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Review

Emerging diabetes therapies and technologies

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ABSTRACT

The prevalence of diabetes is increasing globally and is expected to increase to 439 million people by the year 2030. Several studies have shown that improved glycemic control measured by glycosylated hemoglobin (A1c) in patients with type 1 and type 2 diabetes results in a reduction of both the micro- and macrovascular complications associated with the disease. The recent introduction of new oral medications, insulin analogs (long and rapid acting), insulin pens and pumps, better SMBG meters and continuous glucose monitoring (CGM) have all resulted in improvement of glycemic control. Closed-loop devices currently in development aim to integrate the CGM and pump system in order to more closely mimic the human pancreas. The other upcoming new basal insulin (Degludec), prandial insulin, other new technologies and improved oral therapies will significantly improve patient acceptance of intensive therapy, glycemic control and quality of life in patients with diabetes.

Contents

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Abbreviations: CSII, continuous subcutaneous insulin infusion; CGM, continuous glucose monitoring; DKA, diabetic ketoacidosis; DPP-IV, dipeptidyl peptidase-IV; EMEA, European Medicines Agency; FDA, Food and Drug Administration; FCL, fully closed-loop; GRAS, generally regarded as safe; GLP-1, glucagon-like peptide-1; GIP, glucose-dependent insulinotropic peptide; A1c, glycosylated hemoglobin; HCL, hybrid closed-loop; IU, insulin units; MDI, multiple daily injections; NPH, neutral protamine Hagedorn; NPL, neutral protamine lispro; SMBG, self-monitoring of blood glucose; SGLT2, sodium-glucose transporter-2; T1D, type 1 diabetes; T2D, type 2 diabetes; US, United States.

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1. Introduction

The International Diabetes Foundation estimates that there were 366 million adults aged 20–79 with diabetes worldwide in 2011 and this is expected to rise 552 million by the year 2030 [1] with most of the increase coming from developing countries. Type 1 diabetes (T1D) is caused by the autoimmune destruction of beta cells of the pancreas and results in the reduction or elimination of biological insulin production. This requires patients to administer exogenous insulin along with self-monitoring of blood glucose (SMBG) to control blood glucose levels. Patients with type 2 diabetes (T2D), frequently associated with obesity, are not usually dependent on exogenous insulin administration but may require it if hyperglycemia cannot be controlled with diet or oral medications, especially after longer standing T2D. The Diabetes Prevention Program, a 2.8-year randomized clinical trial, found that the incidence of diabetes was reduced by 58% with intensive lifestyle modification and by 31% with dimethylbiguanide (Metformin) therapy for high risk adults [2]. In addition to insulin, many patients with progressive T1D may be using dimethylbiguanide and other oral antidiabetic medications traditionally used for the treatment of T2D due to the associated high BMI and insulin resistance [3]. Studies have shown that improved glycemic control measured by glycated hemoglobin (A1c) in patients with T1D and T2D results in a reduction of both the micro- and macrovascular complications associated with diabetes [4–6]. The recent introduction of new oral medications, insulin analogs (long and rapid acting), insulin pens and pumps, better SMBG meters, continuous glucose monitoring (CGM) and closed-loop devices have all resulted in improvement of glycemic control.

2. Insulin analogs (Fig. 1a and b)

Since the discovery of insulin, various formulations have been developed for subcutaneous administration in an attempt to emulate the physiological insulin response. Initially, different animal insulins (porcine or bovine) [7] were used for treatment, but they varied greatly in potency, contained many impurities and resulted in significant elevation of circulating insulin antibodies. The first basal (long-acting) insulin, protamine zinc, was developed in the 1930s and could be used twice a day without regular insulin [7]. After the introduction of neutral protamine Hagedorn (NPH) and Lente insulin (ultralente, semilente and lente) in the 1950s, diabetes treatment practices moved toward a regimen of twice-daily NPH (basal) with regular insulin (prandial) to provide improved insulin coverage. The development of purified pork insulin and recombinant human insulin in the early 1980s almost completely eliminated insulin allergy, insulin antibody formation and immune-mediated lipoatrophy. Modification of the amino acid sequence on the β-chain has led to the development of insulin with different pharmacokinetics and pharmacodynamics [8]. Insulin analogs are continuing to be developed with profiles that give more flexibility in treatment with reduced risk of hypoglycemia. Early basal analogs produced blood concentrations with prominent peak effect. The peak levels may result in nocturnal hypoglycemia leading to fasting hyperglycemia [9]. These early insulin analogs also had variability in their subcutaneous absorption as they needed to be properly resuspended by mixing, which contributed to unpredictable blood glucose control [9].

The introduction of basal insulin analogs such as glargine and detemir (amino acid changes depicted in Fig. 1a) are commonly used alone or in combination with prandial (fast-acting) insulin analogs (Fig. 1b). These basal analogs have a longer duration and smoother profile [8]. There is lack of peak activity, more predictable absorption and less intra- and inter-individual variability [8,9]. Significantly improved control can potentially be achieved with either of these analogs [10]. The absorption of regular insulin is too slow to effectively control postprandial hyperglycemia resulting in pre-prandial hypoglycemia [9]. A rapid onset and shorter duration of action was achieved by inhibiting the dimer and hexamer formation through amino acid changes on the chain from B26-30 [8]. The faster onset also allows for a reduction in the time needed between an injection and meal and better compliance and convenience. The development of better prandial insulin analogs, lispro, aspart and glulisine (Fig. 1b) has helped to improve postprandial blood glucose and variability of absorption, however, hypoglycemia benefits are unclear based on meta-analysis results [11].

The new longer acting insulin degludec (Fig. 1a), not approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMEA), is effective for up 24 h, though it may have some spillover effect allowing some patients to reduce injection frequency [12]. Like glargine and detemir, the action profile is relatively flat, without a prominent peak. A premixed insulin combination of degludec and aspart is also being investigated [12]. Lilly is also investigating a new basal insulin, LY2605541, currently in phase 1/2 trials (conceptual slide is shown in Fig. 1a). BIOD-Smart Basal (Biodel) insulin, designed to release insulin dependent on blood glucose concentration, is in the preclinical stage of development [13]. An alternate way to produce a flat insulin profile is to use an insulin patch or patch pump. Another area of research is developing ultra-fast acting insulin (not FDA approved) to more accurately reproduce the physiologic prandial insulin release. One formulation, VIAject