Insulin

Making Sense of Current Options

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KEYWORDS

• Insulin • Glargine U-300 • Insulin degludec • Basaglar • Lispro U-200 • Afrezza • Regular U-500 • Insulin therapy

KEY POINTS

- The evolution of insulin replacement products has sought to advance insulin replacement designs to mimic natural insulin secretory patterns with increasing accuracy.
- Newer insulins include longer acting basal insulins with reduced day-to-day variability, and concentrated and inhaled prandial insulins to more effectively cover postprandial insulin needs.
- Combination products are also evolving, including combinations of the longer-acting basal insulins with rapid-acting or glucagonlike protein-1 receptor agonists, to allow further individualization of therapies.
- These newer insulin products can be integrated and used with existing insulin replacement program designs that consider patient physiologic needs, self-care abilities, comorbidities, and cost.

THE HISTORY AND EVOLUTION OF INSULIN

Insulin was discovered in 1921 by the team of Drs. Frederick G. Banting, Charles Best, and James Collip at the University of Toronto. Although insulin was first extracted from a dog's pancreas, public demand necessitated the use of porcine and bovine sources.[1] These early insulins had a relatively short duration of action and needed to be injected multiple times each day. The high antigenicity of these products also resulted in great interpatient and intrapatient variability in action, both peaking and duration.

Subsequent development of newer insulins sought to prolong the time action profile to extend the duration of action and with the goal of reducing the number of daily injections. It was not until the mid 20th century that further understanding of the natural physiologic insulin secretory pattern lead to the realization that mimicking those patterns was a more appropriate goal of therapy than reducing the number of daily

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injections. Natural physiologic insulin secretion is characterized by basal insulin release throughout the day, with additional rapid release of insulin in response to carbohydrate ingestion (prandial insulin release).

In the early 1980s, to overcome the disadvantages of insulin from porcine, bovine, and combinations of both, and to help with the animal source supply problem associated with increasing incidence of diabetes, biosynthetic insulin was developed using recombinant DNA technology. These insulins were identical in amino acid sequence to human insulin and were first approved by the US Food and Drug Administration (FDA) in 1982.[2]

The problems with the action profiles and extreme variability of the early insulin preparations have largely been addressed by progressive improvements in formulations. When combined with the knowledge of physiologic insulin secretion, we evolved into the use of regimens that incorporate both the basal and bolus insulin. The first recombinant DNA human insulin analog, insulin lispro (Humalog, Eli Lilly, Indianapolis, IN) a rapid-acting bolus insulin, was approved by the FDA in 1996,[3] followed by the approval of the basal analog glargine (Lantus; Sanofi-Aventis, Bridgewater, NJ) in 2000.[4] The more predictable action profiles of the long-acting analog insulins (insulin glargine and detemir) are associated with lower rates of hypoglycemia, particularly nocturnal hypoglycemia, than NPH.[5] Less hypoglycemia can also reduce weight gain.[6] These advances, coupled with improvement in both needle devices and insulin delivery systems such as pens, continued to facilitate the use of insulin therapy.[7]

In 2016, we now fully embrace the need for insulin products that match the secretion of the endogenous insulin as closely as possible. The Diabetes Control and Complications Trial (DCCT), and the follow-up study, Epidemiology of Diabetes Interventions and Complications, which clearly showed that physiologic insulin replacement for type 1 diabetes reduces microvascular and neuropathic complications of diabetes, and the impact of early intervention with physiologic insulin replacement was seen for many years.[8] In truth, the DCCT was conducted before the insulin analogs were developed, and physiologic control was achieved using combinations of regular, NPH, Lente, and Ultralente insulins. The basal analogs that we have had since 2000, although an improvement, still do not create a smooth ideal basal insulin action, because they do seem to have a peak effect and uneven action over 24 hours, leading to problems such as hypoglycemia and hyperglycemia as late effects.[9] The aim of the newer basal insulins that are being introduced into the market is to have a truly basal effect with a flat activity profile and increased duration of action to mimic endogenous basal insulin secretion as closely as possible. As the duration of insulin activity increases, being able to provide basal insulin action reliably for a full 24 hours with 1 daily injection may lead to better patient adherence and reduce some of the hesitation to initiate insulin therapy. The relative time action profiles for the various types of insulins currently available are illustrated in **Fig. 1**.[10]

BASAL INSULINS

Long-acting (basal) insulin analogs have contributed significantly to the advancement of diabetes management. The initial long-acting basal insulin analogs that have been available in the market, insulins glargine and detemir, were developed to mimic the peakless and continuous kinetic profile of physiologic basal insulin secretion. The advantages of early long-acting analogs (insulin detemir and insulin glargine 100 U/mL or U-100) over NPH are a reduced incidence of nocturnal and overall hypoglycemia as well as a better ability to mimic endogenous basal insulin production.[5] However, clamp studies and clinical data show that the glucose-lowering effect of these early