Insulin Therapy

The Old, The New and The Novel—An Overview

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KEYWORDS

• Diabetes • Type 2 diabetes • Insulin therapy • Novel therapy • Special populations

KEY POINTS

- The primary role of insulin therapy is to address the defect of β-cell failure.
- The goal of insulin therapy is to mimic normal insulin physiology.
- Although new and novel insulin formulations are available, there is still a role for neutral protamine Hagedorn and Regular insulin in diabetes management.
- Use of newer basal insulin formulations results in prolonged insulin action times and less hypoglycemia.
- Special considerations need be made when evaluating insulin therapy for older adults, pregnant women, persons with gastroparesis or those who are post gastric bypass.

INTRODUCTION

Diabetes is a group of diseases characterized by insufficient insulin production or inappropriate use. According to Dr Defronzo,[1] the pathophysiology of the disease is composed of etiologic mechanisms, which he refers to as the ominous octet. The octect consists of β-cell failure, decreased peripheral glucose use (muscle), increased hepatic glucose production (liver), adipocyte insulin resistance, increased glucagon secretion (α-cell), reduced incretin secretion and sensitivity (gastrointestinal), central nervous system insulin resistance from neurotransmitter dysfunction (brain), and enhanced glucose reabsorption (kidney).[1]

From the early days of the triumvirate to the current time of the ominous octet, β-cell decline leading to decreased insulin production has played a dominant role in diabetes. The total lack of insulin or impairment in production eventually leads to the need for exogenous insulin.

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Type 2 diabetes mellitus (T2DM) affects approximately 29 million people (9.3% of the population) in the United States.[2] The cost of care is increasing consistently. Factors associated with cost of care include treatment of diabetes complications owing to poor glycemic control. Knowing that T2DM is a progressive disease leading to the requirement for insulin therapy over time would suggest that increasing numbers of patients will be on insulin therapy. However, despite the increase in prevalence of diabetes from 1988 to 2004 by 382%, synthesis of National Health and Nutrition Examination Survey data by Selvin and colleagues[3] revealed that the proportion of patients on insulin therapy has remained essentially unchanged from 1988 to 2004 (30.3%) to 2005 to 2012 (29.1%).

Over the last century since its discovery, insulin has been instrumental in prolonging the life of persons with diabetes as well as improving the quality of life. From the initial isolation of insulin in 1921 to present-day innovations (**Table 1**), the elusive goal has been to more closely approximate normal insulin physiology. Insulin was referred to by Cefalu and colleagues[4] as the "black dress"—that item that is essential, goes with everything and can be accessorized for any occasion. According to Owens and colleagues,[5] the lives of an estimated 5.1 million persons with type 1 diabetes worldwide were prolonged by approximately 1.5 years in 2000 alone. It was reported that, in 2001, more than 300 insulin analogues had been produced (although all have not reached the market), with more to come.[6] With all of the insulins currently available in the United States[7] (**Table 2**), how does one decide what insulin to use, when to use it, and in what patient, to get the best possible results?

NORMAL INSULIN PHYSIOLOGY

Plasma glucose levels in healthy individuals fluctuate within a very narrow range (63–126 mg/dL) despite nutritional intake, exercise, and other iatrogenic, physiologic, and

Table 1
The history of insulin

Year	Type of Insulin	Manufacturer
1922	Pancreatic extraction for human use	Eli Lilly
1930	Neutral protamine Hagedorn (NPH)	Novo-Nordisk
1978–1982	Humulin R (rapid) and NPH	Genentech and Lilly
1996	Lispro	Lilly
2000	Aspart	Novo Nordisk
2000	Glargine	Sanofi
2004	Glulisine	Sanofi
2005	Detemir	Novo-Nordisk
2006	Exubera[a]	Sanofi and Pfizer
2014	Afrezza	Sanofi
2015	u-300 glargine	Sanofi
2015	u-200 Lispro	Lilly
2016	Degludec	Novo Nordisk
2016	Basaglar	Lilly
1952/1994	u-500 regular	Lilly

[a] No longer available.

Data from Quianzon CC, Cheikh I. History of insulin. J Community Hosp Intern Med Perspect 2012;2(2). doi: 10.3402/jchimp.v212.18701.