

Inhaled Insulin: Extending the Horizons of Inhalation Therapy

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Introduction
Epidemiology of Diabetes
Role of Insulin
Barriers to Insulin Therapy
Alternative Devices for Insulin Delivery
Inhaled Insulin Formulation
Delivery System
Effect of Airflow and Breathing Pattern on Particle Deposition
Indications
Clinical Studies
Adverse Effects and Limitations of Inhaled Insulin
Place of Inhaled Insulin in Diabetes Therapy
Conclusion

Targeted glycemic control in patients with type 1 and type 2 diabetes is grossly inadequate, despite data demonstrating reduced microvascular and macrovascular diabetic complications with intensive treatment. A significant proportion of individuals with poorly-controlled type 2 diabetes are resistant to initiating treatment with insulin. Several decades-long search for alternative forms of insulin delivery has finally resulted in the U.S. Food and Drug Administration's approval of the first inhaled insulin delivery system, Exubera. Inhaled insulin provides hope that minimizing barriers to initiating insulin therapy will improve the overall glycemic control in both type 1 and type 2 diabetic patients. Inhaled insulin is a powder formulation that has been approved for pre-meal administration in both type 1 and type 2 diabetic patients. The delivery system for Exubera employs compressed air for producing an aerosol, which is then inhaled by the patient. Insulin is transported across the alveolar-epithelial barrier into the blood and has onset of glucose-lowering activity within 10–20 min of inhalation. The duration of action of inhaled insulin is similar to that of subcutaneous regular insulin. Although there are some limitations to the use of inhaled insulin, the potential to improve adherence and thereby achieve target glycohemoglobin levels ($\leq 6.5\text{--}7.0\%$) in poorly controlled diabetic patients outweigh its disadvantages. *Key words: diabetes, inhaled insulin, aerosol.* [Respir Care 2007;52(7):911–922. © 2007 Daedalus Enterprises]

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Introduction

Diabetes mellitus refers to a group of metabolic derangements in glucose control caused by varying degrees of deficiency in insulin production and peripheral utilization. Deficiency of insulin produces a chronic syndrome of hyperglycemic effects. Type 1 diabetes mellitus results from pancreatic β -cell destruction and subsequent absolute insulin deficiency. Type 2 diabetes mellitus, the most prevalent form, is a consequence of progressive worsening in insulin secretory function and peripheral resistance to its action. Although not lacking in the ability to produce insulin, many patients with type 2 diabetes ultimately require insulin treatment.¹

Diabetes mellitus is a growing problem in the United States, accounting for a substantial financial and health care burden, with the number of diagnosed cases projected to triple in the next 50 years. Over one in four of currently diagnosed patients with diabetes use insulin;² however, an even higher proportion of patients with diabetes actually require treatment with insulin. Insulin continues to be sub-optimally utilized, due to psychosocial barriers to current insulin delivery systems (Table 1). Interest in alternative, noninvasive modes of insulin delivery led to the approval of an inhaled insulin system (Exubera, Pfizer, New York, and Nektar, Mountain View, California) by the Food and Drug Administration (FDA). In this review we will explore the clinical utility, application, advantages, and limitations of the Exubera inhaled insulin system in diabetes mellitus.

Table 1. Barriers to Insulin Use in Type 2 Diabetes Mellitus

Patient-Related	
Perception of poor compliance with other treatments	
Unnatural way of treating diabetes	
Weight gain	
Need for repeated injections	
Pain from injection	
Fear of worsening diabetes	
Complex form of treatment	
Hypoglycemia due to insulin	
Scheduling difficulties	
Poor quality of life	
Insulin will not treat the diabetes	
Increases diabetic complications	
Social stigma	
Clinician-Related	
Complex form of treatment	
Hypoglycemia	
Poor efficacy in type 2 diabetes	
Weight gain	
Lack of resources for teaching in office	
Lack of resources for frequent monitoring	

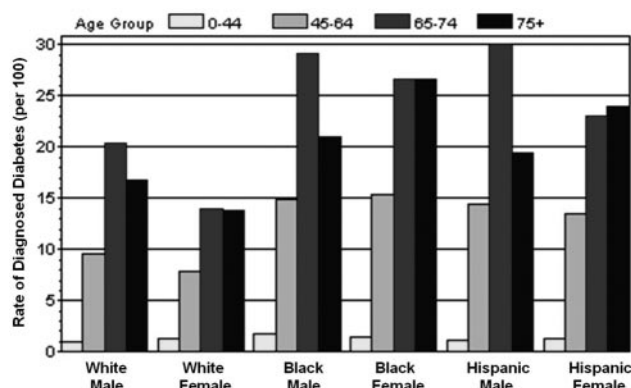


Fig. 1. Age-specific prevalence of diagnosed diabetes, by race/ethnicity and sex, in the United States in 2004. (From Reference 2.)

Epidemiology of Diabetes

Diabetes mellitus contributes to a rising health care burden in the United States. Since 1997, the prevalence of diagnosed diabetes mellitus increased from 10.4 million to 14.6 million people, with an additional 6.2 million undiagnosed cases accounting for associated morbidities and health care utilization.² Diabetes mellitus is the sixth leading cause of death, claiming about 72,000 lives annually. The overall prevalence of diabetes is about 2–4 times higher in Hispanics, African Americans, and Native Americans (Fig. 1)—groups in which health care access and utilization is known to be the lowest.³ By the year 2050, the prevalence of diabetes mellitus is expected to increase to 29 million diagnosed cases, with the greatest increase projected to occur in elderly women and African American men.⁴ The elderly population will bear the brunt of the increase in prevalence of diabetes mellitus, with half of the increase anticipated to occur in people over 65 years of age (Fig. 1).^{2,5} In 2002 alone, a total of \$132 billion was spent either directly or indirectly (disability, work loss, or premature death) on patients with diabetes mellitus. Health care dollars are often spent due to poor control of diabetes and its associated complications. With 28% of all diabetic patients using insulin,² the management of the disease and prevention of further complications are heavily dependent on adherence to insulin therapy.

Role of Insulin

The metabolic effects of insulin, a 51-amino acid peptide pancreatic hormone, allow for appropriate functioning of all organs in the body.⁶ Metabolism of glucose,^{6,7} fats,^{6,8–11} ketones,^{6,12} and proteins^{13,14} all depend on adequate production and utilization of the insulin hormone. Insulin may also play a role in steroid synthesis,^{15,16} vasodilation via activation of nitric oxide,^{17,18} inhibition of

fibrinolysis by stimulating production of plasminogen activator inhibitor-1,^{19–21} and normal growth via anabolic effects on protein and lipid metabolism.⁶ Thus, deficiency in insulin production or utilization affects a variety of metabolic processes throughout the body.

Patients with type 1 diabetes mellitus account for about 5–10% of the total diabetic population.^{2,5} In such patients, the insulin-producing β islet cells of the pancreas are completely destroyed and there is near complete absence of insulin production. Therefore, all patients with type 1 diabetes require insulin replacement. Type 1 diabetics are treated with either “conventional” insulin therapy (up to twice-daily dosing of combination formulations of short-acting and long-acting insulin) or “intensive” insulin therapy (physiologic dosing with long-acting/continuous insulin and pre-meal boluses of short-acting insulin).^{22,23} Physiologic insulin dosing in “intensive” therapy is accomplished by daily or twice-daily administration of long-acting insulin (glargine or neutral protamine hagedorn [NPH], respectively) or continuous short-acting insulin via subcutaneous pump. This is supplemented with pre-meal administration of rapid-acting (regular insulin) or very-rapid-acting insulin (lispro); the dose of these are determined by the pre-meal glucose level, composition of impending meal, and level of impending activity. When compared with the “conventional treatment” group in the Diabetes Control and Complications Trial, the “intensive treatment” group experienced fewer complications of retinopathy, nephropathy, and neuropathy.²²

The pathogenesis of type 2 diabetes is complicated and is characterized by impaired insulin secretion^{24–27} and peripheral insulin resistance.^{26,28,29} Reduced insulin secretion in the pre-diabetic or early diabetic states leads to chronic hyperglycemia, the toxic effects of which may contribute to deteriorating pancreatic β -cell function.^{30,31} Consequently, many type 2 diabetics eventually require some form of insulin to control their hyperglycemia. Factors that suggest earlier need for insulin include substantial weight loss at any age, severe hypoglycemic or hyperglycemic symptoms, heavy ketonuria, first presentation with diabetic ketoacidosis, and difficult-to-control hyperglycemia.³² Unfortunately, insulin therapy is often delayed in type 2 diabetics, for a variety of reasons,³³ despite data that confirm reduced microvascular and macrovascular complications in type 2 diabetes when a more intensive treatment plan, often requiring insulin, is implemented.^{34–37}

Barriers to Insulin Therapy

Resistance to initiating insulin therapy in type 2 diabetics permeates both the health care system and the patient population (Table 1). Reluctance to use insulin is often due to poor education of both patients and their physicians on the benefits of insulin therapy. Patient opposition to initi-

ating treatment occurs mostly for psychosocial reasons. Since diet and exercise are impressed upon type 2 diabetics as factors that can improve glycemic control, starting insulin is perceived as a sign of poor adherence on their part, and as a sign of worsening disease. So they resist, hoping that their disease will not worsen if they can “manage” on oral agents and lifestyle modification. Injections are considered by some patients as unnatural and associated with complications such as hypoglycemia. Often patients fear the unpleasantness associated with injections, such as pain, frequent dosing, social stigma, and scheduling difficulties. Weight gain is another concern, especially for diabetic women.^{33,38}

Physicians also contribute to delayed insulin initiation. Type 1 diabetics are often started on insulin therapy by pediatricians and are subsequently inherited by adult physicians. In patients with adult-onset type 1 diabetes, the diagnosis is often delayed unless the patient is obviously underweight. It is often assumed that adult-onset diabetes is always of the type 2 variety. About 10% of adult type 1 diabetics are erroneously diagnosed as having type 2 diabetes mellitus.^{39–41} Misdiagnosis leads to delayed insulin initiation in such patients. Another common misconception among physicians is that type 2 diabetics do not need insulin treatment, but only agents that promote insulin secretion. Fear of hypoglycemia and patient weight gain are potential adverse effects that prevent clinicians from considering insulin treatment. If the clinician thinks of insulin as a therapeutic option, delay in starting treatment may be due to a lack of office resources to educate the patient on insulin administration technique. Furthermore, some offices may not be adequately equipped and staffed to support the requirements for frequent glucose control monitoring.^{33,38}

The subcutaneous delivery of insulin has received negative publicity because of the above-described problems with insulin injections. As a result, the goal of adequate glycemic control in diabetics remains elusive. The American Diabetes Association and the American College of Endocrinology recommend target glycohemoglobin (HbA1c) levels below 7.0% and 6.5%, respectively. However, the national United States median HbA1c levels have been reported to be between 8.6% and 8.9%.^{42–46} The National Health and Nutrition Examination Survey (NHANES) is an ongoing national data-collection initiative conducted by the National Center for Health Statistics. These surveys are performed on the civilian population, and they collect such data as blood pressure, caloric intake, smoking status, and vaccinations. Data pertinent to diabetics, such as self-reported diabetic complications, types of diabetic medications being taken, and duration of diagnosis, are also collected. NHANES III focused on ethnic differences in glycemic control. Over half of the NHANES III subjects studied had HbA1c levels greater

than 7%, and poorest control was noted in the Hispanic group.^{47,48} We know from the United Kingdom Prospective Diabetes Study Group that intensive glycemic control in type 2 diabetics (sulfonylureas and/or insulin), resulting in 11% lower HbA1c than conventional glycemic control (diet and counseling alone), reduced microvascular diabetic complications risk by 25%.³⁶ Similar results were found in the Diabetes Control and Complications Trial for insulin-dependent diabetics; the intensive treatment group (≥ 3 times daily insulin, with specific glycemic targets) delayed the risk of microvascular complications by 35–70%, compared with the conventional treatment group (once or twice daily insulin guided by symptoms).²² Thus, better control of diabetes with insulin has enormous social and economic implications.

Alternative Devices for Insulin Delivery

Because of poor patient adherence to injections, alternative modes of insulin delivery have been investigated for decades. These include: insulin pens, for ease of administration and transport; insulin jet injectors, which emit a fine spray mist at high pressure for absorption through the skin; subcutaneous infusion ports; external insulin pumps; and inhaled insulin. Other insulin delivery techniques under investigation include implantable pumps that are refilled every 2 months; continuous-delivery insulin patches; insulin pills; buccal and intranasal sprays; and surgically implanted artificial pancreas.^{49,50}

Among devices that are approved and those still under investigation, very few noninvasive options exist for insulin delivery. Inhaled insulin delivery has been explored for over a decade, and one formulation was approved by the FDA in January 2006. This noninvasive alternative is associated with significantly greater patient satisfaction and quality-of-life scores, because it is painless, has social acceptance, and is easy to use, among other factors.^{51–54} Patient satisfaction was measured objectively, with the Patient Satisfaction With Insulin Therapy questionnaire.⁵⁵

Inhaled Insulin Formulation

The first approved form of inhaled human insulin (Exubera) is of recombinant deoxyribonucleic acid (rDNA) origin. Exubera is a spray-dried insulin powder approved for use in type 1 or type 2 diabetes.⁵⁶ Excipients (mannitol, glycine, and sodium citrate) are added to the dried insulin to create the final product, which is a large, low-density powder particle consisting of 60% insulin. The powder is packaged in small blisters.⁵⁷ The formulation is stable at room temperature and its packaging protects the drug from moisture. The aerosolized insulin has a mass median aerodynamic diameter of approximately 3 μm , which is an

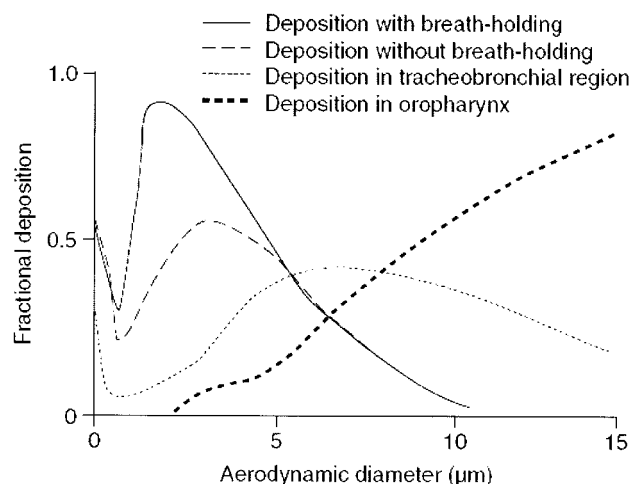


Fig. 2. Fractional particle deposition to the lung is critically dependent on mass median aerodynamic diameter. (From Reference 58, with permission.)

optimal size for enhanced alveolar deposition (Fig. 2), with low oropharyngeal and large-airway deposition.⁵⁸

There are 2 blister sizes. One contains 1 mg of powder, which translates to 2.7 units of injected insulin. The other contains 3 mg of powder, which translates to 8 units of injected insulin. Compared with smaller particles, the specially formulated low-density particles of insulin do not aggregate, which improves alveolar deposition. The slightly larger particle size also reduces phagocytic clearance.⁵⁹ Once deposited in the alveoli, the insulin particles are transported to the adjacent capillaries through vesicles, via a process called transcytosis.^{60–63}

After systemic absorption, inhaled insulin has a rapid onset of action, occurring within 20 min of administration, similar to that of insulin lispro or insulin aspart, and its duration of action is similar to that of subcutaneous regular insulin (Fig. 3). The time to half-maximum glucose-lowering effect occurring before the maximum glucose infusion rate ($t_{\text{GIR early 50\%}}$) correlates with the onset of action of inhaled insulin. Rave and co-workers reported that ($t_{\text{GIR early 50\%}}$) of inhaled insulin was shorter than that of subcutaneous regular insulin (32 min vs 48 min, respectively, $p < 0.001$). The duration of action of inhaled insulin, determined by the time to half of the maximum glucose infusion rate after the maximum glucose infusion rate ($t_{\text{GIR late 50\%}}$), was longer than the duration of lispro (387 min vs 313 min, $p < 0.01$).^{64,65} The pharmacodynamics of inhaled insulin indicate that it is a viable, and possibly better, option for short-acting insulin delivery in diabetic patients, especially because of its ease of use and reduction in adverse effects of injected insulin.

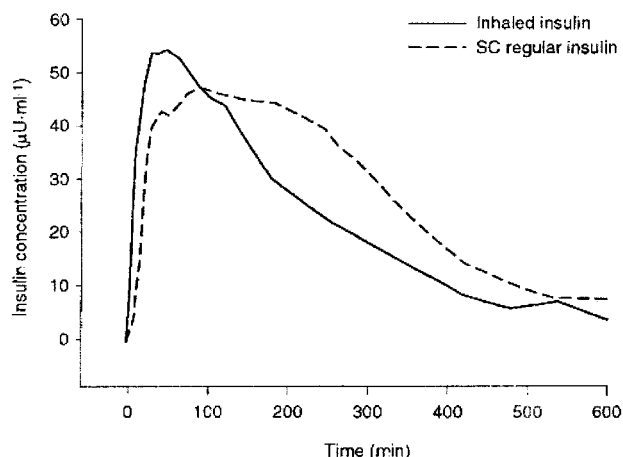


Fig. 3. Serum insulin concentration-time profile in 17 nondiabetic volunteers after inhalation of 6 mg insulin or subcutaneous (SC) injection of 18 units of regular insulin. (From Reference 64, with permission.)

Delivery System

Exubera, the first approved inhaled insulin preparation, is delivered with an aerosol device called the Exubera inhaler, designed by Nektar. The device is a dry powder inhaler (DPI) system that uses compressed air for drug dispersion. The blister units are packaged on a perforated aluminum card. The cards with the 1-mg blisters are printed in green ink and marked with one raised bar, and the cards with the 3-mg blisters are printed in blue ink and marked with 3 raised bars, for easy identification. The inhaler



Fig. 4. Left and center: Exubera inhaled insulin delivery system. (Courtesy of Pfizer.) Right: Lilly/Alkermes inhaled insulin delivery system. (Courtesy of Lilly/Alkermes.)

consists of an inhaler base, a chamber, and an Exubera release unit (Figs. 4 left, center, and 5). The drug blisters should be stored at room temperature (59–86°F) and used within 3 months of opening the foil wrap. The inhaler can be used for up to one year after initial use.

The recommended method of inhaling Exubera is described in Table 2. Briefly, the base is separated from the chamber by pulling on the black ring. The aluminum wrapped blister is placed into the slot with the printed side up. The blue handle is pulled out and squeezed until snapped shut. The blue button (facing the patient) is then pushed. This punctures the blister and an aerosol cloud of dried insulin is released into the clear chamber. With the mouthpiece turned toward the patient for activation, the lips are sealed around the mouthpiece and the insulin is inhaled with one slow, deep breath (see Fig. 5).⁶⁶ A video clip demonstrating the use of Exubera inhaler can also be found

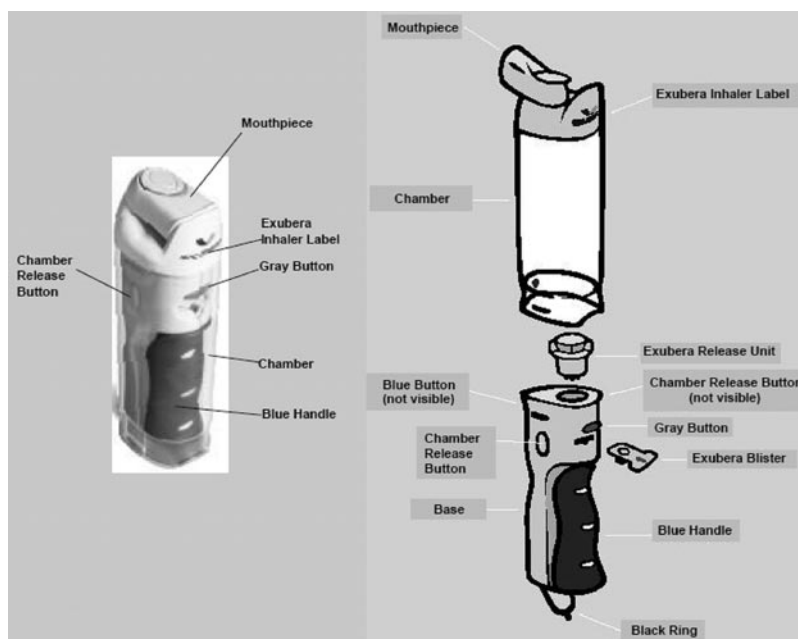


Fig. 5. Exubera inhaler system. (Courtesy of Pfizer.)

Table 2. Use and Cleaning of the Exubera Inhaler

Use	
1.	Hold Exubera inhaler in hand, with the words "Exubera Inhaler" facing you
2.	Pull base out of chamber by pulling black ring until it locks in place.
3.	Hold blister (in aluminum packaging) with printed side up and insert into slot
4.	Make sure mouthpiece is closed
5.	Pull out blue handle
6.	Squeeze blue handle until it snaps shut
7.	Stand or sit up straight
8.	Hold the inhaler with blue button facing you
9.	Push blue button until it clicks and the insulin cloud fills the transparent chamber
10.	If the insulin cloud does not appear, press the gray button to remove the blister and re-insert the blister into the slot
11.	After the insulin cloud is visible, breathe out normally and turn the mouthpiece to face you
12.	Place mouthpiece into mouth and form a seal around it
13.	Take one slow, deep breath
14.	Take mouthpiece out of mouth and hold breath for 5 seconds
15.	Breathe out normally
16.	Turn mouthpiece back to closed position
17.	Press gray button and remove used blister
18.	Squeeze the chamber-release buttons and replace the base into the chamber
Cleaning	
1.	Pull black ring until base locks into open position
2.	Squeeze chamber-release buttons and pull base completely out of chamber
3.	Clean chamber once a week, with a clean, damp, soft cloth, using mild soap and warm water
4.	Ensure complete dryness before re-assembling the unit
5.	Wipe only the outside surfaces of the base

as a supplement to the recently published article on inhaled insulin in the *New England Journal of Medicine*.⁶⁷

Other inhalation delivery systems are currently being investigated in clinical trials. The human inhaled insulin powder (HIIP) by Alkermes/Lilly (see Fig. 4 right) is delivered with a breath-actuated DPI that is smaller than the Exubera device, which allows for ease of use and transport. The HIIP unit also works by puncturing a blister of insulin. These blisters come in 0.9-mg (2 insulin units) and 2.6-mg (6 insulin units) doses, which should be administered within 15 min of starting a meal.⁶⁸ Nebulizers, metered-dose inhalers, other DPIs, and aqueous mist inhalers of insulin are also being investigated.^{69,70} Inhalation devices under investigation include: the aqueous mist inhaler AERx iDMS (Aradigm and Novo Nordisk); the breath-activated liquid insulin formulation designed for the Aerodose Inhaler (Aerogen); the AIR inhaled insulin system (HIIP, Alkermes/Eli Lilly) described above; the Alveair delivery system (Coremed), which uses a polymer/bioadhesive mechanism to create 1.9- μm insulin particles for

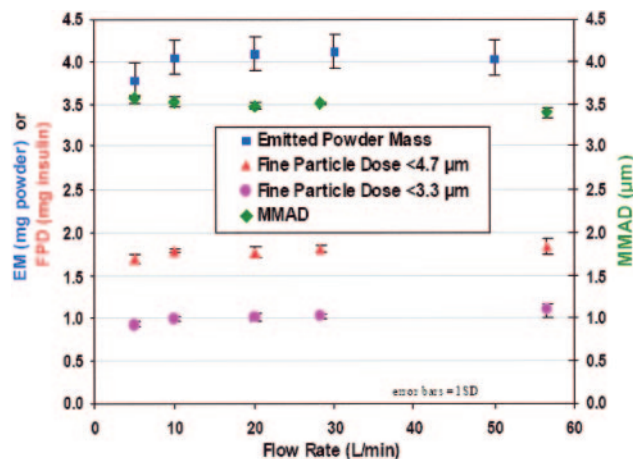


Fig. 6. In vitro studies have demonstrated lack of variability in emitted mass and particle size, despite variable flow rates. EM = emitted mass. FPD = fine-particle dose. MMAD = mass median aerodynamic diameter. (From Reference 57, with permission.)

deep lung deposition; the capsule-based high-impedance Technosphere Inhaler (Mannkind Pharmaceuticals) used with the Medtone DPI, which is a formulation of latticed microspheres that dissolve at the neutral pH of the alveolar surface; and a metered-dose inhaler type system being investigated by Kos Pharmaceuticals. Various formulations of inhaled insulin that are being investigated have been reviewed in detail by Jani et al (2007)⁷¹ and Owens et al (2003).⁷²

Effect of Airflow and Breathing Pattern on Particle Deposition

Although Exubera is packaged in nominal doses of 1 mg and 3 mg per blister, the amount of insulin delivered is variable between any 2 patients and between any 2 doses with one patient, because delivery of a DPI formulation is often dependent on the patient's inspiratory flow rate. The actual dose delivered to the lung in vivo may depend on additional factors, such as the breath-hold maneuver and variable breathing patterns of the patient. The breath-hold maneuver is expected to produce greater lung deposition (see Fig. 2), but it does not seem to correlate with increased bioavailability of insulin in patients.⁷² The Exubera system is unique, because the powder is aerosolized by compressed air prior to inhalation, thereby avoiding the effect of inhalation flow rate on aerosol production observed with other DPIs. In vitro studies of the Exubera formulation have shown that inhalation flow rates do not affect the mass median aerodynamic diameter, fine-particle dose, or emitted powder mass of the drug (Fig. 6). Moreover, the variability in the glycemic metabolic effect of Exubera is comparable to that observed with subcutaneous delivery.⁵⁷

Indications

The FDA approved inhaled recombinant human insulin (Exubera) for adult patients with type 1 or type 2 diabetes. Patients with type 1 diabetes may be started on inhaled insulin as an adjunct to long-acting subcutaneous insulin. Poor glycemic control in patients with type 2 diabetes currently being managed with oral agents or with poor adherence to injectable insulin, could be improved with the Exubera inhaler.^{73–76} These patients are often initially resistant to use of invasive forms of insulin. In both type 1 and type 2 diabetes, inhaled insulin is indicated to replace pre-meal subcutaneous regular insulin and is not indicated for long-term maintenance therapy.

Two other groups of patients in whom inhaled insulin could be considered are pregnant women and morbidly obese diabetic patients. Gestational diabetes may not be an appropriate indication because inhaled insulin is pregnancy category C, and there is lack of sufficient data in that group. However, the manufacturer of Exubera does not prohibit its use in pregnancy.⁶⁷ In the morbidly obese, subcutaneous insulin may be poorly absorbed, and inhaled insulin use may be preferred because its absorption is not limited by body mass index.⁶⁷

According to the Exubera package insert, the pharmacokinetics of inhaled insulin in pediatric, adolescent, and geriatric patients was similar to those in adults. Sex, ethnicity, or obesity differences were not noted either.⁶⁷ Therefore, all of these groups may safely use this product. Since the effects of inhaled insulin in patients with renal or hepatic impairment are unknown at this time, caution is needed when prescribing to these groups of patients.⁶⁷

Clinical Studies

In type 1 diabetes, inhaled human insulin is used as a pre-meal bolus, to replace short-acting subcutaneous insulin, in conjunction with long-acting subcutaneous insulin, such as once-daily insulin glargine or twice-daily insulin NPH. In type 2 diabetes, inhaled insulin may be used as a single agent, 10 min prior to a meal, or in a combination regimen with long-acting subcutaneous insulin or oral anti-hyperglycemic agents.⁶⁹ For initial pre-meal dosing, Dunn and Curran suggested the equation:

$$\text{pre-meal dose (mg)} = \text{body weight (kg)} \times 0.05 \text{ mg/kg}$$

Subsequent doses could be titrated as needed for glucose concentrations, time of day, exercise timing, meal size, and meal composition.^{67,69}

In patients with upper respiratory infection, close monitoring of glucose control is needed because of decreased airway absorption. The use of bronchodilators in temporal

relation to inhaled insulin use also needs to be standardized to a schedule because of the potential for bronchodilators to alter inhaled human insulin absorption.^{67,77} Baseline lung-function testing with bi-annual follow-up is recommended. Inhaled insulin should be discontinued if the forced expiratory volume in the first second (FEV₁) or the diffusion capacity of the lung for carbon monoxide (D_{LCO}) is less than 70% of predicted or declines by more than 20% from the baseline value. Exubera is not recommended for patients with underlying lung disease such as asthma or chronic obstructive pulmonary disease. Inhaled insulin is contraindicated in smokers. Patients must abstain from smoking for at least 6 months prior to starting inhaled insulin.⁶⁷

A meta-analysis by Ceglia et al on the efficacy of inhaled insulin therapy in patients with diabetes included data from 16 open-label trials.⁷⁸ Glycemic outcomes of inhaled versus subcutaneous insulin in patients with type 1 and type 2 diabetes found a small but statistically significant decrease in HbA1c, which favored subcutaneous forms of treatment (Fig. 7). Although not a comparison trial, Cefalu et al found a decrease in HbA1c in patients with type 2 diabetes who were previously poorly controlled with 2–3 times daily subcutaneous insulin.⁷³ These investigators observed that the mean HbA1c decreased from a baseline of 8.67% to 7.96% at the end of a 12-week trial with pre-meal inhaled insulin treatment as a supplement to ultralente at bedtime.⁷³ These data support the benefit of inhaled insulin in type 2 diabetics with poor glycemic control.

When comparing inhaled insulin with oral hypoglycemic agents, the former achieved lower targets of HbA1c. However, the 2 studies that were larger, of longer duration, and reached the 7% HbA1c target recommended by the American Diabetes Association,^{77,79} showed only small, yet statistically significant, advantages of inhaled insulin over oral hypoglycemic agents (Fig. 8).

Adverse Effects and Limitations of Inhaled Insulin

Inhaled human insulin appears to be efficacious in reducing blood glucose levels and is convenient to use, with a high patient satisfaction rate. However, several adverse effects and limitations to the use of inhaled insulin require that patients be closely monitored while using this drug.

The inability to use inhaled insulin in smokers or patients with a history of lung disease is one of its major limitations. Twenty-five percent of patients with diabetes are tobacco smokers. Absorbance of insulin is decreased in nondiabetic patients with asthma, and it is increased in nondiabetic former smokers and in patients with chronic obstructive pulmonary disease.^{78,80} However, it is unclear whether increased absorbance in smokers translates to increased hypoglycemic effects. Lack of expected hypogly-

INHALED INSULIN

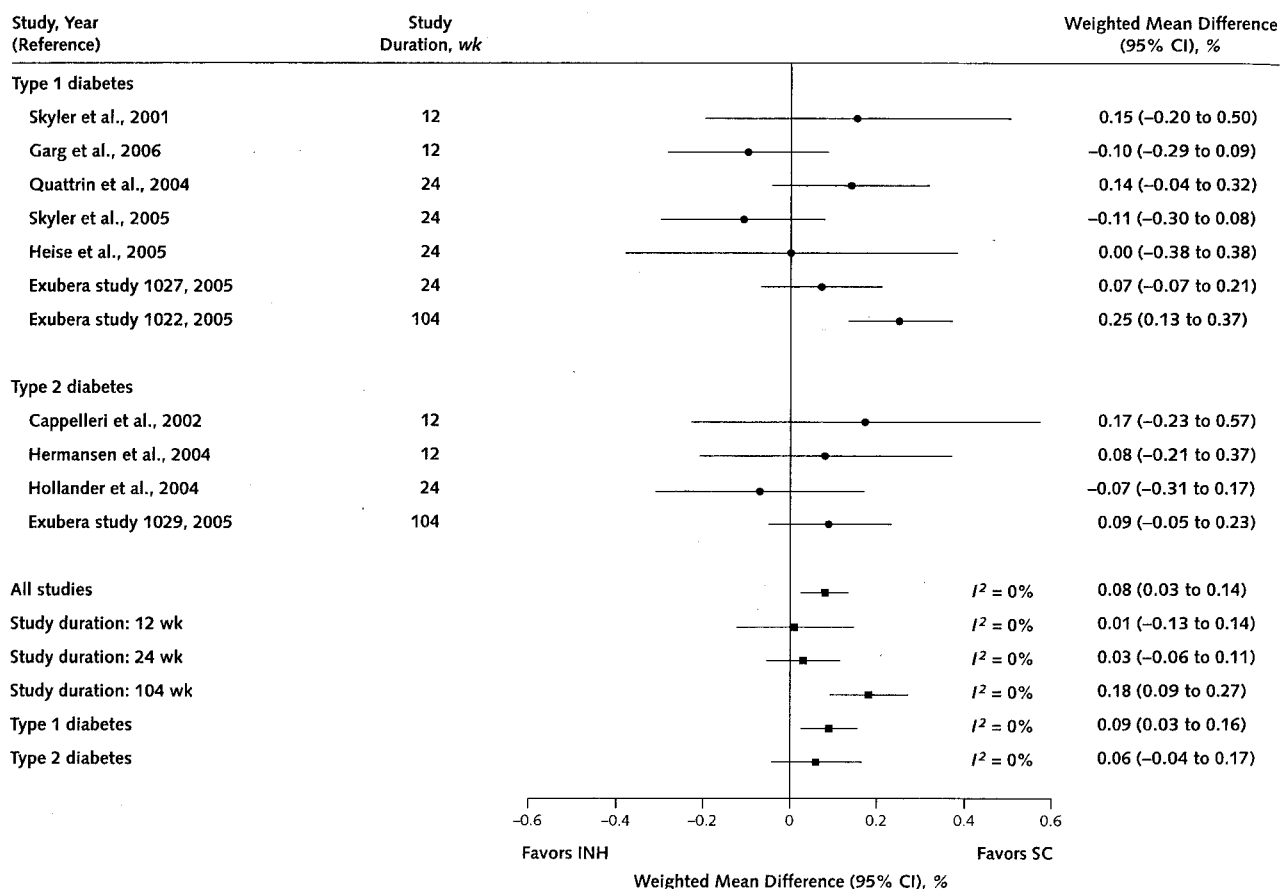


Fig. 7. In a meta-analysis directed at examining the efficacy of inhaled insulin (INH), there was a small advantage in reducing glycohemoglobin (HbA1c) with subcutaneous (SC) insulin, when compared with inhaled insulin in type 1 and type 2 diabetes. CI = confidence interval. (From Reference 78, with permission.)

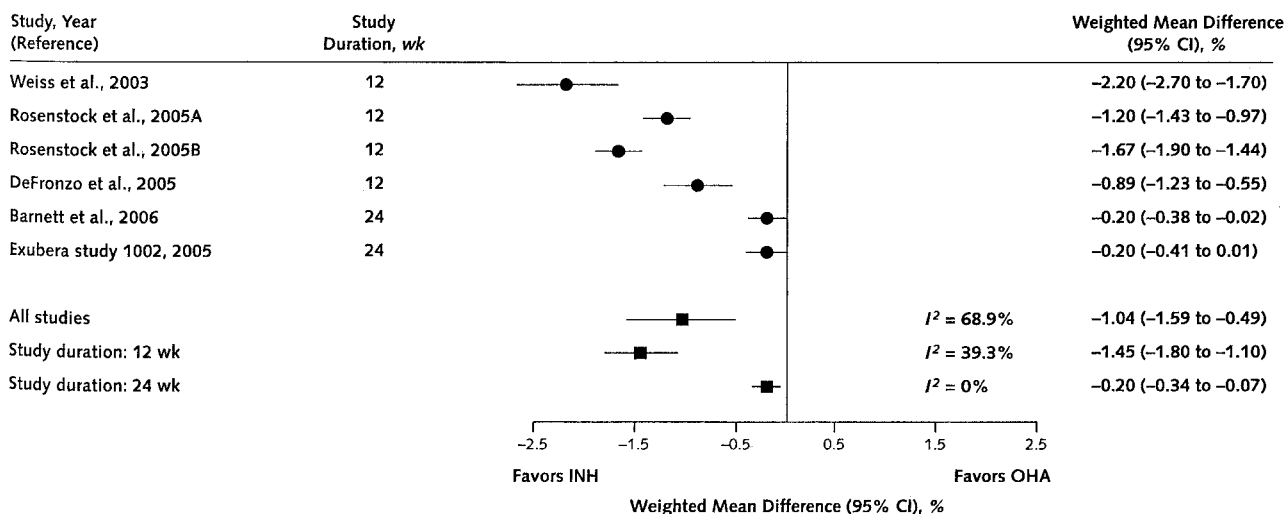


Fig. 8. Ceglia et al demonstrated a favorable effect of inhaled insulin (INH) compared with oral hypoglycemic agents (OHA) in reducing glycohemoglobin (HbA1c). CI = confidence interval. (From Reference 78, with permission.)

emic effects may be due to lower insulin sensitivity and glucose utilization in smokers.⁸¹ Alteration in smoking

habits were shown to influence inhaled insulin pharmacokinetics, although most of these observations were made in

studies of nondiabetic smokers.^{78,81–83} Peak plasma concentrations were 2–5-fold higher, area under the curve from 0–6 hours on a plasma-concentration/time curve was 2–5 times higher, and the time to peak serum concentrations was also faster in smokers than in nonsmokers (31 min vs 53 min, respectively).^{82,83} These data form the basis for the recommended contraindication to the use of inhaled human insulin in smokers.

Cough occurs in 21% of patients who use inhaled insulin, compared with 4–8% in comparator diabetic groups.^{32,84} Cough occurs soon after initiating treatment and often decreases in frequency and severity over time.⁷⁸ The presence of acute respiratory issues, such as bronchitis, is known to alter medication absorption. Caution should also be exercised in patients using bronchodilators. The time of bronchodilator use, in relation to inhaled insulin use, should not be changed because of the potential for altered absorption of insulin.

In patients with type 1 diabetes treated with inhaled versus subcutaneous insulin, a weighted mean reduction in D_{LCO} of -0.902 mL/min/mm Hg was found in the inhaled insulin groups that were treated for less than 24 weeks, but not in the study that was followed for 2 years.^{53,68,77,85–87} These D_{LCO} reductions revert back to baseline when inhaled insulin is discontinued, which suggests reversibility and possible impermanence of D_{LCO} reduction.^{68,88} No D_{LCO} reduction was found in type 2 diabetics monitored for 2 years.⁷⁷ A small but statistically significant decline in forced expiratory volume in the first second (FEV_1) occurs in patients who receive inhaled human insulin, compared with subcutaneous insulin in type 1 diabetes, and compared with oral hypoglycemic agents in type 2 diabetes (weighted mean difference -0.031 L).^{51,53,74–77,79,85–88} FEV_1 continued to decline until 6 months, at which time it stabilized.⁷⁸ However, one small study by the Inhaled Insulin Study Group in 2001 reported no significant changes in either spirometry or D_{LCO} .⁷³

Several nonrespiratory issues are also important to consider when inhaled insulin is employed. When compared with oral anti-hyperglycemic agents, inhaled human insulin had a 3-fold higher occurrence of hypoglycemia.⁷⁸ Similar to other insulin preparations, weight gain of 2–3.6 kg occurred with inhaled human insulin; this was higher than that observed in patients using oral anti-hyperglycemic agents for type 2 diabetes.⁶⁷ This effect was seen in patients whose glucose levels were previously poorly controlled with oral agents over a 24-week period.⁸⁹ Inhaled human insulin also increases circulating insulin antibodies.^{68,85} However, no association with altered outcomes of dosing, glucose control, allergies, adverse pulmonary effects, or hypoglycemic effects have been documented.^{78,90} Other adverse effects, such as chest pain, dry mouth, and otitis media, are infrequently observed.⁷⁸

Although marketed for ease and convenience of insulin administration, the Exubera delivery system is quite large and cumbersome to use. But the benefits of avoiding injection use may outweigh that issue. Exubera is packaged in 1-mg and 3-mg blisters, which equate to about 2.7 units and 8 units of insulin. However, the mathematics of dosing may cause errors in administration and nonreproducible dose delivery and thereby variable intra-dose hypoglycemic effects. To date, most studies that have compared inhaled insulin to subcutaneous insulin were designed on a noninferiority basis.^{51,53,67,68,85–88,91} In contrast, the studies that compared inhaled insulin with oral agents were designed for a superiority effect.^{67,74–76,79} Despite all the above-mentioned issues with inhaled insulin, many patients prefer its use over frequent injection forms of insulin.^{78,92}

Place of Inhaled Insulin in Diabetes Therapy

Type 1 or insulin-dependent type 2 diabetic patients are heavily dependent on accurate dosing and tight glycemic control to prevent acute, potentially severe hyperglycemia. Since studies based on the “superiority” principle were only performed in comparison with oral anti-hyperglycemic agents,⁷⁸ there is no clear advantage to replacing traditional insulin delivery systems with inhaled insulin. However, those patients treated with several oral agents with fair-to-poor control and who are resistant to the idea of injection treatment are excellent candidates for inhaled human insulin. Improved glycemic control in type 2 diabetics could be achieved at an earlier stage, when oral anti-hyperglycemic agents and inhaled human insulin combination therapy is considered as a bridge to converting to “insulin only” regimens. Patients with poor subcutaneous absorption and nonadherent insulin-dependent patients may also benefit from inhaled human insulin use. Potential candidates need to be screened for pre-existing airways disease or smoking history, and they need to be closely monitored for appropriate glycemic control until further clinical experience is attained. Patients also need extensive education on the limitations of the formulation, so that inhaled human insulin is avoided during states of potentially altered absorption (acute bronchitis or bronchodilator use).

Conclusion

Despite the availability of data that support appropriate glycemic targets in diabetic patients, less than half the diabetic population is adequately controlled. Limitations to achieving good control of blood sugar revolve around lack of physician education on the utility of insulin and patient resistance to insulin use. Inhaled insulin offers a highly patient-favorable alternative to injectable forms of insulin, especially in type 2 diabetes, thereby offering prom-

ise to improve medication adherence and glycemic goals. In the indicated groups of type 1 and type 2 diabetes, inhaled insulin is a viable new option when used with less frequently dosed long-acting insulin or oral hypoglycemic agents, respectively. Although underlying pulmonary disease poses a limitation to its use, the other significant adverse effects of inhaled insulin are similar to those of injection formulations. With close glycemic monitoring and education on appropriate use, patients who were previously opposed to insulin treatment could demonstrate improved diabetes control with inhaled insulin and meet the goals recommended by the American Diabetes Association and the American College of Endocrinology. Newer inhaled insulin formulations and delivery systems are being investigated to increase access and ease of use. The place of inhaled insulin in the treatment of diabetes is likely to evolve with the approval of other preparations for clinical use, and with increased familiarity of patients and clinicians with the inhaled route of insulin administration.

REFERENCES

1. Committee Report. Report of the Expert Committee on the diagnosis and classification of diabetes mellitus. *Diabetes Care* 2002;25:S5–S20.
2. National Diabetes Surveillance System. Prevalence of diabetes: age-specific prevalence of diagnosed diabetes, by race/ethnicity and sex, United States, 2005. Centers for Disease Control and Prevention. 6 October 2005. Available at: <http://www.cdc.gov/diabetes/statistics/prev/national/fig2004.htm>. [Internet]. (Accessed May 9, 2007.)
3. National Health Interview Survey (NHIS). National Center for Health Statistics, CDC. 11 January 2007. Accessed 16 January 2007. http://www.cdc.gov/nchs/data/nhis/earlyrelease/200612_01.pdf
4. Boyle JP, Honeycutt AA, Venkat Narayan KM, Hoerger TJ, Geiss LS, Chen H, Thompson TJ. Projection of diabetes burden through 2050: impact of changing demography and disease prevalence in the U.S. *Diabetes Care* 2001;24(11):1936–1940.
5. Turina M, Christ-Crain M, Polk HC Jr. Diabetes and hyperglycemia: strict glycemic control. *Crit Care Med* 2006;34(9 Suppl):S291–S300.
6. Mantzoros C, Serdy S. Insulin action. UpToDate February 27, 2006.
7. Kahn BB. Lilly lecture 1995. Glucose transport: pivotal step in insulin action. *Diabetes* 1996;45(11):1644–1654.
8. Enoksson S, Degerman E, Hagstrom-Toft E, Large V, Arner P. Various phosphodiesterase subtypes mediate the in vivo antilipolytic effect of insulin on adipose tissue and skeletal muscle in man. *Diabetologia* 1998;41(5):560–568.
9. Farese RV Jr, Yost TJ, Eckel RH. Tissue-specific regulation of lipoprotein lipase activity by insulin/glucose in normal-weight humans. *Metabolism* 1991;40(2):214–216.
10. Stralfors P, Bjorgell P, Belfrage P. Hormonal regulation of hormone-sensitive lipase in intact adipocytes: identification of phosphorylated sites and effects on the phosphorylation by lipolytic hormones and insulin. *Proc Natl Acad Sci USA* 1984;81(11):3317–3321.
11. Vaughan M, Steinberg D. Glyceride biosynthesis, glyceride breakdown, and glycogen breakdown in adipose tissue: mechanism and regulation. In: Renold AE, Cahill GF, editors. *Handbook of physiology, adipose tissue*, Vol 24. Washington DC: American Physiological Society; 1965:239.
12. Keller U, Gerber PP, Stauffacher W. Fatty acid-independent inhibition of hepatic ketone body production by insulin in humans. *Am J Physiol* 1988;254(6 Pt 1):E694–E699.
13. Flakoll PJ, Kulaylat M, Frexes-Steed M, Hourani H, Brown LL, Hill JO, Abumrad NN. Amino acids augment insulin's suppression of whole body proteolysis. *Am J Physiol* 1989;257(6 Pt 1):E839–E847.
14. Jefferson LS. Lilly Lecture 1979: role of insulin in the regulation of protein synthesis. *Diabetes* 1980;29(6):487–496.
15. Adashi EY, Hsueh AJ, Yen SS. Insulin enhancement of luteinizing hormone and follicle-stimulating hormone release by cultured pituitary cells. *Endocrinology* 1981;108(4):1441–1449.
16. Rosenfeld RL, Barnes RB, Cara JF, Lucky AW. Dysregulation of cytochrome P450c 17 alpha as the cause of polycystic ovarian syndrome. *Fertil Steril* 1990;53(5):785–791.
17. Abramson DI, Schkloven N, Margolis MN, Mirsky IA. Influence of massive doses of insulin on peripheral blood flow in man. *Am J Physiol* 1939;128:124–132.
18. Steinberg HO, Brechtel G, Johnson A, Fineberg N, Baron AD. Insulin-mediated skeletal muscle vasodilation is nitric oxide dependent: a novel action of insulin to increase nitric oxide release. *J Clin Invest* 1994;94(3):1172–1179.
19. Juhan-Vague I, Alessi MC, Vague P. Thrombogenic and fibrinolytic factors and cardiovascular risk in non-insulin-dependent diabetes mellitus. *Ann Med* 1996;28(4):371–380.
20. Nordt TK, Sawa H, Fujii S, Sobel BE. Induction of plasminogen activator inhibitor type-1 (PAI-1) by proinsulin and insulin in vivo. *Circulation* 1995;91(3):764–770.
21. Schneider DJ, Nordt TK, Sobel BE. Attenuated fibrinolysis and accelerated atherogenesis in type II diabetic patients. *Diabetes* 1993;42(1):1–7.
22. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329(14):977–986.
23. McCulloch DK. Insulin therapy in type 1 diabetes mellitus. UpToDate July 11, 2006.
24. Chen KW, Boyko EJ, Bergstrom RW, Leonetti DL, Newell-Morris L, Wahl PW, Fujimoto WY. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM: 5-year follow-up of initially nondiabetic Japanese-American men. *Diabetes Care* 1995;18(6):747–753.
25. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Decreased insulin secretion and increased insulin resistance are independently related to the 7-year risk of NIDDM in Mexican-Americans. *Diabetes* 1995;44(12):1386–1391.
26. McCulloch DK, Robertson RP. Pathogenesis of type 2 diabetes mellitus. UpToDate August 27, 2006.
27. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. *J Clin Invest* 1999;104(6):787–794.
28. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states: sequence of events leading to non-insulin-dependent diabetes mellitus. *J Clin Invest* 1994;94(5):1714–1721.
29. Kahn CR. Banting Lecture. Insulin action, diabetogenesis, and the cause of type II diabetes. *Diabetes* 1994;43(8):1066–1084.
30. Li Y, Xu W, Liao Z, Yao B, Chin X, Huang Z, et al. Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of β -cell function. *Diabetes Care* 2004;27(11):2597–2602.
31. Moran A, Zhang HJ, Olson LK, Harmon JS, Poytout V, Robertson RP. Differentiation of glucose toxicity from beta cell exhaustion during the evolution of defective insulin gene expression in the pancreatic islet cell line, HIT-T15. *J Clin Invest* 1997;99(3):534–539.
32. McCulloch DK. General principles of insulin therapy in diabetes mellitus. UpToDate August 3, 2006.

33. Brunton S, Carmichael B, Funnell M, Lorber D, Rakel R, Rubin R. Type 2 diabetes: the role of insulin. *J Fam Pract* 2005;54(5):445–452.
34. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, et al; PROactive investigators. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAZone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 2005; 366(9493):1279–1289.
35. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. *Diabetes Res Clin Pract* 1995;28(2):103–117.
36. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352(9131):837–853. *Erratum in Lancet* 1999;354(9178):602.
37. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 1998;352(9131): 854–865. *Erratum in: Lancet* 1998;352(9139):1558.
38. Davis SN, Renda SM. Psychological insulin resistance: overcoming barriers to starting insulin therapy. *Diabetes Educ* 2006;32 Suppl 4:146S–152S.
39. Harris MI, Robbins DC. Prevalence of adult-onset IDDM in the U.S. population. *Diabetes Care* 1994;17(11):1337–1340.
40. Landin-Olsson M, Nilsson KO, Lernmark A, Sundkvist G. Islet cell antibodies and fasting C-peptide predict insulin requirement at diagnosis of diabetes mellitus. *Diabetologia* 1990;33(9):561–568.
41. Niskanen LK, Tuomi T, Karjalainen J, Groop LC, Uusitupa MI. GAD antibodies in NIDDM. Ten-year follow-up from the diagnosis. *Diabetes Care* 1995;18(12):1557–1565.
42. AMA, JCAHO, NCQA: Coordinated performance measures for the management of adult diabetes (Consensus Statement article on line), 2001. Available from <http://care.diabetesjournals.org>. Last accessed May 10, 2007.
43. Bureau of Health Professions National Center for Health Workforce Information and Analysis. HRSA state profile for Montana. Dec 2000. Available at <ftp://ftp.hrsa.gov/bhpr/workforceprofiles/MT.pdf>. [Internet]. Last accessed May 9, 2007.
44. O'Connor PJ, Rush WA, Peterson J, Morben P, Cherney L, Keogh C, Lasch S. Continuous quality improvement can improve glycemic control for HMO patients with diabetes. *Arch Fam Med* 1996;5(9): 502–506.
45. Stolar MW. Clinical management of the NIDDM patient: impact of the American Diabetes Association practice guidelines, 1985–1993. Endocrine Fellows Foundation Study Group. *Diabetes Care* 1995; 18(5):701–707.
46. U.S. Census Bureau demographic data. Available at <http://www.census.gov/index.html>. [Internet]. Last accessed May 9, 2007.
47. Harris MI. Racial and ethnic differences in health care access and health outcomes for adults with type 2 diabetes. *Diabetes Care* 2001; 24(3):454–459.
48. Resnick HE, Foster GL, Bardsley J, Ratner RE. Achievement of American Diabetes Association clinical practice recommendations among U.S. adults with diabetes, 1999–2002: the National Health and Nutrition Examination Survey. *Diabetes Care* 2006;29(3):531–537.
49. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), NIH. Alternative devices for taking insulin. Published January 2006. Available at <http://diabetes.niddk.nih.gov/dm/pubs/insulin/index.htm>. [Internet]. Last accessed May 9, 2007.
50. Patton JS, Bukar JG, Eldon MA. Clinical pharmacokinetics and pharmacodynamics of inhaled insulin. *Clin Pharmacokinet* 2004;43(12): 781–801.
51. Cappelleri JC, Cefalu WT, Rosenstock J, Kourides IA, Gerber RA. Treatment satisfaction in type 2 diabetes: a comparison between an inhaled insulin regimen and a subcutaneous insulin regimen. *Clin Ther* 2002;24(4):552–564.
52. Gerber RA, Cappelleri JC, Kourides IA, Gelfand RA. Treatment satisfaction with inhaled insulin in patients with type 1 diabetes: a randomized controlled trial. *Diabetes Care* 2001;24(9):1556–1559.
53. Quattrin T, Bélanger A, Bohannon NJV, Schwartz SL; for the Exubera Phase III Study Group. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 2004; 27(11): 2622–2627.
54. Testa MA, Turner RR, Hayes JF, et al. Intensive therapy and patient satisfaction in type 1 diabetes: a randomized trial of injected vs. inhaled insulin (abstract no. 8) *Diabetologia* 2001;44(Suppl 1):4.
55. Cappelleri JC, Gerber RA, Kourides IA, Gelfand RA. Development and factor analysis of a questionnaire to measure patient satisfaction with injected and inhaled insulin for type 1 diabetes. *Diabetes Care* 2000;23(12):1799–1803.
56. Lenzer J. Inhaled insulin is approved in Europe and United States. *BMJ* 2006;332(7537):321.
57. Harper N. Pharmaceutical development of Exubera. Pfizer and Nektar. 24 May 2006. MBC drug delivery symposium. Available at <http://massbio.org/attachments/pfizer.pdf>. Accessed January 19, 2007.
58. Byron PR. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. *J Pharm Sci* 1986; 75(5):433–438. *Erratum in: J Pharm Sci* 1986;75(12):1207.
59. Lombry C, Edwards DA, Preat V, Vanbever R. Alveolar macrophages are a primary barrier to pulmonary absorption of macromolecules. *Am J Physiol Lung Cell Mol Physiol* 2004;286(5):L1002–L1008.
60. Barnett AH. Exubera inhaled insulin: a review. *Int J Clin Pract* 2004;58(4):394–401.
61. Edwards DA, Ben-Jebria A, Langer R. Recent advances in pulmonary drug delivery using large, porous inhaled particles. *J Appl Physiol* 1998;85(2):379–385.
62. Newhouse MT. Tennis anyone? The lungs as a new court for systemic therapy. *CMAJ* 1999;161(10):1287–1288.
63. Patton JS. Mechanisms of macromolecule absorption by the lungs. *Adv Drug Deliv Rev* 1996;19(1):3–36.
64. Rave K, Bott S, Heinemann L, Sha S, Becker RHA, Willavize SA, Heise T. Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. *Diabetes Care* 2005;28(5):1077–1082.
65. Rave KM, Nosek L, De La Peña A, Seger M, Ernest CS, Heinemann L, et al. Dose response of inhaled dry-powder insulin and dose equivalence to subcutaneous insulin lispro. *Diabetes Care* 2005; 28(10):2400–2405.
66. Exubera (insulin human [rDNA origin]) inhalation powder. New York: Pfizer; January 2006 package insert.
67. McMahon GT, Arky RA. Inhaled insulin for diabetes mellitus. *N Engl J Med* 2007;356(5):497–502.
68. Garg S, Rosenstock J, Silverman BL, Sun B, Konkoy CS, de la Peña A, Muchmore DB. Efficacy and safety of preprandial human insulin inhalation powder versus injectable insulin in patients with type 1 diabetes. *Diabetologia* 2006;49(5):891–899.
69. Dunn C, Curran MP. Inhaled human insulin (Exubera): a review of its use in adult patients with diabetes mellitus. *Drugs* 2006;66(7): 1013–1032.

70. Harsch IA. Inhaled insulins: their potential in the treatment of diabetes mellitus. *Treat Endocrinol* 2005;4(3):131–138.
71. Jani R, Triplitt C, Reasner C, DeFronzo RA. First approved inhaled insulin therapy for diabetes mellitus. *Expert Opin Drug Deliv* 2007;4(1):63–76. *Erratum in: Expert Opin Drug Deliv* 2007;4(2):191.
72. Owens DR, Zinman B, Bolli G. Alternative routes of insulin delivery. *Diabet Med* 2003;20(11):886–898.
73. Cefalu WT, Skyler JS, Kourides IA, Landschulz WH, Balagtas CC, Cheng S, Gelfand RA; Inhaled Insulin Study Group. Inhaled human insulin treatment in patients with type 2 diabetes mellitus. *Ann Intern Med* 2001;134(3):203–207.
74. DeFronzo RA, Bergenstal RM, Cefalu WT, Pullman J, Lerman S, Bode BW, Phillips LS for the Exubera Phase III Study Group. Efficacy of inhaled insulin in patients with type 2 diabetes not controlled with diet and exercise: a 12-week, randomized, comparative trial. *Diabetes Care* 2005; 28: 1922–1928.
75. Rosenstock J, Zinman B, Murphy LJ, Clement SC, Moore P, Bowering CK, et al. Inhaled insulin improves glycemic control when substituted for or added to oral combination therapy in type 2 diabetes: a randomized, controlled trial. *Ann Intern Med* 2005;143(8):549–558.
76. Weiss SR, Cheng SL, Kourides IA, Gelfand RA, Landschulz WH; Inhaled Insulin Phase II Study Group. Inhaled insulin provides improved glycemic control in patients with type 2 diabetes mellitus inadequately controlled with oral agents: a randomized controlled trial. *Arch Intern Med* 2003;163(19):2277–2282.
77. Advisory Committee Briefing Document: Exubera (insulin [rDNA origin] powder for oral inhalation). [Internet]. Available at www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4169B1_01_01-Pfizer-Exubera.pdf. Last accessed May 9, 2007.
78. Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann Intern Med* 2006;145(9):665–675.
79. Barnett AH, Dreyer M, Lange P, Serdarevic-Pehar M; on behalf of the Exubera Phase III Study Group. An open, randomized, parallel-group study to compare the efficacy and safety profile of inhaled human insulin (Exubera) with metformin as adjunctive therapy in patients with type 2 diabetes poorly controlled on a sulfonylurea. *Diabetes Care* 2006;29(6):1282–1287.
80. Inhaled insulin (Exubera). *Med Lett Drugs Ther* 2006;48(1239):57–58.
81. Wise S, Chien J, Yeo K, Richardson C. Smoking enhances absorption of insulin but reduces glucodynamic effects in individuals using the Lilly-Dura inhaled insulin system. *Diabet Med* 2006;23(5):510–515.
82. Becker RHA, Sha S, Frick AD, Fountaine RJ. The effect of smoking cessation and subsequent resumption on absorption of inhaled insulin. *Diabetes Care* 2006;29(2):277–282.
83. Sha S, Becker RHA, Willvise SA, et al. The effect of smoking cessation on the absorption of inhaled insulin (Exubera) (abstract). *Diabetes* 2002;51 Suppl 2:133.
84. Cefalu WT. Evolving strategies for insulin delivery and therapy. *Drugs* 2004;64(11):1149–1161.
85. Heise T, Bott S, Tusek C, Stephan J-A, Kawabata T, Finco-Kent D, et al. The effect of insulin antibodies on the metabolic action of inhaled and subcutaneous insulin: a prospective randomized pharmacodynamic study. *Diabetes Care* 2005;28(9):2161–2169.
86. Skyler JS, Cefalu WT, Kourides IA, Landschulz WH, Balagtas CC, Cheng SL, Gelfand RA. Efficacy of inhaled human insulin in type 1 diabetes mellitus: a randomized proof-of-concept study. *Lancet* 2001;357(9253):331–335.
87. Skyler JS, Weinstock RS, Raskin P, Yale JF, Barrett E, Gerich JE, Gerstein HC; Inhaled Insulin Phase III Type 1 Diabetes Study Group. Use of inhaled insulin in a basal/ bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. *Diabetes Care* 2005;28(7):1630–1635.
88. Hollander PA, Blonde L, Rowe R, Mehta AE, Milburn JL, Hershon KS, et al. Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 2 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 2004;27(10):2356–2362.
89. Barnett AH, Exubera Phase III Study Group. Efficacy and one-year pulmonary safety of inhaled insulin (Exubera) as adjunctive therapy with metformin or glibenclamide in type 2 diabetes patients poorly controlled on oral agent monotherapy (abstract). *Diabetes* 2004;53 Suppl 2:107.
90. Teeter JG, Riese RJ. Dissociation of lung function changes with humoral immunity during inhaled human insulin therapy. *Am J Respir Crit Care Med* 2006;173(11):1194–1200.
91. Hermansen K, Ronnema T, Petersen AH, Bellaire S, Adamson U. Intensive therapy with inhaled insulin via the AERx insulin diabetes management system: a 12-week proof-of-concept trial in patients with type 2 diabetes. *Diabetes Care* 2004;27(1):162–167.
92. Freemantle N, Blonde L, Duhot D, Hompesch M, Eggertsen R, Hobbs FDR, et al. Availability of inhaled insulin promotes greater perceived acceptance of insulin therapy in patients with type 2 diabetes. *Diabetes Care* 2005;28(2):427–428.