Insulin Replacement Therapy

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Insulin Replacement Therapy is an excellent review of
strategies to effectively dose and adjust insulin for
patients with type 1 and type 2 diabetes. It is authored by
our faculty member, Evelyne Fleury Milfort.

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Insulin Replacement Therapy
Minimizing Complications and Side Effects

by Evelyne Fleury-Milfort, NP

Objectives: The purpose of this article is to educate nurse practitioners about insulin replacement therapy. After reading this article, the nurse practitioner should be able to:

* define insulin replacement therapy and discuss appropriate candidates for this form of insulin management

* describe the major components of insulin replacement therapy

* identify criteria for choosing insulin regimen modalities

* explain the initiation and titration process for multiple daily injections and insulin pump therapy.

Insulin therapy is the cornerstone of treatment for all patients with type 1 diabetes and for patients with type 2 diabetes who reach severe beta cell failure. Multiple studies have documented the importance of optimal glucose control to prevent the devastating complications of the disease. The best strategy to achieve optimal glucose control is to imitate normal insulin delivery. This continuing education article discusses strategies for the initiation and titration of insulin replacement therapy.

Current State of Diabetes

Diabetes has reached an epidemic level in the United States. In 2007, diabetes cost $174 billion in direct medical expenditures and lost productivity.[1]Numerous studies have demonstrated the importance of blood glucose control for the prevention of diabetes complications.[2-4]In addition, increasing evidence shows that glucose variability with frequent excursions may contribute to diabetes complications.[5]

Based on the mounting evidence for glucose control, the American Diabetes Association (ADA) and the American Association of Clinical Endocrinologists (AACE) published target glycemic goals (Table 1), clinical standards and protocols to guide health care professionals in optimizing blood glucose control.[6,7]These documents emphasize the need to help patients reach glycemic targets based on normal insulin delivery. To achieve these targets, providers must pay close attention to achieving control of fasting as well as postmeal glucose levels. They also must aim to decrease blood glucose variability.

Insulin Replacement Therapy

Insulin replacement therapy, also referred to as intensive insulin therapy or basal-bolus therapy, is a comprehensive approach to helping patients achieve optimal blood glucose control by mimicking the

physiologic delivery of insulin. This approach uses current understanding of factors affecting glucose homeostasis to empower patients to use flexible insulin dosing to match their lifestyles and preferences (Table 2).

Rationale

People without diabetes secrete insulin in two basic patterns, background and prandial. The background pattern is a continuous secretion of small amounts of insulin at relatively constant levels, which restricts hepatic glucose production and lipolysis in the unfed state. This secretion is closely linked to changes in glycemia, so that the level falls during fasting states and increased physical activity and rises when blood glucose increases under the influence of counterregulatory hormone secretion. Prandial insulin is secreted rapidly in levels proportional to the glucose rise that results from food ingestion. This higher insulin level suppresses lipolysis and glucose production, and it stimulates the uptake of ingested glucose by the tissues.

The goal of contemporary diabetes management is to achieve and preserve a glycemic level as close to normal as possible. Normoglycemia can reduce acute complications (hypoglycemia, hyperglycemia, diabetic ketoacidosis), reduce microvascular and macrovascular complications, enhance quality of life and reduce the fiscal burden of the disease. For patients who require insulin, this goal can be accomplished with insulin regimens in which basal insulin formulation is used to mimic normal physiologic insulin secretion. Short- or rapid-acting insulin formulation can help simulate the prandial insulin response to nutrient intake.

Type 1 Diabetes

Type 1 diabetes is characterized by an absolute insulin deficiency. For these patients, a basal-bolus regimen with a long-acting analog and a short- or rapid-acting insulin analog is the most physiologic insulin regimen and the best option for optimal glycemic control.[8,9]

Type 2 Diabetes

Type 2 diabetes is a progressive disease characterized by two metabolic problems: insulin resistance and progressive beta cell failure. Insulin supplementation is generally implemented, along with oral antidiabetic agents, as insulin secretion declines. Patients with type 2 diabetes become severely insulin deficient when the secretory capacity of the pancreatic beta cells can no longer compensate for the increased insulin secretion required by the resistant state. Insulin therapy for patients with type 2 diabetes should be tailored to mimic normal basal and bolus insulin secretion, just as for patients with type 1 diabetes.

Candidates for Replacement

Insulin replacement therapy is recommended for most patients with type 1 diabetes and for patients with type 2 diabetes who meet the criteria in Table 3.[10]

For patients with type 2 diabetes, insulin replacement therapy is the best choice when lifestyle intervention, oral hypoglycemic agents and supplementation with a simpler insulin regimen (e.g., basal insulin, premixed insulin or split-mixed regimen) are no longer sufficient to maintain glycemic goals.

Components of Replacement Therapy

The components of insulin replacement therapy are meal planning, frequent blood glucose monitoring, self-management training and patient support.

Because the rise in blood glucose after a meal is primarily due to ingested carbohydrate, the ideal approach to controlling postmeal excursions is to match the insulin dose peak to the carbohydrate intake. This can be achieved with consistent carbohydrate intake or carbohydrate counting.

Consistent carbohydrate intake is a modality in which the patient has a "carbohydrate budget" to use for each meal. This approach to planning is useful for patients who are being introduced to insulin replacement because it may better stabilize blood sugar and assess response to prandial insulin. Use of premeasured foods such as frozen dinners can be useful for that purpose.

The other approach to meal planning is carbohydrate counting. For each patient, a specific dose of insulin is required when carbohydrates are ingested. This dose of necessary insulin, referred to as carbohydrate-to-insulin ratio, is later adjusted based on postprandial glucose levels.

Self-monitoring of blood glucose (SMBG) is a critical component of insulin replacement therapy. The results of fasting and postprandial testing are useful to help evaluate response to therapy and to make appropriate treatment adjustments. This information also helps identify blood sugar patterns and glucose variability.

For patients, blood glucose testing is an important tool for obtaining timely feedback about glycemic response to food intake, activity and medications, and to make insulin adjustment for hyperglycemia or physical activity. SMBG is critical to the detection of hypoglycemia and to the management of unusual situations, such as sick days or steroid therapy.

Patients on insulin replacement therapy must check their blood glucose levels four times a day — before each meal and at bedtime. They should also test before physical activity or driving, and whenever they suspect hypoglycemia. In addition, instruct patients to periodically test their blood sugar 2 hours after meals to evaluate and correct postmeal glucose excursion. To assess for nocturnal hypoglycemia, patients occasionally should monitor their blood sugar between 2 a.m. and 3 a.m., especially in the presence of fasting hyperglycemia or other potential signs of nocturnal hypoglycemia (e.g., nightmare, morning headache, night sweats). Blood glucose should be tested more often after dosage change, with change of schedule, and during illness.

Advise patients to keep a record of insulin doses, physical activity and the amount of food (especially carbohydrate) ingested, especially 1 to 2 weeks before appointments. An electronic logbook of glucose readings is useful to help verify and analyze the data from the glucose meter.

Education is also critical to the success of insulin replacement therapy, and it must be integrated into ongoing patient care. Table 4 outlines topics to be covered.

Ongoing patient assessment is necessary, and it should include weekly visits at the start of therapy. Since insulin replacement therapy is a multifaceted and complex regimen, psychosocial support is needed.

Insulin Replacement Regimens

The selection of an insulin formulation is based on its pharmacokinetic properties. Basal coverage uses long- or intermediate-acting insulins. Short- or rapid-acting insulin preparations replace the normal prandial secretion. Corrective or supplemental doses of short- or rapid-acting insulin can

control premeal or between-meal glucose excursions or correct hyperglycemia. For patients with type 2 diabetes, insulin replacement therapy can also be introduced using premixed insulins with biphasic action. Table 5 outlines the time-action curves of available insulins.

Basal Insulins

Neutral protamine hagedorn (NPH) has a 20-hour duration of action and a distinct peak and trough effect. When used as basal insulin, it must be given two or more times each day to minimize excursion. When dosed at bedtime, NPH will cover the natural rise of blood glucose in early morning (dawn phenomenon). But if it is dosed too early in the evening, NPH may cause nocturnal hypoglycemia from the peak action earlier in the night. NPH insulin can be useful for patients on steroid therapy and patients who do not want to inject insulin at lunchtime.

Long-Acting Analogs

Two basal analog insulins, glargine (Lantus) and detemir (Levemir), exhibit a more physiologic action profile than NPH insulin. Compared with NPH, each basal analog insulin has a longer duration of action, a relatively flat action profile and less variability in absorption. These features make them more predictable in terms of glucose-lowering action, and they likely contribute to a lower incidence of hypoglycemia in patients who use them. These insulins are usually dosed once a day (morning or evening), which facilitates patient compliance. For once-daily dosing, instruct the patient to inject at the same time each day.

Although the two basal analog insulins have similar properties, there are some differences between them. Detemir is bound to albumin, which confers a more stable plasma level at steady state. A recent 2-week, double-blind, randomized study of patients with type 1 diabetes showed that although detemir maintains a hypoglycemic action similar to glargine for the first 12 hours after injection, its hypoglycemic effect drops in the ensuing 12 hours, whereas glargine's action continues for 24 hours.[9]Therefore, detemir should be administered twice a day for better around-the-clock coverage. Avoid a large subcutaneous depot by splitting the glargine dose when more than 50 units are used.

Another difference between these two basal insulins — which may be of particular importance for overweight patients — is that detemir is associated with less weight gain than NPH in patients with type 2 diabetes.[10]Bolus Insulins

Regular insulin has a later onset than the rapid-acting analogs. Its use is associated with several limitations, including the need to administer the dose 30 to 45 minutes prior to a meal. In addition, hypoglycemia may occur several hours after a meal.

But regular insulin works well in patients with gastroparesis who have unpredictable or slow digestion, patients who consistently eat carbohydrate snacks between meals, and older patients who eat more slowly. In addition, because fatty foods delay carbohydrate digestion, the addition of a few units of regular insulin to an injection of rapid-acting insulin can cover the delayed rise in postprandial glucose.

Rapid-Acting Analogs

Compared with regular insulin, the action profile of the rapid-acting analogs (lispro [Humalog], aspart [Novolog], glulisine [Apidra]) more closely mimics the endogenous insulin response to a meal. These insulins are also absorbed more rapidly and have an earlier, higher peak concentration and a

shorter duration of action. These features allow more flexibility in meal timing, allowing patients to better match insulin dose to actual carbohydrate intake.

Another advantage conferred by rapid-acting insulins is that patients can inject at the start of a meal or 10 to 20 minutes afterward, depending on the insulin preparation and their blood sugar level. These characteristics potentially translate to better patient adherence to appropriate mealtime timing of insulin, as well as fewer postprandial glycemic excursions and a lower risk of late postprandial hypoglycemia. But the short duration of action requires additional injection for carbohydrate snacks eaten more than 2 hours after a meal, and, if the basal insulin is not well adjusted, it may be associated with hyperglycemia before the next meal.

Premixed Insulins

Several premixed insulin preparations are also available. These insulin formulations provide a biphasic pattern of insulin action with a fixed ratio. Postmeal dosing is possible for some premixed analog preparations. Although their activity does not mimic physiologic insulin secretion, the premixed insulins can be useful to provide a simpler near-replacement insulin regimen for some patients with type 2 diabetes.

Replacement Modalities

In patients with type 2 diabetes, insulin therapy is often implemented in a stepwise approach based on glycemic profile.11A common starting point is basal insulin or once-daily premixed insulin, along with secretagogues and sensitizers. Basal dose plus short- or rapid-acting insulin is then administered at the largest meal to correct postprandial glucose excursions. As patients become more insulin deficient, they are transitioned to basal insulin with rapid-acting insulin dosed at two meals (split-mixed regimen or premixed insulin), at which time the secretagogue is stopped but insulin sensitizers continue. Later, when the secretory capacity of the beta cells worsens, patients are moved to full insulin replacement with a basal-bolus regimen that delivers long-acting insulin and rapid-acting or short-acting insulin at each meal.

One regimen I have used successfully in endocrinology practice is premixed insulin dosed three times daily. This approach can be a good choice for patients with type 2 diabetes who did not achieve target on a twice-a-day premixed regimen, who have stable glycemic activity and who have consistent carbohydrate intake. The 1-2-3 Trial proved that it is possible to use biphasic insulin aspart 70/30 (Novolog mixed 70/30) in a stepwise approach up to three times daily to achieve glucose targets.12This approach may be appropriate and effective using other premixed insulin formulations as well. The ADA and the AACE have each published guidelines for initiating and titrating insulin in patients with type 2 diabetes, including how to transition these patients to a basal bolus regimen.7,8

Basal-Bolus Regimen

A basal-bolus regimen is appropriate for all patients with type 1 diabetes and for patients with type 2 diabetes who have severe insulin deficiency. This regimen can be implemented in two ways: multiple daily injections (MDI) using a long-acting insulin analog in combination with a rapid-acting insulin analog or by continuous subcutaneous insulin infusion (CSII) using only rapid-acting insulin. Guidelines for initiation and titration, described in the sections below, should be modified as needed to accommodate the needs, preferences and abilities of individual patients.

Initial Basal Insulin

Total insulin dose is determined using this formula: 0.3 units/kg body weight to 1.0 unit/kg body weight with 40% to 50% of basal dose and 40% to 50% of basal dose with glargine or detemir at bedtime. Insulin requirements may be affected by many factors (e.g., physical activity, kidney problems), and patients with type 2 diabetes who are on insulin sensitizers may need less insulin. Some patients may require twice-daily dosing of basal insulin for greater blood glucose stability, especially if they need more than 50 units or if they are unable to take insulin at the same time every day.

Initial Meal Bolus Calculations

The prandial insulin dose usually makes up 45% to 60% of the total daily dose. An individualized insulin-to-carbohydrate ratio provides greater flexibility in meal planning for more sophisticated patients who are able and willing to learn how to estimate carbohydrate intake. Several methods are available to calculate the initial prandial or meal bolus dose.

Some providers distribute the initial prandial dose by giving 15% of rapid-acting insulin before breakfast, 15% before lunch and 20% before dinner. Dosage adjustments are made where necessary. Under this option, the larger percent should be attributed to the patient's largest meal, which is not always dinner. Other providers empirically use the most common ratio, 1 unit per 15 grams of carbohydrate. Patients with type 2 diabetes who are more insulin resistant may require 1 unit of insulin per 10 grams of carbohydrate. When initiating this method or the carbohydrate counting algorithms described below, use a consistent carbohydrate distribution to facilitate the insulin-to-carbohydrate titration.

One method of calculating prandial insulin is based on pattern analysis, in which the patient tests his or her blood sugar before a meal and gives the predetermined insulin dose for predetermined carbohydrate content. The patient then tests his or her blood sugar 2 hours after the meal. The goal is to adjust the 2-hour prandial dose so that the postprandial excursion is less than 40 mg/dL to 60 mg/dL postmeal or the blood sugar is less than 140 mg/dL.

In yet another method, the carbohydrate-to-insulin ratio (CIR) or carbohydrate factor is determined based on the patient's weight. The ratio is estimated by multiplying the patient's weight in pounds by 2.8, and the result is divided by the total daily dose (TDD). Therefore, CIR = (2.8 x weight in pounds)/TDD.13

So, for a patient who weighs 160 pounds and has a TDD of 48 units, the CIR will be 2.8 x 160 = 448; 448/48 = 9. This patient will need to take 1 unit of insulin for each 9 grams of carbohydrate intake. If this patient is eating a meal that contains 45 grams of carbohydrate, the prandial dose will be 45/9 = 5 units of fast-acting insulin for that meal. Other methods include dividing the corrective dose or sensitivity by 3 to obtain the carbohydrate dose or using the "500 rule," in which the total daily dose is divided by 500 to derive the corrective dose (500/TDD = CIR).14In the example 500/50 = 10, the carbohydrate-to-insulin ratio will be 1 unit per 10 grams of carbohydrate, with a total daily dose of 50 units.

Corrective Insulin Algorithm

The final step in the initiation of insulin replacement therapy is establishing individualized glucose targets for premeal readings and providing an algorithm to correct hyperglycemia. The corrective insulin dose algorithm or scale, also referred to as correction factor, sensitivity factor or supplemental insulin dose, represents the expected fall in blood glucose in mg/dL per 1 unit of injected rapid-acting

insulin, or the patient's insulin sensitivity. Several algorithms can determine this corrective insulin scale.

Some providers start empirically with 1 unit/50 mg/dL, meaning that for this patient, one unit of rapid-acting insulin is expected to decrease the blood sugar by 50 mg/dL. So, to calculate the corrective dose, the patient must subtract his or her target blood sugar from the current level and divide the difference by 50 to obtain the corrective dose: Corrective dose = current blood glucose - target blood glucose/sensitivity. Using this formula, if a patient obtains a preprandial blood sugar of 150 mg/dL and has a target blood sugar of 100 mg/dL, the corrective dose will be 150 mg/dL - 100 mg/dL = 50 mg/dL/50 = 1 unit of rapid-acting insulin.

Other statistically derived methods to determine corrective insulin dose include the 1700 Rule.15In this method, dividing 1,700 by the patient's total daily dose of insulin yields the corrective dose. So for the patient who is on a total daily dose of 48 units, determine the corrective dose by dividing 1,700 by the total daily dose (1,700 Ö 48 = 35). This means that the patient will add 1 unit of rapid-acting insulin for every 35 mg/dL that the premeal blood glucose is above the target of 100 mg/dL. Other so-called rules, such as the 1800 rule and the 1500 rule, have also been proposed.15

Multiple Daily Injections

Multiple daily injections (MDI) can be a good choice for patients who are not interested in pump therapy or who do not meet the selection criteria for CSII. This type of regimen presents several issues, particularly variable action or absorption of long-acting insulin, which can cause subcutaneous depot.

The fact that insulin can only be delivered in 1-unit or 0.5-unit increments with some syringes or pen devices limits the fine-tuning of the insulin dose, and this can be a problem for insulin-sensitive patients. Additionally, the required number of injections increases the risk for lipodystrophy.

Another issue with MDI is the portability of the injection device. Patients may miss doses when equipment is not available due to forgetfulness or unplanned eating away from home.

Lastly, MDI requires patients to perform mathematical calculations to determine boluses. As time passes, they may "guesstimate" their dose, resulting in erratic blood sugar. To help with this problem, some providers assist their patients by making a "cheat sheet" card with the bolus calculation scale, so that they avoid relying on estimations.

Insulin Delivery Devices

Today's advanced pen-type delivery devices make self-injection easier. They are less painful and more accurate than previous equipment. The most common categories are prefilled, disposable devices and reusable devices. The latter require the insertion and changing of a cartridge filled with insulin. The main limitation to widespread use of insulin pens is lack of insurance coverage.

Many of these pen devices are insulin-specific, so the selection of an insulin type may dictate device choice. A disposable device may be best for a patient with a busy lifestyle who needs to keep a pen in the office, car, travel kit or sports bag, or for a patient who has an unpredictable eating schedule. A prefilled device may be a better choice for patients with limited manual dexterity and for some with visual impairments.

Insulin Pumps

Insulin pumps represent another drug delivery choice for patients on replacement therapy. These battery-operated devices can be programmed to deliver continuous microdoses of rapid-acting insulin. The patient can administer boluses of larger amounts of insulin as needed to cover the carbohydrate in meals or snacks, and to counteract hyperglycemia. Although pumps are used more often by patients with type 1 diabetes, these devices provide a more physiologic delivery of insulin and can be an option for patients with type 2 diabetes who need more flexibility.

Pumps are available with various insulin delivery features. The so-called "smart pumps" help calculate doses and prevent insulin stacking (giving frequent boluses). The ADA and the ACE recommend considering CSII for patients who meet established selection criteria.7Initiating and Titrating CSII

The initial bolus calculation for patients on CSII is similar to that for MDI. But because CSII is more efficient than MDI, patients may require less total daily insulin, especially if their blood glucose is not uncontrolled. The patient is usually started on one hourly basal rate, generally calculated by taking 80% of one-half of the TDD and dividing it by 24. For example, for the patient who had a TDD of 48 units (for whom we calculated a basal dose of 19 units), the hourly basal rate would be 19 units/24 hours = 0.8 units per hour.

Evaluating Effectiveness

After the initiation of basal-bolus insulin therapy, the patient should test his or her blood sugar before meals, at bedtime and at least three times per week between 2 a.m. and 3 a.m. Review the patient's SMBG record on a weekly basis to assess blood glucose profile and to make appropriate adjustments to basal and bolus insulin components. First adjust the basal dose to the target fasting blood glucose value, then ensure that the patient is not experiencing nocturnal hypoglycemia. Use blood glucose levels before lunch, before dinner and at bedtime to adjust the morning, noon and dinner prandial doses, respectively.

Adjusting Basal Insulin Dosage

When adjusting the basal regimen, dosage can be increased every 3 to 7 days until fasting blood sugar is within target range and the patient does not have nocturnal hypoglycemia. Some providers recommend switching the glargine to the morning if the patient experiences nocturnal hypoglycemia.

For patients on CSII, adjust the initial basal rate based on glycemic profile to appropriately cover periods with a pattern of high or low blood glucose levels. For example, a patient with a pattern of high early morning blood glucose needs a higher basal rate during that period, but he or she may need a lower rate if a pattern of low blood sugar before dinner is identified.

When adjusting the basal rate, do so in small steps (0.05 units to 0.1 units per hour), unless a major adjustment is required for illness, stress, steroid therapy, etc. Make the changes 1.5 to 2 hours before the problem tends to crop up. When adjusting insulin pump settings, remember that the total basal rate is usually 40% to 65% of the total daily dose. Therefore, evaluate the bolus-basal balance at each visit, and readjust as needed. The basal dosage is correct when the patient fasts or skips a meal and blood glucose levels remain stable within target ranges.

Adjusting Bolus Insulin Regimens

To adjust the meal bolus dosage, test the blood glucose before meals and 2 hours after the start of each meal. Adjust the rapid-acting insulin dose until the readings are within 40 mg/dL to 60 mg/dL of each other. If the postbreakfast or prelunch blood glucose level is not within target, adjust the breakfast bolus. For postlunch or predinner fluctuations, adjust the lunch bolus. For postdinner or bedtime irregularities, adjust the dinner bolus. Patients who take a morning dose of long-acting insulin may require less rapid-acting insulin at lunchtime.

If postmeal blood sugar is high but premeal readings are low or in range, identify blood glucose patterns before adjusting the prandial insulin dose. To do so, review the patient's food intake for appropriate carbohydrate counting.

Ask about high-fat food intake (which can delay the absorption of carbohydrate), uncovered between-meal carbohydrate snacks and the timing of the bolus injection before suggesting a solution. Strategies to correct the problem may include changing the timing of the prandial dose from just before the meal to 15 to 20 minutes before food intake, adjustment of the basal insulin dose, or patient education.

Correction boluses that account for more than 10% of the total daily insulin dose may be an indication of inadequate basal or bolus doses. After pattern analysis, integrate the excess correction bolus dose into the basal or bolus dose based on where corrections were most needed.

Prevention of Hypoglycemia

Intensified insulin therapy reduces autonomic and symptomatic responses to hypoglycemia. But multiple studies have shown that hypoglycemia unawareness and the epinephrine response to hypoglycemia can be restored by meticulous avoidance of hypoglycemia.16,17Table 6 outlines strategies to prevent hypoglycemia in patients on insulin replacement therapy.

Putting It Into Practice

For most patients with type 1 diabetes and for insulin-deficient patients with type 2 diabetes, near-physiologic insulin replacement with MDI or CSII is an appropriate and effective option. Insulin replacement therapy has the potential to reduce A1clevels, glucose variability, hypoglycemia episodes and diabetes complications. It also has the potential to improve quality of life. Insulin replacement therapy is a complex undertaking that requires thorough patient education and ongoing support. Nurse practitioners are uniquely suited to providing both.

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