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# Inhaled Insulin: A Much-Needed Needleless Paradigm Shift in Diabetes Management

**Jimmy J Thomas[1*], Stuti Mishra[2], Pakinam Talaat[1], Niya Jamaludheen[3]**

[1]Medicine/ Medicentres Clinic/ Fakeeh University Hospital/ Dubai Silicon Oasis/ Dubai/ United Arab Emirates

[2]OBGYN/ Medicentres Clinic/ Fakeeh University Hospital/ Dubai Silicon Oasis/ Dubai/ United Arab Emirates

[3]DM Healthcare/ Al Rafa Poyclinic/ International City/ Dubai/ United Arab Emirates

[*]**Corresponding author:** Jimmy J Thomas, M.B.B.S, M.D (Med), M.Sc Diabetes (UK), M.Sc Acute Medicine (UK), M.Sc Endocrinology (UK) Medicine/ Medicentres Clinic/ Fakeeh University Hospital/ Dubai Silicon Oasis/ Dubai/ United Arab Emirates

**Co-authors:**

Dr. Stuti Mishra (Second Author), M.B.B.S, M.D, FRCOG

Dr. Pakinam Talaat (Third Author), M.B.B.S, AAARM Board Certified

Dr. Niya Jamaludheen (Fourth Author), M.B.B.S, MRCP, IMT, Diploma is Internal Medicine (Edinburgh)

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**Abstract**

The growing global pandemic of uncontrolled sugars in both type 1 and type 2 diabetics have been a cause of concern for many decades. Time and money invested into the discovery of newer drugs that act on various key enzymes and signaling pathways have helped in curb this expanding pandemic, temporarily. Insulin remains the gold standard of treatment; however, this is often shunned by patients and their healthcare professionals (clinical inertia) alike, owing to the route of delivery of this drug. Ultra short acting analogues of insulin, though help control prandial glucose spikes, do require 2-3 doses based on the meals. In addition to it, long acting basal insulin is often required to mimic the normal physiological insulin baseline levels. This makes an average insulin jab of 2-4 per day, which many find quite distressing. Patients are often overwhelmed with the act of finger prick for checking their blood glucose levels at frequent intervals, and the thought of monitoring blood glucose has often been a deterrent owing to a large group of patients guessing their sugar values pre and post meal. Insulin treatment warrants a stricter monitoring of blood glucose and at times in those with either hypoglycemic spells or those with uncontrolled hyperglycemia; multiple finger pricks might be required. The variances in blood glucose readings on numerous Point of Care (POC) glucometer devices also do not help the cause and only adds to the already existing frustration. Focus on alternate and novel routes of drug delivery of existing molecules help in shifting the paradigm of therapy to more favorable outcomes. This article will discuss one such therapeutic paradigm changes towards the drug delivery of insulin.

**Keywords:** Inhaled Insulin; Exubera; Afrezza; Hba1c Reduction; Postprandial Blood Glucose

**List of Abbreviations**

| | | | | | |
|---|---|---|---|---|---|
| POC | : | Point of Care | CSII Infusion | : | Continuous Subcutaneous Insulin |
| HbA1c | : | Glycosylated Hemoglobin | MDI | : | Multiple daily insulin injections |
| | | | IU | : | International unit |
| | | | Kg | : | Kilograms |

| | | |
|---|---|---|
| AERx iDMS System | : | AERx insulin Diabetes Management |
| TI | : | Technosphere Insulin |
| FDKP | : | Fumaryl diketopiperazine powder |
| RHI | : | Regular Human Insulin |
| OHAs | : | Oral Hypoglycemic Agents |
| NPH | : | Neutral Protamine Hagedorn |
| Mmol | : | Millimole |
| RCT | : | Randomized controlled trial |
| AID | : | Automated insulin delivery |
| CGM | : | Continuous glucose monitoring |
| RAA | : | Rapid acting analog |
| HR-QOL | : | Health-related quality of life |
| FEV(1) | : | Forced expiratory volume in 1 second |
| FVC | : | Forced vital capacity |
| TLC | : | Total lung capacity |
| DL(CO) monoxide | : | Lung diffusion capacity for carbon |
| DKA | : | Diabetic ketoacidosis |

**Inhaled Insulins: A much needed needleless paradigm shift in Diabetes management.**

## Introduction

Alternatives to injectable insulin delivery have always been a fascination in advancements in technologies for Diabetes treatment. With the burden of both type 1 and type 2 diabetes increasing worldwide, the need for newer formulations with longer half-lives (basal insulins), in addition to those which have a rapid onset of onset with a shorter duration of action (prandial insulins), have been contributing towards increasing patient compliance and preventing micro- and macro- vascular complications of the disease. In parallel, one of the most commonly associated dislikes with insulin delivery is its injectable form. Continuous Subcutaneous Insulin Infusion (CSII) do show better glycemic control than Multiple Daily Insulin injections (MDI), the usefulness of this device is limited to a subset of diabetic patients [1]. The lack of other modalities of delivery has contributed to the delay in initiation and continuation of insulin therapy for many diabetes patients globally.

## Brief History

Historically, the earliest works recorded in delivery of insulin via the inhaled route was in the 1920s. Administering insulin in a mildly diabetic patient who, after inhaling normal oral insulin with an inhalation device; while maintaining a constant carbohydrate load, showed a decrease in blood glucose levels. His urine sugars also had become negative. This, however, was short lived and his blood glucose levels began to increase again after stopping the insulin inhalation [2].

Earlier human experiments in four diabetic subjects using an aerosol delivery of insulin, the subjects inhaled a nebulized mist of Regular porcine-bovine insulin. While it was observed that ultrasonic nebulizers had destroyed the biologic activity of the insulin molecule, therefore, particle size of the mist was kept to 2 microns. In each of the test diabetic patients, it was shown that following the nebulizations, serum insulin levels increased within 15 minutes while peaking at 30 minutes and blood sugars levels decreased simultaneously. This showed that insulin not only crossed the respiratory tract mucosae but also retained its biologic activity [3].

Aerosol formulations of insulin which contained suspended insulin zinc crystals in fluorocarbon propellant and oleyl alcohol to improve the insulin suspension and prevent valve clogging; were initially evaluated for temperature dependent stability and potencies. It was seen that at 7, 25 and 37 degrees, the predicted shelf life was approximately 19 years, 11 and 2 months, respectively [4].

Normal individuals, when regular or crystalline insulin with sodium glycocholate as surfactant intranasally administered induced hypoglycemia and elevations in serum immunoreactive insulin concentrations. A potency ratio of 1:8 was seen for intranasal versus intravenous insulin. In a cross over study, 4 insulin-dependent diabetics were administered insulin once intranasally and once subcutaneously in a ratio of 1:9. It was seen that the intranasal insulin was more effective than the subcutaneous insulin in preventing morning post breakfast hyperglycaemia [5].

A study involving Type 1 diabetics was performed to assess the potential of intranasal insulin as an adjunct to subcutaneous insulin. Intranasal aerosolized insulin containing laureth-9 as a surfactant was administered to 8 patients who were fasting, 15 patients who were on mixed meals and 8 patients who were on long term home care. When administered, intranasal insulin at 1U/kg bodyweight in 1% laureth-9 surfactant, it was quickly absorbed in approximately 15 minutes and it decreased plasma glucose levels by 50% in 45 minutes and 120 minutes in fasting normal controls and fasting type 1 diabetics, respectively. The most

common side effect observed was nasal irritation which increased proportionally to the concentration of surfactant. When compared to an intranasal placebo, the 2-hour postprandial glucose in the subjects increased by 38mg/dl versus 191mg/dl, respectively. In a 3 months outpatient study using aerosolized intranasal insulin versus subcutaneous insulin; it was shown to have comparable glycemic control when used with Ultralente insulin. Therefore, inhaled aerosol insulin could be considered as another method for adjunct insulin treatment for better control of fasting and postprandial hyperglycemia [6].

A nonrandomized, placebo-controlled trial, involving 6 non-obese type 2 diabetic patients was performed to investigate the efficacy of an aerosolized dose of insulin in normalizing plasma glucose levels during the fasting state. 1U/ kg body weight of porcine insulin was given by oral aerosol inhalation using a nebulizer at a flow rate of 17L/min. It was seen that the fasting blood sugars decreased in a5 patients and the 6$^{th}$ patient had an almost normal blood sugar reading. The average maximum seen decrease in blood sugars from the baseline was 55%±10% (n=6) vs 13%±9% after a placebo aerosol inhalation. This demonstrated that aerosol oral inhaled insulin was well tolerated and could effectively decrease or normalize blood glucose levels in non-obese type 2 diabetic patients [7].

A double-blind, randomized, controlled intervention study, performed on 8 health non-diabetic volunteers, was performed to study the biologic effects of nebulized insulin. The subjects were administered regular human insulin (doses of 40, 80 and 160 units) or 0.9% normal saline as oral nebulizations. It was observed that at 160 units of inhaled nebulized insulin, there was a significant decrease in blood glucose levels and a corresponding increase in the serum insulin concentrations along with a decrease in serum C peptide levels [4.3±0.2 to 2.8±0.2 mmol L-1 ($P < 0.001$), 9.5±1.5 to 26.1±2.5 mU L-1 ($P < 0.001$), 0.48±0.03 to 0.12±0.02 mmol L-1 ($P < 0.001$)]. None of the volunteers had any adverse effects and none had any significant changes in pulmonary function tests. This concluded that if healthy subjects showed the above response, then this modality of insulin deliver could similarly benefit diabetic patients too [8].

**The pulmonary route:**

In comparison to other potential routes of drug administration, i.e. buccal, nasal, conjunctival, and oral; the pulmonary route offers a large number of advantages. The alveolar absorptive area is approximately 70- 140 m$^2$, which makes for plenty of space for the drug to diffuse into the blood stream. This when combined with the large network of blood vessels perfusing the alveoli (about 5L/min), a thin alveolar epithelium (0.1-0.2 microns) and a short distance between the epithelial surface and blood (0.5-1.0 microns) make it an ideal route for drug delivery. Additional advantages offered by this route involve the relative low concentrations of enzymes like proteases and peptidases that might denature the insulin, the rapid mixing of the insulin with the mucus layer in the alveoli and the absence of the first pass metabolism by the liver [9].

Although lucrative, disadvantages of this route include problems faced by the aerosols, its nebulization process, the synchronicity with the breathing process and the stability and ease of use of the device itself. The nebulizations process should be effective to deliver the correct size of the drug particle (1-3 microns) to reach the lower airways and alveoli, without it being deposited in the upper airways. The breathing technique, i.e., to time the inspiration along with the release of the aerosol, is important to make sure the drug is not deposited in the oral cavity or oropharynx. Other impediments include diseases of the lungs or even the issues pertaining to the properties of the delivery vehicle or adjunct chemicals like water / lipid solubility, molecular weight or liphophilicity. Sometimes, additives which stabilize the drug, or inhibit phagocytosis or enhance absorption can cause local tissue irritation and inflammation [10].

**Make or break: Exubera versus AERx versus Technosphere Insulin (TI)**

A dry powder formulation of rapid acting insulin called Exubera from Pfizer, was the first U.S. Food and Drug Administration (FDA) approved inhaled insulin that was made commercially available, in 2006, for the treatment of both type 1 and type 2 diabetics. It was non-inferior to subcutaneous mixed regular and NPH insulin and contributed to HbA1c lowering in both type1 and type 2 diabetes patients. It was safe to be used along with long acting injectable insulin or with oral antidiabetic agents (OHAs) as monotherapy or combination therapy [11,12]. Despite its results, in October 2007, Pfizer withdrew Exubera from the market, owing to poor sales volumes. The size of the device and dosing in milligrams (mg) rather than International Units (IU) contributed to its poor take up among the diabetic patients.

The AERx insulin Diabetes Management System (AERx iDMS), from Novo Nordisk, unlike Pfizer's Exubera, produces a fine aerosol mist of liquid insulin. The device, although bulky too, is smaller than the Exubera device and has visual cues to guide the patients breathing thereby allowing a better delivery of the drug. The insulin is automatically delivered during the breathing manouever, which makes certain that more of the insulin reaches the lungs and not deposited in the upper airways [13]. Novo Nordisk decided to not go ahead with the development of this inhaled insulin despite being in Phase 3 trials, following Pfizers experience. Although dry powder formulations are more stable and can make for lighter, less sophisticated devices; they contain more complex formulations, drug carrier toxicology, and also possibly contribute to a higher rate of immunogenicity. Meanwhile, liquid technology formulations,

make for easier dosing, and contribute lesser to immunogenicity. Unfortunately, the latter is also dependent on temperature and humidity based aerosol particle stability, and the need for more complex devices to ensure effective bioavailability [14].

The Technosphere Insulin (TI, Afrezza) from MannKind Corporation is the only currently available inhaled insulin in the market for diabetic patients. Like Exubera, this is a dry powder formulation where recombinant human insulin absorbed into Technosphere particles formed with the excipient carrier, fumaryl diketopiperazine powder (FDKP). The FDKP automatically self assembles using hydrogen bonds to form microspheres in an acidic environment. Once inhaled, the particles dissolve in the pulmonary neutral pH environment and are rapidly absorbed into the systemic circulation. The proportion of the drug reaching the lung versus the oropharynx and stomach are 59% versus 30% versus 10%, respectively. The device is small and pre-filled single use cartridges are loaded prior to use. Drug carrier size is maintained at 2-3 microns, ensuring it reaching the alveoli [15].

**Clinical studies with Afrezza in Type 1 and Type 2 Diabetes**

A randomized, open-label, four-way crossover study was done in 11 healthy, non-smoking volunteers on 25, 50 or 100 U TI and 10 IU Regular Human Insulin (RHI) administered subcutaneously to evaluate the pharmacokinetics (PK) and Pharmacodynamics (PD) of TI (Afrezza) using a euglycaemic clamp technique. Results showed peak insulin concentrations (C(max)) were reached approximately 2 hr earlier than RHI (12-17 min for TI vs. 134 min for RHI). Afrezza was more rapidly absorbed and more rapidly eliminated than RHI, resulting in a faster onset and short duration of action [16].

Another double-blind, placebo-controlled, randomized, multicenter, parallel-group study was performed to compare the efficacy, safety, and tolerability of Afrezza with placebo in insulin-naive type 2 diabetic patients poorly controlled with OHAs. 126 patients were randomly assigned to two groups, one receiving Afrezza and another receiving placebo, for 12 weeks of treatment. It was seen that, when compared to placebo, the Afrezza group had a 7.9% ofHbA1c reduction from a mean baseline, a decrease of 56% of postprandial glucose excursions and maximum reduction of postprandial glucose levels by 43% [17].

An open-label, multicentre, randomized, non-inferiority trial was performed in type 1 diabetic adults (>18 years) to compare HbA1c change from baseline to week 24 of Afrezza (n = 174) compared to those on subcutaneous insulin aspart (n = 171), while both on basal insulin (insulin glargine, insulin detemir, or NPH insulin). The mean HbA1c reduction at week 24 was -0.21%(-2.3mmol/mol) from a baseline of 7.94% (63.3mmol/mol) in the Afrezza group versus a -0.40% (-4.4 mmol/mol) from a baseline of 7.92% (63.1mmol/mol) for the insulin aspart group. The former also had fewer hypoglycemias when compared to the latter group. It was also observed that the Afrezza group had a miniscule, non-significant amount of weight loss (-0.4 kg) compared to a weight gain (+0.9 kg) in the insulin aspart patients (P = 0.0102). It showed a non inferiority of Afrezza to Insulin aspart when used along with basal insulin in type 1 diabetics [18].

A Randomized Controlled Trial (RCT) conducted in 19 centres in the US, for 17 weeks, involving 123 type 1 adult (>18 years) patients, to receive either Afrezza with a basal insulin (degludec) versus a control group who continue their usual insulin delivery method consisting of Automated Insulin Delivery (AID) system, a nonautomated pump, or multiple daily insulin injections (MDI). The primary outcome was to show noninferiority between the groups (HbA1c) at the end of 17 weeks. It was seen that the improvement in HbA1c from baseline by >0.5% was seen in 21% in the Afrezza group and 5% in the control group. Similarly, a worsening in the HbA1c by >0.5% was seen in 26% in the Afrezza group versus 3% in the control group. 30% of patients in the Afrezza group and 17% in the control group achieved an HbA1c of <7% at the end of 17 weeks. Hypoglycemic episodes as measured by continuous glucose monitoring (CGM), showed little difference between the groups for those <54 mg/dl (P value 0.002 for noninferiority) and for <70mg/dl (P value < 0.001 for noninferiority). Mild transient cough was seen in 23% of the Afrezza group and other respiratory symptoms seen in the same group were shortness in breath (5 patients), wheezing (2 patients) and bronchospasm (1 patient). This showed that Afrezza with basal insulin (degludec) was noninferior to the usual care regimen in the control group [19].

A study performed to look at the data evaluating health-related quality of life (HR-QOL) through the use of the standardized short-form 36 (SF-36) and Insulin Treatment Questionnaire in type 2 diabetics was done. 171 patients were randomized to receive Afrezza, 162 patients to receive metformin with a secretagogue, or 169 to receive a combination of Afrezza with metformin and secretagogue. At the end of 12 weeks, both the arms using Afrezza reported a higher patient satisfaction than the non- Afrezza group [20].

One of the most frequent questions that linger in the mind of inhaled insulin users and prospective new recruits is the effect on the pulmonary function. A randomized, open label, multicentre study performed at 220 sites, was done to evaluate the changes in pulmonary function in patients using Afrezza or usual ant diabetes care. Both type 1 and type 2 diabetic patients were categorized into cohorts of those receiving Afrezza (730 patients), or those on routine care (824 patients) or those without diabetes and not on any specific care (145 patients). Over a period of 2 years, these patients were monitored via Pulmonary function tests [forced expiratory volume in 1 s (FEV(1)), forced vital capacity (FVC), total lung capacity (TLC) and lung diffusion capacity for carbon monoxide

(DL(CO))]. With the passage of time, it was observed that lung function declined in all 3 groups; however the greatest decline in the first 3 months was in those on Afrezza. However, in the subsequent 21 months, there was no statistical significant changes in the rate of change (slope) in FEV(1), FVC and DL(CO). A mild, transient cough which occurred immediately post inhalation was the most common seen side effect with the Afrezza group [21].

The AFFINITY -1 study was a randomized, phase 3, multicentre study, over 24 weeks in 375 type 1 diabetic adults (>18 years) who were randomized to receive either basal insulin plus either Afrezza or subcutaneous insulin aspart. The Afrezza group showed fewer statistically significantly level 1 (≤ 3.9 mmol/l) and level 2 (< 3.0 mmol/l) hypoglycemic events and lower incidence of level 3 (requiring external assistance for recovery) hypoglycemia when compared to the insulin aspart group. Higher rates of hypoglycemia were observed 30-60 min after meals, but significantly lower rates 2-6 h after meals in those who were on Afrezza [22].

The AFFINITY -2 trials was a randomized, double-blind, placebo-controlled study, over 24 weeks, involving insulin-naïve T2DM patients whose disease was uncontrolled with metformin alone or with at least two OHAs. There was s significantly greater reduction of HbA1c from baseline ($P < 0.001$) and a larger number of patients that achieved a HbA1c of <7% ($P = 0.0005$), in those who were receiving Afrezza. Additionally, the placebo group showed an average weight loss of 1.13 kilograms, while the Afrezza group showed a weight gain of 0.49 kilograms [23].

An ongoing study, INHALE-3 is a Phase 4, randomized, multicentre trial in 19 locations, over 17 weeks, involving type 1 diabetic adults (≥18 years) using multiple daily injections (MDI), an automated insulin delivery (AID) system, or a pump without automation, and continuous glucose monitoring (CGM) 1:1 to an insulin regimen of insulin degludec plus inhaled insulin (Afrezza) and CGM or continuation of usual care. The primary endpoint is to evaluate the change in HbA1c from baseline [24].

A randomized controlled trial (RCT) conducted in 19 centres in the US, for 17 weeks, involving 122 type 1 adult (>18 years) patients, to receive either Afrezza or a rapid acting analog (RAA) insulin along with to continue their usual insulin delivery method consisting of Automated Insulin Delivery (AID) system, a nonautomated pump, or multiple daily insulin injections (MDI). The primary outcome was to evaluate the treatment group difference in area under the curve for glucose >180 mg/dL (AUC180) over 2 hours. It was seen that the AUC180 was 40 ± 44 mg/dL versus 50 ± 42 mg/dL in the Afrezza versus RAA group, respectively. The former had a smaller glucose excursion ($P = 0.01$) and a shorter peak glucose ($P = 0.01$). Thus, adults using Afrezza had a significantly less reduction in post prandial blood sugars when compared to rapid acting insulin analogues [25].

The most common side effects that were commonly encountered in most Afrezza clinical trials were hypoglycemia (67%), acute bronchospasm in asthmatic patients (29%), cough (26-29%), throat pain (6%), > 15% decrease in FEV1 (6%), headache (5%), bronchitis (3%), fatigue (2%), reduction in lung function (3%) and urinary tract infections (2%). Other potential adverse effects that have not had enough significant evidence, however have been seen include lung cancer and diabetic ketoacidosis (DKA) [26,27].

## Conclusion

The treatment of diabetes is constantly evolving with newer medications being added to the armamentarium. In addition to new specific target systems to help in controlling sugars, novel innovations to mechanisms of delivery should also be investigated for effectiveness and improved compliance of medications.

Afrezza represents a novel mechanism of delivery for a much needed medication in the control of postprandial hyperglycemia seen in diabetes. Although not the first, it has certainly stood the test of time and has contributed greatly in the control of postprandial hyperglycemia in both insulin naïve and treated diabetic patients along with those who have been poorly controlled on OHAs.

The changing pulmonary landscape, post COVID-19, has served as a challenge in anticipating long term effectiveness and potential complications that may arise in using this route for medications. More research is required to evaluate the above-mentioned effects and also investigate its effectiveness in control of prandial glucose increase in specific populations like children, pregnant women and the elderly.

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