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Review Article

Inhaled insulin in diabetes management: a review of efficacy, safety, and patient-centered outcomes

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ABSTRACT

Inhaled insulin offers a non-invasive alternative to subcutaneous insulin for managing diabetes mellitus. Technosphere insulin (TI), marketed as Afrezza, delivers ultra-rapid-acting insulin via the pulmonary route, facilitating rapid absorption and improved post-prandial glucose (PPG) control. Clinical trials have demonstrated that TI achieves non-inferior glycaemic control compared to subcutaneous rapid-acting insulins in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM), with notable reductions in HbA1c and enhanced PPG outcomes. TI's fast onset (peak concentration ~15 minutes) and short duration reduce late hypoglycaemia risk. Studies also report improved patient satisfaction due to greater ease of use and reduced injection burden, supporting better treatment adherence. The most common adverse effect is mild, transient cough; small reversible declines in pulmonary function (FEV1) have been observed, necessitating careful patient selection and monitoring. Inhaled insulin is contraindicated in individuals with chronic lung diseases or recent smoking history. Future research should explore its use in paediatric and pregnant populations and assess long-term safety, adherence, and cost-effectiveness. With expanding evidence from trials like INHALE-3, inhaled insulin represents a valuable addition to the diabetes treatment landscape, particularly for patients seeking flexible and patient-centred insulin therapy.

Keywords: Inhaled insulin, Technosphere insulin, Afrezza, Diabetes management, Pulmonary delivery, Glycaemic control, Ultra-rapid insulin

INTRODUCTION

Diabetes mellitus is a collection of metabolic diseases of carbohydrate metabolism in which improper gluconeogenesis and glycogenolysis cause glucose to be underused as an energy source or overproduced, producing hyperglycaemia.[1] The global epidemic of diabetes mellitus and its sequelae presents a significant worldwide health hazard. In 2019, global diabetes prevalence was 9.3% (463 million) and is projected to rise to 10.2% (578 million) by 2030 and 10.9% (700 million) by 2045. Prevalence is higher in urban (10.8%) than rural (7.2%) areas, and in high-income (10.4%) than low-income nations (4.0%). Estimated to be 7.5% (374 million) worldwide in 2019, impaired glucose tolerance is expected to rise to 8.0% (454 million) by 2030 and to 8.6% (548 million) by 2045.[2]

Evolution of insulin therapy

For over a century, insulin has been used to treat diabetes. Today's insulin options are the result of years of research and development. Insulin has evolved from poorly defined animal pancreatic extracts to pure, carefully regulated formulations that can be prescribed and injected with great precision and predictability. The insulin formulation and molecule have been modified to resemble the normal insulin response. Insulin and insulin formulations must create either a low basal level or mealtime insulin spikes.[3]

Frederick Banting and Charles Best's discovery of insulin in 1921 turned type 1 diabetes from a death sentence into a treatable chronic illness. Rapid clinical use of insulin transformed diabetes treatment and sparked a boom in molecular structure, pharmacokinetic, and therapeutic use research.[4]

Need for non-invasive insulin delivery

Subcutaneous insulin administration in diabetes treatment offers advantages; however, it also has significant drawbacks. These include the risk of hyperinsulinemia, which can lead to severe hypoglycaemia, stimulation of smooth muscle cell proliferation, glucose incorporation into arterial wall lipids, lipohypertrophy, and atherosclerosis, contributing to both micro and macroangiopathy.[5] In addition, patients often face considerable barriers to subcutaneous insulin therapy, including anxiety about injections, the complexity and burden of dosing schedules, challenges with self-injection, concerns about hypoglycaemia and weight gain, interference with daily routines, and social discomfort.[6] Consequently, identifying a non-invasive alternative is essential for enhancing patients' quality of life.[5] Although oral delivery seems the most practical, however, this method has encountered problems more significantly, with bioavailability. Investigated to bypass this restriction perhaps are chitosan matrix systems and nanomaterials. In several trials, nasal, oral, buccal, and ocular insulin administration have been demonstrated to lower serum/plasma glucose concentrations effectively; nonetheless, significant challenges remain.[7]

Overview of inhaled insulin

Inhaled insulin products were developed as a non-invasive alternative to injectable insulin. The first such product, Exubera, was launched in 2006 but withdrawn within a year due to its bulky delivery device, cost issues, low physician acceptance, and limited absorption efficiency.[8]

Subsequent concerns also emerged regarding possible links to lung cancer in users, particularly smokers.[9] Building on these learnings, Afrezza (TI) was approved by the FDA in June 2014. It features a compact inhaler and ultra-rapid-acting profile, making it a viable option for mealtime insulin delivery.[10] According to the American Diabetes Association's 2025 standards of care, insulin analogues or inhaled insulin are preferred over injectable human insulins for most adults with type 1 diabetes to reduce the risk of hypoglycaemia.[11] MannKind corporation developed Afrezza using technosphere technology and licensed it for use in individuals over 18 years old with T1 and T2DM. In August 2014, MannKind corporation entered into a global licensing agreement with Sanofi. On December 11, 2024, India's Central Drugs Standard Control Organisation (CDSCO) granted approval for Afrezza (insulin human) inhalation powder for adult patients. Cipla Limited secured exclusive rights to distribute and market the drug in India.[9]

Formulation and mechanism of action

TI is an inhalation powder consisting of recombinant human insulin adsorbed onto Technosphere microparticles created from the inert excipient Fumaryl diketopiperazine (FDKP). FDKP has good solubility in water at neutral or alkaline pH levels. Under slightly acidic circumstances, FDKP conducts intramolecular self-assembly and crystallises into microparticles with a median diameter of around 2.0-2.5 µm. These particles are within the ideal size range for deep lung delivery; bigger particles are often deposited in the mouth, throat, or upper airways, while smaller particles may be expelled. The low bulk density and uniform particle size enhance aerodynamic characteristics that promote the transport of TI to the deep lung. Upon reaching the deep lung, the particles swiftly disintegrate in the alveoli's neutral or basic physiological pH, facilitating the quick absorption of insulin and FDKP into the systemic circulation; FDKP is physiologically inactive and eliminated unaltered in the urine.[12]

PHARMACOKINETICS AND PHARMACO-DYNAMICS

Onset, peak, and duration of action

TI is a dry powder of human (recombinant DNA) insulin designed to adhere to Technosphere microparticles for administration via the pulmonary route. The powder dissolves instantly upon inhalation, providing rapid delivery of insulin and achieving peak concentrations approximately 15 minutes after administration.[13]

Absorption and metabolism

The carrier of these insulin particles, FDKP, is an inert excipient that encapsulates peptides and proteins within microspheres. The particles dissolve in the neutral pH environment of the lungs, and their small size allows for efficient distribution and absorption into circulation. The absorption into systemic circulation occurs more rapidly; however, the insulin utilised with TI is regular human insulin. After insulin enters the bloodstream, its metabolism and elimination processes resemble regular human insulin. The FDKP is taken up by the bloodstream and is eliminated unchanged mainly via the kidneys.[14]

Comparison with subcutaneous insulin

TI provided the primary glucose-lowering effect within 3 hours following inhalation, accounting for roughly 71% of the total glucose infusion rate (GIR). In contrast, subcutaneous regular human insulin (SC RHI) contributed only 27% of the GIR. This is due to the rapid and pronounced onset of action with TI, which is comparable to IV injection of RHI. No other clinically effective insulin formulation has shown such a quick onset of action. A greater total dose of subcutaneous RHI would be necessary to achieve a comparable glucose-lowering effect as TI in critical first 3 hours after subcutaneous RHI

administration. Significant residual activity (i.e., 73%) after SC RHI administration at 3 hours mark may necessitate consumption of an extra snack to avert late hypoglycaemia.[15]

CLINICAL EFFICACY

Clinical trials assessing TI, an ultra-rapid-acting inhaled insulin, have shown its effectiveness in reducing HbA1c and enhancing PPG control. A 12-week study involving 20 patients with T2DM demonstrated a notable reduction in HbA1c of 1.6% (from 9.0% to 7.4%, p<0.0001) alongside an increase in time-in-range from 42.2% to 65.7% (p<0.0002).[16] In a 24-week randomised study in T1DM, HbA1c drop with TI (-0.21%) was non-inferior to insulin aspart (-0.40%), therefore fulfilling the non-inferiority margin of 0.4%. Patients receiving TI experienced a modest weight reduction (-0.4 kg), in contrast to those on aspart who showed a weight increase (+0.9 kg) (p=0.0102). Additionally, the incidence of hypoglycaemic events was lower in the TI group compared to the aspart group (9.8 vs. 14.0 events per patient-month, p<0.0001).[17] TI absorbs and acts quicker than subcutaneous insulin.

Table 1: Summary of clinical studies of TI in type 1 and 2 diabetes mellitus patients.

Author(s)	Year	Main inclusion criteria (N)	Intervention and duration	Efficacy outcomes	Safety outcomes
Hirsch et al[18]	2025	T1DM adults (n=123), HbA1c <11.0% AID/MDI users	TI + Degludec vs. usual care, 17 weeks	Non-inferior HbA1c reduction (0.11%, p=0.01); better postprandial control	Well tolerated, mild cough (23%), hypo-glycaemia similar to control
Hirsch et al[19]	2024	T1DM adults (n=122), HbA1c <11.0% AID/MDI	TI vs. rapid-acting analogue insulin, 17 weeks	Lower PPG excursion (p=0.02), shorter time to peak glucose (p=0.006)	Lower hypoglycaemia, cough was observed
Grant et al[20]	2022	T1DM adults >12 months (n=30), HbA1c ≤9% stable insulin regimen	TI vs. SC Lispro, single-centre crossover study	TI had faster onset (7-15 min vs. 21-38 min for LIS); total exposure lower	No severe hypoglycaemia; cough was reported by 10% of volunteers in TI group
Levin et al[16]	2021	T2DM patients (n=20), HbA1c 7.5-11.5%, uncontrolled on oral medications or insulin	TI rapid titration for 12 weeks	HbA1c decreased by -1.6% (p<0.0001); TIR increased from 42.2% to 65.7% (p<0.0002)	Minimal hypoglycaemia
Hoogwerf et al[21]	2021	T2DM adults (n=309), HbA1c 7.0-11.5%, on insulin glargine for ≥3 months	Insulin glargine followed by TI vs. Insulin Aspart, 24 weeks	HbA1c reduction: TI -1.05% vs. IA-1.31% (p=0.06); TI led to weight loss (0.78 kg, p=0.0016)	Lower hypoglycaemia incidence [43% in TI vs 54% in IA, p=0.035]; mild cough in TI group (5.3%)
Seaquist et al[22] (affinity-1 study)	2019	T1DM adults (n=375), HbA1c 7.5-10.0%, on basal insulin + prandial insulin	TI+ basal insulin vs. Insulin Aspart + basal insulin, 24 weeks	-	Lower hypoglycaemia rates across HbA1c levels (Level 1 hypo-glycaemia: 38.0%, p<0.001; level 2 hypo-glycaemia: -38.0%, p<0.001; level 3 hypo-glycaemia: -50.4%, p=0.05]
McGill et al[23]	2021	T1DM adults (n=138), HbA1c 7.0-9.0%, stable insulin regimen	TI vs. Insulin Lispro, 16 weeks	HbA1c change: -0.1% for TI vs. no change in LIS lower post-meal glucose at 1 hr (-66 mg/dL, p<0.0001) and 2 hr (-34 mg/dL, p<0.05)	Cough in 30% of TI group
Rüppel et al[24]	2017	Healthy adults (n=32), crossover euglycemic clamp study	TI vs. RHI, pharmacokinetic modelling study	TI ED50 was 5-fold higher than RHI; faster absorption (12-15 min)	Safe in healthy volunteers; no severe adverse effects
Bode et al[17]	2015	T1DM adults (n=345), HbA1c ≤9% basal insulin users	TI vs. Insulin Aspart, 24 weeks	Mean change in HbA1c: TI: -0.21%, 95% CI-0.33 to -0.09 vs. Aspart: -0.40%, 95% CI-0.52 to -0.28 (non-inferior); fewer hypoglycaemic events	Lower hypoglycaemia (p<0.0001); mild cough in TI users (31.6%)
Rave et al[15]	2008	T2DM patients (n=13), HbA1c ≤9%, intensive insulin therapy	TI (48 U) vs. SC RHI (24 U), cross-over glucose clamp study	TI T_{max}: 17 min vs. SC RHI: 135 min (p=0.0001); 60% glucose disposal in 3h with TI	Lower intra-subject variability with TI; no severe adverse events

*AID-automated insulin delivery; MDI-metered dose inhaler; T2DM-type 2 diabetes mellitus; T1DM-type 1 diabetes mellitus; TI-technosphere insulin; SC-subcutaneous; RHI-recombinant human insulin; HbA1c-glycosylated haemoglobin.

Maximum insulin concentration (C_{max}) was obtained in 17 minutes for TI in a glucose clamp experiment against 135 minutes for subcutaneous insulin (p=0.0001). Whereas subcutaneous insulin showed just 30% of its action in the first three hours, over 60% of the glucose-lowering effect of TI happened in this period. The early PPG disposal rate with TI was much greater, hence it can be a good choice to reduce post-prandial hyperglycaemia (Table 1).[15]

GLYCAEMIC CONTROL (HbA1c REDUCTION)

A prominent sign of glycaemic control and a necessary assessment of the therapeutic effectiveness of insulin treatments is HbA1c decrease. Target HbA1c values in T1DM and T2DM have demonstrated encouraging outcomes using inhaled insulin. Effective glycaemic control was shown by Hirsch et al reporting a non-inferior HbA1c decrease of 0.11% (p=0.01) with TI compared to usual therapy in persons with T1DM.[18] Levin et al found a notable 1.6% HbA1c drop in T2DM patients from 9.0% to 7.4% (p<0.0001) following 12 weeks of TI medication.[16] Comparable effectiveness was shown by Hoogwerf et al who recorded an HbA1c drop of 1.05% in the TI group against 1.31 percentages in the insulin aspart group (p=0.06).[21]

McGill et al reported similar HbA1c control between TI and insulin lispro for T1DM patients after 16 weeks.[23] Also, Bode et al found that TI lowered HbA1c by 0.21% compared to 0.40% with insulin aspart, which met the conditions for not being weaker.[17]

TI demonstrated comparable or non-inferior HbA1c reduction to rapid-acting subcutaneous insulins across studies in T1DM and T2DM. It consistently showed faster onset and better PPG control. In T2DM, TI led to substantial HbA1c reductions and improved time-in-range. Overall, TI offers effective glycaemic control with rapid action (Table 1).

PPG MANAGEMENT

In diabetes treatment, post-meal glucose levels are connected to cardiovascular problems; hence, PPG control is essential. Because of its quick start and brief duration of action, inhaled insulin has demonstrated interesting effects in optimising PPG control. With a shorter time to peak glucose levels than in routine care in T1DM, Hirsch et al showed that TI offered improved post-prandial glucose management.[18] Also, Hirsch et al noted a notable drop in post-prandial glucose excursion (p=0.02) and a shorter time to peak glucose with TI compared to fast-acting analogue insulin.[19]

Grant et al noted that TI attained quicker onset (7-15 minutes), improving PPG control over subcutaneous lispro.[20] With lower 2-hour post-meal glucose levels than insulin aspart, Bode et al reported in a 24-week research that TI allowed quicker post-prandial glucose clearance.[17] Reflecting effective early PPG control, Rave et al also noted that 60% of glucose-lowering benefits occurred during the first three hours post-inhalation.[15] Furthermore validated by Rüppel et al was a correlation between fast insulin absorption with TI and improved early post-meal glucose elimination.[24]

SAFETY AND ADVERSE EFFECTS

Pulmonary function effects

Pulmonary function is a key consideration with inhaled insulin. A two-year trial by Raskin et al showed a modest, non-progressive decline in FEV1 during the first three months of TI therapy, which was not clinically significant.[25] Similarly, a meta-analysis by Pittas et al reported a small, reversible FEV1 reduction with TI compared to subcutaneous insulin.[26] Importantly, these changes were mild, transient, and reversible upon discontinuation of TI.[25,26] TI should not be used in individuals with chronic lung diseases such as asthma or COPD, as it may cause acute bronchospasm. Spirometry (FEV1) should be performed before starting treatment, at 6 months, and annually thereafter, even in the absence of symptoms. TI is contraindicated in patients with active lung cancer. In those with a history or increased risk of lung cancer, the potential benefits should be carefully weighed against the risks.

Hypoglycaemic risk

With inhaled insulin in place of subcutaneous insulin, hypoglycaemia is less likely. Compare with insulin lispro in T1DM patients, McGill et al found that TI was linked to a noticeably decreased risk of mild to severe hypoglycaemia (5.97 vs. 8.01 occurrences per patient; p=0.0269).[23] Similarly, Pittas et al, in a systematic review, reported a reduced risk of severe hypoglycaemia with TI (odds ratio 0.61; 95% CI 0.35-0.92).[26] TI is a safer choice for prandial insulin treatment, as its fast start and shorter duration of action help lower late post-prandial hypoglycaemia.[23,26]

Other adverse events

The most frequently reported adverse effect of inhaled insulin is coughing. McGill et al observed that cough was present in 30% of patients, and it was typically moderate, transient, and occurred immediately after inhalation.[23] Patients receiving TI had a 7.82 times greater incidence of coughing than those on subcutaneous insulin, as Pittas et al reported (odds ratio 7.82; 95% CI 6.14-10.15).[26] Also, throat discomfort was occasionally noted, but these symptoms were often self-limiting.[23,26] Most importantly, no increased long-term pulmonary toxicity or carcinogenic risk was observed.[26]

PATIENT-CENTRED BENEFITS

Through increased comfort and simplicity of usage, inhaled insulin greatly increases patient satisfaction.

Comparatively to 10.6% with subcutaneous insulin, a research study found a 35.1% increase in general satisfaction with inhaled insulin. Furthermore, a 41.3% improvement in convenience/ease of use makes this the favoured choice for insulin administration.[27]

Along with social humiliation about injecting in public, the difficulty of injection and the lifestyle limitations it may impose, often reported obstacles to insulin therapy include fear of insulin injection and perceptions of the possible pain of injection. The elements influencing insulin treatment adherence include frequent injections, interference with everyday life, and dread of injections. TI provides less weight gain, simpler insulin delivery, a reduced risk of hypoglycaemia, and more flexibility to fit different patient lifestyles.[28]

Limitations and challenges

People who smoke or have smoked in the last six months, people with severe asthma, or people in stages III or IV of COPD should not use inhaled insulin. This restriction is in place because smoking might change the pharmacokinetics and pharmacodynamics of insulin that is breathed in. Inhaled insulin doesn't seem to affect lung function in healthy people, but there aren't many studies that look at it in detail enough to say how well it works for people with lung illness.[29] Given the possibility of a sudden bronchospasm, Afrezza is contraindicated in those with chronic lung disease. Before therapy starts, patients should be checked for underlying lung illnesses like COPD or asthma. Furthermore, pulmonary function should be assessed at baseline, following the first six months, and yearly. Patients whose FEV1 declines by 20% or more from baseline should have treatment discontinuation should be considered. Diabetes patients experiencing respiratory symptoms such as coughing, wheezing, or bronchospasm require frequent monitoring. Patients having a history of hypersensitivity to RHI or Afrezza's excipients should not undergo Afrezza treatment. The product is not advised for people who smoke or for the control of DKA; it should not be taken during hypoglycaemic episodes.[30]

FUTURE PERSPECTIVES

Involving 123 persons with type 1 diabetes, the 17-week, randomised controlled INHALE-3 trial is spread among 19 U.S. locations. Participants were either starting a regimen incorporating Afrezza with basal insulin or continuing their regular treatment, which comprised automated insulin delivery devices or several daily injections. The Afrezza group showed notable increases in post-prandial glucose management and HbA1c levels, preliminary data showed. More than half of the participants said they would like to keep using Afrezza after the research ended.[31] Expanding on the positive findings of INHALE-3, future studies will investigate the effects of inhaled insulin in a broader range of patients, particularly those in the pediatric and pregnant populations. Inhaled insulin is essential to diabetes management; these trials hope to prove it.

CONCLUSION

Summary of findings

Particularly, Afrezza, inhaled insulin, has become a promising non-invasive substitute for subcutaneous insulin in diabetes control. Studies have revealed its quick start, good PPG management, and similar HbA1c lowering. Furthermore, more patient satisfaction is provided by inhaled insulin because of its simplicity of use, lower hypoglycaemia risk, and better treatment adherence. Particularly in patients with injection phobia or those suffering from post-prandial hyperglycaemia, clinical trials such as INHALE-3 show non-inferior glycaemic control, therefore confirming its position as a practical insulin delivery route.

Implications for clinical practice

For patients with T1 and 2DM, especially those resistant to injectable insulin treatment, the availability of inhaled insulin increases treatment choices. Its quick absorption qualifies it for post-meal glucose management, lowering the risk of delayed hypoglycaemia associated with subcutaneous insulin. Spirometry screening at therapy initiation and regular monitoring are advised, particularly for individuals who could have pulmonary problems. Despite its benefits, concerns remain regarding transient cough, potential effects on lung function, and its contraindication in individuals who smoke or have pre-existing lung conditions. Thus, clinicians must carefully assess each patient's smoking history, pulmonary function, and individual treatment goals when considering inhaled insulin. For select patients, it may serve as a preferred option for mealtime insulin, supported by growing real-world experience and clinical expertise.

Areas for further research

Paediatrics, pregnant women, and people with comorbidities, among other demographics, should all be included in further long-term trials to assess the safety and effectiveness of inhaled insulin. Comparatively to injectable insulin, research should also investigate its effects on diabetes-related complications, adherence rates, and cost-effectiveness. Furthermore, better inhalation devices and novel formulations might increase bioavailability and usability. Globally expanding studies like INHALE-3 will enable clinical recommendations to be refined and its importance in regular diabetes treatment to be established, therefore improving patient outcomes and quality of life.

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