Update On Insulin Management in Type 2 Diabetes

Introduction
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The Evolution of Insulin Therapy in Diabetes Mellitus
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Individualizing Insulin Therapy
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Advances in Insulin Therapy:
A Review of Insulin Degludec
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LEARNING OBJECTIVES
After reading this supplement, the family physician will be able to:
• Compare the pharmacokinetics and pharmacodynamics of rapid-acting and long-acting insulin analogs with recombinant human insulins
• List the features of pens and other devices used to deliver insulin
• Describe the role of insulin in the management of patients with type 2 diabetes mellitus
• Identify strategies to address patient barriers to insulin therapy
• Identify different approaches to initiate insulin therapy
• Describe the results of phase 3 trials of ultra–long-acting insulin degludec

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Dr. Heile disclosed that he is on the advisory board and is a speaker for Novo Nordisk, and is a speaker for Amylin Pharmaceuticals.

Dr. Schneider disclosed that he is on the advisory board for Novo Nordisk.

Dr. Meneghini disclosed that he is on the advisory board and is a consultant for Novo Nordisk, is on the advisory board for Sanofi Diabetes, is a consultant for Valeritas, and has received grants or research support from Boehringer Ingelheim, Mannkind, and Pfizer. Dr. Meneghini is also a self-managed stock/shareholder in Dexcom.

Dr. Reid disclosed that he is on the advisory boards and speakers’ bureaus for Novo Nordisk and Sanofi.

Dr. King disclosed that he is a speaker and consultant for, and has received research support from, Eli Lilly, Novo Nordisk, and Sanofi.
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Discovery of Insulin

The discovery of insulin in 1921 by Banting and Best ushered in a new age of treatment—and hope—for patients with diabetes mellitus (DM). First administered to 14-year-old Leonard Thompson on January 11, 1922, insulin transformed the lives of patients with type 1 DM (T1DM). No longer were starvation diets the primary mode of treatment. Life saving in patients with T1DM, insulin has since become an important treatment option in patients with type 2 DM (T2DM) as well.

But as is often the case with medical breakthroughs, the discovery of the hormone that first reversed diabetic coma in dogs was only the beginning. Recognizing the crudeness of the pancreatic extract that he called isletin (after the islets of Langerhans, the insulin-producing tissue of the pancreas), Banting turned to chemist James Collip, also at the University of Toronto, who developed a process to remove the toxins and impurities from the pancreatic extract. Banting also recognized the limitation of using dogs as the source of isletin (the name of which was changed to insulin by the university) so he quickly turned to cattle as a more plentiful source. Not surprisingly, the demand for insulin skyrocketed within months of its first testing in humans by Banting and Best, so, in July 1922, licenses for the manufacture of insulin were given to several pharmaceutical companies.

Evolution of Insulin

While the clinical effects of insulin in patients with T1DM were dramatic, such as waking people from diabetic coma, enabling them to consume a normal diet, and improving long-term prognosis, problems were encountered. One was the challenge of balancing normoglycemia without causing hypoglycemia. The early insulin preparations acted relatively quickly and had a peak effect, but they did not provide a continuous, low level of basal insulin in the same manner as did pancreatic β cells. The time-action profile was, therefore, far from physiologically similar to endogenous insulin. The second problem was allergic reactions since the source of the insulin was nonhuman. Resolving these issues was the focus of intensive research over many decades.

To better balance normoglycemia without causing hypoglycemia, intermediate- and long-acting insulins were subsequently developed as basal insulins to prolong the duration of effect. Discovered in 1936, neutral protamine Hagedorn (NPH) insulin was released in 1950 as an intermediate-acting basal insulin. Although NPH insulin remains widely used today, recent guidelines have recommended against its use since the availability of insulin analogs (detemir and glargine), which provide a relatively flat profile for 24 hours and “yield better reproducibility and consistency, both between patients and within patients, with a corresponding reduction in the risk of hypoglycemia.” Other basal insulins such as Lente and Ultralente were introduced in the 1950s and used extensively for many years, but they had important limitations, such as wide variability in absorption and duration of effect, which led to inconsistent blood glucose control.

Along with efforts to prolong the duration of action of insulin, much scientific work was undertaken to reduce the risk for the allergic reactions first encountered with canine insulin, and then with bovine and porcine insulins. While the purity...
of these formulations improved over time with advances in chromatography, allergic reactions remained a limitation for some patients. The use of animal-derived insulins eventually gave way to synthetic human insulins, first approved by the US Food and Drug Administration in 1982. Consisting of the same amino acid sequence as insulin secreted by the human pancreas, synthetic human insulins are less likely to cause allergic reactions and have a faster onset and shorter duration of action compared with animal-derived insulins. The short-acting regular human insulin has now been largely replaced by rapid-acting insulin analogs (aspart, glulisine, and lispro) because the analogs are more physiologically similar to endogenous insulin and provide improved safety and tolerability. While allergic reactions do occur with insulin analogs, the prevalence is low.

**Insulin Analogs**

Some of the early insulin formulations included zinc for the binding of insulin to protamine to alter the pharmacokinetic properties of the drug. With the availability of recombinant DNA technology, it became possible to modify the insulin structure so as to yield analogs of human regular insulin with pharmacokinetic and pharmacodynamic properties that more closely mimic the effects of endogenous insulin secreted by the pancreas (FIGURE 1). Two groups of insulin analogs were developed: (1) those with an onset of action more rapid than that of regular human insulin (ie, the rapid-acting insulin analogs); and (2) those with a duration of action longer than that of NPH human insulin (ie, the long-acting basal insulin analogs) (TABLE 1). Premix insulin formulations are also available that combine a rapid-acting insulin analog with its intermediate-acting protamine suspension.

**Rapid-Acting Insulin Analogs**

The pharmacokinetic and pharmacodynamic profiles of the rapid-acting insulin analogs have been compared with those of short-acting regular human insulin. Many of those investigations have used the euglycemic clamp technique, which allows for the assessment of insulin absorption and insulin activity through simultaneous intravenous infusion of insulin and glucose to maintain a consistent glucose level, with close monitoring of blood glucose levels. Investigations have generally not measured the onset of biologic activity directly but have measured surrogate markers, such as the time to maximum plasma concentration ($t_{max}$). One comparison reported a $t_{max}$ of 70 minutes for insulin aspart compared with 129 minutes for regular human insulin, and 42 minutes for insulin lispro compared with 101 minutes for regular human insulin.

Onset of activity, duration of activity, and glucose-lowering effect are dependent on absorption of the insulin molecules from the injection site. Variability in absorption has been a limitation of some insulins, but variability is lower with the rapid-acting insulin analogs. The variability of $t_{max}$ between injections in the same patient with insulin aspart and regular human insulin has been reported to be 15% and 24% ($P < .05$), respectively. The respective variability of $t_{max}$ between individuals was 20% and 37% ($P < .001$). Greater variability in $t_{max}$ may contribute to greater variability in blood glucose levels as well as risk of hypoglycemia.

The shorter onset of action of the rapid-acting insulin analogs more closely mimics the postprandial physiologic profile of endogenous insulin secretion and activity relative to regular human insulin. Thus it would be expected that the rapid-acting insulin analogs may be administered within 15 minutes of a meal compared with the necessary 30 minutes with regular human insulin. The shorter preprandial administration time with the rapid-acting insulin analogs may improve patient-perceived convenience. Treatment outcomes may also be improved due to less potential for insulin administration to be followed by a missed or incompletely eaten meal.

Because the rapid-acting insulin analogs are more physiologically similar to endogenous insulin and provide a more rapid onset and time to peak activity relative to regular human insulin, the frequency of severe hypoglycemia observed with the rapid-acting insulin analogs after meals...
Also using the euglycemic clamp technique, the pharmacokinetic and pharmacodynamic properties of insulin detemir and insulin glargine were compared with those of NPH insulin in patients with T1DM or T2DM.29-32 One study was a head-to-head comparison of insulin detemir, insulin glargine, and NPH insulin in 54 patients with T1DM.32 Over the 24-hour period following the administration of 4 single subcutaneous doses of 0.4 U/kg, the time-action profiles (ie, the glucose infusion rates over time) of insulin detemir and insulin glargine were reported to be relatively flat, whereas that of NPH insulin had a more pronounced peak (Figure 2).32 Insulin detemir was reported to have significantly less intraindividual pharmacodynamic variability compared with insulin glargine and NPH insulin. The variability (as assessed by the coefficient of variation) of the glucose infusion rate area under the curve for the first 12 hours was 27% for detemir, 46% for glargine, and 59% for NPH insulin (P < .001 vs insulin glargine and NPH insulin). Over the first 24 hours, the coefficients of variation were 27% for detemir, 48% for glargine, and 68% for NPH insulin (P < .001 vs insulin glargine and NPH insulin). With respect to pharmacokinetics, the coefficients of variation of the maximum plasma insulin concentration were 18% for detemir, 34% for glargine, and 24% for NPH insulin.

Despite these pharmacodynamic and pharmacokinetic differences favoring the basal insulin analogs compared with
The evolution of insulin therapy

A recent meta-analysis comparing insulin glargine (once daily) to insulin detemir (once or twice daily) examined data from 4 trials comparing insulin glargine (once daily) to insulin detemir (once or twice daily) for the treatment of type 2 diabetes. Insulin glargine was associated with a lower risk of nocturnal hypoglycemia compared with insulin detemir (relative risk [RR] = 0.54; P < 0.001). The risk for overall hypoglycemia was also reported to be lower with insulin detemir and insulin glargine compared with NPH insulin (RR = 0.68 and RR = 0.89, respectively; P < 0.001 and P = 0.002). The risk for severe hypoglycemia was similar for insulin glargine or insulin detemir compared with that of NPH insulin.

Furthermore, some of the studies included in the systematic reviews used a treat-to-target design, in which equal glucose-lowering efficacy was maintained among treatments, thereby allowing comparisons of other insulin properties. An important difference between the basal insulin analogs and NPH insulin identified in the systematic reviews concerns hypoglycemia, particularly nocturnal hypoglycemia. Detemir and glargine were associated with significant reductions in nocturnal hypoglycemia compared with NPH insulin (both, relative risk [RR] = 0.54; P < 0.001).

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NPH insulin, evidence-based systematic reviews have concluded that overall glucose control is similar among the 3 basal insulins. These findings should be interpreted cautiously since the basal insulins were generally administered once daily in the studies included in the systematic reviews, although a few studies used a twice-daily regimen for insulin detemir or NPH insulin. Furthermore, some of the studies included in the systematic reviews used a treat-to-target design, in which equal glucose-lowering efficacy was maintained among treatments, thereby allowing comparisons of other insulin properties. An important difference between the basal insulin analogs and NPH insulin identified in the systematic reviews concerns hypoglycemia, particularly nocturnal hypoglycemia. Detemir and glargine were associated with significant reductions in nocturnal hypoglycemia compared with NPH insulin (both, relative risk [RR] = 0.54; P < 0.001). The risk for overall hypoglycemia was also reported to be lower with insulin detemir and insulin glargine compared with NPH insulin (RR = 0.68 and RR = 0.89, respectively; P < 0.001 and P = 0.002). The risk for severe hypoglycemia was similar for insulin glargine or insulin detemir compared with that of NPH insulin.

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lastling 24 to 52 weeks and involving 2250 people. The meta-analysis found no differences between the 2 basal insulin analogs with respect to glycemic control, as measured by the percentage of patients who achieved A1C ≤7.0% with or without hypoglycemia. In addition, no significant differences in overall, severe, and nocturnal hypoglycemia were identified. Insulin detemir was associated with less weight gain and insulin glargine with a lower number of injection-site reactions.

**Evolution of Insulin Delivery**

In addition to progressive improvements in purity and the time-action profile of insulin, there have been major advances in the devices used to deliver insulin that provide clinicians greater flexibility to meet patients’ needs and to resolve patients’ concerns. Advances in delivery systems include pens with shorter, smaller gauge, highly polished needles; pens with a “dial-a-dose” gauge that is easier to read; easy portability; and insulin-prefilled pens. These advances improve ease of use and dosage accuracy, likely reduce injection pain, facilitate discrete use in public places, and increase patient acceptance and adherence.

Of note, however, insulin pens must never be used in more than one individual, even if a needle has been changed, as is sometimes done in institutions. A clinical reminder from the US Centers for Disease Control and Prevention in January 2012 cautioned against pen reuse and sharing, citing an incident in which more than 2000 individuals were potentially exposed to the transmission of bloodborne pathogens because of inappropriate reuse and sharing of insulin pens. Another advance in insulin delivery is insulin-pump therapy, which has become even more promising with the advent of continuous glucose-monitoring devices and the availability of rapid-acting insulin analogs.

**Role of Insulin in Diabetes**

Recently, insulin has been recognized as a key treatment option for patients with T2DM, and is no longer considered last-line therapy. When used appropriately, insulin is the most effective glucose-lowering therapy available, with essentially no limit to the magnitude of glucose lowering. Insulin, particularly the insulin analogs, provides many treatment benefits, although some limitations remain.

**Benefits of Insulin**

Basal-bolus therapy using the combination of a rapid-acting insulin analog and a basal insulin analog may closely mimic the release of insulin from the pancreatic β cells. The use of an insulin pump, which uses only a rapid- or short-acting insulin (rapid-acting analog preferred) may also provide insulin in a pattern that most closely mimics endogenous insulin secretion. The administration of insulin via an insulin pump may be a good treatment option in patients with T1DM or those with T2DM who require intensive basal-bolus therapy.

The reduction of microvascular complications, such as nephropathy, neuropathy, and retinopathy, by achieving intensive glycemic control with the use of insulin, has been well established in patients with T1DM or T2DM. Nonetheless, the landscape of glycemic control changed with the completion of the Action to Control Cardiovascular Risks in Diabetes (ACCORD) trial, the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, and Veterans Affairs Diabetes Trial (VADT). Based on the findings from those trials, caution is advised against the indiscriminate setting of very low glycemic targets. Findings from subanalyses of data from those trials suggest that while most patients are likely to achieve a microvascular benefit from intensive control, others may potentially be harmed by cardiovascular events. Those likely to benefit are those with short-duration DM, a long life expectancy, and no significant cardiovascular disease. Those who may be harmed and in whom an A1C goal <7.0% may not be appropriate are those with a history of severe hypoglycemia, a limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbidities, or long-standing DM in whom the more stringent A1C goal may be difficult to attain.

**Misconceptions and Limitations Regarding Insulin**

Insulin therapy is considered by some clinicians and patients to be the most complicated and time-consuming of the glucose-lowering therapies. Concerns about self-injection, the need for dosage adjustment, and cost, as well as the stigma of insulin as last-line therapy, are common. Additionally, in some studies with follow-up to 24 months, patients’ adherence to insulin therapy has been reported to be 54% to 81% in patients with T2DM. When used properly, insulin is the most efficacious glucose-lowering therapy and, therefore, may help motivate patients to adhere to insulin therapy. Hypoglycemia and weight gain are also common concerns of patients and clinicians, although insulin analogs are an improvement compared with older insulins. The risk for hypoglycemia requires that patients be educated regarding the signs and symptoms and actions to be taken should a hypoglycemic episode occur. Self-monitoring of blood glucose is required and is of crucial importance in patients using multiple insulin injections or insulin-pump therapy. Devices for continuous glucose monitoring may also be used to reduce the incidence of hypoglycemia. Because weight gain associated with insulin therapy may be a demotivating factor in patients, lifestyle management and patient educa-
tion are essential. Education should include consequences of poor glycemic control and disease progression, and the expected benefits with regard to quality of life. Using a collaborative approach to individualize therapy and to match the type of insulin and insulin dosing with a patient’s lifestyle habits, such as food intake and daily activities, fosters patient self-management and may help to minimize the risks and maximize the benefits of insulin therapy.

Conclusions

Since its discovery nearly a century ago, insulin has evolved to greater purity, with pharmokinetic and pharmacodynamic profiles that more closely resemble insulin secretion by the pancreas. The insulin analogs are now recommended for treatment of patients with T1DM or T2DM because they are better tolerated and more physiologically similar to endogenous insulin compared with older formulations, including human insulins. Insulin analogs delivered and monitored with current pens and devices provide clinicians with improved ability to better manage patients with DM.

**REFERENCES**


