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Inhaled Insulin - Why Isn't It More Popular?

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Abstract:

Background: Diabetes is a disease affecting an increasing number of patients each year. The medications currently available on the market are not perfect, which is why the search for new and more effective therapies continues. One such option is inhaled insulin, which, despite having been available on the market for nearly 20 years, is still not widely used. This raises the question: why is that?

Aim: A review of the available knowledge on inhaled insulins, including their advantages and disadvantages, as well as potential applications of this medication, with an attempt to answer the question of why they have not replaced subcutaneous insulins on the market.

Methods: A narrative review was conducted using the medical databases PubMed, Google Scholar, and ScienceDirect, identifying studies presenting various aspects of the use of inhaled insulins.

Results: The article presents the history of the introduction of inhaled insulins to the market, the reasons for their limited availability, their safety profile, positive and negative effects of therapy, and the potential use of this medication in the treatment of patients with diabetes.

Conclusion: The analyzed studies demonstrate a relatively high level of safety and efficacy of inhaled insulin therapy. They also highlight concerns and disadvantages associated with this form of treatment and suggest its potential role in the management of patients with diabetes.

Keywords: diabetes; glycemic control; inhaled insulin; insulin; side effects;

1. Introduction:

Regardless of its type, diabetes represents a major challenge for modern medicine. This is due to the growing number of cases, the complexity of the disease, the range of available treatment options, and increased life expectancy, which consequently leads to a greater burden of treatment-related complications and longer disease duration. In 2024, an estimated 589 million adults worldwide were living with diabetes, and this number is projected to reach as many as 853 million by 2050 (Bruce B Duncan et al., 2025). This represents a vast population of patients who require an appropriately selected treatment strategy that is safe and tailored to the individual needs and preferences of the patient, provides good glycemic control and minimizes complications.

Insulin is the mainstay of treatment for type 1 diabetes and may also be required in type 2 diabetes in advanced stages of the disease. Despite its undeniable benefits, long-term insulin therapy creates new challenges. The risk of hypoglycemia, injection-site skin complications, pain, patients' reluctance to undergo subcutaneous injections, and fear of weight gain may all limit treatment effectiveness (Peyrot M et al., 2010; Ronald J Pettis et al., 2018). Advances in diabetes treatment continue to emerge, including new medical devices such as insulin pumps and closed-loop systems, as well as improved insulin formulations, including ultra-rapid-acting and long-acting insulins. Nevertheless, subcutaneous administration remains the standard route of insulin delivery in everyday clinical practice.

This route of administration is associated with a number of problems, including injection-site complications such as abscesses, scar tissue formation, lipohypertrophy, and lipoatrophy, as well as impaired or variable insulin absorption. It may also cause psychological difficulties, such as fear of needles and reluctance to initiate insulin therapy. In response to these challenges, numerous attempts have been made to develop alternative routes of insulin administration. Insulin has been investigated for buccal, oral, intranasal, inhaled delivery, and others. Of these approaches, only inhaled insulin has proven sufficiently safe, effective, and easy to use to receive marketing authorization (Heinemann L et al., 2016).

At first glance, inhaled insulin might seem like an ideal product: it eliminates the pain associated with injections, is easy to administer, avoids complications related to subcutaneous delivery, and could potentially improve patient adherence. Why, then, is inhaled insulin not widely used? Why has it failed to replace subcutaneous insulin on the market? In this article, we aim to provide a comprehensive overview of the advantages and disadvantages of inhaled insulin and to summarize the challenges that have limited its widespread adoption.

2. Methods:

2.1 Materials and methods

Using the available literature from medical databases PubMed, Google Scholar, and ScienceDirect, a search was conducted using keywords such as “inhaled insulin,” “side effects of insulin,” “safety of inhaled insulin,” and “pulmonary safety.” Based on the available abstracts, 25 texts addressing various aspects of inhaled insulin therapy were selected, covering medical, economic, and psychological considerations. The aim was to provide a comprehensive overview of the available knowledge regarding inhaled insulin, its advantages and disadvantages, and its potential applications.

2.2 AI

In this article ChatGPT (OpenAI) was used to assist with the translation and linguistic editing of the text. The final version was reviewed and revised by the authors.

3. Results and Discussion:

3.1 Historical Background

When the first inhaled insulin was introduced to the market in 2007 and began to be used by patients, it was expected to achieve tremendous success. However, after only one year, it was withdrawn from the market and considered a commercial failure. Problems with

frequent hypoglycemic episodes, unpredictable changes in insulin absorption - particularly among smokers and patients with respiratory diseases - as well as declines in pulmonary function cast a shadow over the anticipated success of the drug. It was also found that inhaled insulin increased the incidence of respiratory tract infections, caused persistent cough and inflammation of the airways. Due to the respiratory complications associated with this route of administration, more stringent monitoring requirements were introduced for patients receiving inhaled insulin, including regular spirometry. One study reported a concerning increase in the incidence of lung cancer among patients using the first inhaled insulin. Although this association was never confirmed, both clinicians and patients became increasingly concerned about the use of insulin via the inhaled route. The rapid withdrawal of the drug from the market was also attributed to its high cost compared with subcutaneous insulin, limited availability, and the large, inconvenient, and difficult-to-use inhaler. The higher cost of treatment, cumbersome delivery system, and reports of potentially serious adverse effects discouraged potential users from adopting this form of therapy (Joanna Mitri and Anastassios G. Pittas, 2008; Lutz Heinemann et al., 2016; Rima B. Shah et al., 2016).

In 2014, another attempt was made to introduce inhaled insulin for widespread clinical use. Clinical trials suggested that, in both type 1 and type 2 diabetes, this form of insulin was at least non-inferior to subcutaneously administered insulin. The new formulation also offered an improved delivery system compared with its predecessor: the inhaler was smaller, more convenient, and easier to use and allowed for simpler dosing (Joanna Mitri and Anastassios G. Pittas, 2008).

Unfortunately, studies showed that it could have adverse effects similar to those associated with the previous product. These included a potentially increased risk of lung cancer, progression of pulmonary disease, and airway irritation followed by cough. These adverse effects were sufficiently bothersome to lead some patients to discontinue inhaled insulin therapy during clinical trials (Bruce W. Bode et al., 2015; Joanna Mitri and Anastassios G. Pittas, 2008). This formulation remains available on the market and continues to be extensively studied as it seeks to establish its role in the treatment of patients with diabetes, although its future remains uncertain. In the following sections, we will discuss its advantages and disadvantages, examine and challenge some of the concerns and misconceptions that have arisen around inhaled insulin, and explore its potential applications.

3.2 Method of Administration

Among the possible routes of insulin administration, only three forms are currently widely available: intravenous, subcutaneous, and inhaled (Rima B. Shah et al., 2016). A comparison of these routes is presented in Table 1.

Inhaled insulin is administered using an inhaler. Over the years, these devices have been progressively improved, becoming smaller, more discreet, easier to use, and more precise in dosing (Tricia Santos Cavaiola and Steven Edelman, 2014). Currently, an inhaler that is available on the market fits in the palm of the hand and can be used for 15 days without cleaning, after which it should be replaced. It is therefore a relatively convenient inhaler that requires minimal maintenance and user interaction. The medication, provided as a powder contained in a cartridge, is inserted into the inhaler before administration.

Insulin administration method	Availability	Use of the drug
Subcutaneous	Widely used	The basic form of chronic treatment
Intravenous	Mainly for hospital treatment	In emergencies, during exacerbations of diseases
Inhaled	Available in some countries	Mainly as a mealtime insulin
Other: buccal, oral, intranasal, intramuscular, intraperitoneal, percutaneous and others	Only in research	Currently none

Table 1 Summary of insulin administration methods based on "Insulin delivery methods: Past, present and future" Rima B Shah et. al., 2016

The conversion of subcutaneous insulin doses to inhaled insulin doses was established based on clinical studies. It was determined that 4 units of subcutaneous insulin correspond to 10 units of inhaled insulin. For simplicity, the cartridges are labeled using subcutaneous insulin units to facilitate the transition from subcutaneous administration to inhaled insulin. Cartridges containing 4, 8, and 12 units, expressed as subcutaneous insulin equivalents, are available (Lutz Heinemann et al., 2016). Unfortunately, this provides relatively limited flexibility in dose adjustment compared with insulin pens (typically in increments of 0.5–1 unit) and insulin pumps (in increments as small as 0.01 unit). The doses indicated on the cartridges are slightly lower than the equivalent calculated doses in order to reduce the risk of

hypoglycemia when switching from the traditional route of administration to inhaled insulin. Therefore, to achieve the desired therapeutic effect, patients may require higher doses of inhaled insulin than would be expected from a simple conversion from subcutaneous insulin. Doses should be individually adjusted for each patient. To administer a dose greater than 12 units, more than one inhalation is required, using an appropriate combination of doses depending on the individual needs (Tamara Goldberg and Elaine Wong, 2015).

Inhaled insulin has storage requirements similar to those of subcutaneous insulin. It is best stored in a refrigerator at a temperature of 2–8°C until the expiration date. Once removed from the refrigerator, an opened package should be used within 10 days. Before administration, it is recommended to allow the insulin to reach room temperature for approximately 10 minutes (Tamara Goldberg and Elaine Wong, 2015).

One challenge associated with inhaled insulin is the need to perform the inhalation correctly. Insulin loss with this route of administration may depend on the device itself as well as on patient-independent conditions within the respiratory tract. According to published studies, approximately 60% of the dose reaches the lungs, while 30% is deposited in the oral cavity and approximately 10% in the pharynx and stomach. Therefore, proper inhalation technique is essential to ensure accurate dosing and effective treatment (Tricia Santos Cavaiola and Steven Edelman, 2014).

In summary, the administration of inhaled insulin is relatively simple, convenient, and precise. However, achieving the desired therapeutic effects requires adherence to proper preparation and inhalation techniques, as well as appropriate dose conversion and individual dose adjustment.

3.3 Pharmacokinetics and Pharmacodynamics

The lungs, due to their large functional surface area and extensive blood supply, provide favorable conditions for rapid drug absorption (Lutz Heinemann et al., 2016). This is a highly desirable property in the case of insulin. This route of administration results in a short time between insulin administration and the onset of action. The need to wait for an extended period before eating is often poorly accepted and not consistently followed by patients, which has led to ongoing efforts to develop faster-acting insulin analogues. The time to onset of action of the first inhaled insulin was similar to that of insulin lispro, which was probably another factor contributing to the discontinuation of research into this and similar inhaled insulin formulations (Lutz Heinemann et al., 2016).

Subsequently, research focused on its successor - an inhaled insulin formulation consisting of recombinant human insulin adsorbed onto specially designed microparticles, which improved its pharmacokinetic properties. The particles in this formulation are smaller, resulting in less deposition in the lungs, reduced aggregation, and less airway irritation (Shavita Shahani and Lokesh Shahani, 2015). The ratio of the mass of the dry powder to the total volume of the inhaled dose, together with the uniform particle size, facilitates transport to the lungs. The bioavailability of inhaled insulin in experimental studies was approximately 30% on average (Lutz Heinemann et al., 2016).

In clinical studies, the time to reach peak insulin concentration following inhalation ranged from 8 to 15 minutes, classifying this formulation as ultra-rapid-acting insulin. Its concentrations returned to baseline after approximately 180 minutes. As a result, inhaled insulin can be administered at the beginning of a meal or within 20 minutes after starting a meal, rather than 10–30 minutes before a meal, as is the case with some subcutaneously administered insulins (Lutz Heinemann et al., 2016).

Due to its rapid absorption, inhaled insulin may provide effective control of postprandial glucose excursions, which remain a significant challenge with subcutaneous insulin therapy (Kevin B. Kaiserman et al., 2022). Its rapid onset of action is a major advantage, while its rapid elimination provides an additional benefit. Studies showed that the incidence of hypoglycemic events within 2 hours after insulin administration and a meal was comparable between patients receiving inhaled insulin and those receiving insulin aspart. However, more than 2 hours after the meal, the incidence of hypoglycemia was 2–3 times higher in the subcutaneous insulin group (Bruce W. Bode et al., 2015). The faster elimination of inhaled insulin may therefore reduce the occurrence of unexpected hypoglycemic events several hours after a meal.

The ultra-rapid pharmacodynamic profile of inhaled insulin may thus provide patients with greater flexibility in insulin administration, while its short duration of action may reduce the risk of insulin stacking and unexpected declines in blood glucose levels later after administration (E. R. Seaquist et al., 2019)

3.4 Effects of therapy

Numerous studies comparing different inhaled insulin formulations with subcutaneous insulin have demonstrated a beneficial effect on glycated hemoglobin (HbA1c). The effect

was generally comparable to, or only slightly inferior to, that of subcutaneous insulin. However, it is suspected that with optimal dose adjustment, the therapeutic effects could be even better. This form of insulin has only been available relatively recently, and its somewhat weaker effect on reducing HbA1c may be partly attributable to limited knowledge regarding the most effective methods of administration, including errors in dose adjustment, timing of administration, and failure to account for factors that may affect treatment efficacy (Tricia Santos Cavaiola and Steven Edelman, 2014).

However, a rapid-acting profile is not always the optimal solution. The short duration of action of inhaled insulin may not provide sufficient glycemic control following meals rich in fat and protein. This may require multiple correction doses, which might not be necessary when using longer-acting subcutaneous insulin or an insulin pump with an extended bolus. Researchers have therefore investigated whether the two approaches could be combined. The use of inhaled insulin together with a closed-loop system has been shown to be safe, well tolerated, and associated with better early postprandial glucose control compared with subcutaneous insulin alone. Due to the rapid elimination of inhaled insulin, glucose levels later after the meal (>2 hours) were higher in patients receiving inhaled insulin. At this stage, the closed-loop system should compensate by delivering corrective insulin; however, this was not always successful. The researchers emphasize that optimal glycemic control requires appropriate adjustment of the inhaled insulin dose as well as proper configuration of the closed-loop system. When both components are appropriately matched, this combination of two modern treatment approaches may provide highly satisfactory results (A. Galderisi et al., 2020).

Another potentially beneficial difference between the two routes of insulin administration observed in clinical studies was a reduction in morning blood glucose levels. Results from studies in dogs suggest that this may be attributable to more efficient peripheral glucose utilization following inhaled insulin compared with subcutaneous insulin. However, this mechanism has not yet been sufficiently investigated or fully elucidated (Bruce W. Bode et al., 2015). This may be a particularly beneficial effect, as appropriate morning glucose levels indicate that treatment is maintaining adequate glycemic control during a prolonged period without insulin administration.

Studies have also repeatedly observed weight loss or a smaller increase in body weight among patients receiving inhaled insulin compared with those using subcutaneous insulin. This effect may be particularly desirable in patients with type 2 diabetes, as weight reduction

can contribute to improved insulin sensitivity. The mechanism underlying the potential weight-reducing effect is not fully understood. Several mechanisms have been proposed, including a possible reduction in fear of hypoglycemia among patients using inhaled insulin, which could lead to less defensive eating or additional food intake intended to prevent a drop in blood glucose levels (Bruce W. Bode et al., 2015; Tricia Santos Cavaiola and Steven Edelman, 2014).

3.5 Hypoglycemia

Hypoglycemia is the most common complication associated with all types of insulin, and the same applies to inhaled insulin. The goal of diabetes treatment is to maintain blood glucose levels as stable as possible, avoiding significant fluctuations and episodes of hypoglycemia, while achieving an insulin action profile that most closely resembles physiological insulin secretion. As mentioned in the previous section, the rapid elimination of inhaled insulin may have a beneficial effect by reducing the frequency of hypoglycemic events later after a meal; however, its impact on the overall incidence of hypoglycemia is more complex.

The overall incidence of hypoglycemia, including severe hypoglycemia, observed in studies of inhaled insulin was not higher than that associated with subcutaneous insulin and was significantly lower in some studies. The reduction in hypoglycemic events was particularly noticeable among patients with type 2 diabetes, which is a highly desirable outcome given the relatively common occurrence of impaired awareness of hypoglycemia in this population and the potentially serious consequences of hypoglycemic events in older patients (Tricia Santos Cavaiola and Steven Edelman, 2014).

The AFINITY 1 study demonstrated that patients receiving inhaled insulin experienced a significantly lower incidence of hypoglycemia while achieving non-inferior glycemic control. Data from this study concluded that inhaled insulin may allow treatment intensification with a lower risk of inducing hypoglycemia. It may also benefit patients who have already achieved their target HbA1c levels by reducing the frequency of hypoglycemic events and stabilizing glucose fluctuations (E. R. Seaquist et al., 2019).

In the STAT study, participants monitored their blood glucose levels using continuous glucose monitoring (CGM), allowing for a more detailed analysis of glycemic profiles and comparison of inhaled and subcutaneous insulin therapy. Patients receiving inhaled insulin achieved a comparable time in range (TIR), experienced lower daily glycemic variability, and

spent less time in hypoglycemia compared with those receiving subcutaneous insulin. These findings provide further evidence that inhaled insulin may improve early postprandial glycemic control, increase glycemic stability, and reduce the risk of hypoglycemia (Halis Kaan Akturk et al., 2018).

Thus, inhaled insulin does not appear to increase the risk of hypoglycemia compared with subcutaneous insulin and may even help reduce its occurrence. Nevertheless, as with any form of insulin therapy, caution is required. Patients should be educated about the symptoms and detection of hypoglycemia, as well as appropriate strategies for managing hypoglycemic episodes and their potential consequences, in order to ensure safe and effective treatment (Tamara Goldberg and Elaine Wong, 2015; Tricia Santos Cavaiola and Steven Edelman, 2014).

3.6 Pulmonary Complications

The most common respiratory adverse effect associated with inhaled insulin is airway irritation accompanied by cough. Several studies have confirmed that this complication occurs in approximately 30% of patients. Cough usually developed early after treatment initiation, typically within several minutes after inhalation, and was generally mild in severity. Its frequency reduced as the duration of therapy increased. This adverse effect was not sufficiently severe to cause a large proportion of patients to discontinue inhaled insulin during clinical trials, and it generally diminished over the course of treatment (Tricia Santos Cavaiola and Steven Edelman, 2014).

Initial studies assessing the safety of the first inhaled insulin available on the market demonstrated a more rapid deterioration in spirometric parameters after prolonged treatment compared with patients in the control group. However, subsequent studies showed that the more rapid decline in FEV1 and DLCO occurred primarily during the first 6 months of treatment and then stabilized by approximately the second year, reaching levels comparable to those observed in the control group. These changes were also completely reversible after discontinuation of inhaled insulin (Tricia Santos Cavaiola and Steven Edelman, 2014). The manufacturer of the inhaled insulin currently available on the market recommends excluding pre-existing pulmonary disease before treatment initiation, followed by spirometry at baseline, after 6 months of therapy, and annually thereafter. If a patient's FEV1 decreases by ≥20% from baseline, the benefits and risks of continuing treatment should be reconsidered (Tamara Goldberg and Elaine Wong, 2015).

Insulin is an anabolic hormone. When administered subcutaneously, inadequate rotation of injection sites may lead to complications such as scar tissue formation and lipohypertrophy (Ronald J. Pettis et al., 2018). When inhaled insulin was introduced, concerns arose regarding whether a similar effect could occur in the respiratory tract. In two studies of the first inhaled insulin, a higher incidence of cancer was observed, raising concerns within the medical community that these earlier fears might be confirmed. For example, in one study of the older drug, 6 patients developed cancer among 4,740 participants in the inhaled insulin group, compared with 1 patient among 4,292 participants in the control group (Tricia Santos Cavaiola and Steven Edelman, 2014). In studies of the currently available inhaled insulin, 2 cases were reported among 2,750 patients in the treatment group, compared with 0 cases among 2,169 patients in the control group (Tamara Goldberg and Elaine Wong, 2015). The patients who developed cancer in these studies were long-term smokers. Two additional cases of cancer were reported in nonsmoking patients after completion of the study. However, because the number of cases was small and the available data are insufficient to establish a causal relationship, the FDA and the manufacturer recommend continued oncological vigilance in patients receiving inhaled insulin. They also recommend careful consideration of the potential benefits and risks in patients with a current or previous history of lung cancer, as well as in those with other established risk factors for lung cancer (Tamara Goldberg and Elaine Wong, 2015; Tricia Santos Cavaiola and Steven Edelman, 2014).

3.7 Use in Patients with Respiratory Diseases

The use of inhaled insulin in patients with acute or chronic pulmonary diseases raises concerns regarding both its efficacy and safety, including the potential for worsening symptoms or progression of the underlying disease. The effects of conditions such as asthma and chronic obstructive pulmonary disease (COPD) on the absorption of inhaled insulin have been investigated. These conditions were found to reduce insulin absorption and its pharmacodynamic effect by approximately 30–40%. However, this effect could be mitigated by administering a bronchodilator immediately before inhaled insulin (Tamara Goldberg and Elaine Wong, 2015).

Unfortunately, patients with underlying pulmonary disease may experience an adverse effect known as bronchospasm, which occurred in approximately 30% of participants in some studies. Due to the significant risk of this complication, the manufacturer does not

recommend the use of inhaled insulin in patients with chronic pulmonary diseases. Screening for such conditions is also recommended before initiating treatment with inhaled insulin (Tamara Goldberg and Elaine Wong, 2015).

The effect of acute respiratory diseases on inhaled insulin administration has also been investigated. Respiratory tract infections are among the most common infectious diseases in the general population, affecting both healthy individuals and patients with diabetes. Therefore, it was important to determine whether such infections influence insulin absorption and efficacy or increase the risk or severity of adverse effects.

A study by Philip A. Levin et al. investigated the effect of upper respiratory tract infections on the pharmacokinetics and pharmacodynamics of inhaled insulin. The researchers measured serum concentrations of fumaryldiketopiperazine (FDKP), an excipient used in the investigated formulation, as well as serum insulin, serum C-peptide, and plasma glucose levels. These parameters were assessed both during the upper respiratory tract infection and after the clinical resolution of symptoms. Analysis of the data revealed no significant differences in the measured pharmacokinetic or pharmacodynamic parameters during and after the upper respiratory tract infection (Philip A. Levin et al., 2016).

This and other studies have not demonstrated a significant safety concern associated with inhaled insulin use during respiratory infections. Nevertheless, further research is needed in this area. It should also be emphasized that although an infection does not appear to significantly affect the pharmacokinetics or pharmacodynamics of inhaled insulin, any infection may increase insulin requirements and therefore necessitate appropriate adjustment of insulin doses (Philip A. Levin et al., 2016).

3.8 Use in Smokers

The currently available inhaled insulin is not recommended for individuals who smoke or for those who have recently stopped smoking. In smokers, the drug demonstrates increased and more rapid absorption, as well as less predictable bioavailability, which significantly increases the risk of hypoglycemia. This is probably related to increased permeability of the alveolar epithelium (Tricia Santos Cavaiola and Steven Edelman, 2014; Robert Fountaine et al., 2008).

Smoking cessation rapidly restores the usual absorption pattern of inhaled insulin; however, the potentially life-threatening effects return just as rapidly if smoking is resumed.

One study demonstrated that after 4 weeks of smoking abstinence, inhaled insulin absorption decreased, along with a reduction in insulin requirements of approximately 25–40%. When participants smoked a single cigarette after this period, insulin absorption immediately returned to baseline levels. This is clinically important because a patient who has been abstinent from smoking for an extended period and subsequently begins inhaled insulin therapy could experience significant disruption of glycemic control and potentially life-threatening hypoglycemia after smoking "just one" cigarette. The same study also demonstrated that nicotine replacement therapy (NRT) reduced exposure to inhaled insulin, and patients using NRT who resumed smoking experienced a less pronounced increase in pulmonary insulin absorption. The authors emphasize, however, that this issue requires further investigation (Alan X. Pan et al., 2007).

The effect of passive smoking on the absorption of inhaled insulin has also been investigated. Unlike active smokers, individuals exposed to passive smoke appear to have slightly reduced alveolar permeability, which could theoretically result in impaired insulin absorption. A 2008 study (Robert Fountaine et al., 2008) supported this hypothesis. Participants exposed to acute passive cigarette smoke had a reduced rate and extent of pulmonary insulin absorption; however, this did not appear to adversely affect glycemic control. Since the study investigated only the acute response to passive smoke exposure, the researchers suggested that further studies are needed to assess the effects of chronic exposure. These findings also raise questions about the extent to which environmental factors may influence the efficacy and safety of inhaled insulin.

At present, further research is needed to determine whether inhaled insulin can be safely used in smokers. However, for now, this form of therapy is currently not recommended for this group of patients.

3.9 Children

The safety and efficacy of the currently available inhaled insulin have been established in clinical studies involving children aged 6 years and older with diabetes. At present, there are insufficient data regarding the safety and efficacy of this treatment in children younger than 6 years. The overall efficacy and safety profile in children appears to be similar to that observed in adults (Michael J. Haller et al., 2026).

Children with diabetes experience a higher incidence of hypoglycemia and diabetic ketoacidosis than adults with type 1 diabetes. Achieving the desired therapeutic outcomes can also be more difficult because of the challenges associated with treatment adherence and cooperation. Particularly in younger children, the delayed onset of action of insulin, the need to plan meals, and fear of needles can complicate treatment. In this population, ultra-rapid-acting inhaled insulin could potentially improve treatment outcomes, as has already been demonstrated in some studies. A lower incidence of hypoglycemia, better control of postprandial glucose levels, and avoidance of injection-related fear and reluctance to take medication are potential advantages of inhaled insulin that could help address some of the challenges associated with subcutaneous insulin therapy (Michael J. Haller et al., 2023).

3.10 Physical Exercise

Physical activity increases the effect of subcutaneous insulin. Therefore, patients with diabetes who engage in physical exercise are generally advised to reduce their mealtime insulin doses and/or increase carbohydrate intake around the time of exercise.

The effect of physical activity on the absorption of various inhaled medications, such as terbutaline, is also well established. This phenomenon is thought to result from increased ventilation induced by exercise and lung expansion, which may increase intercellular pores between type I pneumocytes and endothelial cells. However, the exact mechanism is not yet fully understood. This effect has also been investigated in relation to inhaled insulin.

A study involving 12 healthy volunteers produced the following results: when physical activity was initiated immediately after inhalation or 30 minutes after drug administration, insulin absorption and the onset of action were accelerated during the first 2 hours of exercise. However, overall bioavailability was not increased; rather, exercise affected the rate of onset of insulin action and the time to peak insulin concentration. This phenomenon is also known to occur with subcutaneous insulin, and if the effect is confirmed in patients with diabetes using inhaled insulin, appropriate patient education and dose adjustment will be necessary (Astrid Petersen et al., 2008).

3.11 Psychological Aspects

Psychological factors are highly important in diabetes management. Diabetes affects many aspects of patients' lives. It can lead to both physical and psychological complications, involves numerous acute and chronic risks, and may directly threaten life. It is therefore unsurprising that the effects of treatment can evoke a wide range of emotions in patients - from happiness and pride when treatment goals are achieved to doubt, frustration, or reluctance when the desired outcomes are not reached. These emotions influence how patients perceive their treatment, whether they are willing to continue it, and how closely they adhere to medical recommendations, ultimately affecting the effectiveness of pharmacotherapy (Richard R. Rubin and Mark Peyrot, 2010).

Diabetes is a condition in which disease management rests largely on the patient. This can itself be a source of stress. Outside of regular medical appointments, patients are responsible for their day-to-day health and well-being. Treatment accompanies them every day for the rest of their lives. Modern medicine offers not only the possibility of extending the lives of patients with diabetes but also of tailoring treatment to minimize its negative consequences. It is therefore important for therapy to be as easy to manage as possible, minimally burdensome, and associated with as few negative emotions as possible. Oppressive treatment methods may be rejected by patients even when they are effective (Mark Peyrot and Richard R. Rubin, 2011).

Inhaled insulin addresses many of these needs. Avoiding the need for injections is undoubtedly one of its major advantages. It may provide a treatment option for patients who strongly refuse injections, as well as for those who omit doses because of fear of pain. In a disease characterized by considerable stress and anxiety, eliminating at least some of these stressors could have a positive impact on patients' well-being (Richard R. Rubin and Mark Peyrot, 2010).

The use of the latest inhaler devices is relatively straightforward and does not significantly interfere with patients' daily activities. Currently available inhalers are small, convenient, and quick to use. Inhaled insulin may improve patients' perceptions of insulin therapy among those who have previously used insulin and may also increase willingness to initiate insulin therapy among patients who have not previously used insulin. One study reported that participants stated that the availability of inhaled insulin after completion of the study would likely encourage them to initiate insulin therapy despite their previous concerns about insulin treatment (Richard R. Rubin and Mark Peyrot, 2010). Greater treatment

satisfaction and the absence of injection-related anxiety could also potentially improve adherence and persistence with optimal treatment.

The previously discussed lower incidence of hypoglycemia among patients using the inhaled route of insulin administration may also be psychologically important. Hypoglycemia itself can cause stress and fear for one's safety. Patients experiencing frequent hypoglycemic episodes may therefore be particularly interested in a treatment that could reduce their frequency (Tricia Santos Cavaiola and Steven Edelman, 2014). Conversely, the rapid onset of action of inhaled insulin may help prevent large postprandial glucose excursions and high blood glucose levels, along with associated symptoms such as increased irritability (Lutz Heinemann et al., 2016). Considering both of these aspects, inhaled insulin may potentially improve the overall well-being of patients with diabetes by reducing some of the negative psychological consequences of the disease. This could, in turn, reduce treatment dissatisfaction and reluctance to adhere to medical recommendations and continue therapy.

However, switching from subcutaneous to inhaled insulin may also have negative psychological consequences. The dose of inhaled insulin required to achieve the same therapeutic effect is approximately 2–3 times higher than the corresponding subcutaneous dose. For example, a patient who normally administers 8 units of insulin with lunch might require up to 24 units of inhaled insulin. For patients accustomed to administering relatively small doses, this may initially cause anxiety and fear of hypoglycemia. Such concerns would likely diminish over time, but during the initial phase of treatment they could contribute to unstable glycemic control and dissatisfaction with therapy. Therefore, appropriate patient education and support in determining the correct dose conversion are essential to ensure that patients do not avoid the higher doses of inhaled insulin that may be necessary to achieve the desired therapeutic effect (Michael J. Haller et al., 2026).

3.12 Limitations

Despite their undeniable advantages, inhaled insulins have several limitations. Some of these may potentially be overcome in the future, but achieving this will require further research into the efficacy and safety of this form of therapy, as well as possible modifications and improvements to the treatment approach.

At present, inhaled insulin cannot be used as the sole treatment for patients with type 1 diabetes. Due to its rapid-acting profile, it is well suited for mealtime insulin administration

and correction of hyperglycemia. However, basal insulin administered by injection is still necessary to achieve adequate long-term glycemic control. Therefore, inhaled insulin cannot currently eliminate the need for injections entirely. This should be clearly communicated to patients to avoid misunderstandings (Tricia Santos Cavaiola and Steven Edelman, 2014).

For now, inhaled insulin is not approved for use during pregnancy (Tamara Goldberg and Elaine Wong, 2015). Animal studies have demonstrated adverse effects on fetuses, although these effects were observed only at very high insulin doses. Several studies have also investigated the safety of inhaled insulin during pregnancy in humans and reported favorable outcomes. However, its use has not been approved due to insufficient safety data. Switching from subcutaneous to inhaled insulin during pregnancy is not recommended because of the potential risk to the fetus associated with inadequate glycemic control.

Several drug interactions may limit the concomitant use of certain medications with inhaled insulin. Drug interactions may increase the risk of hypoglycemia, enhance or reduce the effect of insulin, or alter the signs and symptoms of hypoglycemia. Such medications include oral antidiabetic agents, salicylates, certain antibiotics, corticosteroids, lithium, hormonal contraceptives, and beta-blockers. Most of these medications also require caution when combined with subcutaneous insulin. When inhaled insulin is used together with other medications, dose adjustment and more frequent monitoring of blood glucose levels may be necessary (Tamara Goldberg and Elaine Wong, 2015).

The effects of impaired renal or hepatic function on the pharmacokinetics and safety of inhaled insulin have not been adequately studied. Until now, the currently available formulation and its predecessors represent relatively new approaches to insulin therapy there are currently limited data regarding the long-term use of inhaled insulin (Nasser Mikhail, 2016).

3.13 Financial Aspects and Availability

Inhaled insulin appears to be a safe and attractive treatment option that could potentially generate considerable interest. Why, then, have so few patients heard of it or had the opportunity to use it? Cost and availability are undoubtedly important factors. At present, inhaled insulin is approved for use only in the United States, Brazil, and India, although it is relatively readily accessible only in the United States. It is currently not approved for use in the European Union.

Another important issue is the relatively high cost of this form of insulin. Current prices range from approximately $271 for 90 cartridges containing 4 units each plus two inhalers to approximately $380 for 60 cartridges containing 8 units each. Such costs may be prohibitive for many patients, particularly given that subcutaneous insulin is considerably more affordable (Tamara Goldberg and Elaine Wong, 2015). In the future, the cost of inhaled insulin therapy may decrease and market availability may expand, potentially making this form of treatment accessible to a larger population of patients.

3.14 Role in Diabetes Management

Due to its ultra-rapid onset of action, safety profile, and convenience, inhaled insulin may have potential applications in several clinical settings. Despite the continued need for basal insulin injections, inhaled insulin may be useful in patients with type 1 diabetes for controlling postprandial glycemia and correcting hyperglycemia without the need for additional injections. This could potentially improve adherence among patients who are reluctant or anxious about injections, reduce postprandial hyperglycemia and glycemic variability, and contribute to better overall glycemic control (Nasser Mikhail, 2016).

In patients with type 2 diabetes who require insulin therapy to achieve optimal glycemic control, reluctance to initiate injectable treatment is relatively common. This may be related to fear of needles, concerns about pain, or apprehension regarding the difficulty of insulin therapy. In such patients, inhaled insulin could potentially prevent delays in initiating insulin treatment and thereby help reduce the risk of diabetes-related complications (Nasser Mikhail, 2016).

Inhaled insulin could also be beneficial for patients who experience hypoglycemia several hours after meals, particularly 4–5 hours after eating. Potential candidates might include individuals who have limited time for meals and need to achieve stable postprandial glycemia as quickly as possible, those who wish to exercise shortly after consumption, or patients who simply prefer not to eat frequently (Nasser Mikhail, 2016).

Another group that could potentially benefit from this form of insulin therapy consists of patients experiencing complications associated with injectable insulin. This includes individuals with multiple areas of lipoatrophy or lipohypertrophy, as well as those with scar tissue or other injection-site changes. Even a temporary change in the route of insulin administration could provide time for these skin complications to improve, which may be

important from both aesthetic and medical perspectives. Injection-site abnormalities can slow insulin absorption, make absorption unpredictable, or, in severe cases, interfere with adequate insulin delivery. Thus, eliminating these complications would probably be valuable for better disease control (Nasser Mikhail, 2016).

4. Conclusion

In this article, we have presented the advantages and disadvantages of inhaled insulin. The main advantages include easy and painless administration, a rapid onset of action, and, consequently, no need to wait before eating after administration, as well as faster correction of hyperglycemia. Other benefits include a lower incidence of hypoglycemia, the potential for weight reduction, improved perceptions of treatment and quality of life, reduced psychological burden associated with diabetes, and, consequently, potentially better treatment adherence.

Inhaled insulin also has several disadvantages. These include adverse effects such as cough, exacerbation of chronic respiratory diseases, restrictions on its use in certain patient populations, the need for pulmonary function monitoring during therapy, high cost, and limited availability. There are also currently insufficient data regarding the long-term use of inhaled insulin (Nasser Mikhail, 2016).

When deciding whether to initiate or discontinue this form of therapy, all of these factors should be taken into consideration. They should be discussed openly with patients, and the potential risks and benefits should be assessed jointly. For many patients, inhaled insulin may represent an interesting alternative to subcutaneous insulin; however, it is not an appropriate option for everyone.

Disclossure

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