## 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**

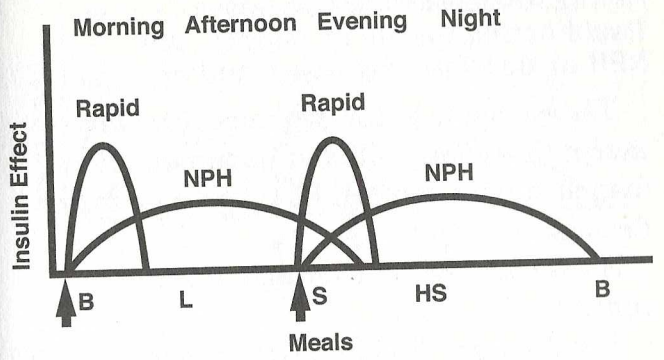
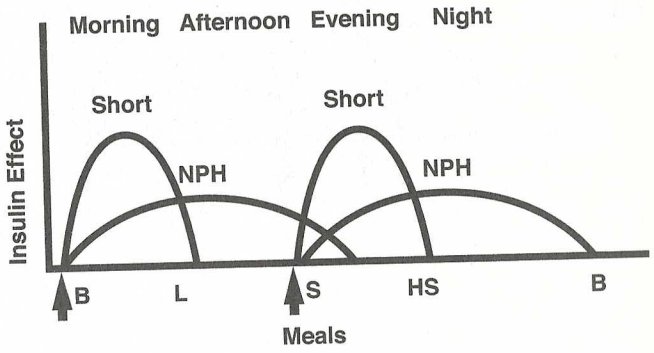



**Figure 2**



### 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**

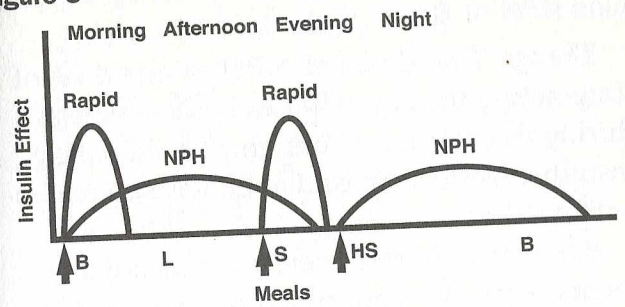
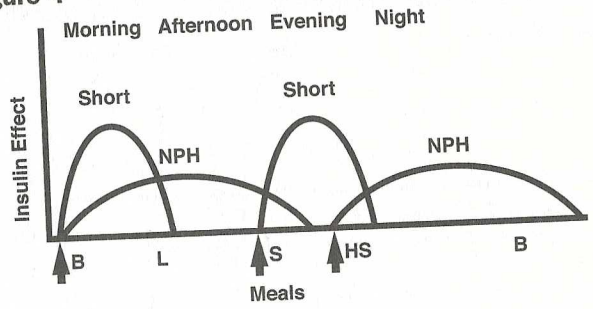



**Figure 4**



### 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**

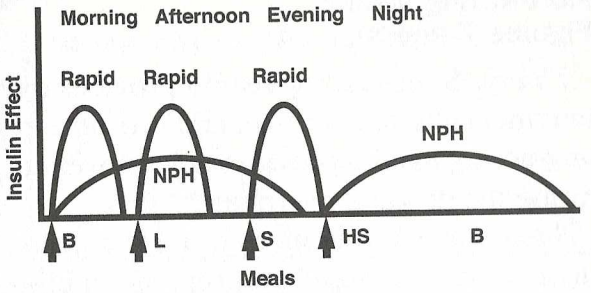
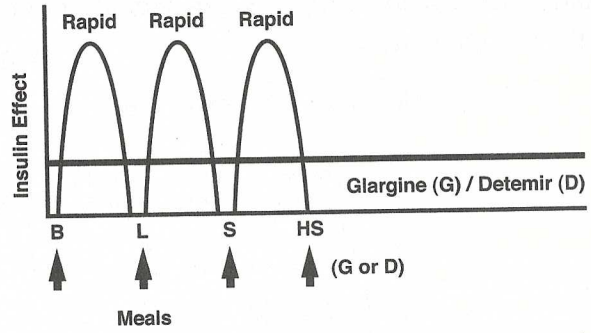



**Figure 6**



### 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**

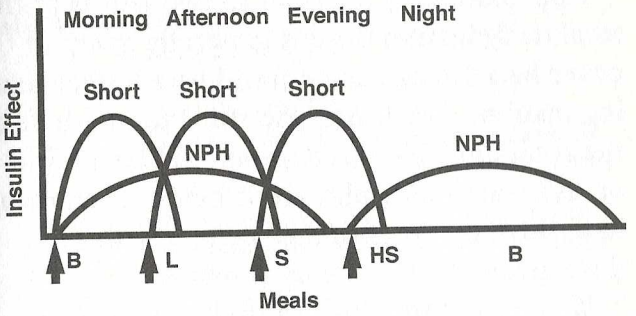
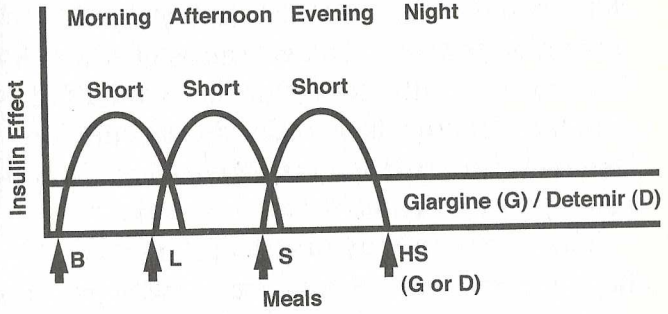



**Figure 8**



## 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:

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

- 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.