Diabetes Treatment, Part 3: Insulin and Incretins

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Editor's note: *This article is the fifth in a 12-part series reviewing the fundamentals of diabetes care for physicians in training. Previous articles in the series can be viewed at the* Clinical Diabetes *website (http://clinical.diabetesjournals.org).*

Insulin is the oldest and the most effective treatment to control glucose levels in diabetic patients. It was first used in the treatment of diabetes by Frederick Banting and Charles Best in 1922. Although originally thought to be a cure for diabetes, it soon became evident that insulin was a method of controlling the disorder. Insulin has been the most versatile of diabetes treatments because it may be used to control any degree of hyperglycemia of type 1 or type 2 diabetes. Although it was initially prepared by isolation from animal pancreatic tissue, insulin is now prepared through recombinant DNA techniques using microorganisms. Use of recombinant insulin has decreased the immunogenicity of commercially available insulin.

Type 1 diabetes is characterized by a loss of ß-cells and therefore an absolute insulin deficiency. The mainstay of therapy, therefore, is insulin treatment. Because the disease does not affect insulin sensitivity, patients typically require small doses of insulin to maintain control of glucose levels. Type 2 diabetes, however, is characterized by preexisting insulin resistance followed by a relative insulin deficiency. As a result of insulin resistance and progressive insulin deficiency, patients with type 2 diabetes typically require higher doses of insulin and gradual upward titration of insulin doses.

Since the discovery of insulin and its use to treat diabetes, insulin has been combined with additives and modified at the molecular level to change its pharmacokinetic properties. Some insulin preparations accelerate insulin's effects in the bloodstream, whereas others prolong the pharmacokinetic profile. These insulin preparations may be used alone or in combination with other insulins in formulating an insulin regimen.

Rapid- and Short-Acting Insulins

Regular insulin. Regular insulin was the first available insulin preparation and therefore the first short-acting insulin. At the time of injection, regular insulin self-associates to form hexamers, which are poorly absorbed into the circulation. Gradually, insulin hexamers dissociate into dimers and monomers, which enter the bloodstream more rapidly. Formation of hexamers delays absorption and activity of regular insulin. Regular insulin tends to have an onset of action 30–60 minutes after injection, a peak effect in 2–3 hours, and a total duration of action of 8–10 hours. Because of its delayed onset, patients are typically instructed to use regular insulin ~ 30 minutes before a meal.

Another disadvantage of regular insulin is that its pharmacokinetic profile does not overlap with the rate of carbohydrate absorption as well as that of insulin analogs (discussed below), and this mismatch can produce postprandial hyperglycemia soon after a meal and delayed hypoglycemia several hours after a meal. This effect may be more pronounced in patients with type 1 diabetes because of their relatively high insulin sensitivity. Regular insulin, however, does have some advantages over other insulin formulations. Because it is bioidentical to endogenous insulin, immunogenicity is very low and much lower than animal insulin preparations. Cost is also a major advantage of regular human insulin, which sells for about one-fourth the price of insulin analogs.[1–3]

Insulin analogs. Three rapid-acting insulin analogs are available in the United States: lispro, aspart, and glulisine. They all contain modifications to the insulin molecule that cause rapid dissociation of hexamers into dimers and monomers after injection. Rapid dissociation leads to rapid absorption. As a result, they may be administered at the beginning of a meal, which many patients find more acceptable and easier to remember.[4] All rapid insulin preparations are available in both vial and pen devices. Lispro and aspart both have an onset in 5–15 minutes, a peak of activity in 30–90 minutes, and a duration of action of 4–6 hours. These insulins deliver approximately twice the maximal concentration and take approximately half as much time to reach maximal concentrations as regular insulin injected subcutaneously.[4,5] Glulisine, the newest insulin analog, has a faster onset than lispro.[6] As a result, it may be administered after a meal rather than immediately before a meal. Rapid-acting insulins exhibit better control of postprandial glucose levels and are less likely to

cause postprandial hypoglycemia than regular insulin. There also may be less variability in insulin levels from injection to injection with rapid-acting insulin analogs.[1] A major disadvantage of these formulations, however, is price. The cost of insulin analogs is approximately four times that of regular human insulin.

Inhaled insulin. In addition to subcutaneous injection, regular insulin may also be inhaled. When inhaled, regular insulin exhibits a different pharmacokinetic profile compared to injection; its onset of action is faster and in fact is similar to that of lispro. Time to maximal effect for inhaled insulin is also similar to lispro, but the duration of action is longer than that of lispro and very similar to that of injected regular insulin.[7] Patients using inhaled insulin, therefore, may use it immediately before a meal as with rapid-acting analogs, but must monitor for a prolonged effect, as with subcutaneous regular human insulin.

Phase III testing did not demonstrate a decline in pulmonary function testing after 6 months of inhaled insulin therapy, but there was a slightly higher incidence of cough.[8] Patients should undergo pulmonary function testing before using inhaled insulin; those with significant pulmonary disease or who have smoked in the past 6 months should not use inhaled insulin. Patients must also have a specialized inhaler to use inhaled insulin. Another disadvantage is price; as with rapid-acting insulin analogs, the price of inhaled insulin preparations is much greater than that of injected regular human insulin. The first commercially available inhaled insulin is scheduled to be withdrawn from the market due to low sales in 2007; however, other versions of inhaled insulin are planned for release in upcoming years.

Intermediate- and Long-Acting Insulins

The effects of regular insulin may be delayed and prolonged by several modifications to either the solution containing the insulin or the insulin molecule itself. The result is insulin that may be used to replace the body's basal insulin requirements. Currently, one intermediate-acting and two long-acting insulins are available in the United States.

Protamine solutions. Addition of protamine to regular insulin yields neutral protamine Hagedorn (NPH) insulin. The onset of NPH insulin is typically in 2–4 hours, with a peak of activity in 4–10 hours and an effective duration of 10–16 hours. Because of its peak action, NPH is associated with a higher incidence of hypoglycemia than insulin detemir or glargine (discussed below), which tend to have less of a peak in action. NPH insulin may be used twice or three times daily as a basal insulin or used in the morning to act as a combination of basal and bolus insulin to cover the noon meal. Rapid-acting insulins, including lispro and aspart, are also available in protamine solutions to prolong their effects. When in such solutions, their long-acting component is very similar to that of NPH.[5] NPH insulin is inexpensive and available without a prescription. A possible shortcoming of NPH is that there may be significant intra-patient variation in absorption, thus causing variations in peak and duration from injection to injection.[3,9]

Zinc solutions. The action profiles of insulin may also be prolonged by addition of zinc to the preparation. Such a solution yields lente and ultralente insulin, which are no longer available in the United States.

Long-acting analogs. Long-acting insulin analogs attempt to replicate the body's basal insulin secretion. Currently, glargine and detemir are available for such therapy. Both are available in vial and pen forms. Glargine was originally released in 2001. Like rapid-acting insulin analogs, glargine is a modified insulin molecule that contains changes in amino acids to alter its absorption into the bloodstream. However, these substitutions in glargine affect its solubility such that it is only soluble in an acidic solution (which is present in the vial of insulin). Once injected beneath the skin, the buffering action of interstitial fluid neutralizes the pH such that glargine is no longer soluble and precipitates under the skin to form a reservoir of insulin. It is the precipitation of insulin out of solution that produces the extended half-life of glargine, which approaches 24 hours.[3,4] Prolonging the action of insulin in this manner reduces its peak effect, and when used in insulin regimens, produces a lower risk of hypoglycemia than NPH.

Glargine is administered once daily, which may improve compliance. However, it is two to three times more expensive than NPH and has not been conclusively shown to reduce hemoglobin A_{1c} (A1C) levels compared to NPH. Injection of glargine, especially in larger doses, may cause a burning sensation likely resulting from the acidity of the solution.

Insulin detemir was released more recently than glargine and uses a different approach to extend its half-life. The insulin molecule is bound to a 14-carbon fatty acid. The addition of the hydrophobic fatty acid leads to albumin affinity, and, therefore, the insulin travels through the bloodstream bound to albumin. Because only the free fractions of the insulin molecules are active, the effective half-life of detemir is prolonged compared to regular insulin. The duration of action of detemir is 14–21 hours at commonly prescribed doses, but like other insulins, the duration is longer at higher doses. It may also have a more predictable glucose-lowering effect than NPH insulin.[10,11]

Detemir is approved for use once or twice daily. It is associated with a lower risk of hypoglycemia than NPH insulin in patients with type 1 or type 2 diabetes.[11,12] Like glargine, it is available as a pen or in a vial, but also like glargine it is much more expensive than NPH and has not been definitively shown to improve A1C compared to NPH.

Insulin Regimens

Traditionally, glucose has been controlled using an injection of NPH and regular insulin in the morning and in the evening (the "spit-mix" regimen). Because these insulins may be mixed, this approach minimizes the number of injections required. Regular insulin from the morning injection acts to control glucose levels after breakfast and with its extended action also assists in meeting basal insulin requirements. NPH, because of its combination of prolonged effect and peak of 4–10 hours, serves for both basal coverage and prandial coverage for the midday meal. The second injection of regular and NPH is typically given at suppertime. As in the morning, the regular insulin component provides prandial coverage for the evening meal, and the NPH component provides for basal insulin overnight. Additional regular insulin may be used at breakfast and supper to correct any hyperglycemia.

This traditional approach can be problematic, however. The overlap in the activity of regular insulin and NPH can cause considerable drops in glucose level, which often requires midmorning and bedtime snacking. Patients must also maintain a relatively inflexible daily schedule in which they eat lunch on time and consume predetermined amounts of carbohydrate based on the amount of NPH they have used hours ahead of time. Delaying lunch would typically result in hypoglycemia, whereas delaying breakfast or supper could cause hyperglycemia, as the effects of the previous dose of NPH wane.[4]

A newer approach to administering insulin involves using the newer long-acting insulin analogs to provide basal insulin coverage through one or two daily injections and rapid-acting insulin analogs to cover mealtime glucose excursions. This "physiological" approach requires at least four injections daily and attempts to more closely replicate the body's normal physiological insulin secretion. As a result, patients have greater flexibility regarding the timing of meals; they typically do not have to eat at a particular time of the day to avoid hypoglycemia (as long as their basal insulin doses are not inappropriately high). Rapid-acting insulin is usually dosed according to the amount of carbohydrate consumed at each meal. Patients should check glucose levels at each meal and administer additional rapid-acting insulin if necessary.[4]

Using a long-acting basal insulin rather than NPH is associated with a lower risk of hypoglycemia in patients with type 1 or type 2 diabetes.[5,9,13,14] However, this approach has not clearly resulted in improved A1C levels in large studies. It should also be noted that the expense of using two forms of insulin analogs is much greater than the cost of a regimen using regular and NPH insulins. Another variant of this approach is to use inhaled regular insulin for postprandial glucose control with basal insulin. Inhaled insulin offers rapid entry to the bloodstream, but its prolonged activity could lead to postprandial hypoglycemia, especially in patients with type 1 diabetes.

Initiating Insulin Therapy

How best to initiate insulin in patients with type 2 diabetes is a common dilemma for many physicians. Because type 1 diabetes is caused by absolute insulin deficiency, all type 1 diabetic patients will require insulin administration. Insulin therapy should therefore be initiated at the time of diagnosis, with a physiological insulin regimen as described above as the preferred approach. Type 2 diabetes, however, is characterized by a slower decline in ß-cell function and the eventual need for insulin therapy, but the timing of insulin initiation can be a source of debate on the part of physicians and dread on the part of patients.

According to a recent joint consensus statement from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes, indications for insulin therapy in type 2 diabetes include A1C > 7% despite lifestyle modification and use of metformin. However, insulin may be delayed until after addition of a sulfonylurea and/or a thiazolidinedione has failed to adequately control glucose levels. Insulin is typically initiated in the form of basal insulin added to existing oral agents at a dose of 0.2 units/kg of body weight/day and increased every 5 days until the fasting glucose level is < 100 mg/dl.[3,15] Other studies have suggested that initiation of insulin in a premixed formulation may be an acceptable alternative.[16] As insulin deficiency progresses in type 2 diabetes, mealtime insulin may be added to control postprandial glucose levels and to allow for correction of hyperglycemia.

Important Considerations

In using and initiating insulin, it is important to remember that certain situations mandate greater caution to help avoid hypoglycemia. The ADA recommends that all patients using multiple insulin injections should check their glucose level three or more times daily and that, even in patients using less frequent insulin injections, self-monitoring of blood glucose levels is useful.[17] This is especially true for avoiding hypoglycemia. It is important to counsel insulin-using patients to check their blood glucose before driving, swimming, or operating heavy machinery and to avoid such activities if they are hypoglycemic.

Certain patient populations have a higher risk of developing hypoglycemia. Patients with renal or hepatic dysfunction are one such population. The liver and kidneys are responsible for virtually all of the body's gluconeogenesis and glycogenolysis as well as degradation of insulin. Patients with hepatic or renal insufficiency therefore have a combination of less endogenous glucose production and a longer insulin half-life, which can expose them to rapid glucose drops. It is important to initiate insulin

at lower doses in these patients and to instruct them to remain vigilant for hypoglycemia.

Other patients who may experience a higher risk of hypoglycemia are those with pancreoprivic diabetes (injury or removal of the pancreas). These patients, in addition to losing β-cells, also have a deficit of α-cells of the pancreas. The result is glucagon deficiency and impaired recovery from hypoglycemia. It is important to instruct these patients about the signs, symptoms, risks, and appropriate treatment of hypoglycemia. They may also require a prescription for an emergency glucagon kit, although it is possible that patients with hepatic insufficiency may have an impaired response to glucagon. Patients should also be instructed to wear medical alert identification.

Incretins and Amylin

Incretins are gastrointestinal peptides that affect glycemic control. Their existence was hypothesized when it was noted that oral glucose stimulated two to three times more insulin release than the same amount of glucose administered intravenously. Subsequent investigation has revealed the presence of several hormones that play a significant role in postprandial glucose control, including amylin, gastric inhibitory peptide (GIP), and glucagon-like peptide 1 (GLP-1). During the past few years, analogs of these hormones have become available for use in controlling diabetes. Because they have only recently been commercially available, many of their mechanisms of action and long-term effects are not yet fully understood.

Pramlintide. Pramlintide is an analog of amylin, a naturally occurring hormone produced along with insulin by pancreatic β-cells. Levels increase postprandially and typically correlate with insulin levels. As with insulin, amylin levels are very low in type 1 diabetes; however, levels may be elevated in patients with insulin resistance.[18–20] Administration of exogenous amylin in the form of pramlintide has been shown to decrease postprandial hyperglycemia in patients with type 1 or type 2 diabetes who are treated with insulin. The major mechanism of action appears to be inhibition of gastric emptying and suppression of glucagon release. Clinically, it also suppresses the appetite in those who receive it.

Pramlintide's improvement in overall glucose control has been modest in clinical trials at ~ 0.3%; however, those using the medication have also experienced weight reduction of ~ 1.0–1.5 kg in patients with type 1 diabetes and ~ 2.0–2.5 kg in patients with type 2 diabetes. Usual dosage for type 1 diabetes is 15 µg before meals, titrated eventually to 60 µg. Patients with type 2 diabetes usually start with a dose of 60 µg at mealtimes, titrated eventually to 120 µg at mealtimes.

Use of pramlintide has been shown to increase the risk of insulin-induced severe hypoglycemia in patients with type 1 diabetes; therefore, patients should start at a low dose as described above and should decrease prandial insulin by 50% and monitor their blood glucose closely for hypoglycemia.[19,21–24] Pramlintide therapy is relatively expensive compared to generic insulin, and pramlintide is not currently available in a pen for administration.

Exenatide. Exenatide is an analog of GLP-1, a naturally occurring incretin produced by the L-cells of the distal ileum. GLP-1 acts to stimulate insulin release from the pancreatic β-cells, suppress glucagon release from the pancreatic α-cells, slow gastric emptying, and increase satiety.[19,25,26] Response to GLP-1 may be slightly blunted in type 2 diabetes.[27] Interestingly, increases in GLP-1 may be responsible for some of the weight loss after roux-en-Y gastric bypass surgery in patients with type 2 diabetes.[28]

Administration of exenatide in patients with type 2 diabetes has similar effects. Clinically, the result is a reduction in A1C of ~ 1%. Preliminary studies suggest that a significant proportion of patients with type 2 diabetes using insulin may be successfully transitioned from insulin to exenatide in addition to their oral agents.[29] Most patients experience significant weight loss of ~ 2.5 kg when exenatide is used in addition to metformin and ~ 1 kg when it is added to a sulfonylurea.[19,30–32]

Exenatide is not indicated for simple weight loss. Patients typically use 5 µg before breakfast and supper, and the dose is increased to 10 µg before breakfast and supper after ~ 1 month. To ease administration, exenatide is available in pens with 5-µg or 10-µg premeasured doses. Like pramlintide, the cost of exenatide is relatively high compared to that of generic insulin and other generic medications. Exenatide is not approved for use in the treatment of type 1 diabetes. It should also be noted that exenatide is indicated for use with sulfonylureas, metformin, or thiazolidinediones but is not approved for use as monotherapy.

Conclusion

Insulin therapy is the oldest and perhaps most versatile of diabetes treatments. Once a crude and imprecise treatment for hyperglycemia, it has become one of the most complex and refined treatments for diabetes today. The major limiting factor in insulin therapy is risk of hypoglycemia. Good understanding of the pharmacokinetics of insulin action and proper management of insulin regimens allow health care providers and patients to control blood glucose levels in most cases.

Increasingly, incretins and amylin are used before insulin therapy to improve glucose control and stimulate weight loss. They are especially useful in type 2 diabetes because of their effects on weight, but the need for injections limits acceptance of these therapies by some patients.

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