

EDITORIAL

Introduction: inhaled insulins: potential therapies for diabetes mellitus

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ABSTRACT

There is no doubt that diabetes is an extensive worldwide problem. Several studies have demonstrated that reducing levels of glycosylated hemoglobin (HbA_{1c}) decreases the risk of developing diabetic complications. Insulin is the most effective glucose-lowering agent available. However, several barriers prevent the initiation and intensification of insulin therapy in patients with diabetes. For example, some studies have shown

a delay of up to 5 years in over 50% of patients with type 2 diabetes uncontrolled with oral antidiabetic agents. Alternative noninvasive options for the administration of insulin, such as inhaled human insulin (Exubera; insulin human [rDNA origin] Inhalation Powder) are likely to increase patient acceptance of insulin, improve glycemic control and thus reduce the overall burden of diabetes.

Introduction

Diabetes is an extensive problem, affecting 194 million people worldwide, and almost 50 million people in Europe alone¹. The Diabetes Control and Complications Trial (DCCT)² and the United Kingdom Prospective Diabetes Study (UKPDS)³, have demonstrated a significant correlation between the levels of glycosylated hemoglobin (HbA_{1c}) and the risk of developing diabetic complications in patients with type 1 or type 2 diabetes, respectively. The risk of developing complications increased over time and was greatest in patients with a long history of poor control.

Both the DCCT and UKPDS studies showed that strict glycemic control could slow, if not prevent, the development of complications. In the DCCT trial, lower HbA_{1c} levels were correlated with greater reductions in the relative risks of developing diabetic retinopathy, neuropathy, and nephropathy². Epidemiological extrapolation of the data from the UKPDS showed that for every percentage point reduction in HbA_{1c}, there was a 21% decrease in the risk of any diabetes-related end point and a 21% reduction in diabetes-related deaths⁴. Furthermore,

the UKPDS showed that an intensive insulin regimen led to a relative risk reduction (RRR) of 25% ($p = 0.0099$) for microvascular complications, and a lower risk for myocardial infarction (RRR 16%; $p = 0.052$), compared with conventional insulin therapy³.

The American Diabetes Association (ADA), the American Association for Clinical Endocrinologists (AACE), and the International Diabetes Federation (IDF) regularly publish international guidelines for diabetes management (Table 1)⁵⁻⁷. The guidelines advocate optimal glycemic targets that help reduce, delay or prevent diabetes-related long-term complications.

However, at present, almost two-thirds of patients do not achieve the required treatment goals for glycemic control (Figure 1)^{8,9}. Furthermore, one report from the United States demonstrated that the rates of glycemic control are worsening⁸, and, as a result, many patients remain at risk of developing diabetic complications. Both of these factors result in the significant burden of diabetes and associated healthcare costs. The total indirect and direct costs of diabetes in the United States have been estimated at over \$132 billion per year¹.

Table 1. Summary of target glycemic goals from the American Diabetes Association (ADA), American Association of Clinical Endocrinologists (AACE), and International Diabetes Federation (IDF) guidelines⁵⁻⁷

Plasma glucose concentrations	ADA	AACE	IDF
Fasting/preprandial	90–130 mg/dL (5.0–7.2 mmol/L)	110 mg/dL (6.0 mmol/L)	110 mg/dL (6.0 mmol/L)
Postprandial	< 180 mg/dL (< 10.0 mmol/L)	140 mg/dL (7.8 mmol/L)	NA
HbA _{1c}	< 7%	6.5%	6.5%

NA = not applicable; HbA_{1c} = glycosylated hemoglobin

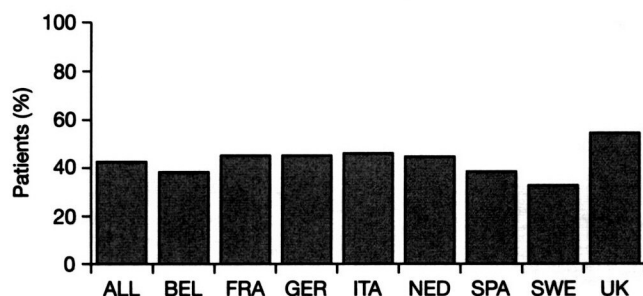


Figure 1. Percent patients with glycosylated hemoglobin (HbA_{1c}) levels < 7.5% overall, and across several individual European countries. Adapted from Liebl et al.⁹

Role of insulin

Exogenous insulin is the most frequently used, and the most physiological, treatment of diabetes. Studies such as the UKPDS have demonstrated that insulin-based regimens, particularly intensive insulin therapy, improve glycemic control and reduce the incidence of complications³. There are many insulin formulations available for patients with diabetes. In recent years, short-acting insulin analogues, such as lispro, aspart, and glulisine, have been developed to closely mimic the physiological serum insulin concentration profile after the ingestion of a meal. Long-acting analogues such as glargine and detemir, have a relatively constant concentration/time profile over 24 hours to provide a steady, basal level of insulin. Therefore, with several daily insulin injections, patients can achieve insulin profiles that aim to mimic insulin profiles observed in non-diabetic patients.

Nevertheless, the difficulty in starting and maintaining insulin injection-based therapeutic regimens remains one of the key issues in diabetic therapy. Patients with type 2 diabetes often delay starting and intensifying insulin therapy. Studies have shown that many different reasons contribute to this reluctance, including technical concerns surrounding injections and emotions related to disease progression^{10,11}. As a result, efforts have focused on finding non-invasive alternatives for insulin administration.

Inhaled insulins

Many non-invasive insulin delivery systems have been investigated. To date, the pulmonary route of

delivery has shown the most promise, as demonstrated by the six inhaled insulin formulations currently in development¹². The advantages of pulmonary delivery, the formulation and inhaler technology, and the pharmacokinetic profiles of each inhaled insulin are discussed in detail by Dr John Patton in the first review article of this supplement¹³.

Inhaled human insulin, Exubera (insulin human [rDNA origin] Inhalation Powder; Pfizer Inc, New York, NY; Nektar Therapeutics, San Carlos, CA, USA), is a dry-powder formulation of regular human subcutaneous insulin that is administered by oral inhalation using a purpose-designed portable pulmonary inhaler. Exubera was approved in the United States and European Union as a short-acting insulin for the treatment of adults with type 1 or type 2 diabetes in January 2006. Exubera provides a unique and effective way to deliver insulin into the bloodstream. The novel dry-powder insulin formulation and innovative inhaler design ensure reliable delivery to the deep lung, and simple flexible dosing¹⁴. Pharmacokinetic and pharmacodynamic data show that Exubera has a time-action profile that is well suited for mealtime insulin administration in patients with diabetes¹⁵.

In various studies, Exubera has achieved and maintained effective glycemic control comparable to subcutaneous fast-acting human insulin regimens in patients with type 1 or type 2 diabetes¹⁶⁻¹⁹. Furthermore, in patients with type 2 diabetes failing oral antidiabetic agents (OAs), those using Exubera alone or in combination with OAs achieved greater improvements in HbA_{1c}²⁰⁻²³. The efficacy and general safety findings are discussed by Dr Stefano Del Prato within the second review article of this supplement²⁴.

Pulmonary function is an important aspect of the safety profile for compounds delivered via the lungs. To date, Exubera is the only inhaled insulin formulation that has extensively investigated pulmonary function in comprehensive detail, with several completed and ongoing Phase 3 studies in patients with type 1 or with type 2 diabetes. Data from these extensive pulmonary safety studies are covered in detail within the review article by Dr Leonardo Fabbri²⁵, and provide reassurance that Exubera is generally well tolerated^{16-23,25}. Declines

in forced expiratory volume in 1 second (FEV₁) have been observed with Exubera treatment relative to comparator; however, the changes in pulmonary function are small. Furthermore, in studies of up to 2 years duration, the rate of change in lung function remained similar to comparator, and the changes were reversible upon discontinuation of treatment. As a precaution, baseline and periodic spirometry measurements should be conducted during Exubera therapy.

The limited information available regarding the efficacy and pulmonary safety of other inhaled insulin formulations²⁶⁻²⁹ is in general agreement with Exubera findings, but more comprehensive studies are expected in the future.

Importantly, non-invasive insulin therapies such as Exubera may increase acceptance of insulin-based therapeutic regimens³⁰. This could encourage the earlier initiation and intensification of insulin, providing a significant opportunity to improve glycemic control, leading to better long-term health outcomes for patients with diabetes.

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Note on research

In preparing this article, the authors searched for references to inhaled insulin in the Medline database and in congress abstracts of the American Association of Clinical Endocrinologists (AACE), the American Diabetes Association (ADA), the American Thoracic Society (ATS), the European Association for the Study of Diabetes (EASD), and the European Respiratory Society (ERS) from 1998 to 2006.

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