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Review Article

# Advancements in Insulin Therapy: A Review

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**Abstract:** Glycemic control is required to prevent microvascular and macrovascular complications of diabetes. Insulin is an important part of therapy in diabetic patients. Insulins have to be injected which is inconvenient and cause many complications. Newer forms of insulin which are delivered through routes other than injections are developed by pharmaceutical companies. The efficacy, bioavailability, side effects of these are studied in various clinical trials and gained approval. This review focuses on the advancements in insulin therapy that helps to overcome the troubles caused by invasive insulin administration.
**Keywords:** Diabetes, insulin, therapy.

## INTRODUCTION

Diabetes mellitus is a group of chronic metabolic disorder characterised by hyperglycemia due to defects in carbohydrate, lipid and protein metabolism [1]. There are two types of diabetes mellitus- type I and type II. Type I diabetes is caused due to destruction of beta cells of langerhans of pancreas and type II diabetes is caused due to decreased sensitivity and resistance of cells to action of insulin [2]. Type I diabetes requires exogenous insulin supply. Type II diabetes can be treated with exercise, oral anti diabetic agents and insulin [3]. Insulin is a peptide hormone produced by the islets of langerhans in pancreas. It is stored in the body as a hexamer i.e. six molecules bound with zinc ion. When the body requires insulin, the hexamer disassociates to form monomer which produces the physiological action. It is available in numerous forms such as regular insulin, short acting insulin, intermediate acting insulin, long acting insulin, basal analogues, concentrated insulin, inhalable insulin and chemically modified insulins. Inhalable insulins and modified insulins are the latest approved forms of insulin. The onset of action, duration of action, the frequency of injection and mode of ingestion varies in each forms of insulin. Inhalable insulins are inhaled via the lungs while other forms are injected subcutaneously into the body. With the advancement in science and technology, artificial insulin preparations are introduced by altering the disassociation process of the hexamer. The efficiency, patient acceptance and satisfaction are important criteria to be assessed.

## INHALABLE INSULIN

The need for multiple daily injection and lack of acceptance of injections made the query for another route by which insulin can be administered to the body for attaining glycemic control. Administration via the pulmonary route provides a greater surface area for absorption and is rapidly absorbed through alveoli [4, 5]. Exubera was available as blisters of 1mg and 3 mg dose. It is formulated as dry powder for inhalation and a special device is used for the inhalation [4, 5]. The dosage calculations are cumbersome for the medical practitioners. It is used in combination with a long acting insulin in type I diabetic patients [6]. It can be used as monotherapy or in combination with oral antidiabetic agents or with long acting insulin in type II diabetic patients [6]. Pulmonary function testing is advised before administration of inhalable insulin. In patients with type 1 diabetes, the inhaled insulin Exubera, administered three times daily prior to meals and a single night-time injection of a long-acting insulin (Humulin U Ultralente), has been compared with a conventional subcutaneous insulin regime (involving regular human insulin administered twice daily with NPH human insulin administered twice daily) in 24-week randomized, open-label trials [6, 7]. The primary efficacy parameter was glycemic control, as measured by the reduction from baseline in haemoglobin A1C (HbA1c). In these trials, the reduction in HbA1c and the rates of hypoglycaemia were comparable in the two treatment groups [6, 7]. Inhaled insulin has a favourable pharmacokinetic profile that makes it efficient in managing post prandial hyperglycemia. It is also effective when used alone or in combination with oral

antidiabetic agents or injectable insulin and hence makes the treatment plan flexible.

Inhaled insulin is contraindicated in patients with lung diseases and in those who smoke or discontinued smoking less than 6 months prior to beginning of therapy [6]. The main disadvantage of inhalable insulin is cough which settled as treatment continued and hypoglycaemia [7] . The bioavailability of the product is only10% of the subcutaneous route due to loss in the upper airways and hence a larger dose is required to achieve glycemic control [9]. Treatment satisfaction, convenience, quality of life and patient compliance were found to be much better than the injectable insulin. Patients are likely to prefer inhaled insulin when it is available [11]. Treatment satisfaction with inhaled insulin is comparable with oral medications in a study in type II diabetic patients [12] Exubera was the first inhalable insulin approved by FDA in 2006 but was later withdrawn due to concern about effect on lung function, high cost and requirement for a bulky inhaler [13]. Afrezza is the one currently available drug device in the form of small easy to use inhaler and the inhalational powder as single-use cartridges [14]. The product has a large patient acceptance worldwide due to the lack of fear of injection. The patient satisfaction rates were very high. It is ultra-rapid-acting insulin which mimics a linear dose-related pharmacokinetic profile in patients of type I and II diabetes mellitus [15]. Maximum plasma drug concentration reached between 10 and 15 min ($T_{max}$) which is very early compared to regular insulin or other rapidly acting insulin analogues (20-45 min). This is important as it mimics first-phase insulin release after food seen in non-diabetic individuals. Duration of action is around 2-3 hrs [15, 16]. 60% of the inhaled drugs gets deposited in the lungs [15]. Inhaled insulin is designed to be used within 20 min of beginning a meal.

## CHEMICALLY MODIFIED INSULIN

Chemically modified insulins were studied under the leadership of Professor Markus Meuwly from the department of chemistry at University of Basel. Replacement of a hydrogen atom of insulin with iodine has shown improved release and bioavailability in the blood stream. The efficacy and affinity of insulin to the receptor is not changed while the availability of insulin to the organism is enhanced by introduction of an iodine atom. Intermolecular interaction between atoms is improved by the replacement of a hydrogen atom with iodine. The advantages of chemically modifying the insulin were predicted using quantum chemistry and molecular dynamics simulations [17]. The changes in stability of the modified insulin were studied using crystallographic and nuclear magnetic resonance experiments. The artificial insulin thus produced helps in optimising the therapy in diabetic patients. It also has an important role in protein engineering.

## TRANSDERMAL INSULIN

Transdermal administration of insulin avoids the complications and other disadvantages of injections and other routes of administration. Insulin is delivered over 12 hours. It employs a microneedle through which the drug is introduced into the body. Use of microneedle does not cause pain and produce advantages of high degree of patient acceptance, convenience and by pass the first pass metabolism in liver [18]. Permeation through the skin is tough. Physical enhancement techniques like iontophoresis, ultrasound/sonophoresis, microneedles, electroporation, laser ablation and chemical enhancers are required for improving transdermal penetration. Chemical enhancers alter the lipid structure of the stratum corneum altering its barrier properties and increase its permeability for drugs. Iontophoresis is a technique that uses a small electric current to enhance the transdermal delivery of compounds through the skin [19]. Microneedle technology is cost-effective, minimally invasive, and controllable approach to transdermal drug delivery. Micron sized channels are created which disrupts the stratum corneum barrier. Interstitial fluid get filled up in the channels producing hydrophilic pathways. Upon creation of the microchannels, interstitial fluid fills up the channels, resulting in hydrophilic pathways [20]. Microneedles deliver the drug into the epidermis without disruption of nerve endings [21]. Transferosulin employs transformers which are particles similar to lyposomes but are more deformable and can easily pass through the skin. Their membrane contains phospholipids and insulin is carried inside the hydrophilic. Studies in type I diabetic patients showed similar pharmacokinetic profile to long acting human insulin (Ultratard) with less intraindividual variability in insulin absorption [22].

## CONCLUSION

As the field of medical science advances, newer insulin formulations are discovered. As insulin is an inevitable agent for patients with diabetes these new formulations are gaining importance in medicine. Scientists are busy with exploring the possible ways to achieve their goal. A chemist Danny chou, PhD from the university of Utah, exclaimed that he is looking forward for smart insulins that are controlled by circulating blood sugar levels. These are insulins with brain. Smart insulin will be active when the body needs it and when the blood glucose level gets normal it gets stopped. Such a preparation will help maintain glycemic control without any complications.

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