

# Optimizing insulin regimens in type 1 diabetes

## How to help patients get control of their life

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This is the second of three articles on insulin therapy.

**Preview:** The advances in insulin therapy in the past 5 years, including the introduction of insulin analogues, have made blood glucose control in patients with type 1 diabetes much more attainable. Diabetic patients can now achieve a better quality of life, including spontaneity and flexibility in lifestyle, than was possible with earlier insulin products. Here, Dr Bohannon discusses the latest improvements in acute and basal insulin therapy and presents three algorithms she has developed to help patients individualize their insulin regimens in relation to their eating and exercise patterns.

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As diabetes care becomes an increasing focus in primary care, physicians need to be familiar with the recent advances in types of insulin products available and the subsequent changes in diabetes treatment. Having a basic understanding of the pathophysiology of type 1 diabetes is important in order to rationally prescribe the new insulin therapies.

### Pathophysiology of type 1 diabetes

Type 1 diabetes is usually due to autoimmune destruction of the beta cells of the islets of Langerhans, although occasionally idiopathic forms of no apparent cause can result from loss of beta cells. In addition, type 1 diabetes may occur in persons who have lost insulin-secretory capacity as a result of severe pancreatitis, those who have undergone pancreatectomy because of cancer or trauma, and those who have lost beta cell function

because of hemochromatosis, other diseases, or toxins (eg, ingestion of Vacor rat poison). In general, persons with type 1 diabetes have no, or extremely little, insulin-secretory capacity and are therefore dependent on exogenous insulin to survive. Without it, they die of ketoacidosis.

The body usually puts out a small amount of insulin continually throughout the day and night, irrespective of meals. This background, or basal, insulin is secreted in small bursts every 9 to 11 minutes. It is responsible for maintaining suppression of ketogenesis (formation of ketoacids by the liver) and control of lipolysis (fat breakdown), gluconeogenesis, and glycogenolysis, as well as supplying adequate insulin for basal glucose uptake by the peripheral tissues. Basal insulin comprises about 50% of the total daily amount of insulin secreted by the pancreas when a person is on a weight maintenance diet. The other 50% is secreted as a "bolus" in response to the rise in blood glucose level that occurs with meals.

Ketoacidosis results from lack of insulin, which is necessary not only to put glucose into insulin-sensitive cells (primarily muscle and fat) but also to prevent ketogenesis in the liver. If insulin levels are not adequate at all times to regulate lipolysis in adipose tissue, the fat cells release excessive amounts of free fatty acids and glycerol as breakdown products of triglycerides, the storage form of fat in cells. The free fatty acids circulate to the liver, where they are taken up and broken down into ketoacids. The ketoacids then are released into the bloodstream and cause ketoacidosis. The glycerol from the triglyceride breakdown acts as a substrate for glucose production by the liver, contributing further to the hyperglycemia, which occurs because there is inadequate insulin to encourage peripheral tissues to take up glucose. More insulin is needed by the liver to turn off ketogenesis once it has started than is needed to keep ketogenesis suppressed by a constant low level of circulating basal insulin.

In a normal pancreas, an increase in blood glucose level of 3 mg/dL (0.167 mmol/L) (eg, from 80 to 83 mg/dL [4.44 to 4.61 mmol/L]) triggers the onset of first-phase insulin secretion. As the blood glucose level rises, more insulin is secreted to control the degree of postprandial hyperglycemia. Typically in a nondiabetic person, the blood glucose level peaks about 1 hour after a meal or glucose ingestion, and the serum insulin level peaks at about the same time. The concurrent increases in insulin and blood glucose levels then lead to a drop in glucose level as a result of both suppression of endogenous glucose production by the liver and the increase in glucose uptake and utilization by the peripheral tissues, particularly muscle and fat.

The rapid outpouring of insulin in response to the rise in blood glucose level is very important. Not only does it encourage glucose uptake by the peripheral tissues, it also suppresses hepatic glucose production which, in the basal state between meals, is necessary to prevent hypoglycemia. If the liver were not capable of producing glucose between meals, we would all die of hypoglycemia within 8 hours after our last meal, because the brain, muscles, and adipose tissue would have taken up glucose from the bloodstream for their basic

survival, resulting in hypoglycemia. In the postprandial state, the first effects of the rapid rise in insulin level are suppression of hepatic glucose production (by suppressing glycogenolysis and gluconeogenesis) and suppression of lipolysis. Only somewhat later does it increase peripheral glucose uptake and utilization or storage by muscle and fat. In adipose tissue, free fatty acids and glucose are taken up from the bloodstream and stored as triglycerides in the cells.

When the ambient blood glucose level is subacutely elevated, the beta cell temporarily does not respond to a further rise in glucose as a stimulus for first-phase insulin secretion. This is called the glucotoxicity effect, and it occurs in humans at a blood glucose level of about 115 mg/dL (6.38 mmol/L). The effect of fasting plasma glucose on the acute insulin response is shown in figure 1.

### **Advances in treatment**

In the treatment of type 1 diabetes, it is important to recreate both types of insulin secretion (ie, to provide for constant, 24-hour-a-day basal insulinization and also to mimic acute insulin release in response to meals). Regular insulin (the older "fast-acting" insulin) was never truly fast-acting or similar to normal physiologic response. It was just the fastest of several relatively slow-acting insulins that were available. Because regular insulin given subcutaneously peaks 2 to 4 hours after administration and continues to have significant blood glucose-lowering action for 6 to 8 hours, it is far from ideal for mimicking the physiologic rapid increase in endogenous insulin secretion, which peaks 1 hour postprandially.

Thankfully, two truly rapid-acting insulin analogues that far more closely mimic natural acute-phase insulin secretion have become available in the last 5 years. (Other analogues are currently in clinical trials.) Not only are lispro insulin (Humalog) and aspart insulin (NovoLog) far more physiologic in their timing of action, they are also far more convenient for the patient. These agents can be dosed from 15 minutes before to immediately after a meal while still greatly improving control of postprandial blood glucose levels. In contrast,

regular insulin ideally should be taken a half hour to an hour before a meal. Because of the inconvenience, patients rarely followed this recommendation, and as a result, their glycemic control suffered.

The dosing of meal-related insulin in type 1 diabetes used to be far more rigid than is currently necessary, now that the tools are available to greatly improve not only glucose control but also quality of life, spontaneity, and variability in lifestyle patterns. In the past, standard therapy involved a daily regimen of a mixture of regular insulin plus isophane insulin suspension (NPH) before breakfast and dinner, often in preestablished doses, and a fixed diet that needed to be consumed at the proper times and without variation in order to achieve the best glucose control possible on that regimen. Now patients with type 1 diabetes can have a much freer lifestyle, eating when and what they want, while still maintaining excellent glycemic control by counting carbohydrates, checking blood glucose levels, and adjusting the rapid-acting insulin dose appropriately.

### **Algorithms for individualizing regimens**

In my practice, patients with type 1 diabetes are given three algorithms that are individualized on the basis of their responses to carbohydrate intake, insulin therapy, and exercise. To refine each one generally takes a couple of months and involves intensive glucose testing, record keeping, and education, preferably by a certified diabetes educator. All three algorithms involve use of rapid-acting (lispro or aspart) insulin.

#### **Carbohydrate algorithm (see end page)**

The carbohydrate algorithm (see box at the end of this article) is a tool that patients can use to calculate the amount of insulin needed to dispose into the tissues the amount of carbohydrate to be consumed. It is imperative that patients know how to count carbohydrates accurately; otherwise, they will not be able to adequately control their blood glucose response to meals. Fortunately, federal law now requires that all packaged foods bear nutritional labeling that lists the amount of carbohydrate, fat, protein, saturated fat, sugars, and

fiber. Also, many carbohydrate-counting books give the carbohydrate content of raw foods based on the size or weight of a portion (eg, a 2-in diameter apple has 15 g of carbohydrate).

Certain concepts about meals and carbohydrate should be discussed with patients. One of them is that a high-fat meal (eg, pizza, fettuccine Alfredo, steak with baked potato and lots of sour cream and butter) tends to slow the absorption of carbohydrate from the intestine. Consequently, the rapid-acting insulin given before the meal may peak relatively too soon, causing low blood glucose levels shortly after the meal or high blood glucose levels several hours later, or both. This situation can be avoided by taking the insulin soon after the meal rather than before it or even by giving the total rapid-acting dose in two separate injections a half hour to an hour apart. Patients who have an insulin pump may choose to use a square-wave bolus. For example, if 8 units is needed for the meal, the patient might give an infusion of 4 U/hr for 2 hours rather than a bolus of 8 units all at once.

#### **High-blood-glucose supplement algorithm (see end page)**

The appropriate supplementary insulin dose for high blood glucose levels also needs to be discovered by repeated trials and testing (see box at the end of this article). This algorithm should be determined separately from the meal-associated carbohydrate algorithm. Therefore, it is best to refine the algorithm when the blood glucose level is fairly stable, beginning 3 hours or more after the last meal or last dose of rapid-acting insulin and when no intermediate-acting or long-acting insulin peak is expected.

It is important to instruct patients not to give a high-blood-glucose supplement dose if it has been less than 3 hours since their last rapid-acting insulin dose, because the previous insulin dose would not yet have had its full effect and hypoglycemia may result. However, if the patient has taken a supplementary dose within the last hour and is going to eat carbohydrate, he or she should take an insulin dose according to the carbohydrate algorithm to cover that meal or snack but should not take a high-blood-glucose supplement dose at that

time, even if the blood glucose level is still high before the meal or snack. This instruction should be reviewed repeatedly with patients, and they should be asked to explain it back to you in order to verify that they understand it. The carbohydrate algorithm dose of insulin should be taken whenever the patient is going to eat carbohydrate unless, of course, the carbohydrate is being ingested to treat hypoglycemia.

### Exercise algorithm (see end page)

The exercise algorithm (see box at the end of this article) is usually the last to be calculated, after the patient has a good handle on carbohydrate counting and has developed appropriate carbohydrate and high-blood-glucose supplement algorithms. Again, establishing this algorithm takes some effort, but once all three algorithms are implemented, they free the patient to live a variable and active lifestyle while still maintaining excellent glucose control. The exercise algorithm is determined at a time when blood glucose levels are stable (ie, more than 3 hours after the last meal or rapid-acting insulin dose and when no intermediate-acting or long-acting insulin peak is expected). Ideally, the blood glucose level is somewhat high (140 to 180 mg/dL [7.77 to 9.99 mmol/L]) but not over 200 mg/dL (11.10 mmol/L), which would indicate that the basal insulinization is very inadequate.

If the blood glucose level is high before a meal and exercise is planned after the meal, then instead of eating extra carbohydrate to cover the exercise or taking extra insulin to bring down the high premeal blood glucose level, the patient can exercise to a level that will result in the equivalent blood glucose-lowering effect that would have been expected from the deleted dose of high-blood-glucose insulin supplement. For example, a patient knows that a half hour of bicycling will lower his blood glucose level by 30 mg/dL, and he is planning to bicycle for a half hour after a picnic lunch. If he needs 1 unit of rapid-acting insulin for every 15 g of carbohydrate consumed, then he could eat 30 g more carbohydrate at lunch (eg, half a turkey sandwich on sliced bread plus a 2-in apple), or he could take 2 units less insulin before lunch, knowing that the exercise after lunch should bring down his blood glucose level.

In addition, if his blood glucose level was 180 mg/dL (9.99 mmol/L) before lunch and his high-blood-glucose supplement algorithm is 1 unit for every 30 mg/dL (1.67 mmol/L) higher than 120 mg/dL (6.66 mmol/L), he could take the carbohydrate dose calculated for the meal but omit the extra 2 units he should have taken according to the high-blood-glucose supplement algorithm, because he will be exercising the right amount to lower his blood glucose level after the meal. Using exercise instead of insulin in this situation allows the patient to more easily lose weight as a result of the exercise. If, instead, the blood glucose level was 100 mg/dL (5.55 mmol/L) before the picnic, he could just omit 2 units of the carbohydrate algorithm fast-acting insulin and exercise instead of taking the normal amount of insulin for the picnic. Alternatively, he could eat 30 g of carbohydrate before exercising without taking additional insulin to cover it.

### Basal insulin therapy

Until the long-acting, nonpeaking insulin analogue glargine (Lantus) became available in 2001, the standard insulins used to provide background insulinization were NPH, insulin zinc suspension (lente), and insulin zinc suspension, extended (ultralente), all of which have peaks of action (table 1) (1-3). Studies indicate that human ultralente, although long-acting, has a peak activity comparable to that of NPH for the same amount given subcutaneously, but the peak occurs much later and is much broader. The peak action time of both agents varies widely among patients.

**Table 1. Pharmacokinetics of current insulin preparations**

Insulin	Onset	Peak	Effective duration
Lispro (Humalog)	<15 min	1 hr	4-5 hr
Regular	0.5-1 hr	2-3 hr	5-8 hr

**Table 1. Pharmacokinetics of current insulin preparations**

<b>Insulin</b>	<b>Onset</b>	<b>Peak</b>	<b>Effective duration</b>
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(Table 1 Continued)

NPH, lente	2-4 hr	6-8 hr	6-16 hr
Ultralente	4 hr	Variable	18-22 hr
Glargine (Lantus)	1-2 hr	Flat, predictable	22-24 hr

NPH, isophane insulin suspension.

*Compiled from Barnett and Owens (1), Lepore et al (2), and White et al (3).*

The standard background insulins also have much greater intraindividual variability from day to day than both the rapid-acting insulin analogues and the long-acting glargine. Other factors that can affect insulin uptake and bioavailability of these insulins include site of injection, cigarette smoking (15% variability for one cigarette), use of hot tubs, and exercising of the area of injection. These variables are far less of a problem with glargine insulin or with the rapid-acting insulin analogues.

As mentioned, it is important to develop the algorithms for rapid-acting insulin when a peak of an intermediate-acting or long-acting insulin is not expected. However, it is more difficult to determine appropriate carbohydrate and high-blood-glucose supplement algorithms for patients who take NPH, lente, or ultralente rather than glargine as the basal insulin. For example, a patient takes a dose of NPH or lente along with a fast-acting or rapid-acting insulin dose before breakfast. In the late morning, her blood glucose level is high. Because she wants to determine her high-blood-glucose supplement algorithm, she gives a supplement dose of rapid-acting insulin and then skips lunch to assess the

effect of the supplement. In so doing, she may become hypoglycemic within 3 hours, not so much because of the high-blood-glucose supplement dose but because she missed lunch and the NPH insulin peaked at that time.

Compared with NPH, glargine has been shown to consistently cause less nocturnal hypoglycemia when it is administered at bedtime and hemoglobin A<sub>1c</sub> control is equivalent. This effect is achieved without an increase in daytime hypoglycemia, despite the fact that glargine lasts 24 hours in most patients. Although some studies in type 2 diabetes have shown that glargine gives somewhat better control when dosed in the morning, I still prefer to begin glargine therapy with a bedtime dose and adjust it to achieve fasting blood glucose levels of less than 100 mg/dL (5.55 mmol/L) or, at most, less than 120 mg/dL (6.66 mmol/L), if possible without causing nocturnal hypoglycemia. It is much easier to determine the appropriate dose when glargine is given at bedtime, without a snack, and the fasting blood glucose level is tested about 8 hours later.

There is less time to adjust the dose in patients with type 1 diabetes than in those with type 2 diabetes, because it is imperative that basal insulinization is adequate to prevent diabetic ketoacidosis. When switching patients from other insulin regimens to a once-daily basal dose of glargine plus meal-associated rapid-acting insulin, I usually add up the total daily dose of all types of insulin and give 40% to 50% of it as a once-daily bedtime dose of glargine on the day of the switch (having given the last dose of intermediate-acting insulin that morning or the last dose of ultralente insulin the night before). The patient is then instructed to adjust the glargine dose on the basis of fasting blood glucose levels, increasing it by 1 unit daily for 3 days if the fasting level is greater than 120 mg/dL, 1 unit every 2 to 4 days if the level is 100 to 120 mg/dL, and 1 unit every 3 to 7 days until the level is mostly less than 100 mg/dL. Patients should stop dose titration if hypoglycemia occurs that does not have another cause (ie, rapid-acting insulin, alcohol consumption, or exercise).

It should be made clear to the patient that only hypoglycemia that is attributable to the glargine

should stop the upward titration of the dose. For example, if a patient becomes hypoglycemic during the night after drinking a lot of alcohol that evening, I would consider the hypoglycemia to be a side effect of the alcohol, not the glargine. I then would reinforce the educational efforts with the patient about the inappropriateness of consuming more than two alcoholic beverages in one sitting. Should this situation occur again, the patient is instructed to check the blood glucose level in the middle of the night and to eat a snack if necessary.

Likewise, if a patient takes some rapid-acting insulin at bedtime (perhaps because of a high blood glucose level at that time) and then becomes hypoglycemic, I would not attribute that hypoglycemia to the glargine. Rather, I would reinforce to the patient that during the titration phase, rapid-acting insulin should not be taken at bedtime even if the blood glucose level is high (as long as it is less than 300 mg/dL [16.65 mmol/L]). If basal insulinization is adequate, the blood glucose level would be expected to decline slowly during the night toward a more acceptable level by the next morning, even in the absence of a high-blood-glucose supplemental dose of insulin at bedtime.

When switching patients from a 70/30 or mixed fast-acting insulin and NPH or lente insulin twice daily to a basal-bolus regimen, I usually calculate the total daily dose of insulin (all types) and begin by having the patient take 40% to 50% of it as glargine in one dose at bedtime. Then the patient titrates the dose on the basis of fasting blood glucose level, as previously described. In this scheme, 40% to 50% of the total daily dose is given as lispro or aspart divided between the meals according to carbohydrate content.

In patients with type 1 diabetes, especially those taking small doses (more often than in those with type 2), glargine may not last the full 24 hours. It is important to determine whether the glargine is not lasting long enough or whether not enough fast-acting insulin is being given for the carbohydrate in the preceding meal. This can be determined by doing several skip-a-meal studies on different days, in which the patient checks the blood glucose level 3 hours after lunch to be sure it is below 120 mg/dL

(6.66 mmol/L). (A glucose level higher than 120 mg/dL 3 hours after a meal indicates to me that the patient did not receive enough "bolus" rapid-acting insulin before the previous meal.) The blood glucose level is then checked hourly, but no calories are consumed until bedtime.

If the glucose level rises and continues to rise until time for the evening glargine dose, this would indicate that the basal glargine dose at that time is not adequate for glycemic control. If the fasting glucose levels are consistently acceptable, this means that the glargine is wearing off prematurely and not lasting 24 hours. (The test should be done several times to ensure that the effects are reproducible and to determine the time at which the dose seems to be wearing off.) However, if the glucose levels remain acceptable throughout the evening when no calories are consumed, the high blood glucose levels previously noted before or after dinner were probably due to an inadequate rapid-acting insulin dose at lunch or dinner, respectively.

If the effect of glargine seems to be wearing off prematurely, it typically occurs between 18 to 24 hours after the last injection, a time that usually encompasses dinner. Although the total daily glargine dose could be equally divided between two injections about 12 hours apart, that would involve an additional injection because glargine cannot be mixed in the same syringe with any other insulin or other liquid, and this is often unnecessary.

Patients who need to take insulin before meals can continue with the glargine dose at bedtime but add 1 to 2 units of regular insulin to the lispro or aspart insulin (in the same syringe) before dinner. The regular insulin acts as a short pseudo-basal dose to maintain insulinization during the time between when the rapid-acting insulin wears off and the next glargine dose begins working. This obviates the extra injection of glargine.

### **Emergency precautions**

All patients with type 1 diabetes and others taking any type of insulin should have a prescription for glucagon (Glucagon Emergency Kit). Family

members and anyone else who might be in a position to have to treat the patient for hypoglycemia should know where the glucagon kit is kept and how to use it. I always encourage patients to have family members and others close to them administer at least one of their usual insulin shots to overcome the fear of giving injections. On more than one occasion I have consulted on a case of severe hypoglycemia that occurred in the presence of a spouse, in which the diabetic person was unconscious or convulsing and suffered grave bodily harm because the spouse was too timid or anxious to give the glucagon injection, even though it was available in the home. I also encourage family members who are capable of giving an injection to give routine insulin injections to the diabetic patient on a regular basis, at least once a month, to stay proficient and negate the fear factor. Often children are less anxious than adults and more likely to quickly learn the glucagon procedure, which can be lifesaving for their sibling or parent.

## Conclusion

It is becoming easier for knowledgeable, motivated patients with type 1 diabetes to achieve and maintain excellent blood glucose control. This is possible because of the greatly improved tools that have become available, including more physiologic insulins, both those that mimic normal basal insulinization and those that have rapid peaks that simulate normal postprandial insulin secretion. In addition, the advent of diabetes teaching centers and certified diabetes educators who can work closely with patients to teach and motivate them regarding self-care, carbohydrate counting, glucose monitoring, insulin adjustment, and so on has made good glycemic control achievable and the future much brighter for people with diabetes.

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## **Carbohydrate algorithm**

For an adult of average weight with an average activity level, the carbohydrate algorithm may start with 1 unit of rapid-acting insulin analogue for every 15 g of carbohydrate to be ingested. After the patient has applied the initial formula and kept excellent records about the carbohydrate intake at each meal, the amount of insulin given, and the blood glucose levels both before and 2 to 3 hours after the meal, the appropriateness of that algorithm can be determined.

If blood glucose levels are routinely too high (>140 mg/dL [7.77 mmol/L]) at 2 hours after a meal, it is evident that more insulin needs to be given for that amount of carbohydrate. Thus, the algorithm might be changed to 1 unit of rapid-acting insulin for every 12 g of carbohydrate and then fine-tuned further as needed. If the patient becomes hypoglycemic within 3 hours after the meal, the algorithm would obviously need to be adjusted in the other direction (eg, 1 unit of rapid-acting insulin for every 18 g of carbohydrate). In my experience, most patients with type 1 diabetes need 1 unit of rapid-acting insulin for between 8 g and 16 g of carbohydrate. However, some children may need 1 unit for 20 g of carbohydrate, and some obese patients may need 1 unit for every 5 g. The appropriate ratio must be individually determined, and a certified diabetes educator can be very helpful in this regard.

## **High-blood-glucose supplement algorithm**

For an adult of average weight, I usually start with an algorithm of 1 unit of lispro or aspart insulin for every 30 mg/dL (1.67 mmol/L) of blood glucose higher than 120 mg/dL (6.66 mmol/L), but no more than 3 units as the supplementary dose at one time. This means that if it has been more than 3 hours since the last meal or rapid-acting insulin dose and the blood glucose level is 180 mg/dL (9.99 mmol/L), the patient would take 2 units of lispro or aspart, avoid eating and exercising (other than usual activities of daily living), and test again 3 hours later. If the blood glucose level is still higher than 120 mg/dL, the algorithm is insufficient.

I then instruct the patient to use the algorithm several more times when the blood glucose levels are elevated by different amounts. If it is obvious that the algorithm is insufficient, it can be changed to 1 unit of rapid-acting insulin for every 25 mg/dL (1.39 mmol/L) of blood glucose above 125 mg/dL (6.94 mmol/L), or 1 unit for every 20 mg/dL (1.11 mmol/L) above 120 mg/dL, and so on. I encourage patients to titrate on the basis of half-unit increments, which are measurable in an insulin syringe. Patients who have an insulin pump can use much smaller increments (eg, 0.3 units for every 10 mg/dL [0.56 mmol/L] above 120 mg/dL).

## **Exercise algorithm**

To determine the exercise algorithm, the patient should choose an exercise that he or she is likely to do on a regular basis and should exercise at a specific level for a fixed duration (eg, riding an exercise bicycle for 15 minutes at 12 mph or jogging 1.5 miles in 15 minutes). The blood glucose level should be checked before the exercise session, immediately after exercise, and 45 minutes later. If half an hour of a specific exercise regularly tends to lower the blood glucose level by about 30 mg/dL (1.67 mmol/L), then before engaging in that activity in the future, the patient can consume the amount of carbohydrate that he or she knows will raise the blood glucose level by 30 mg/dL. Or, if the blood glucose level is elevated right before exercising (ie, 150 mg/dL [8.33 mmol/L]), the patient can proceed, knowing that the glucose level is likely to come down into a more normal range within an hour after the exercise session.