Insulin Strategies for Primary Care Providers

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Primary care providers care for more than 75% of patients with diabetes.[1–4] With the recent introduction of two new insulin analogs, it seems appropriate to review insulin therapy for primary practitioners. This is particularly relevant because ~30–50% of patients with type 1 diabetes in the United States are still using single or twice-daily injections, an outdated and nonphysiological process.[5,6] Education about insulin physiology and the use of insulin in patients with diabetes should enable primary care providers to come closer to physiological insulin replacement and return glucose levels to near-normal concentrations.

Insulin use in diabetes is an integral component of the management of about 30–40% of the 10.3 million Americans diagnosed as having diabetes.[7] This review is designed to help health care practitioners become familiar with the different types of insulin that are now available and how each should be used to optimize treatment for the large population of patients with diabetes.

Types of Insulin
Most insulin now is made biosynthetically, purified, and then treated enzymatically to yield human insulin.[8]

Rapid-Acting Insulin
Insulin lispro (Humalog) is an insulin analog that differs from human insulin in amino acid sequence but binds to insulin receptors and thus functions in a manner similar to human insulin. Specifically, lysine at position 29 is switched with proline at position 28 to form insulin that does not self-associate in solution. Insulin aspart (Novolog) is human insulin in which the proline at position 28 is substituted with aspartic acid, also inhibiting self-aggregation. Because human insulin regularly forms aggregates in solution and because only insulin monomers and dimers are readily absorbed across capillary endothelium, the absence of self-aggregation yields an insulin that is rapidly absorbed from the subcutaneous injection site.

Pharmacodynamically, lispro and aspart bind as well to insulin receptors as does human insulin, but lispro has a slightly elevated affinity for the Insulin-like Growth Factor 1 (IGF-1) receptor ($156 \pm 16\%$ for lispro vs. $81 \pm 9\%$ for aspart).[9] Both lispro and aspart have low mitogenic potency despite the elevated IGF-1 receptor affinity of lispro, indicating that a minor increase in IGF-1 affinity is not a sufficient stimulus to provide a mitogenic stimulus to a cell line.[9]

Both lispro and aspart have an onset of action within 15 min, a peak in activity at 60–90 min, and a duration of action of 3–5 h. Both result in fewer hypoglycemic episodes compared to regular insulin.[10] These analogs function very well in continuous subcutaneous insulin infusion (CSII) systems (insulin pumps), resulting in lower HbA_{1c} concentrations and postprandial blood glucose levels than regular insulin, with less hypoglycemia.[11,12]

The addition of neutral protamine to lispro creates an intermediate-acting insulin that has been used in 75/25 and 50/50 combinations with lispro as twice-daily injections.[13] The 50/50 mixture is not yet available in the United States.

Short-Acting Insulin
Regular insulin is the prototype of short-acting insulin, which is, unfortunately, an inappropriate description. It has an onset of action 15–60 min after injection, a peak effect 2–4 h after injection, and a duration of action of ranging from 5 to 8 h.[14] For best results, the slow onset of regular insulin requires it to be administered 30–60 min before meals, which is certainly not a convenient way for busy or hungry people with diabetes to prepare for meals. However, the slow onset of action does not hold true for intravenous administration, making regular insulin appropriate for intravenous treatment of diabetes.[15]

Intermediate-Acting Insulin
Neutral protamine Hagedorn insulin, better known as NPH insulin, is regular

IN BRIEF

Primary care providers take care of the majority of patients with diabetes in the United States. The introduction of new insulin analogs over the past few years should help primary practitioners and their patients with diabetes achieve physiological insulin replacement and near-normal glucose levels. This article reviews currently available insulins and replacement of insulin in a physiological manner for patients with type 1 or type 2 diabetes and provides examples of patients for whom insulin dosages changed over time.

insulin combined with stoichiometric amounts of protamine, resulting in a poorly soluble insulin-protamine complex. NPH has an onset of action 2 h after injection, a peak effect 6–10 h after injection, and a duration of action ranging from 13 to 20 h. From a practical point of view, most patients get little effect after 13–15 h.

Lente insulins were developed by combining regular insulin and zinc in an acetate buffer to form a crystalline compound that dissolves poorly in the subcutaneous body fluid. Semilente insulin, no longer available, was a more amorphous compound and had a peak and duration of action slightly longer than that of regular insulin.

Long-Acting Insulin

Ultralente is very stable crystalline insulin that has its peak activity 8–10 h after injection and a duration of action of ~20 h.

Insulin glargine (Lantus) is an insulin analog with two modifications to human insulin. The first is the addition of two positive charges (two arginine molecules) to the C-terminus of the b-chain, which shifts the isoelectric point from a pH of 5.4 to 6.7, making the molecule more soluble at a slightly acidic pH and less soluble at the physiological pH of subcutaneous tissue. The second modification, the replacement of A21 asparagine by glycine, stabilizes the molecule.

When injected subcutaneously, glargine, which is a clear solution, forms a microprecipitate at the physiological, neutral pH of the subcutaneous space. Slow dissolution of the glargine precipitate at the site of injection results in relatively constant and peakless delivery over 24 h. Clinical trials have demonstrated lower fasting glucose levels and less hypoglycemia with glargine than with NPH.[10]

Glargine has ~50–60% the affinity of human insulin for the insulin receptor, an in vitro potency (based on lipogenesis) of 60%, but equivalent in vivo potency because the plasma concentrations

reached are twice those of insulin.[16] Glargine also has up to six times greater affinity for IGF-1 receptors than does human insulin.[9] Concern about one study showing progression of retinopathy in type 2 diabetes was diminished because the most common retinal side effect of IGF-1 is optic disc swelling, and that was not noted in the study.

An important difference between glargine and NPH is that glargine is clear in solution, whereas NPH is cloudy. This may be a disadvantage for patients who have relied on the cloudy solution of NPH, lente, and ultralente to visually distinguish them from the clear solution of regular insulin and lispro. Patients should be advised to mark their vials clearly.

On the other hand, the advantage of glargine's clarity over "cloudy insulins" is that it can be injected without first being re-suspended (usually by rolling the vial or cartridge), which is a major cause of variability in absorption of the intermediate-acting insulins. Patients' inability to accurately re-suspend NPH in cartridges before injection was shown to result in variation in NPH content from 5 to 214%.[17]

Detemir is a long-acting insulin still under development. Detemir is covalently acylated with fatty acids on lysine at position 29, which increases its binding to albumin and thus delays its absorption from subcutaneous tissue.[18] The large size of detemir may also reduce its rate of transendothelial transport.[19]

Pharmacodynamically, detemir has decreased insulin and IGF-1 receptor affinity.[9] In patients with type 1 diabetes, detemir and NPH were equally effective in maintaining glycemic control, although detemir was administered at a higher molar dose. There was less intra-subject variation in fasting glucose with detemir during the last 4 days of the study, and results indicate that there was a reduced risk of hypoglycemia compared with NPH.[20] More studies are needed to determine the usefulness of this unique insulin, especially in the presence of a large flux of free fatty acid.

Physiological Principles of Insulin Replacement

Prandial Insulin

The concentration of glucose in the plasma of healthy individuals remains within a normal range despite large fluctuations in nutritional intake (think of Thanksgiving) and physical activity (a marathon). The fundamental reason for this is the precise balance between insulin secretion from pancreatic β-cells and insulin action on sensitive tissues, primarily adipose tissue, liver, and muscle. After healthy individuals eat, their plasma glucose concentration increases rapidly, peaks in 30–60 min, and returns to basal concentrations within 2–3 h.[21]

Normal plasma insulin concentrations have a similar pattern. Initially, the insulin response to glucose intake during a meal is characterized by a rapid increase in insulin secretion that is completed within 10 min (first phase). This is followed by a sustained secretion of insulin above basal rates, which can last for several hours before declining to basal rates (second phase).[22–24] All patients with type 1 diabetes and those with type 2 diabetes who no longer produce adequate endogenous insulin need replacement of insulin that mimics these phases of insulin production.

Insulin administered at mealtimes to mimic the first-phase response of insulin production is called "prandial insulin." It should be regular insulin or a rapid-acting insulin analog so that the insulin is able to enter the bloodstream quickly enough to cover the initial elevation in glucose. To assist in this process, a lag time is instituted between insulin injection and food consumption to allow optimization of timing between insulin release from the subcutaneous depot and the initial glucose rise. The more rapid-acting the insulin, the shorter the lag time needed before food consumption. For example, lispro or aspart can be given just before meals but optimally should have a lag time of 10–15 min. Regular insulin requires a longer lag

time of 30–60 min, with even longer lag times required for premeal hyperglycemia.

Prandial insulin, however, must mimic not only the first phase of insulin production, but also the second-phase response to cover the elevation of glucose during and after meals. Prandial insulin therefore must have continued absorption over the mealtime glucose rise. Meals during which glucose is likely to be elevated over a shorter period of time, such as high-carbohydrate meals, are better controlled with rapid-acting lispro or aspart. Meals that will likely have a prolonged second phase, such as high-protein or high-fat meals, may be better covered by regular insulin, which has a more prolonged duration of action. (Regular insulin still is not acting physiologically here, however, because it fails to adequately cover the initial rise in glucose.) Prandial insulin may therefore be either rapid-acting for smaller, more carbohydrate-rich meals or regular for meals that are higher in fat or protein. Many patients find that using combinations of regular insulin and either lispro or aspart works well for certain mixed meals.

Post-glycemic glucose excursion, defined as the change in glucose from the pre-prandial level, has been clearly demonstrated to be lower with lispro than with regular insulin.[8,25] However, lispro has not been found to lower overall HbA$_{1c}$ concentrations more than regular insulin.[10] This likely is a result of inadequate basal insulin coverage (discussed below) when lispro dissipates before the next meal. Therefore, if adequate basal insulin were to be provided, patients should benefit from lower HbA$_{1c}$ concentrations over time. Deterioration of post-prandial glucose control has not been seen with aspart, suggesting that aspart has a longer duration of action than does lispro.[26]

People with diabetes can adjust the type and dose of prandial insulin they use on a per-meal basis if they know or plan the types of meals they are about to consume.

Post-Absorptive (Basal) Insulin
In individuals without diabetes, once food has been absorbed and glucose is no longer elevated in the bloodstream (the normal fasting state, also called the post-absorptive state), hepatic glucose production increases while the secretion of insulin is inhibited. This "basal insulin" concentration is that amount of insulin required in the post-absorptive state to restrain endogenous glucose output primarily from the liver. Basal insulin also limits lipolysis and excess flux of free fatty acids to the liver.

The lack of adequate basal insulin stimulates hormone-sensitive lipase and free fatty acid release from fat stores, which in turn stimulates hepatic production and release of ketone bodies, leading to ketogenesis in patients with type 1 diabetes. This is not usually seen in patients with type 2 diabetes because insulin resistance and therefore continued high levels of insulin during the post-prandial state maintain inhibition of hormone-sensitive lipase.

Basal insulin may also be administered through CSII with an insulin pump. Glucose excursions during meals are covered by boluses of insulin delivered by the pump. Most insulin used for CSII is rapid-acting because HbA$_{1c}$ concentrations were found to be significantly lower after 3 months of CSII with lispro compared to regular insulin.[27] However, one recent study showed no difference in HbA$_{1c}$ concentrations whether lispro was delivered via CSII or as multiple daily injections using NPH as the basal component.[28]

Administration of Insulin

Insulin Algorithm
One of the most confusing issues in the treatment of diabetes concerns the "insulin sliding scale."[29] This is a regimen usually practiced in hospitals where glucose monitoring may occur only when nursing staff are available to check blood glucose levels. This is a retrospective correction of hyperglycemia with short-acting insulin without regard to

caloric intake or physiological insulin delivery. Under this regimen, blood glucose checked at bedtime is treated with the same type of insulin despite the fact that no further caloric intake is planned for the rest of the night, which almost guarantees the occurrence of nocturnal hypoglycemia.

A better tool for managing diabetes is the insulin algorithm. This requires patients to check their blood glucose before meals and adjust the insulin they administer before eating based on both the glucose level and the caloric value of the anticipated meal. For example, a patient checks her blood glucose before lunch and finds that it is 170 mg/dl. Because her normal lunchtime dose of aspart is 6 units for a meal containing 60 g carbohydrate (1 unit for every 10 g carbohydrate), she needs to supplement 1–2 units of aspart for every 50 mg/dl her blood glucose is above her target value of 120 mg/dl. She therefore administers 6+2, or 8 units of aspart before eating lunch. If she also wanted to eat 10 g more carbohydrate than usual, she would need to take an additional 1 unit of aspart to cover the extra 10 g carbohydrate. In this case, she would administer 6+2+1, or 9 units of aspart before lunch instead of her usual 6 units.

Patients' understanding of the relationship between carbohydrate counting and insulin requirements improves with experience, but the assistance of a dietitian is almost always necessary. In patients with type 1 diabetes, the amount of lispro or aspart injected before meals may be small initially (i.e., 1 unit for every 15–20 g carbohydrate). This dose would be increased every 3 days or so as patients come to understand how they respond to a particular dose of insulin and how well that dose covers the amount of carbohydrate they consume. This information requires frequent self-monitoring of blood glucose before and after meals. In patients with type 2 diabetes, the initial dose of prandial insulin may be significantly higher because of insulin resistance.

If patients note hypoglycemia before a meal, they can administer their usual dose of lispro or aspart and then begin eating immediately to prevent further hypoglycemia. In such cases, the lag time can also be eliminated with regular insulin. Patients commonly make the mistake of omitting all prandial insulin in the presence of premeal hypoglycemia. Even if the basal insulin dose is otherwise correct, this will result in very high glucose levels (often >300 or 400 mg/dl in type 1 diabetes) during and after the meal

Once-Daily Insulin

This regimen is considered non-physiological because it does not mimic normal insulin secretion, which consists of both basal and prandial insulin release. However, it may still be used effectively for patients with type 2 diabetes when oral regimens become inadequate for maintaining glycemia within the target range. In such cases, the oral regimen should be continued with insulin added at bedtime to suppress nocturnal hepatic glucose production.[30] Typically, patients require 0.3–0.4 unit/kg/day of intermediate-acting insulin or glargine, although initial doses may be much more conservative.

There may be an increased risk of hypoglycemia in patients with type 2 diabetes with bedtime NPH. Rosenstock et al.[31] did not see nocturnal hypoglycemia in patients with type 2 diabetes who were given bedtime NPH; however, data from those subjects were pooled with data from subjects given a single nightly injection of glargine. Ultralente has a lower serum peak level than NPH and therefore may be preferable to NPH because of decreased nocturnal hypoglycemia.[8]

Another option would be to use an intermediate-acting insulin with a prandial insulin once daily before dinner, particularly if bedtime glucose levels are unacceptably high. This can often be accomplished conveniently with a premixed insulin (either 70% NPH, 30% regular or 75% neutral protamine lispro,

25% lispro). Because many patients with type 2 diabetes start insulin so late in the disease process when there is little insulin secretion, this once-daily injection regimen often will not be sufficient to achieve glycemic targets.

Twice-Daily Insulin Regimens

The administration of basal insulin twice a day may suffice for patients with type 2 diabetes who still have significant endogenous insulin production. Injection of basal insulin to mimic insulin normally produced during the post-absorptive state is usually accomplished by utilizing a long-acting insulin, such as ultralente, or an intermediate-acting insulin, such as NPH.

In one option for a twice-daily regimen, one injection occurs before breakfast to cover basal glucose production during the day. A second shot is then administered at bedtime to inhibit nocturnal hepatic glucose production. Again, many patients with type 2 diabetes will do well with this non-physiological regimen, which is inappropriate for those with type 1 diabetes with endogenous insulin deficiency.

In a different option for twice-daily injections, regular insulin or lispro can be mixed with NPH or ultralente insulin in the same syringe. The shorter-acting insulin should be drawn into the syringe first to avoid contaminating the short-acting insulin preparation with longer-acting insulin. The zinc in ultralente retards the onset of action of the regular insulin and so it should be immediately injected after withdrawal from the vial.

Regular insulin is not affected by mixture with NPH and therefore is sold in premixed combinations of 70/30 or 50/50 NPH and regular. These mixtures limit patients' ability to alter the dose of either insulin individually, although additional prandial insulin may be added for premeal hyperglycemia. This is not as convenient if the premixed insulin is being used with a pre-filled pen device. With severe insulin deficiency as seen in type 1 or long-standing type 2 diabetes, premixed insulins

will not provide enough flexibility to reach glycemic targets.

When regular insulin is combined with intermediate-acting insulin, the extended duration of action can overlap with nocturnal basal insulin, causing hypoglycemia in the early hours of the morning. A bedtime snack is therefore recommended for patients who use this combination. This same overlap can cause pre-prandial hypoglycemia at lunchtime. This hypoglycemia is not seen as frequently with the rapid-acting analogs in combination with intermediate-acting insulin, negating the requirement of a bedtime snack. If patients choose to have a bedtime snack, however, they may need to include a small dose of a rapid-acting insulin analog with their snack.

Flexible Insulin Regimens

The same flexible insulin regimens used in patients with type 1 diabetes are also used in patients with type 2 diabetes. Intermediate-acting (basal) insulin may be administered at bedtime, although it is usually used twice daily. Some use it more frequently. Prandial insulin is provided by rapid- or short-acting insulin administered with each meal. In type 1 diabetes, patients' weight is used to determine the total amount of insulin needed as 0.4–0.8 units/kg/day, although some women may require less than this amount. Patients with type 2 diabetes frequently require >1.0 unit/kg/day. As a rule of thumb, approximately half of the total daily insulin dose is basal insulin.

With NPH-based regimens, it becomes difficult to separate the basal from the prandial insulin because NPH may act as both. For example, if NPH is administered in the morning, it would serve as basal insulin in the late morning after breakfast is absorbed, as prandial insulin partly if not totally responsible for the lunch meal, and then as basal insulin again for the time period after lunch is absorbed.

This is one of the primary disadvantages of using large doses of NPH in the morning. Furthermore, large doses of

morning NPH can result in late-morning hypoglycemia or, at the very least, leave patients with little if any flexibility in the timing of their lunch. One way to minimize this problem is to use small doses of morning NPH with a prandial dose of rapid- or short-acting lunchtime insulin.

Regimens of three daily injections became popular in the 1980s. NPH and regular insulin were administered in the morning, with the NPH acting as both basal and prandial insulin. Regular insulin was administered at dinner, and NPH was then provided at bedtime. This was an improvement over the traditional twice-daily long-acting or mixed regimens, but the problems associated with this regimen are now obvious. First, there was no flexibility with the timing of the midday meal. Second, there was frequent hyperglycemia when the morning insulin dissipated before supper. And finally, there was more nocturnal hypoglycemia from both the long duration of the dinnertime regular insulin and the early action of the bedtime NPH.

By adding a prandial lunchtime injection, the morning NPH could be decreased, if not eliminated. This resulted in much greater flexibility and the ability to change the timing of meals, especially the midday meal. Unfortunately, because of the peaking action of NPH and ultralente, this regimen was still far from perfect and often resulted in erratic glucose levels. Many providers and patients decided to eliminate multiple injections altogether and proceed to insulin pump therapy using first regular insulin and later lispro and aspart as both basal and prandial insulins.

The introduction of glargine in 2001 was, in our opinion, an important milestone in efforts to maximize insulin therapy. With this new, long-acting insulin, prandial and basal insulins can be identified more accurately, and initial dosing is simplified.

Let's look at several examples. The first case involves a 55-year-old woman with a 15-year history of type 2 diabetes. She weighs 80 kg. She was started on 10 units of bedtime NPH 3 years ago and

successfully reduced her HbA_{1c} concentration from 9.2 to 6.8%. Over time, however, bedtime insulin alone was not successful in controlling her evening glycemia despite increasing the dose to 30 units/day (0.38 units/kg/day).

She was started on a pre-mixed dose of 70/30 NPH and regular both before breakfast and before dinner. Her dose was increased to 40 units in the morning, 30 units before dinner (0.88 units/kg/day), and for about a year she did well maintaining her HbA_{1c} between 6.9 and 7.4%.

More recently, her pre-dinner and fasting glucose levels have been increasing, and adding more insulin has resulted in pre-lunch and nocturnal hypoglycemia. She was tried on a pre-mixed combination of 75/25 neutral protamine-lispro and lispro, but this did not improve her fasting glycemia, and her pre-dinner glucose levels were actually higher on this insulin.

It was then decided to stop the pre-mixed insulin in favor of using lispro with each meal and NPH at bedtime. She was now taking 15–20 units of lispro with each meal and 25 units NPH at bedtime (~1 unit/kg/day). On this regimen she did much better in keeping her HbA_{1c} concentration consistently between 6.5 and 7%. She did have occasional nocturnal hypoglycemia, and in 2001 she was switched to glargine at bedtime administered in the same dose as the NPH. After 6 months on this regimen, she had no episodes of nocturnal hypoglycemia.

The good news about this case is that her control is now within published goals.[32] However, she would prefer to take fewer injections than her current four per day. Sometimes, this is possible as evidenced by the fact that she did well for some time on a less complicated regimen. This is a common scenario because the natural history of the progression of β-cell deficiency requires not only more insulin, but also a more physiological regimen. Certainly, this patient could have been maintained on two daily injections of NPH and regular insulin,

but it would have been much more difficult (if not impossible) for her to achieve her glycemic targets. In our opinion, the most common mistake made with individuals who have insulin-requiring type 2 diabetes and severe insulin deficiency is not providing prandial insulin with meals.

Our next example involves a 70-kg, 32-year-old man with a 10-year history of type 1 diabetes. There is no history of severe hypoglycemia (defined as requiring the assistance of another person). He presents on twice-daily NPH and regular insulin, with a total dose of 50 units/day given as 20 units of NPH plus 10 units of regular before breakfast and 10 units of NPH plus 10 units of regular before dinner. His HbA_{1c} is 8.8%, and he has little understanding about how to adjust insulin based on food intake. He does however add additional regular insulin for premeal glucose levels above 200 mg/dl.

We would start by helping this patient become comfortable adding either lispro or aspart with meals for premeal hyperglycemia. A more appropriate glycemic target would be 150 mg/dl, and one possible algorithm to start with would be to add 1 unit of lispro or aspart for every 50 mg/dl above 150 mg/dl.

We would then teach him how to match prandial insulin with food because most patients do well with carbohydrate counting. While he is learning this, we would put him on a more logical insulin regimen using glargine as the basal component.

We would leave his total insulin dose the same because it seems appropriate at 0.7 units/kg/day. Because about half of the total dose is basal insulin, we would start at 50 units ÷ 2 = 25 units. The glargine package insert[33] suggests that when switching from NPH to glargine, one should start with 80% of the total current dose of NPH. Because our patient was using 30 units/day or NPH, we would therefore give 30 units × 0.80 = 24 units of glargine/day.

For this patient, then, either calculation results in about the same dose. The

problem occurs when someone comes in on a regimen with NPH alone or with little prandial insulin. Thus, when calculating initial glargine doses, it is wise to determine whether the current basal dose of NPH is about half the total dose.

While our patient is still learning to count carbohydrates, we would have to take an educated guess about how much prandial insulin to use. We would only use lispro or aspart to start (perhaps later adding regular insulin for high-fat meals). If about 25 units will be required for his total prandial dose, a simple way to start is to take a brief diet history and determine what percentage of calories he consumes at each meal. This particular patient eats a very small breakfast (10% of his total daily calories) with a larger lunch (30% of daily calories) and a large dinner (60% of daily calories). Therefore, we suggest about 3 units of prandial insulin with breakfast, 7 units with lunch, and 14 units with dinner. Our patient feels that the dinner dose is too high, and it is decided that he will use only 10 units at dinner as a starting point. Over time, more precise requirements will become obvious, but we need to emphasize that frequent self-monitoring of blood glucose and dietary instruction are necessary to maximize his chances of success.

Conclusion

A variety of basal and prandial insulins are now available for health care providers to help manage hyperglycemia in patients with diabetes. These new insulins can be combined or added to established insulins in flexible regimens that can and should be individualized with patients to achieve glycemic control. Utilizing an insulin algorithm and carbohydrate counting not only educates patients about their diabetes but further improves their glycemic control and gives them added control over their diabetes and lifestyle. Insulin pens and insulin pumps provide further diversity for insulin delivery. No matter what the insulin regimen or means of insulin administration, however, successful diabetes management requires frequent self-monitoring of blood glucose.

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