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# Insulin Therapy for Diabetes

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Additional information is available at the end of the chapter

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## 1. Introduction

Diabetes affects 25.8 million people, or 8.3% of the U.S. population. Among people with diabetes, 26% are insulin users.[1] Therapy with insulin is effective at lowering blood glucose in patients with diabetes. Insulin is a key player in the control of diabetes for patients with type 1, and it is required at later stages by patients with type 2. Hyperglycemia in type 1 diabetes is a result of the deficiency of insulin, and in type 2 diabetes hyperglycemia is due to impaired tissue response to insulin.

The discovery of insulin is hailed as one of the most dramatic events in the history of the treatment of disease. It was isolated in 1921, with its first clinical use in 1922.[2] The major advances achieved in this area include the human insulin analogue synthesis. Insulin delivery systems currently available for insulin administration include syringes, infusion pumps, jet injectors, and pens. The traditional and most predictable method for insulin administration is by subcutaneous injections. The major drawback of current forms of insulin therapy is their invasive nature. In type 1 diabetes, good glycemic control usually requires at least two, three, or more daily insulin injections. To decrease the suffering, the use of supersonic injectors, infusion pumps, sharp needles, and pens has been adopted.

Such invasive and intensive techniques have spurred the search for alternative, more pleasant methods for administering insulin. Several non-invasive approaches for insulin delivery are being pursued. The ultimate goal is to eliminate the need to deliver insulin exogenously and for patients to regain the ability to produce and use their own insulin. The success of the administration route is measured by its ability to elicit effective and predictable lowering of blood glucose level, therefore minimizing the risk of diabetic complications. Newer methods explored include the artificial pancreas with a closed-loop system, transdermal insulin, and

buccal, oral, pulmonary, nasal, ocular, and rectal routes. This chapter focuses on the new methods that are being explored for use in the future.

## 2. Current methods in insulin therapy

Current methods of insulin delivery include using syringes, continuous subcutaneous insulin infusion (CSII), and insulin pens. Use of syringes is the most common method, and there is a wide choice of products that are easy to read and operate. CSII, also referred to as an insulin pump system, is designed to provide a continuous supply of insulin infusion around the clock and can be individualized and adjusted as per the specific needs of the patient. CSII is a way to simulate the physiology of daily insulin secretion where an appropriate level of insulin is delivered. The use of an insulin pump is superior to multi-dose insulin injections because it is easier to use and therefore provides the patient with more flexibility. A disadvantage is that insulin pump therapy is expensive compared to the use of traditional syringes and vials.

Insulin pen devices offer an alternative method for insulin delivery that is more accurate and less painful versus vials and syringes.[3] Reusable insulin pens offer a number of advantages including durability and flexibility in carrying a multiple days' supply.

## 3. Future trends (Table 1)

**Injectable insulin:** Two promising new insulin preparations include a long-acting basal insulin analogue called insulin degludec and an ultrafast-acting insulin analogue, human insulin Linjeta™ (formally called VIAject®).

Insulin degludec is novel, ultra-long-acting basal insulin.[4] Insulin degludec is almost identical to human insulin in structure except for the last amino acid deleted from the B-chain and addition of a glutamyl link from LysB29 to a hexadecandioic fatty acid.[4] It forms soluble multi-hexamers after subcutaneous injection, resulting in an ultra-long action profile with a half life of more than 24 hours.

Insulin degludec has proven to be non-inferior to currently available, long-acting insulin analogue insulin glargine in trials carried out in both type 1 and type 2 diabetes.[5-6] In an exploratory phase 2 trial in subjects with type 1 diabetes, insulin degludec was found to be safe and well tolerated and had comparable glycemic control to insulin glargine, but with reduced rates of hypoglycemia.[7] In a multicenter phase 3 clinical trial in adults with type 1 diabetes, at one year, compared to insulin glargine, glycemic control was similar to glycemic control using glargine with decreased nocturnal hypoglycemia.[6] Similarly, in an open-label phase 3 non-inferiority trial in type 2 diabetes patients, improvement in glycemic control was comparable to insulin glargine at one year follow-up (drop in HbA1C by 1.1% in the degludec group and 1.2% in the glargine group) with fewer hypoglycemic episodes in insulin degludec users.[5] Insulin degludec is not yet approved by the FDA.

Linjeta™, formally called VIAject®, is recombinant human insulin with a fast onset of action. In a study of pharmacodynamics and pharmacokinetic properties of an ultrafast insulin, it was found to have an earlier onset of action and shorter time to maximal plasma insulin concentration. VIAject®, compared to human insulin, had less within-subject variability of plasma insulin.[8] In a double blind, three-way crossover study with VIAject® compared to lispro insulin, VIAject® was found to be bioequivalent to the previously used formulation and had a faster absorption/onset of action than insulin lispro.[9] VIAject® is currently undergoing two pivotal phase 3 clinical studies for both type 1 and type 2 diabetes. Since the VIAject® pharmacodynamics mimic 1<sup>st</sup> phase release insulin and the amount of insulin circulating several hours after a meal, it leads to possible reduction in hypoglycemia, and it is predicted to possibly prevent weight gain.[8]

**Artificial pancreas:** Closed-loop insulin delivery is an emerging therapeutic approach for people with type 1 diabetes. [10] Even with the use of continuous glucose monitors and insulin pumps, most people with type 1 diabetes do not achieve glycemic goals and continue to have unacceptable rates of hypoglycemia. The goal of closed-loop therapy is to achieve good glycemic control with the use of a control algorithm that directs insulin delivery according to glucose levels while reducing the risk of hypoglycemia. Insulin delivery in the closed-loop system is modulated at intervals of 1-15 minutes, depending on interstitial glucose levels. The uniqueness of this approach is the real-time response of insulin delivery to the glucose levels, similar to that of the beta-cell. The algorithms that are most relevant include the proportional-integral-derivative control (PID) and the model-predictive control (MPC).[11]

Several areas need improvement to have a near normal closed-loop system. First and foremost is the rapid onset of action. The lag period of current fast-acting insulin analogs is 90-120 minutes. Current trials show promise. In a phase 2 study with or without recombinant human hyaluronidase (rHuPH20) that accelerates insulin absorption in healthy volunteers, both lispro and recombinant human insulin with rHuPH20 produced earlier and greater peak insulin concentrations, improved postprandial glycemic control, and reduced hypoglycemia.[12]

Rapid acting insulins are being developed that use monomeric insulins that cannot form hexamers.[13] As mentioned earlier, ultrafast insulin VIAject®, a formulation of human soluble insulin, improves the rate of insulin absorption. It has been reported in a study to evaluate its pharmacodynamics and pharmacokinetic properties that VIAject® has higher metabolic activity in the first two hours after injection.[14] True closed-loop systems, which determine minute-to-minute insulin delivery based on continuous glucose sensor data in real time, have shown promise in small inpatient feasibility studies using a variety of algorithmic and hormonal approaches.

**Buccal delivery of insulin:** The buccal delivery system for insulin delivers insulin through an aerosol spray into the oral cavity and hence differs from inhalers. The insulin is absorbed through the inside of the cheeks and in the back of the mouth instead of the lungs. In vivo studies performed on diabetic rats showed promising results with stable blood glucose profile with a significant hypoglycemic response after 7 hours using buccal insulin.[15] Similar studies in the rabbit and rat have shown that buccal spray of insulin is an effective insulin delivery system, which is promising for clinical trial and future clinical application.[16] Though

promising in rat models, they are not appropriate models because rats have a keratinized buccal mucosa. The only animal models with comparable human buccal permeability are pigs.

**Oral-lyn™:** Genex Biotechnology Corporation (Toronto, Canada) is developing a buccal insulin formulation based on RapidMist™, an advanced buccal drug delivery technology. [17] Oral-lyn™ is a liquid formulation of human regular insulin with a spray propellant for prandial insulin therapy. The formulation results in an aerosol with relatively large micelles where the majority of the particles have a mean size  $>10\ \mu\text{m}$  and therefore cannot go into the lungs. Each puff is claimed to deliver 10 U of insulin. The absorption rate of administered insulin as a puff is 10%, and that corresponds to 1 U when 1 puff of 10 U is delivered, which means 10 puffs will deliver 10 U insulin for a meal.[17]

Clinical studies in healthy volunteers and subjects with type 1 and type 2 diabetes have shown that the oral insulin spray was absorbed in direct relation to the amount given, and it had a rapid onset and a shorter duration compared with regular insulin given subcutaneously. In all of the studies conducted, the oral insulin spray was generally well tolerated. The only side effects included mild episodes of transient dizziness in some healthy volunteers and subjects with type 1 diabetes.[18] The product is on the market in a number of countries (e.g., Ecuador and India).[17] Without appropriately designed and performed phase 3 trials at hand, it is not possible to make any clear statement about the benefits/risk ratio of the different buccal insulins.[17]

**Oral insulin:** Oral insulin has benefits in terms of compliance among patients, as well as physiological advantages because oral insulin can mimic the physiological fate of insulin through first pass to the liver, directly and effectively inhibiting hepatic glucose production. [19] Since the initial discovery of insulin by Banting and Best in 1922, the oral form of insulin has been the elusive goal. Difficulties encountered for oral insulin delivery, since it is a protein, include degradation by the low pH of the stomach and the digestive enzymes in the stomach and small intestine. The major barrier for insulin absorption is the intestinal epithelium. All these factors lead to low bioavailability, and that leads to significant inter- and intra-subject variability.

Nanotechnologies have brought some hope for improved delivery of insulin. Nanotechnology applications for delivery of hydrophilic drugs such as insulin might be achieved using biodegradable polymers such as chitosan, which has been extensively exploited for the preparation of nanoparticles for oral controlled delivery of several therapeutic agents.[20-24] In recent years, chitosan cross-linked to various hydrophobic polymers has been utilized for the preparation of orally delivered drugs because of improved permeation and sustained release characteristics.[25-26]

The newer products that are being tried include water-soluble, long-acting insulin derivative, [(2-sulfo)-9-fluorenylmethoxycarbonyl]3-insulin,[27] vitamin B12-dextran nano particles,[28] lipid nanoparticles,[29] and PEGylated calcium phosphate nanoparticles as oral carriers for insulin.[30] Protection of insulin from the gastric environment has been achieved by coating the nanoparticles with a pH-sensitive polymer that dissolves in the intestine at mild alkaline

pH. In rats, oral insulin nanoformulation significantly ( $P < 0.05$ ) reduced blood glucose in normal and diabetic rats.[31]

Biocon (Bangalore, India) is manufacturing IN-105, which is in late phase 3.[17] IN-105 is a human recombinant insulin conjugated with polyethylene glycol via an acetyl chain. It is orally bioavailable and stable at ambient conditions. Preclinical studies in different species have shown acceptable efficacy and safety. Its maximal circulating insulin levels after oral administration of 5 mg were observed after 20 minutes, and the maximum drop in glucose occurred at 40 minutes after oral administration. Phase 1 and phase 2 trials demonstrated that the absorption of IN-105 and the reduction in blood glucose levels were proportional to the dose administered.[32]

**Inhaled insulin:** The inhaled products fall into two main groups: the dry powder formulations and solution, which are delivered through different inhaler systems. Exubera<sup>®</sup>, containing rapid-acting insulin in powder form, was studied in patients with type 1 and type 2 diabetes mellitus.[33-34] The results of a patient preference study, using a comparison of utility scores, showed a greater preference for the inhaled route over insulin injection.[35] However, issues like cost, the bulkiness of the device, and the small number of studies in subjects with underlying respiratory disease prevented widespread use of this new mode of delivery.[36-37] Exubera<sup>®</sup> was available for less than one year, and then Pfizer took it off the market in 2007 because the drug failed to gain market acceptance.

**Afrezza<sup>®</sup>:** (MannKind Corporation, Valencia, CA, USA) is recombinant human insulin, using the Technosphere<sup>®</sup> concept and administered using a next-generation inhaler called Dreamboat<sup>®</sup>. Technosphere<sup>®</sup> is a drug delivery system created by micro particles (2-3  $\mu\text{m}$ ) that form microspheres, which are then lyophilized into a dry powder for inhalation.[38]

**Transdermal insulin:** Transdermal insulin delivery is a needle-free alternative and avoids the disadvantages associated with other alternative routes such as the pulmonary and nasal routes. Permeation of compounds is limited to small, lipophilic molecules. The stratum corneum, the outermost layer of the skin, constitutes the major barrier for insulin permeation to reach useful levels. Several chemical and physical enhancement techniques such as iontophoresis, ultrasound/sonophoresis, micro-needles, electroporation, laser ablation, and chemical enhancers have been explored to overcome the stratum corneum barrier to increase skin permeability.

Methods to improve transdermal delivery:

1. Chemical enhancers, which alter the lipid structure of the stratum.
2. Iontophoresis, which enhances the transdermal delivery of compounds via the use of a small electric current.[39]
3. Micro-needle technology, which involves the creation of micron-sized channels in the skin, thereby disrupting the stratum corneum barrier[40] and delivering the drug into the epidermis without disruption of nerve endings.[41]
4. Sonophoresis, which uses ultrasound and has been shown to increase skin permeability of insulin. It is still being evaluated.[42]

## 4. Conclusions

Effective glycemic control remains an important clinical goal. Patient barriers to accepting insulin initiation include fear of hypoglycemia, weight gain, and the inflexible timing of scheduled insulin doses, leading to adherence issues. Additionally, the invasive nature of the insulin syringe, pump, and pen remains an obstacle for patients. Of the alternatives to subcutaneous and injected insulin, intranasal, inhalable, and oral insulin could prove to be the most cost-effective ones. Oral insulin in particular could prove to be promising, especially since as a therapy it seems to have progressed with nanotechnology research, allowing for several types of encapsulations to bypass the gastric acidic environment. Artificial pancreas or closing the loop with insulin pumps that deliver insulin in response to sensors also appears to be promising.

Method	Mechanism
Artificial pancreas	Insulin pump controlled by algorithm with glucose monitor
Buccal insulin	Insulin through an aerosol spray
Oral insulin	Various nanoparticle encasings bound to insulin
Inhalable insulin	Insulin absorbed through alveolar membranes
Transdermal insulin (patches)	Insulin absorbed through pores in skin opened with ultrasound energy, microdermabrasion, etc.
Intranasal insulin	Absorbed through nasal mucosae

**Table 1.** Methods for Future Types of Insulin Therapy

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