be the most cost-effective and clinically effective treatment to normalize blood glucose levels. In this handbook, you will find solutions to the many

common challenges involved in prescribing insulin—from choosing insulin regimens, to addressing patient reluctance to start insulin therapy, to minimizing the weight gain that often accompanies improved glycemic control.

Please be aware that there are no standards for how to best use insulin therapy. Every patient is unique, and the insulin regimen must be individualized. Self-monitoring of blood glucose (SMBG) and following proven regimens of starting an insulin dose and making adjustments dependent on blood glucose measurements allows the patient to achieve excellent blood glucose management and minimize the risk for problems.

The American Diabetes Association has published this third edition of *Practical Insulin: A Handbook for Prescribing Providers* in the hope that it will assist you in initiating and maintaining insulin therapy for your patients with type 1 or type 2 diabetes and encourage you to continue your training in insulin therapy. It should be noted that one barrier to insulin use in type 2 diabetes patients can be physician reluctance or "resistance." This is due in large part to concerns about a prospective patient's unwillingness to self-administer injections and fear of low blood

glucose levels. It must be emphasized that insulin can be effectively and safely used, and giving positive support to the patient using insulin can help assure optimal management of blood glucose.

Patient Selection

Insulin therapy is appropriate for patients with type 1 or type 2 diabetes.

The absolute insulin deficiency of established type 1 diabetes can only be treated effectively with multiple daily insulin injections or continuous subcutaneous insulin infusion (the insulin pump).

Because people with type 2 diabetes are somewhere along the continuum from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance, insulin therapy is less straightforward. However, insulin therapy is a necessity in type 2 diabetes for:

- patients unable to adequately control their blood glucose levels with maximum-dose combinations of oral glucose-lowering medications and/or an injectable incretin mimetic (such as exenatide or liraglutide)

- patients undergoing surgery
- patients who cannot tolerate oral glucose-lowering medications and/or an incretin mimetic
- patients with renal or hepatic disease or allergies that preclude the use of oral glucose-lowering medications and/or an incretin mimetic
- women who are planning pregnancy or are already pregnant
- patients who are hospitalized

Insulin therapy is often instituted for type 2 diabetes patients who:

- cannot control their diabetes with diet and exercise alone
- are highly symptomatic with severe hyperglycemia, e.g., with glucose levels frequently >250 mg/dl
- are newly diagnosed with very high glucose levels
- have progressive microvascular complications

Insulin Choices

The insulin primarily in use today is recombinant DNA technology insulin. It is produced in virtually unlimited quantities of highest purity in either the exact amino acid sequence of native human insulin or as rapid- or long-acting human analogs, in which the amino acid sequence is intentionally altered to achieve the desired pharmacokinetic characteristics (Tables 1 and 2).

Table 1: Insulins Available in the United States (2011)

Product	Manufacturer
Rapid-acting Insulin Analogs	
Humalog (insulin lispro)*	Lilly
NovoLog (insulin aspart)*	Novo Nordisk
Apidra (insulin glulisine) †	Sanofi-Aventis
Short-acting Insulin	
Humulin R (regular)	Lilly
Novolin R (regular)	Novo Nordisk
Intermediate-acting Insulin	
Humulin N (NPH)†	Lilly
Novolin N (NPH)	Novo Nordisk
Long-acting Insulin	
Lantus (insulin glargine)*	Aventis
Levemir (insulin detemir)†	Novo Nordisk
Combinations	
Humulin 70/30 (70% NPH, 30% regular)†	Lilly
Humalog 75/25 (75% insulin lispro protamine suspension [NPL], 25% insulin lispro)†	Lilly
Humalog 50/50 (50% NPL, 50% lispro)†	Lilly
Novolin 70/30 (70% NPH, 30% regular)	Novo Nordisk
Novolog 70/30 (70% insulin aspart protamine, 30% insulin aspart)†	Novo Nordisk

*Available in prefilled disposable pen injectors and cartridges for pen injectors in addition to vials.
†Available in prefilled disposable pen injectors in addition to vials.

Table 2: Insulins by Comparative Action

	Onset (h)	Peak (h)	Effective duration (h)
Rapid acting			
Insulin lispro (analog)	<0.3–0.5	0.5–2.5	3–6.5
Insulin aspart (analog)	<0.25	0.5–1.0	3–5
Insulin glulisine (analog)	<0.25	1–1.5	3–5
Short acting			
Regular (soluble)	0.5–1	2–3	3–6
Intermediate acting			
NPH (isophane)	2–4	4–10	10–16
Long acting			
Insulin glargine (analog)	2–4	Relatively flat	20–24
Insulin detemir (analog)	0.8–2 (dose dependent)	Relatively flat	Dose dependent; 12 h for 0.2 U/kg; 20 h for 0.4 U/kg, up to 24 h.
Combinations			
70% NPH, 30% regular	0.5–1	Dual	10–16
75% NPL, 25% lispro	<0.25	Dual	10–16
50% NPL, 50% lispro	<0.25	Dual	10–16
70% aspart protamine, 30% aspart	<0.25	Dual	15–18

Currently Available Insulin

In normal physiology, there is a low rate of insulin release between meals, sufficient to inhibit the overproduction of glucose and ketone bodies by the liver that otherwise would occur. This insulin production between meals and overnight is referred to as basal insulin production. With meals, there are bursts of insulin sufficient to prevent hyperglycemia, promoting retention of nutrients as storage forms of energy, referred to as prandial insulin secretion (see Figure 9 in the Appendices, p. 60). Although regular insulin may be better suited for prandial coverage and NPH better suited for basal coverage, nevertheless regular and NPH insulin each may provide some basal and some prandial coverage, depending on the time of administration. Insulin analogs on the other hand have been designed with timing of action intended to provide coverage as either

prandial (rapid-acting analogs) or basal insulin (long-acting analogs).

Insulin Lispro, Insulin Aspart, and Insulin Glulisine

Rapid-acting insulin analogs are intended to mimic meal-stimulated insulin secretion, which is when the normal pancreas responds to food by releasing a bolus of insulin. Their fast onset improves our ability to match insulin dose to carbohydrate (CHO) intake and to ensure that insulin and glucose reach the blood at approximately the same moment. Rapid-acting insulins should be taken no more than 15 minutes before the meal starts, but may also be given immediately (within 20 minutes) after the meal for individuals (such as children and older adults) in whom caloric intake is often difficult to predict or to diabetes patients with gastroparesis who have unpredictable absorption of CHO. The short duration of action of these insulins may lead to hyperglycemia before the next meal unless adequate basal insulin is provided, and they are associated with less between meal hypoglycemia when compared to regular insulin.

Regular

Although also intended to allow matching of food and insulin at meals, the relatively slow onset of regular insulin—generally it must be taken 30–45 minutes before the meal starts—produces a longer, and less predictable, lag time (time between injection and noticeable glucose-lowering effects). Regardless, it can be used as the short-acting insulin in a multiple-injection regimen. Regular insulin can also be incorporated as follows:

- It can be given with rapid-acting insulin to provide a bridge between meals, e.g., the prebreakfast injection of rapid-acting insulin will not necessarily cover a midmorning snack.
- Because the effects of regular insulin can last up to 6 h, regular insulin contributes to the basal insulin and can keep glucose levels from rising when the time between meals is long.
- When a meal containing high fat levels delays CHO digestion, adding or substituting some regular to the premeal rapid-acting insulin will ensure insulin availability when needed.
- When there is delayed gastric emptying.

NPH

This insulin is excellent for treating the hyperglycemia due to the "dawn phenomenon." Because the peak activity is at 4–10 hours, NPH taken at bedtime will work during the early morning (4:00–8:00 a.m.), when the glucose increase can be quite significant in patients with a strong dawn phenomenon. Also, NPH taken before breakfast can keep glucose levels normalized between late morning—when the effects of insulin lispro, insulin aspart, or insulin glulisine diminish—and lunch, as well as provide some coverage for the midday meal due to its afternoon peak.

Insulin Glargine

This true basal insulin provides a flat, smooth action over approximately 24 h in most patients. The absorption from the subcutaneous depot is very predictable and controlled by its altered solubility at neutral pH. Insulin glargine cannot be mixed with other insulin preparations in the same syringe. Glargine is usually given once daily, either in the evening or in the morning. Glargine is often used in conjunction with oral agents in patients with type 2 diabetes, or as a basal/bolus regimen in conjunction with a

rapid-acting insulin analog. It is important to note that some patients benefit from injecting insulin glargine twice daily. Some patients experience a shorter duration of action (e.g., 20 hours of coverage), so splitting the dose and injecting twice daily helps afford 24 hours of basal coverage.

Insulin Detemir

Insulin detemir is another basal insulin that is injected once or twice a day. Like glargine, it is usually added to oral agents in type 2 diabetes or used in conjunction with a rapid-acting insulin that is taken before meals. Insulin detemir achieves a long duration of action by binding of the insulin with albumin.

Insulin Absorption

Perhaps the most perplexing aspect of insulin therapy is the variability in insulin absorption between patients and within a single patient from one day, or time of day, to the next. Note that the action times for the various insulin preparations shown in Table 3 are generalized.

Table 3: Insulin Absorption Rate

	Absorption continuum		
	Less variable		**More variable**
Insulin type	lispro, aspart, glulisine, glargine, detemir		Regular, NPH
Injection volume	small (<10 U)		larger
	Faster		**Slower**
Injection route	IV (regular only)	IM	SC
Injection site	abdomen	arm	thigh

The reality is that rates of absorption can vary as much as 20–40% from one day to the next in any patient because of local tissue

reactions and changes in insulin sensitivity, blood flow, depth of injection, and amount of insulin injected. The presence of edema may influence absorption of insulin. Changes in insulin sensitivity also occur over weeks to months. The patient's records of SMBG are, in most cases, reliable indicators on which to base insulin therapy adjustments.

To facilitate more predictable absorption, consider the following:

- **Injection site:** Potential subcutaneous injection sites include the abdomen (avoiding 1–2 inches around the navel), upper thighs, hips/buttocks, or back of the upper arms. However, injections into the abdomen, with its larger overall blood circulation and higher body heat, provide the quickest and most predictable absorption of rapid-acting and regular insulin. Avoidance of edematous sites is advisable. Note that injections of long-acting insulin add to the basal insulin supply, so the injection site usually has little discernable influence on rate of absorption.
- **Injection site rotation:** Patients can either choose one body area for injection and rotate within that area or rotate among body areas. Systematic rotation

prevents lipohypertrophy, a result of insulin stimulation of fat cell growth, which delays insulin absorption.

- **Injection size:** Variability in insulin absorption is increased and net absorption is decreased as the volume (number of units) of insulin increases with a single injection. For patients with significant insulin resistance who are using large doses of insulin, several smaller injections may help decrease the variability in absorption.
- **Injection depth:** Patients should practice injecting at a consistent depth.
- **Blood flow:** Practices that increase regional blood flow (e.g., exercise, local massage/friction, hot showers, or soaks/saunas) speed absorption and lessen predictability of insulin action.

Mixing Insulins

Most insulin mixtures today are NPH or NPH-type insulin with either regular or rapid-acting insulins. The insulin manufacturers also premix NPH or NPH-like insulin with their regular or rapid-acting insulin to make it more convenient for the patient. The effect of mixing NPH-type insulin and a rapid-acting insulin analog is to create a biphasic action profile.

Table 4 shows the insulin mixtures commonly used. When mixing insulins in one syringe, the rapid- or short-acting insulin should be drawn up first. Only insulins from the same manufacturer are recommended for mixing. The acidic nature of insulin glargine and the unique formulation of insulin detemir preclude them from being mixed with other insulins.

Table 4: Insulins That Can Be Mixed in the Same Syringe

NPH plus	Regular plus	Glargine/ detemir
insulin lispro	insulin lispro	*Do not mix with other insulins*
insulin aspart	insulin aspart*	
insulin glulisine	insulin glulisine*	
regular	NPH	

*Likely, but not yet examined.

A commercially prepared mixture of NPH and regular insulin (70%/30%) or of protamine suspensions of rapid-acting analogs and the respective rapid-acting analog (75%/25% NPL/lispro, 50%/50% NPL/lispro, or 70%/30% aspart protamine/aspart) are very stable. These premixed insulins are less useful when there is the need to vary the dose of only one of the insulin components. Their primary advantages are convenience and accuracy, particularly for patients with visual impairments or problems with manual dexterity for whom mixing insulin would be difficult or unreliable. For patient convenience, most premixed insulin products are available in insulin pens.

Insulin Regimens

Ideally, the insulin regimen mimics physiologic insulin secretory patterns (see Figure 9 in the Appendices, p. 60) to the greatest extent possible, containing basal and meal-stimulated (bolus) release of insulin. Insulin pump therapy or multiple daily insulin injections are the two methods that most closely mimic natural insulin secretion in response to meals or hepatic glucose release.

The first step in choosing an insulin regimen is to establish glycemic goals. For many adult patients, this means that more than one-half of SMBG results should fall within the following ranges:

- **Preprandial:** 70–130 mg/dl
- **Bedtime:** 100–140 mg/dl
- **Postprandial (1–2 h):** <180 mg/dl

Note that blood glucose measurements throughout this handbook are indicated in

terms of plasma values. Most glucose meters now display plasma values, which are about 10–15% higher than those for whole blood and for which different goals were given in older publications.

It is very important to individualize blood glucose goals for the patient's age, health status, history of significant hypoglycemia, lifestyle, and personal goals. For example, it would be reasonable to modify the preprandial goal to 100–140 mg/dl or higher for a type 1 diabetes patient with severe or asymptomatic hypoglycemia. Pregnant women with either type 1 or type 2 diabetes require meticulous glycemic control; a recent consensus statement recommended premeal, bedtime, and overnight glucose values between 60–99 mg/dl and peak postprandial glucose goals of 100–129 mg/dl if they can be achieved without excessive hypoglycemia.

Insulin for Type 1 Patients

All patients with type 1 diabetes should begin an intensive insulin regimen to cover both basal and prandial (mealtime) insulin needs. Patients should be encouraged to find injection and/or administration schedules and methods (multiple daily injection vs. subcutaneous insulin infusion) that best meet their lifestyles. This will require collaboration between the patient and the practitioner. Many patients will likely be put on one of the following sample injection regimens.

- Those willing to perform four injections per day would use a rapid- or short-acting insulin (lispro, aspart, glulisine, or regular) before each meal with a longer-acting component usually added at bedtime (glargine or detemir) or at both breakfast and bedtime (NPH).

Sample Injection Regimens

2 Injections/Day—mixed or pre-mixed insulin (NPH plus a short- or rapid-acting insulin) (Figures 1 and 2).

Theory: Postprandial glucose levels for breakfast and supper are covered by short- or rapid-acting insulin; lunch and overnight glucose levels are covered by NPH.

Advantage: Two injections per day.

Disadvantages: 1) NPH given at supper peaks during the night and often does not last overnight until breakfast, leading to nocturnal hypoglycemia and/or high prebreakfast glucose levels; 2) Inflexibility in dealing with midday glucose levels because the NPH dose is set at breakfast based on expectations of food and activity for the day; life is often unpredictable. It would be rare for a type 1 patient to achieve adequate glucose control with this regimen.

Figure 1

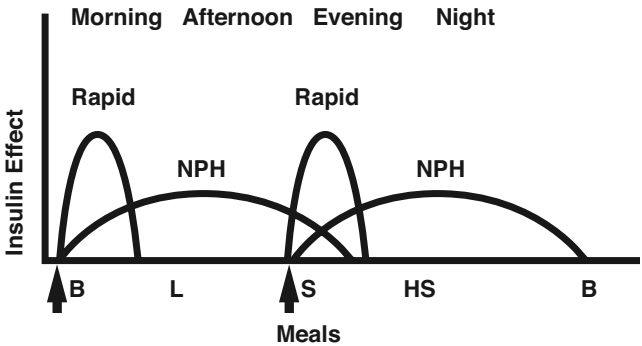
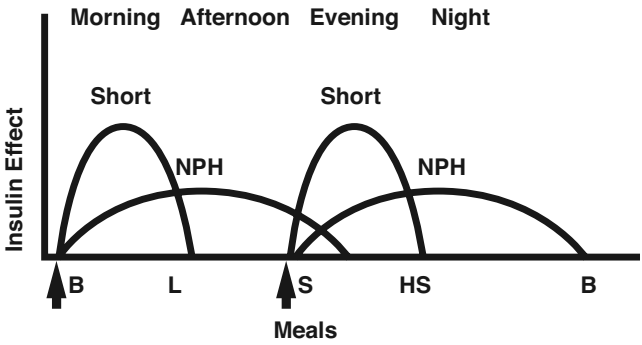


Figure 2



3 Injections/Day Using NPH and Rapid-Acting Analog before Breakfast, Rapid-Acting Insulin at Supper, and NPH at Bedtime (Figures 3 and 4).

Theory: Same as for two injections/day except that giving NPH at bedtime rather than at supper controls blood glucose better through the night.

Advantage: Better overnight glucose control.

Disadvantage: Still inflexible at midday. Again, it would be rare for a type 1 patient to achieve adequate glucose control with this regimen.

Figure 3

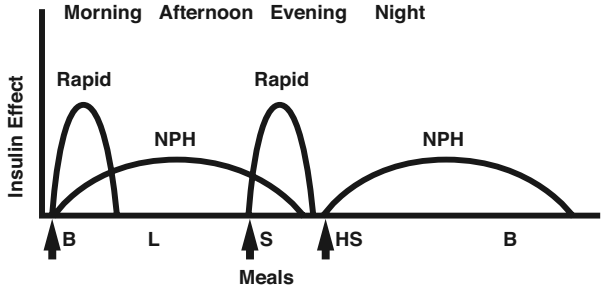
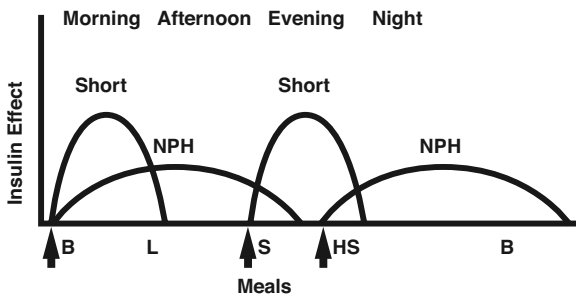


Figure 4



4 Injections/Day Using Rapid-Acting Insulin plus NPH or Basal (Figures 5 and 6).

Theory: Two doses of NPH or one dose of long-acting insulin provides basal coverage during the day and overnight. Rapid-acting insulin covers postprandial glucose increases with each meal.

Advantage: Allows meal-to-meal adjustments of insulin dose based on preprandial blood glucose levels, CHO intake, and activity and permits greater freedom of timing of the meals.

Figure 5

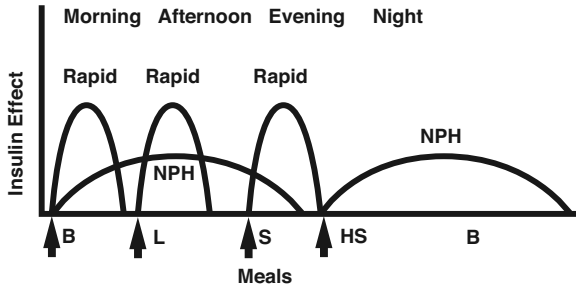
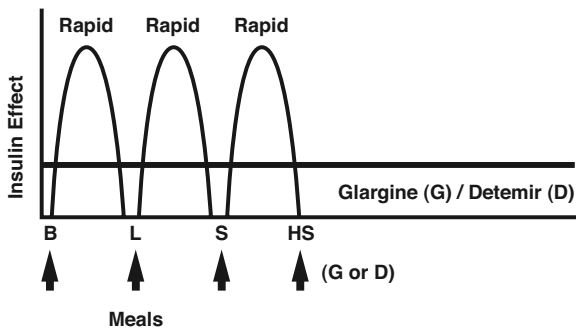


Figure 6



4 Injections/Day Using Short-Acting Insulin (Figures 7 and 8).

Theory: Short-acting insulin provides daytime/meal glucose control, and one dose of long-acting insulin provides basal coverage during the day and overnight.

Advantage: Allows meal-to-meal adjustments of insulin based on preprandial blood glucose levels, CHO intake, and activity.

Disadvantage: The long duration of regular insulin may lead to delayed, especially nocturnal, hypoglycemia.

Figure 7

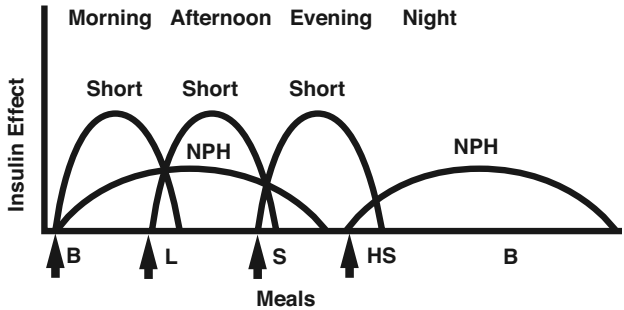
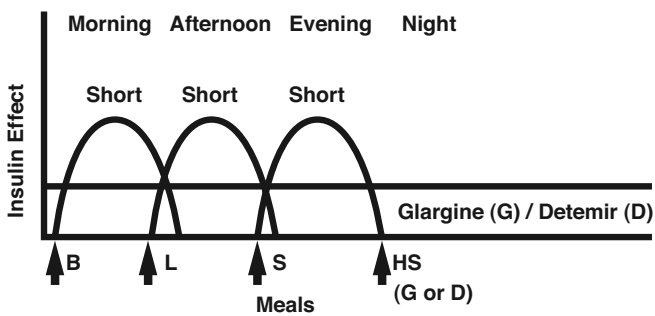


Figure 8



Determining Total Insulin Dose

Approximately one-half to two-thirds of the total daily insulin dose is generally given to cover basal needs and should be a longer-acting insulin. The other one-third to one-half of the total daily insulin dose should be a rapid- or short-acting insulin given before each meal to control postprandial glycemia, with the dose given in proportion to meals.

When initiating insulin therapy, baseline total daily insulin dose is often calculated as 0.6 × body weight in kilograms (kg). For the average 70-kg patient, baseline daily insulin dose would be 42 units/day (range 35–50 units/day), one-half to two-thirds of which is basal and the other one-third to one-half of which covers meals. Modify this calculation based on the patient's activity level and physical condition (Table 5).

The initial daily insulin doses may be higher in the first week because many patients are initially insulin resistant. These are simply useful starting points, with subsequent insulin adjustments made on the basis of the patient's SMBG results.

As stated in the Introduction, there is no consensus about how to best institute and maintain insulin therapy. The endocrinologists

Table 5: Initial Insulin Doses—Type 1 Diabetes Patients

Dose (units/kg/day)	Patient
0.5	Conditioned athlete
0.6	Motivated exerciser, woman in 1st phase (follicular) of menstrual cycle
0.7	Woman in last week (luteal phase) of menstrual cycle or in 1st trimester of pregnancy, adult mildly ill with a virus, child starting puberty
0.8	Woman in 2nd trimester of pregnancy, child in mid-puberty, adult with a severe or localized viral infection
0.9	Woman in 3rd trimester of pregnancy, adult ill with bacterial infection
1.0	Woman at term of pregnancy, adult with a severe bacterial infection or illness, child at peak pubescence
1.5–2.0	Child at peak pubescence who is ill

who shared their expertise for this handbook suggested the following methods:

- A traditional approach is to begin with a four-injection regimen (a rapid-acting analog at each meal and a basal injection of insulin glargine or insulin detemir) where the total daily dose is calculated as 0.5 or 0.6 units insulin/wt kg. Approximately one-half of the total daily dose is given as basal insulin, while the remaining one-half is divided between the three rapid-acting injections (one-sixth of the total daily dose per meal, depending on dietary habits).

This calculation serves as a starting point and should be adjusted according to patient-specific needs.

Example:
80-kg male, total daily dose 48 units (80 × 0.6)
Basal insulin dose: 24 units of insulin glargine or insulin detemir daily
Mealtime insulin: 8 units of rapid-acting insulin with each meal (24 remaining units/3 meals = 8 units/meal). The number of units given per meal can and should be adjusted based on distribution of CHO intake throughout the day with each meal.

- Another approach to determining total daily dose is to determine basal and bolus doses separately, as follows:
  The basal insulin dose can be calculated as:
  - **Insulin glargine:** 0.3 × wt kg (or one-half of total daily dose) given at bedtime or before breakfast (once every 24 h)
  - **Insulin detemir:** 0.3 × wt kg given at bedtime or before breakfast (given once or twice a day)
  - **NPH:** NPH can also be used to cover basal needs, particularly when cost of the long-acting insulin analogs is prohibitive.

- ❑ 0.2 × wt kg before breakfast plus 0.1 x wt kg at bedtime, or
- ❑ 0.1 × wt kg three times per day (if given every 8 h to make it work as a basal insulin)

Optimal basal therapy results in blood glucose levels in the fasting state between 70 and 130 mg/dl. The first morning blood sugar of the day is the reading that should be utilized to adjust the basal insulin dose to achieve the desired fasting blood glucose. The bolus insulin dose can be calculated as:

- 0.1 × wt kg (or one-sixth the total daily insulin dose) administered with breakfast, lunch, and supper

Bolus insulin is given to:

- counteract the postprandial glucose increase
- correct premeal glucose levels out of the 70–130 mg/dl target range

Most of the postprandial blood glucose increase is due to the CHO content in the meal. Patients can count grams of total CHO provided on food labels. In general, 1 unit of short-acting insulin covers 10–15 g CHO for most patients with type 1 diabetes.

However, it is important to calculate each patient's individual insulin-to-CHO ratio (see Appendices) so that patients can learn to adjust their insulin dose to CHO intake. Note that if meals include a large amount of fat, glucose availability will be delayed.

If the premeal glucose level is in the normal range, bolus insulin covers food only. Low premeal glucose levels require less bolus insulin, and high premeal levels require enough insulin to bring glucose back to normal in addition to insulin to cover food (see "Correction Insulin Doses"). Note the periods covered by each insulin dose (Table 6).

Table 6: Adjusting Insulin Doses

If glucose levels are out of target at	Adjust this insulin component
Postbreakfast/prelunch	Prebreakfast rapid/short insulin
Postlunch/presupper	Prelunch rapid/short insulin and/or morning NPH
Midafternoon	Morning NPH or long-acting insulin analog
Postsupper/bedtime	Presupper rapid/short insulin
Early morning	Evening NPH or long-acting insulin analog

Honeymoon Phase

A few weeks after a diagnosis of type 1 diabetes, some patients enter the "honeymoon" phase, which is characterized by increased endogenous insulin secretion for weeks to months. Insulin requirements during this phase may drop to 0.2–0.6 units/kg/day. However, it is important to maintain the insulin injection routine: evidence suggests that exogenous insulin administration may help to preserve β-cell function, which may improve glycemic stability and reduce the risk of complications in the long term. Ask the patient to monitor blood glucose frequently and report results to assist in the calculation of insulin dosages that do not induce hypoglycemia. Usually, blood glucose levels are less labile during this phase.

As endogenous insulin secretion slows and ceases, patient insulin requirements increase to those given in Table 5, usually within 1 year after diagnosis. Continue to use patient records of SMBG to determine insulin dosages and regimen.

Correction Insulin Doses

There are several methods for making occasional corrections to the premeal rapid- or short-acting insulin dose in response to out-of-target glucose levels. (Persistent out-of-target fasting glucose levels require adjustment of insulin given at night to cover basal needs.) The methods are based on consideration of patterns discerned in the patient's glucose monitoring records; the patient's previous experience with insulin dose, food intake, and exercise; and the patient's projections for food intake and exercise during the period to be covered by the corrected dose. It will take several similar-situation corrections for the patient to create an individualized list of "standard" corrective responses. As with glucose monitoring records and records of insulin dose, food intake, and activity, encourage patients to record insulin adjustments and resulting glucose levels.

- Corrections are usually made in increments of 1–2 units of rapid- or short-acting insulin. Some calculate correction doses as 3% of total daily insulin requirement. These represent starting points; insulin corrections must be individualized.
- A second correction method is based on the patient's body weight (Table 7). For a 60-kg patient, corrections would be made in increments of ~1 unit insulin (60 × 0.6 = 36 units total daily dose; 36 × 0.03 = 1 unit). For this individual, each unit of rapid-acting insulin covers 10 g CHO.

Table 7: Sample Mealtime Dose Calculation for a 60-kg Patient with Insulin-to-CHO Ratio of 1:10

Premeal BG (mg/dl)	CHO g in food	Insulin for food (units)	Correction insulin (units)	Total dose (units)
<70	40	4	–1	3
70–110	50	5	—	5
70–110	30	3	—	3
110–200	50	5	+1	6
>200	40	4	+2	6

NOTE: Insulin doses vary by patient needs and sensitivity to insulin; thus, have patients frequently monitor blood glucose levels.

- Another correction method uses the following formula:

$$\frac{1500}{\text{wt kt}} = X$$

$$\frac{(\text{glucose level} - \text{desired glucose level})}{X} = \text{insulin supplement}$$

Example:
80-kg patient who is 60 mg/dl above target glucose level would require a 3-unit supplement based on the following calculations:

$$\frac{1500}{80\ \text{kg}} = 18.75 \qquad \frac{(200 - 150\ \text{mg/dl})}{18.75} = \sim 3\ \text{units}$$

- Another correction method focuses on timing the premeal insulin to compensate for out-of-target premeal glucose levels (see "Timing Insulin").

Timing Insulin

To prevent excessively high postprandial glucose levels, lag time (time between injection and noticeable glucose-lowering effects) should be consistent for every insulin injection given to cover meals. Patients should be

educated regarding the appropriate lag time for their mealtime insulin depending on if they are using a rapid-acting insulin (aspart, lispro, or glulisine) versus regular insulin. The advantage of rapid-acting analogs is that patients can inject immediately prior to meals if they experience difficulty with injection timing.

Many type 1 diabetes patients now use insulin pumps that are programmed to continuously provide a basal rate of insulin, allowing the patient to bolus insulin to handle CHO intake or adjust blood glucose levels. Rapid-acting insulins are almost always the desired insulin for use in insulin pumps.

Adjustments for Exercise

When initiating an exercise routine, encourage type 1 diabetes patients to exercise at the same time every day, for the same duration, and at the same intensity, to facilitate consistent therapy adjustments that will reduce the chances of severe hypoglycemia. In addition, SMBG before and after exercise will help identify necessary changes in food or insulin intake and educate the patient about his or her individual glycemic response to exercise. Once a patient with type 1 diabetes understands how to adjust their insulin and food intake in relation to exercise, they will

be better able to anticipate the adjustments needed for varying types of physical activity.

The following guidelines apply primarily to patients with type 1 diabetes. If a type 2 diabetes patient does experience exercise-induced hypoglycemia, however, the following guidelines can be helpful.

- When the patient plans to exercise after a meal, begin by cutting the meal-related rapid- or short-acting insulin dose in half. Use SMBG results to determine whether the lowered dose resulted in hyperglycemia, glucose within the target range (70–110 mg/dl), or hypoglycemia. If needed, adjust up or down by 3% of total daily insulin requirements to prepare for a similar bout of exercise (similar in timing, duration, intensity).
- When the patient plans to exercise before eating, he or she may need to eat supplementary CHO. This is a simpler option than reducing the basal insulin dose preprandially.

Insulin for Type 2 Patients

Patients with type 2 diabetes may lie anywhere on the continuum of predominant insulin resistance with relative insulin deficiency to a predominant secretory defect and insulin deficiency with insulin resistance. Diet and exercise constitute the first course of therapy for type 2 diabetes and remain central to therapy, even with the addition of pharmacologic treatments. Nutrition therapy should include calorie restriction for weight loss.

Use of oral agents, combinations of oral agents, and injectable incretin mimetics, such as exenatide and liraglutide, may postpone the need for insulin treatment for many years. This period may produce acceptable A1C levels, but the disease usually progresses. Insulin, if given in sufficient doses often enough, is capable of restoring glycemia to near normal in most patients with type 2 diabetes.

Adding Insulin to Oral Agent Therapy

Adding a simple insulin regimen to monotherapy or combination therapy with oral agents will improve glycemic levels in patients unable to reach glycemic goals with oral agents alone, and is convenient for the patient, thus improving compliance and acceptance.

- **Fasting levels above target:** The oral agent(s) can be used to control glucose levels during the day, and the insulin can be used to better control fasting (prebreakfast) levels.

  A single bedtime injection of insulin glargine, detemir, or NPH can be added to the current dose of the oral agent. To prevent hypoglycemia, a conservative starting dose is 0.2 units/kg, titrating up in increments of 2 units every 3 days based on fasting blood glucose levels. Patients may be instructed to titrate their own dose upward based on fasting glucose values until target fasting goals are achieved. Results must be carefully monitored with SMBG done at least twice daily: before breakfast and before bedtime. More frequent SMBG may

be recommended to further fine-tune therapy.

- **Fasting levels at target; values during day above target:** If, once the fasting level is normal, glucose levels during the day are out of the target range, consider:
  - ❑ if using bedtime NPH, adding a second injection of NPH before breakfast at a dose of 0.2 × body weight in kilograms (kg), while continuing the bedtime dose;
  - ❑ adding regular or a rapid-acting insulin before meals. As a starting point, patients can usually begin with approximately 4 units and adjust by 2 units every 3 days until blood glucose is in the desired range; or
  - ❑ following an insulin protocol as for type 1 diabetes (using an insulin pump also produces good blood glucose outcomes).

Insulin-Only Therapy

Typically, patients with type 2 diabetes begin an insulin regimen with one bedtime injection of insulin glargine, detemir, or NPH to control fasting hyperglycemia while beginning or continuing therapy with oral

medications to control meal-related glycemic increases and/or reduce insulin resistance (Table 8). However, when the daytime glucose levels are frequently >250 mg/dl (uncontrolled by maximal doses of oral medications and/or injectable incretin mimetics), insulin deficiency may be profound, and many patients benefit from treatment similar to that for type 1 diabetes, using a rapid-acting insulin before meals in conjunction with basal insulin.

Table 8: Sample Insulin Regimens for Type 2 Diabetes Patients

Before breakfast	Before lunch	Before evening meal	At bedtime
More Common			
—	—	—	Glargine, detemir, or NPH
NPH	—	—	NPH
NPH+rapid/ short	—	NPH+rapid/ short	—
Rapid/short	—	Rapid/short	Glargine/detemir
Less Common			
NPH+rapid/ short	—	Rapid/short	NPH
Rapid/short	Rapid/short	Rapid/short	Glargine/ detemir
NPH+rapid/ short	Rapid/short	Rapid/short	NPH

Troubleshooting

Patient Resistance to Starting Insulin

Many type 2 diabetes patients would be better controlled on insulin but resist beginning injections despite rising glycemic levels. Education is the key to gaining patient acceptance when insulin therapy is indicated.

- Reinforce the short-term benefits of improved glycemia, including decreased nocturia and improved energy level.
- Reinforce or reintroduce information about the importance of controlling glucose levels and how it relates to the health of kidneys, eyes, and nerves and to overall well-being.
- Teach patients with type 2 diabetes that the disease course includes progressive β-cell failure and that insulin therapy is a normal part of the treatment of the condition, not a sign of failure on the part of the patient.

- Avoid using the prospect of insulin therapy as a threat to increase adherence to lifestyle change or other therapies.
- Suggest that the patient try a bedtime injection routine of insulin glargine, detemir, or NPH for 1–2 months, then plan to discuss whether the patient feels better and has more energy.
- Point out that newer needles make insulin therapy essentially painless and much more convenient than before, and offer alternatives to syringes, such as pen injectors.
- Provide or refer the patient for diabetes self-management education on handling and filling syringes and making injections as comfortable as possible, and for ongoing self-management support.

Weight Gain

Minimizing weight gain, or promoting weight loss, in patients with type 2 diabetes is vital. Weight loss of even a modest amount reduces insulin resistance and improves glycemic control. Instituting insulin, sulfonylurea, or thiazolidinedione therapy is associated with weight gain in part because, as glycemic control improves, glucose is captured by the

body instead of being lost in the urine and promotes growth of adipose tissue.

A single injection of insulin glargine, detemir, or NPH before bedtime can be associated with modest weight gain. Metformin plus bedtime insulin glargine, detemir, or NPH seems to blunt this effect. Patients beginning insulin therapy should be advised to decrease calorie intake and increase exercise to minimize or avoid weight gain.

Fasting (Morning) Hyperglycemia

Fasting (morning) hyperglycemia is common when the evening basal dose of insulin is inadequate or when NPH is given with the evening meal instead of at bedtime. The early morning rise in glycemic levels due to the dawn phenomenon combined with waning NPH insulin create high prebreakfast glucose levels. In NPH users the solution is to delay injection of the NPH insulin until bedtime or to substitute longer-acting insulin glargine or detemir for NPH. If NPH is being given at bedtime or insulin glargine or detemir is being used, the dose may need to be increased until target levels are achieved.

A strong dawn phenomenon response that cannot be accommodated with these maneuvers may be resolved with an insulin pump.

The pump can be programmed to provide a lower basal dose between midnight and 4 a.m. and an increased basal amount between 4 a.m. and 8 a.m.

Hypoglycemia

Hypoglycemia is defined as blood glucose values <70 mg/dl in most patients. Patient symptoms vary; patients with hypoglycemia unawareness—primarily those with type 1 diabetes who have had frequent bouts of hypoglycemia—may have no symptoms and are at particular risk for severe hypoglycemia (see "Hypoglycemia Unawareness"). Each individual must learn to recognize when to perform SMBG to confirm suspected lows.

Patients with type 1 diabetes can learn to avoid exercise-related hypoglycemia with careful planning that includes adjusting either the premeal rapid- or short-acting insulin dose or CHO intake (see "Adjustments for Exercise"). Patients with type 2 diabetes generally experience less exercise-induced hypoglycemia; however those on intensive insulin regimens may experience more exercise-induced hypoglycemia and should be aware of the signs and symptoms of hypoglycemia and its appropriate treatment.

Mild hypoglycemia can be treated by the "rule of 15": treat with 15 g fat-free CHO, wait 15 minutes, and then repeat SMBG. Levels still below target range warrant repeating the treatment. Once normal blood glucose is achieved, a snack may be necessary when a meal is not imminent to avoid a repeated low blood sugar.

When the patient has severe hypoglycemia and glucose cannot be given orally, subcutaneous or intramuscular glucagon is indicated (Table 9). Patients should be encouraged to always carry glucose/dextrose tablets with them to rapidly treat low blood glucose levels.

Table 9: Glucagon Doses

Product	Body weight (kg)	Dose (mg)
Glucagon	<20	0.5
	≥20	1.0
GlucaGen	<25	0.5
	≥25	1.0

Hypoglycemia Unawareness

Some patients lose their ability to recognize normal warning symptoms of hypoglycemia, or the symptoms are absent or blunted. These patients are at high risk to progress to severe hypoglycemia. Hypoglycemia unawareness develops more commonly in type 1 diabetes

patients who have frequent hypoglycemic episodes and have had diabetes for a long time. In fact, the best predictor of whether or not someone will experience this is a high incidence of antecedent hypoglycemia. Preventing hypoglycemia can reverse hypoglycemia unawareness. Hypoglycemia awareness training can also improve patient recognition of early manifestations of hypoglycemia and prevent episodes of severe hypoglycemia.

Patient SMBG Records

Although most blood glucose meters have memory, it is extremely valuable for patients to keep written records of every test result. Patterns become discernable when compiled by the patient, and it is the patient who benefits from recognizing the cause–effect relationships and making adjustments accordingly. It is also helpful in pattern recognition for the patient to note:

- concurrent doses of insulin or other diabetes medications
- CHO intake
- exercise
- hypoglycemia
- corrections in insulin dose for out-of-target premeal glucose levels or for exercise

Reviewing several weeks of such records with the patient will allow you to spot trends

requiring insulin regimen adjustment. Ask patients to note any results outside of the target range in their log and follow the previously developed action plan (see "Correction Insulin Doses"). These records will allow the patient and the practitioner to make educated adjustments to therapy given any trends identified through the patients' blood glucose and activity log.

Ideally, newly diagnosed type 1 patients, or patients new to insulin, should perform SMBG at least four times per day: before each meal and at bedtime. In addition, checking between meals and at 3:00 a.m. may be necessary, particularly initially or to prevent anticipated hypoglycemia. Continuous glucose monitoring systems have been developed that can provide patients with a glucose value in real time as well as warn the patient or his or her caregiver when glucose levels are too high or too low. Such devices can be very helpful for patients with diabetes, but their considerable expense often necessitates preauthorization processes with health insurers.

Experienced, motivated patients should be encouraged to use premeal values to calculate meal-related short-acting doses, and postprandial values to calculate the insulin-to-CHO ratio (see Appendices).

Patient Education

Perhaps the most important aspect of diabetes care is the patient–health care provider relationship. The essential element of this partnership is patient education. Encourage your patients to learn all they can about how to successfully control their glucose levels, including appropriate insulin dose adjustments in response to SMBG.

Stress to your patients that testing, record keeping, healthy eating, and exercise are for their benefit, not yours. Healthy living with diabetes is directly due to their success at diabetes self-management.

A wide variety of patient education materials are available from the American Diabetes Association. Your patients can reach the American Diabetes Association Call Center at 1-800-DIABETES and visit the ADA website at www.diabetes.org.

The American Diabetes Association has a wide variety of medical management publications for health care professionals, such as these books:

Medical Management of Type 1 Diabetes
Medical Management of Type 2 Diabetes
Medical Management of Pregnancy Complicated by Diabetes
Therapy for Diabetes Mellitus and Related Disorders
Intensive Diabetes Management
Clinical Care of the Diabetic Foot
Complementary and Alternative Medicine Supplement Use in People with Diabetes: A Clinician's Guide

For more information on these and other professional titles published by the ADA:

- Visit the ADA online bookstore at *http://shopdiabetes.org*
- Call 1-800-232-3472
- Visit any nationwide bookseller

Appendices

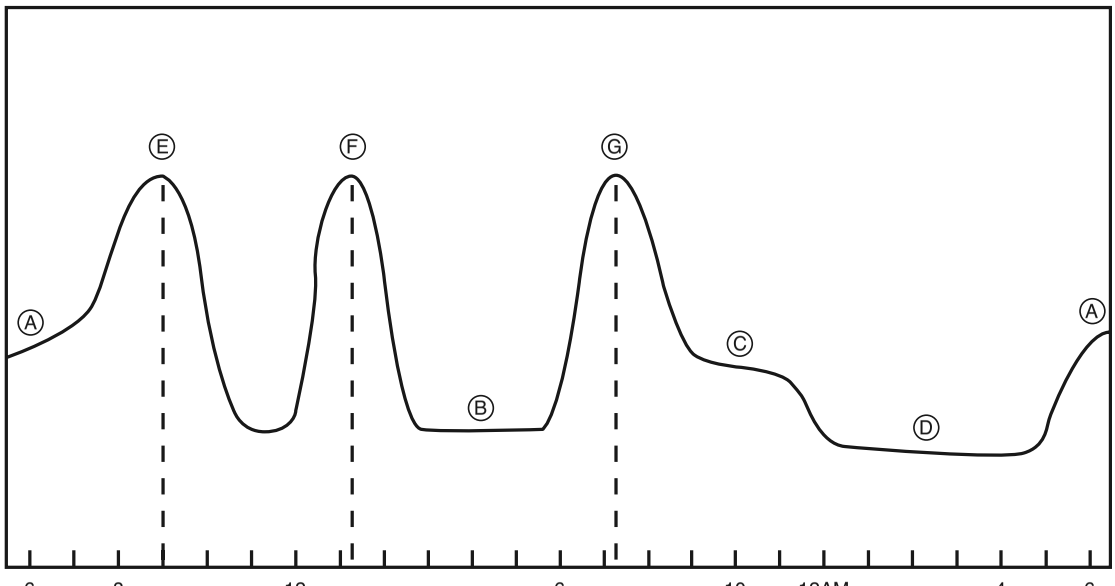
Endogenous Insulin Action (Figure 9)

Insulin is produced in the islets of Langerhans by β-cells and secreted in response to rising blood glucose levels. β-cells sense glycemic levels and if functioning normally maintain euglycemia by: 1) basal release of insulin; and 2) postprandial bolus release of insulin. (See next page for figure.)

Insulin Storage

Unopened vials, cartridges, and pens of insulin should be refrigerated at 36–46°F and used until the expiration date. Vial stoppers will maintain a sufficient seal for about 100 punctures, and once opened, insulin vials can be stored at room temperature for about a month. Injecting cold insulin can be uncomfortable. Follow the manufacturer's recommendations for storing open insulin pens or cartridges (Table 10).

Figure 9: 24-h Physiologic Insulin Secretion in Response to Glucose Levels



A: The "dawn phenomenon" starts at 4:00 a.m. and reaches its peak by 7:00–8:00 a.m. This peak is sustained until 10:00 a.m., when levels fall. The dawn phenomenon may be a result of growth hormone and cortisol, insulin agonists, which begin to rise at 4:00 a.m., peak at 8:00 a.m., and fall at 10:00 a.m. Thus, in the early morning, insulin levels must rise to keep blood glucose levels normal.

B: During the day, the basal insulin level is a result of stress, illness, activity, and body weight. Typically, the hourly insulin secretion rate is

$$\frac{0.3 \times \text{body weight in kilograms}}{24 \text{ h}}$$

C: Because people are generally less active during the evening, insulin requirements tend to be slightly higher from 6:00 p.m. to 12:00 a.m. However, the increased insulin requirement is an individualized response, and therefore therapy must be tailored to each patient.
D: The hormones are at their nadir from 12:00 a.m. to 4:00 a.m., so insulin requirements are minimal.
E–G: The meal-related insulin requirement is based on CHO content and timing of the meal. Because breakfast occurs during the peak of the growth hormone and cortisol surges, more insulin may be required for each 10 g CHO consumed:

- Breakfast: 1.5 units insulin/10 g CHO
- Lunch and supper: 1.0 units insulin/10 g CHO

Table 10: Storage of Opened Insulin Pens and Cartridges

Products	Days at Room Temperature
Lilly	
Humulin R, Humulin N, Humulin 70/30, Humalog, and Humalog 75/25 and 50/50 vials; Humalog pen; Humalog cartridges	28
Humulin N pen	14
Humalog 75/25, Humalog 50/50, and Humulin 70/30 pens	10
Novo Nordisk	
Novolog 10-ml vial, pen, and 3-ml cartridges	28
Novolin R, N, and 70/30 10-ml vials	28
Novolog 70/30 vial	28
Novolog 70/30 pen and 3-ml cartridges	14
Levemir 10-ml vials, 3-ml FlexPen	42
Aventis	
Lantus 10-ml vial, pen	28
Apidra 10-ml vial, cartridge	28

Freezing, exposure to direct sunlight, or high temperatures (>86°F) will decrease insulin potency. Instruct patients to examine insulin appearance before drawing up the injection. NPH insulin should appear uniformly cloudy without clumping or sediment after gentle resuspension; rapid- and short-acting insulins, insulin glargine, and insulin detemir should appear clear.

Insulin Potency

Insulin potency is measured in units. All preparations sold in the U.S. are available in unit-100 strength, indicating 100 units/ml. Lilly manufactures a regular human insulin that is available by prescription only in a U-500 strength (500 units/ml), which is reserved for special circumstances, such as severe insulin resistance. Insulin-treated patients who are traveling to other countries should be aware that insulin obtained there may be a different strength than U-100.

Additives

All insulin preparations contain spoilage retardants. In addition, NPH (neutral protamine Hagedorn) contains an absorption-inhibiting substance that prolongs the action and contributes to the uniformly cloudy appearance. Regular insulin, insulin lispro, insulin aspart, insulin glulisine, insulin detemir, and insulin glargine preparations are clear.

Because of component precipitation, NPH and insulin combinations should be rolled gently between the hands to mix the components before drawing up the dose. Shaking incorporates air, creating the problem of air bubbles in the syringe.

Insulin Delivery

Options, in order of increasing cost of use, include syringes, pens with disposable cartridges, prefilled disposable pens, and the insulin pump. Consider the patient's ability to prepare and inject each insulin dose when recommending a delivery method. The use of an insulin pump requires considerable patient education and office staff support until mastered. Patients using a pump must be motivated and committed to meticulous self-management and monitoring.

Insulin Pumps

Motivated patients who are performing multiple injections and SMBG per day and who desire flexibility to compensate for unscheduled activities may be candidates for an insulin pump. Also, patients with a strong dawn phenomenon or with severe hypoglycemia may have better control of these problems with pumps. Any patient starting insulin pump therapy requires education and support above and beyond the usual until he or she becomes skilled at pump use and troubleshooting. Consider referring patients for education sessions with a health care team experienced in pump therapy.

Since 2006 the FDA has approved several continuous glucose monitors that send real-time interstitial fluid glucose values to the insulin pump for viewing. Because interstitial fluid glucose correlates highly with blood glucose, this allows patients to evaluate their glucose values in real time. Such devices may be a welcome addition to pump therapy.

Rapid-acting insulins—lispro, aspart, and glulisine—are well suited for use in pumps. In general, the basal infusion rate for a pump is calculated as 0.3 units/kg body weight divided over 24 h. Pumps are generally programmed by dividing the day into four parts. Table 11 illustrates a basic basal pump program, although each patient's program will need to be refined to fit individual requirements.

Table 11: Basal Insulin Pump Program

Period	Requirement	Rationale
12:00–4:00 a.m.	50% less basal	Anti-insulin hormones (growth hormone and cortisol) at lowest effectiveness
4:00–10:00 a.m.	50% more basal	Largest effects of anti-insulin hormones
10:00 a.m.–6:00 p.m.	Basal	Basal dose is affected by stress, exercise, illness, etc., and should be adjusted as needs become evident
6:00 p.m.–12:00 a.m.	Basal	

To refine basal settings, have the patient perform SMBG at the end of each of the periods outlined in Table 11 to determine whether adjustments are needed. For instance, at the 4:00 a.m. test, blood glucose should be 70–130 mg/dl. If blood glucose is out of this range, increase or decrease the basal insulin for the preceding 3–4 h in increments of 0.10 units/h.

Bolus doses are given to cover CHO content of food in meals. A reasonable starting point is to assume that 1 unit of rapid- or short-acting insulin covers 10 g CHO. However, fine-tuning requires calculation of the individual's insulin-to-CHO ratio (see "Determining Insulin-to-CHO Ratio").

Determining Insulin-to-CHO Ratio

For many patients, a 1:10 or 1:15 insulin-to-CHO ratio holds true. However, other patients have a different ratio or may have a 1:10 ratio except when eating certain foods. Insulin-resistant patients may require much more insulin per carbohydrate serving. Ratios at breakfast may be lower than at other meals if the relative percentage of calories from CHO is higher, which is common.

If glucose levels 1–2 hours after eating consistently exceed 160 mg/dl, when pre-meal glucose was in target, the premeal insulin-to-CHO ratio requires recalculation. The following two examples show insulin-to-CHO ratio calculations. Encourage your patients to perform this calculation after different meals and different foods to understand their typical insulin-to-CHO ratio.

Example 1:

A patient with premeal glucose levels in the target range is experiencing consistently elevated postprandial blood glucose levels. The patient consumed 50 g CHO at lunch and took 5 units short-acting insulin to cover the meal. One-hour postprandial glucose was 200 mg/dl (40 mg/dl too high), indicating that: 1) the total prelunch insulin dose was 2 units too small (if each unit reduces the patient's glucose level by 20 mg/dl); and 2) the patient needs a larger (more insulin per gram of CHO) insulin-to-CHO ratio. To recalculate the ratio:

Insulin taken for food	5 units
Additional insulin needed	2 units
Total dose should have been	7 units

If 7 units would have been correct for 50 g CHO, then

$$\frac{50\text{g CHO}}{7\text{ units}} = 7.14\text{g CHO/unit} = \text{a 1:7 insulin:CHO}$$

This patient would better match insulin to CHO using 1 unit of insulin for every 7 g CHO in meals.

Example 2:
Same meal composition, different patient, within target premeal glucose level but a 2-h postprandial glucose level of 240 mg/dl. Therefore, 4 extra units should have been added (if each unit reduces the patient's glucose level by 20 mg/dl) to the 5 units for food. This ratio is calculated as:

$$\frac{50\text{g CHO}}{9\text{ units}} = 5.56\text{g CHO/unit} = \text{a 1:6 insulin:CHO}$$

This patient would better match insulin to CHO using 1 unit of insulin for every 6 g CHO in meals.