LEADING ARTICLE

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Evolving Strategies for Insulin Delivery and Therapy

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Abstract

It has now been conclusively proven that adequate control of blood glucose delays or prevents the progression of diabetic complications. In order to achieve the suggested targets for glycaemic control necessary to reduce the incidence of diabetic complications, it has been established that a more intensive insulin regimen requiring multiple insulin injections is required for patients with type 1 diabetes mellitus. For patients with type 2 diabetes, oral antidiabetic therapy is generally used initially, but given the natural history of type 2 diabetes and the need to achieve improved glycaemic control, earlier use of insulin has been promoted. However, the use of insulin in more intensive regimens for the patient with type 1 diabetes or for earlier treatment of the patient with type 2 diabetes is not routine. Many factors are responsible for this observation. Nevertheless, available device options such as insulin pens or insulin pumps are routinely available for implementation of intensive insulin therapy. However, a major limitation for advancing to intensive insulin therapy is that the only viable way to administer insulin is through injection. Delivery options that use dermal, nasal and oral approaches have been explored. The oral approach may include gastrointestinal, buccal or pulmonary uptake. Recent evidence shows that delivery of insulin via the oral cavity with uptake occurring in the pulmonary alveoli may be the most viable clinical option in the future.

The benefits of glycaemic control in patients with diabetes mellitus has been well documented, as the results from major trials have demonstrated conclusively that glycaemic control can prevent or delay the progression of diabetic complications such as retinopathy, nephropathy and neuropathy. These findings were initially reported for patients with type 1 diabetes, comparing intensive insulin therapy to conventional insulin therapy in the Diabetes Control and Complications Trial.[1,2] However, these observations have also been shown to apply to patients with type 2 diabetes.[3,4] Additional evidence from the landmark study in type 2 diabetes, that is, the UK Prospective Diabetes Study (UKPDS),[5] suggests that there may be no threshold for glycosylated haemoglobin (HbA_{1c}) below which one should not expect a reduction in complications. In support of this, the European Prospective Investigation into Cancer in Norfolk (EPIC-Norfolk) population study trial[6] demonstrated that lowered HbA_{1c} is associated with a lower rate of cardiovascular disease, even in non-diabetic individuals. The favourable findings of these studies have prompted suggestions for lowered target values for HbA_{1c}. In order to achieve optimal glycaemic control, the use of insulin in a more intensive physiolog-

ical replacement regimen, in addition to the use of insulin earlier in the course of management for patients with type 2 diabetes, has gained considerable support.

The rationale for more intensive use of insulin, particularly in type 2 diabetes, is also supported by the natural history of the disease itself. Type 2 diabetes is characterised by an antecedent phase of insulin resistance that requires a compensatory increase in insulin secretion to maintain euglycaemia. However, it is now observed that a progressive loss of the insulin secretory capacity of β cells appears to begin years before the clinical diagnosis of diabetes. This pancreatic dysfunction, given the presence of insulin resistance, results in a state of 'relative' insulin deficiency leading to hyperglycaemia. It is at this stage that impaired glucose tolerance and impaired fasting glucose may be present. With worsening pancreatic dysfunction and the inability to fully compensate for the degree of insulin resistance, clinically overt type 2 diabetes becomes present.[7] This concept was well appreciated in a study evaluating the natural history of type 2 diabetes in the Pima Indians of southwestern USA.[8] In this study, it was found that individuals who did not develop diabetes, when followed over time, were able to secrete enough insulin to compensate for any given degree of insulin resistance and thereby maintain carbohydrate tolerance and avoid diabetes.[8] Essentially, individuals who were able to compensate for the increased insulin resistance with a higher insulin response maintained an euglycaemic and non-diabetic state. Therefore, individuals who are observed to develop clinical diabetes, at any given level of insulin resistance, may be described as having an insulin response that does not fully compensate adequately to maintain euglycaemia.[8,9]

In addition to the recognition that β-cell dysfunction is a key pathophysiological parameter of type 2 diabetes, it was also observed in the UKPDS that progressive β-cell failure continued as glycaemic control gradually deteriorated, regardless of initial therapy. Because of the progressive nature of the disease, combination oral therapy or insulin may be needed at this stage to effectively treat the hyperglycaemia.[3] These observations are extremely relevant as traditional initial management of type 2 diabetes has typically relied on monotherapy with oral antihyperglycaemic agents. When monotherapy with an oral agent fails to control blood glucose, it is considered the standard of care to progress to a combination of oral therapies in an effort to obtain glycaemic control.[10,11] As the disease progresses and β cells are at near complete dysfunction, even combination oral antihyperglycaemic therapy may not be effective to maintain glucose control. Near-normal glucose levels are rarely achieved and more than half of patients with type 2 diabetes have HbA_{1c} values above 8.0%.[12] It is at this stage that insulin is considered, but it has historically been considered a treatment of last resort. However, observations from recent trials suggest that insulin, either as monotherapy or in combination with oral agents, may be needed to optimise the management of patients with type 2 diabetes, and may be needed much earlier in the course of the disease than has been previously appreciated.

1. Rationale for Restoring Insulin Secretory Profiles

The goal for delivering exogenous insulin in a patient with diabetes is to mimic as closely as possible the normal physiological insulin secretion seen in non-diabetic individuals. This concept is extremely important given the insulin secretory defects described for both type 1 and type 2 diabetes. Whereas it is well known that the pathophysiology of type 1 diabetes involves autoimmune destruction of the pancreas requiring initiation of insulin therapy from its onset, it has been accepted that type 2 diabetes can be considered a state of inadequate insulin secretion as well, although from an entirely different pathophysiological process. The normal insulin secretory profile in response to glucose consists of a first phase, corresponding to an acute release of insulin (generally <10 minutes), and a second phase corresponding to a sustained release of insulin from immediately releasable insulin stores and protein synthesis within the β cells. Whereas

both first and second phases are deficient for the patient with type 1 diabetes, the pattern observed in type 2 diabetes is characterised by a lack of first-phase insulin response but a preserved second-phase response.[13] Restoring these profiles in both type 1 and type 2 diabetes with exogenous insulin remains a major goal of clinical medicine.

2. Current Clinical Strategies for Exogenous Insulin Therapy

In order to restore the normal endogenous insulin secretory profile in patients with diabetes, it is necessary to consider replacement as providing both basal and post-meal insulin needs, that is, the basal-bolus concept[14] (figure 1). With this strategy, insulin provided for basal (fasting) needs suppresses glucose production between meals and overnight, requires nearly constant plasma levels and represents generally less than half of daily insulin requirements. In contrast, the requirement for insulin at mealtimes (prandial) coverage is referred to as 'bolus' insulin needs. The bolus insulin limits hyperglycaemia after meals and, ideally, should have an immediate rise and sharp peak in plasma levels to effectively control glycaemic excursions (figure 1). Insulin provided as boluses represents 10–20% of total daily insulin requirement at each meal.

The ability to adhere to the basal-bolus concept on a clinical level has become more feasible given the release of the newer fast-acting and basal insulin formulations.[15] The currently available insulin formulations differ based on time-activity profiles[16-23] (table I). The rapid-acting insulins, such as lispro and aspart, have a more rapid onset and shorter duration of action compared with regular insulin, which allows the insulin regimen to more closely mimic the normal endogenous insulin profile.[15,21,22] In addition, other short-acting analogues that will be able to address the post-prandial needs, such as glulisine, are in development.[24] Both of the available analogues (lispro and aspart) provide the required meal-related bolus in insulin secretion when given at mealtimes; therefore, they provide good postprandial control of the glycaemic excursion.[15,21,22] In addition, based on the time-activity profile, patients can inject themselves immediately before the meal and provide a dose to match the carbohydrate content of the meal.[25]

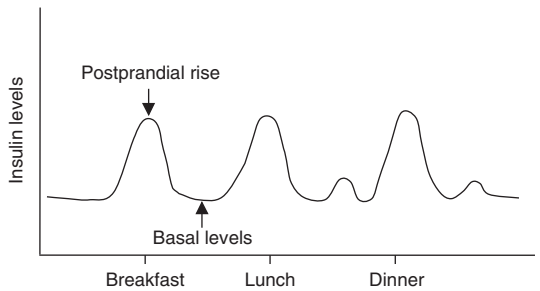

Fig. 1. Schematic representing meal 'bolus' and 'basal' insulin needs (reproduced from Cefalu,[14] with permission of Taylor & Francis [http://www.tandf.co.uk/journals/titles/07853890.html]).

The short-acting insulin formulations (i.e. regular insulins) have been a mainstay of diabetic management for years; however, a major shortcoming of regular insulin use is the difficulty in matching postprandial insulin availability to postprandial requirements. Regular insulin provides a slower onset and more prolonged duration of action than is required for effective postprandial glucose control. As a result, large doses of regular insulin given to reduce postprandial hyperglycaemia may predispose the patient to episodes of hypoglycaemia at later time points.[26] If reduced doses are given at the meal to reduce the chance of later hypoglycaemia, adequate postprandial control may not be achieved.

The third category of formulations includes the intermediate acting insulins (Neutral Protamine Hagedorn [NPH] insulin and insulin lente). Traditional use of the intermediate-acting formulations has generally been to provide injections twice daily to provide 24-hour basal insulin coverage. The limitation of these formulations as true basal insulin relates to the fact that the peak and nadir are not truly representative of normal endogenous basal insulin release.

The last category is the long-acting insulin formulations, represented by insulin ultralente and insulin glargine.[18,27] A new long-acting insulin preparation, determir, has also been shown to be a true basal insulin preparation and shows consistency

Table I. Characteristics of modern insulin formulations

Insulin formulation	Onset of action	Peak (h)	Duration of action (h)
Lispro/aspart	5–15 min	1–2	4–6
Human regular	30–60 min	2–4	6–10
Human Neutral Protamine Hagedorn (NPH)/lente	1–2h	4–8	10–20
Human ultralente	2–4h	Unpredictable	16–20
Glargine	1–2h	Flat	~24

in the pharmacokinetic profile across treatment groups.[28] However, insulin ultralente has also been shown to peak (though later than that observed with NPH insulin), while insulin glargine and insulin detemir appear to be to more representative of a true basal insulin based on an almost peakless profile.[27] Compared with NPH insulin given once or twice daily, insulin glargine may be effective in lowering fasting plasma glucose with fewer episodes of nocturnal hypoglycaemia.[25,29,30]

The insulin formulations discussed above can be administered individually, but for convenience, preparations combining intermediate-acting NPH insulin or Neutral Protamine Lispro (NPL) insulin and regular or short-acting insulins (e.g. mixtures containing 70% NPH and 30% regular insulin [70/30] or 75% NPL and 25% lispro [75/25]) are available.[19] Recently, a 70/30 mixture containing 30% insulin aspart has become available. Additional mixtures have been evaluated and consist of 85% NPH insulin and 15% regular human insulin (85/15), 50% NPH and 50% regular insulin (50/50), in addition to 50% insulin lispro/50% NPL (50/50).[31-33]

Available insulin formulations allow the clinician to design a regimen that can be highly individualised for the specific needs of the patient. Thus, when the insulin regimen is accompanied by assessment of caloric intake (i.e. 'carbohydrate counting') and self monitoring of blood glucose, the insulin can be titrated to effectively optimise glucose control by providing not only basal insulin coverage, but matching prandial needs.[15] Despite the availability of new formulations that allow physiological insulin replacement and the demonstrated benefits of improved glycaemic control, advancing the patient to intensive insulin therapy has not achieved widespread acceptance. A major limitation of intensive insulin therapy is that in order to optimise glucose control, the regimen may require multiple insulin injections that in turn may increase the complexity and effort required to comply with the regimen.

3. Barriers to Insulin Therapy

Despite the newer insulin formulations and strategies that allow the clinician to mimic normal endogenous insulin secretory profiles, intensive insulin therapy has not achieved widespread acceptance because of barriers to its use from both patients and physicians. Specifically, there may be concerns from the patient about fear, inconvenience, pain or the anxiety of insulin injections.[34,35] Furthermore, the patient may feel as if they are advancing to insulin therapy because they have been noncompliant with their treatment regimen.[36] In addition, the perception is that use of insulin signifies progression to a more serious phase of their disease; some patients view insulin use as a 'prelude to death'.[37]

Resistance of physicians to using intensive insulin therapy may be secondary to concerns of possible associated adverse events (i.e. weight gain, hypoglycaemia, increased cardiovascular risk).[37] Thus, providers who care for patients with type 2 diabetes may accept less than optimal control on combination oral therapy because of these concerns or the concerns relayed to them by the patients. While weight gain and hypoglycaemia may accompany intensive treatment of diabetes, lessons learned from the UKPDS (where patients randomised to insulin gained 4kg and had higher rates of hypoglycaemic episodes than the diet treated group) strongly suggest a significant clinical benefit in reduction of complications such as retinopathy and nephropathy.[3]

At one time, it was postulated that the hyperinsulinaemia resulting from exogenous insulin therapy

may have adverse cardiovascular outcomes in patients with type 2 diabetes. However, the concern that cardiovascular risk is increased from exogenous insulin therapy lacks support from clinical research trials. Specifically, the UKPDS reported no data which suggested that either sulphonylurea or insulin therapy increased cardiovascular risk. In fact, a 16% risk reduction for myocardial infarction (including nonfatal and fatal myocardial infarction and sudden death) was observed that approached clinical significance ($p = 0.052$).[3] Other studies that initiated insulin therapy for cardiovascular diseases at hospitalisation (e.g. the Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction [DIGAMI] study[38]) have suggested a protective effect of insulin therapy after acute myocardial infarction. Thus, advancement to intensive insulin therapy would represent a management challenge, but one that needs to be undertaken given the long-term tissue damage that is observed with chronic hyperglycaemia.

4. Approaches for Non-invasive Insulin Delivery

In addition to achieving insulin delivery without injections, the delivery system should ideally provide insulin in a way that mimics normal endogenous secretory profiles, as can be done with the available insulin formulations.[15] Thus, the major goals when considering a practical non-invasive insulin delivery system are: (i) eliminating injections; (ii) preserving a more physiological insulin profile with exogenous insulin therapy; and (iii) preserving the physiological route for internal insulin (i.e. first passage through the liver). Achieving these goals for non-invasive insulin delivery will allow for more intensive insulin delivery, a regimen clinically proven to improve glycaemia significantly and reduce complications, while enhancing patient compliance. In an effort to achieve these goals, research has been conducted that has evaluated insulin delivery via dermal, nasal and oral routes.

4.1 Transdermal Approach

4.1.1 Insulin Pen Injectors

One of the major advances in insulin delivery has been an innovation that has made self-injection easier and more convenient with use of the insulin pen injector. These devices are small, convenient, disposable and use smaller gauge needles that may result in less painful injections than conventional injections.[39] Another positive feature of the device is that the desired dose of insulin can be precisely selected with a dial.[40] These devices can also deliver the new fast-acting insulin analogues. Insulin pen injectors should facilitate compliance with multiple injections, allowing a more physiological insulin pharmacokinetic profile.[41]

4.1.2 Jet Injectors

Jet injectors administer insulin without needles by delivering a high-pressure stream of insulin into subcutaneous tissue. This approach is appealing because of the lack of needles, but the discomfort associated with jet injectors is not reported to be less than that observed with injections.[40] Insulin delivered with the jet injector was proposed to be more precise and more quickly absorbed than subcutaneous needle delivery; however, the time-activity profile of the insulin can be altered, which can create problems with glycaemic control.[42] Although these devices were first proposed over 40 years ago, they appear to have limited use for the treatment of diabetes.[40,42] However, if a patient has severe anxiety or a phobia toward needles, these devices may potentially help.

4.1.3 Iontophoresis

Iontophoresis refers to transdermal delivery of insulin or other peptides by a direct electric current. This concept is analogous to that observed with passive transdermal medication patches currently in widespread clinical use. Current transdermal systems, for example, deliver nicotine for smoking cessation programmes or hormone therapy for postmenopausal women. However, iontophoresis enhances the transdermal delivery of drug ions into the skin and surrounding tissues using low level electrical current. Proof of concept for this approach has

been demonstrated, as iontophoretic delivery of bovine insulin produced a concentration-dependent reduction in plasma glucose levels when evaluated in a study of diabetic rats.[43] In that study, however, the method did not appear as effective in rats that had not been depilated. These observations would suggest that: (i) the creams used with the iontophoretic device acted as a penetration enhancer only in animals that had been treated in advance with a depilatory cream rather than having their hair removed with scissors; or (ii) depilation was effective in reducing the skin's barrier function. In contrast, a significant fall in plasma glucose in the rats was demonstrated with iontophoretic delivery of a monomeric human insulin analogue.[43] Before this technique becomes a clinical reality, the specific factors that modulate absorption and delivery of transdermal insulin using this approach will need to be elucidated.

4.1.4 Low-Frequency Ultrasound

The permeability of human skin to macromolecules can be increased several-fold with use of low-frequency ultrasound waves. As such, this technique has been evaluated as a means of non-invasively administering insulin. It has been estimated that the permeability achieved by 1 hour of sonophoresis performed three times daily may allow for a typical daily dose of insulin (about 36U) to be delivered transdermally.[44] Although this approach is potentially feasible, one concern is that the rate of insulin delivery is too slow to provide for effective insulin coverage of mealtime glucose excursions; therefore, it does not mimic normal physiology. Further study is required to improve efficiency and ensure safety before clinical application can be considered.[44]

4.1.5 Transfersomes

Transfersomes are lipid vesicles made of soybean phosphatidylcholine and have the property of deformability, which makes them flexible enough to pass through pores much smaller than themselves; for example, despite being some 1000 times larger, transfersomes may pass through pores with an efficacy similar to water. Therefore, this technology offers potential, and has shown effectiveness, for transdermal delivery of insulin and other macromolecules. Early tests have demonstrated that when the vesicles are loaded with insulin and applied to intact skin in a sufficient quantity, insulin may be transported with at least 50% of the bioefficiency of a subcutaneous injection[45] (figure 2). The absorption of insulin with this technology is not rapid enough for effective insulin coverage for meals, as is the concern with other transdermal systems. However, it may be feasible in the future to deliver constant basal levels, as estimates are that a skin surface area of approximately 40 cm^2 is sufficient to cover the basal daily insulin requirements of most patients with type 1 diabetes.[45] Future studies are needed to determine the clinical utility of this approach.

4.2 Intranasal Approach

Delivery of insulin using an intranasal approach was first suggested over 65 years ago, but it was not until the 1980s that this approach was seriously evaluated.[40,46] Feasibility has been demonstrated, as intranasal insulin (60 or 120U) given pre-meal to 17 patients with type 2 diabetes and compared with placebo resulted in reductions in postprandial

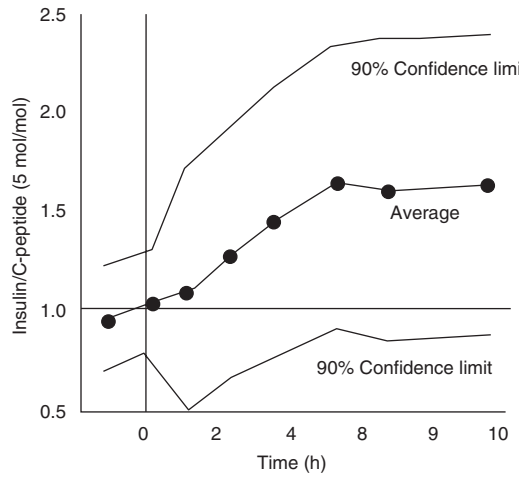

Fig. 2. Change in the systemic insulin/C-peptide molar ratio as a function of time after epicutaneous Transfersulin administrations. The data represent the results of six experiments done on a non-diabetic volunteer with various amounts of different transfersulin formulations [reproduced from Cevc et al.,[45] with permission from Elsevier].

glucose at both 60 and 120 minutes.[47] However, the major limitation of this approach is one of poor bioavailability across the mucous membranes. This was demonstrated in studies by Hilsted et al.[48] in 31 patients, as they reported doses of intranasal insulin that were approximately 20 times higher than those needed with subcutaneous injection.[48] In addition, glycaemic control worsened slightly, but significantly, during nasal insulin treatment compared with subcutaneous insulin, despite the large doses of insulin.[48] To overcome the problem of limited bioavailability, absorption-enhancing compounds such as bile salts and polyethylene ether derivatives have been evaluated for nasal insulin and have resulted in increased absorption and effective biological activity. It appears, however, that the chance of nasal irritation has increased with these changes.[47,49,50] The feasibility of intranasal insulin has been demonstrated, but limitations do exist and further studies are needed to establish long-term safety and efficacy.

4.3 Oral Approach

Insulin delivered orally, when considered generally, can be considered as having uptake occur within either the gastrointestinal tract, buccal mucosa or lung alveoli.

4.3.1 Gastrointestinal Delivery

If absorption occurs via the gastrointestinal tract, a theoretical advantage is that the insulin uptake mirrors the enterohepatic transport of endogenous insulin.[51] However, as insulin molecules tend to be too large and hydrophilic to cross the mucosa, uptake of insulin via the gastrointestinal tract is limited by an extremely low bioavailability (i.e. ≤0.5%). An additional limitation is the extensive enzymatic and chemical degradation of insulin within the enzymatic barrier of the gastrointestinal tract mucosa.[52] Several approaches have been suggested to overcome this problem, such as protease inhibitors aimed at limiting degradation, absorption enhancers and enclosing insulin within microspheres, and, thereby, protecting it against hydrolysation or enzymatic degradation.[51,53,54] Thus, strategies to enhance gastrointestinal uptake of insulin are being explored.

Proof of concept for oral insulin has been shown for hexyl-insulin-monoconjugate-2 (HIM2), a native recombinant insulin with a small polyethylene glycol 7-hexyl group attached to the position B29 amino acid lysine, currently in development. Preclinical pharmacokinetic and safety data for HIM2 are beginning to emerge. Ongoing phase I and II clinical trials suggest that oral HIM2 has a bioavailability of approximately 5% and may result in an acceptable glucose lowering effect.[55] In addition, another recent preliminary study demonstrated the feasibility of using an oral delivery agent to facilitate human insulin absorption.[56] Although oral delivery with conjugated insulin holds promise for the future, substantially more clinical research is required.

4.3.2 Buccal Delivery

Oral insulin delivery that relies upon uptake by the buccal mucosa and oropharynx appears to be feasible for more widespread clinical testing, as insulin appears to be rapidly absorbed into the systemic circulation with this approach.[52,57] In particular, a liquid aerosol preparation has been evaluated for buccal uptake in patients with both type 1 and type 2 diabetes.[58,59] In patients with type 2 diabetes, the serum glucose, insulin and C-peptide levels obtained postprandially with this formulation, when given before a meal, were found to be comparable with that of subcutaneous insulin.[59] This formulation appears to show additive glycaemic effects when given to patients with type 2 diabetes on oral therapy only. In a study of 24 patients with type 2 diabetes, approximately 100U of oral insulin was provided before each meal in this cohort who had worsening glycaemic control on oral therapy. The buccal insulin combined with oral agents significantly decreased postprandial glucose levels when compared with oral agents alone (10.3 vs 14.5 mmol/L)[58] [figure 3].

A study of 22 patients with well controlled type 1 diabetes compared the pharmacokinetic profiles of regular insulin, insulin lispro and oral insulin spray (with an absorption enhancer). However, as only

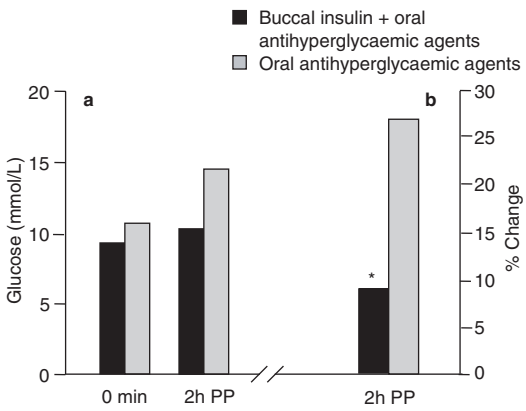

Fig. 3. Average pre-meal (0 minutes at breakfast, lunch and dinner) and post-meal glucose (2 hours postprandial [PP]) values in patients with type 2 diabetes mellitus obtained with oral antihyperglycaemic agents alone or oral antihyperglycaemic agents plus buccal insulin prior to meals (**a**). The percentage change in average 2-hour PP values was significantly lower with oral antihyperglycaemic agents plus buccal insulin versus oral antihyperglycaemic agents alone (**b**) [reproduced from Levin et al.,[58] with permission from The American Diabetes Association, © 2001 American Diabetes Association]. * $p < 0.001$.

four patients received insulin lispro, the sample size was too small to determine significant differences between treatment groups.[60] Another study in 30 patients with type 1 diabetes suggested that there were no significant differences in postprandial glucose control between those treated with buccal insulin and those treated with subcutaneous insulin, although plasma insulin levels were reported to peak more rapidly with buccal administration.[61] Buccal insulin, therefore, has also demonstrated proof of concept; unfortunately, the studies to date demonstrating efficacy are presented as abstracts only, and safety and adverse effect profiles for this approach have not been presented for large numbers of subjects.

4.4 Pulmonary Approach

Finally, insulin delivered through the oral cavity can also be considered to have its uptake in the pulmonary bed. However, the idea of pulmonary delivery of insulin is not a new idea, as the first report of inhaled insulin was noted in 1925;[62] truly remarkable given that this was reported very shortly after the first clinical use of insulin.[63] The high permeability of the lung's large surface area makes it an ideal route for the administration of insulin. The lung has hundreds of millions of alveoli that are richly vascularised and where drug absorption takes place. In addition, the surface area is quite large, as the alveolar capillaries provide a total surface area of 50–140m^2 for absorption.[64,65] Therefore, these characteristics allow absorption of insulin to be much enhanced across pulmonary mucosae compared with either nasal or buccal surfaces, even in the absence of enhancing chemicals.[57]

Insulin delivered in this way is believed to be transported across the alveolar cells by transcytosis, but this has yet to be conclusively proven. Once deposited in the alveoli, the inhaled insulin molecules are taken up into vesicles, transported across the epithelial cells and then released into the interstitial fluid between the epithelium and the alveolar capillary endothelium. The insulin is once again taken up into vesicles, transported across the capillary endothelium and released into the bloodstream, where it exerts a rapid systemic effect[64-68] (figure 4). This process is extremely rapid and pulmonary uptake results in a very rapid peak in insulin levels, that is, after 15–20 minutes.[66,69,70] Therefore, the physiological and anatomic barriers that limit successful implementation of other routes of non-invasive insulin delivery do not appear to be a major concern when one considers the feasibility of pulmonary delivery of insulin, based in large part on the favourable anatomy of the lung.

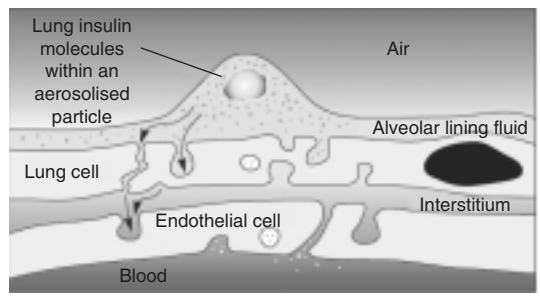

Fig. 4. Pulmonary transport of insulin and uptake mechanism (reproduced from Klonoff,[68] with permission).

There have been numerous studies evaluating the clinical effect of pulmonary uptake of insulin. Heinemann et al.[71] compared the pharmacodynamics of microcrystalline dry human insulin powder 99U, subcutaneous injections of regular human insulin 10U and intravenous regular human insulin 5U in a study of 11 healthy individuals using a euglycaemic clamp.[71] The results suggested that the bioavailability of inhaled insulin was approximately 10% compared with injectable insulin, and inhaled insulin had a much faster onset of action compared with that observed with subcutaneous insulin (31 versus 52 minutes).[71] The time-action profile of inhaled insulin 6mg versus subcutaneous regular insulin 18U and insulin lispro 18U was evaluated by Heise et al.[72] with a euglycaemic glucose clamp in 18 healthy, nonsmoking males. Inhaled insulin showed a faster onset of action than subcutaneous regular insulin and even insulin lispro. In addition, the duration of action was intermediate between that of insulin lispro and regular insulin (382, 309 and 413 minutes, respectively). This more rapid onset of action would allow for more effective post-meal glucose coverage; therefore, insulin delivery via the pulmonary bed appears to be more physiological than conventional regular insulin.

Rapid absorption of insulin with pulmonary delivery also occurs in patients with diabetes, as both Laube et al.[73] and Gelfand et al.[74] reported that inhaled insulin produced a more rapid peak and fall of plasma insulin levels than subcutaneous insulin. In addition, it was shown that preprandial insulin 45U was absorbed rapidly and showed similar pharmacodynamics to subcutaneous insulin 8U given 30 minutes before a meal in a study of 20 patients with type 1 diabetes.[75] In a study of 15 patients with type 2 diabetes, pulmonary delivery of insulin had a shorter time to peak action than subcutaneous insulin and gave comparable dosage reproducibility.[76]

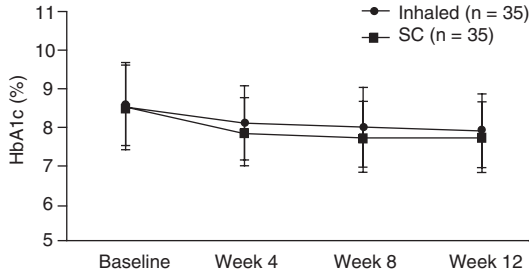

Fig. 5. Glycosylated haemoglobin (HbA_{1c}) values over 12 weeks in patients with type 1 diabetes mellitus treated with inhaled insulin or subcutaneous (SC) insulin (reproduced from Skyler et al.,[77] with permission from Elsevier).

4.4.1 Clinical Trials of Inhaled Insulin

The efficacy and tolerability of inhaled insulin have been assessed in phase II and phase III clinical trials.

The open-label phase II trials with the inhaled insulin Exubera® [1] included a 1-month run-in during which patients were evaluated for glycaemic control and pulmonary function. A 3-month treatment phase involved home blood glucose monitoring, weekly visits to the treatment centre and final pulmonary function tests. The control group continued to receive their regular regimen of two to three insulin injections daily, while patients in the experimental group received pre-meal inhaled insulin as well as a bedtime subcutaneous injection of ultralente insulin. In a phase II study involving 73 patients with type 1 diabetes mellitus, changes in HbA_{1c} were indistinguishable between the inhaled insulin group and the control group treated with their usual insulin regimen over a 12-week treatment period[77] (figure 5). Change in fasting and postprandial glucose concentrations, and occurrence and severity of hypoglycaemia, were similar between the two groups. Further, pulmonary function was stable over this short-term study period. A phase II study involving 69 patients with poorly controlled type 2 diabetes demonstrated that by adding inhaled insulin to oral antihyperglycaemic agents, a significant improvement in glycaemic control could be obtained. In that study, HbA_{1c} values dropped by more than 2% in the combination group, whereas no change com-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

pared with baseline was observed in the group randomised to oral antihyperglycaemic agents alone.[78] Another randomised 3-month study of 26 patients with type 2 diabetes on a stable insulin schedule (two to three injections daily for ≥1 month) found that inhaled insulin significantly improved glycaemic control compared with baseline, with a decrease in HbA_{1c} of $0.71 \pm 0.72\%$ (figure 6). Pulmonary function was stable and the patients showed no significant weight change.[26]

Several phase III studies have been reported. In a 6-month study of 334 patients with type 1 diabetes, it was determined that HbA_{1c} values were comparable in the conventional insulin-treated patients and those who received inhaled insulin plus a single bedtime insulin ultralente injection. However, it found that patients receiving inhaled insulin reported enhanced overall satisfaction, quality of life and acceptance of intensive insulin therapy.[79] A phase III study of 309 patients with type 2 diabetes mellitus suboptimally controlled on oral therapies revealed improved glycaemic control with inhaled insulin alone and in combination with oral agents. Glycaemic control, as assessed by HbA_{1c}, improved in the patients taking inhaled insulin alone and in combination by 1.2% and 1.9%, respectively, when compared with oral agents alone. In terms of patient satisfaction, the two groups using inhaled insulin generally preferred the inhaled insulin over their previous regimen.[80]

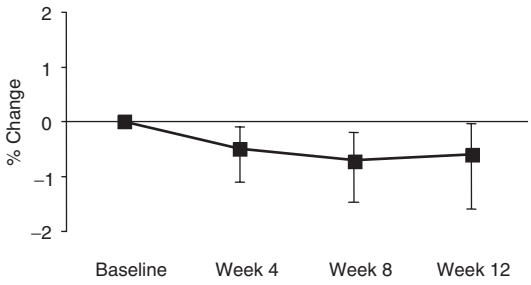

Fig. 6. Percent change in glycosylated haemoglobin (HbA_{1c}) values in patients with type 2 diabetes mellitus receiving inhaled insulin. Error bars represent 1SD (reproduced from Cefalu et al.,[26] with permission; the American College of Physicians is not responsible for the accuracy of any translation of this figure).

4.4.2 Adverse Events and Benefits

The frequency and nature of adverse events reported with inhaled insulins appear, in general, to be comparable with subcutaneous insulin, with the exception of cough (although this decreases in incidence and prevalence with continued use). Patients treated with inhaled insulin have been shown to develop increased serum insulin antibody levels. However, this observation did not result in any apparent clinical change.[81,82] Pulmonary function tests, including forced expiratory volume in 1 second, forced vital capacity, total lung capacity and carbon monoxide diffusing capacity (DL_{CO}) have been conducted for all inhaled insulin studies, and some studies reported a statistically significant decrease in the more variable DL_{CO} relative to subcutaneous insulin.[83,84] Further studies are ongoing to characterise the insulin antibody and DL_{CO} changes, and to determine clinical significance or a methodological basis for these findings.

5. Conclusion

There is little doubt that the ability to control blood glucose is key to the prevention and delay of diabetic complications. With the release of the new insulin formulations, more physiological insulin regimens can be designed to optimise glycaemic control. Yet barriers remain in the implementation of more intensive insulin regimens in addition to earlier use of insulin for patients with type 2 diabetes.

One of the main barriers is that insulin therapy can only be given with syringes and, combined with the patient's related fears and anxiety about injections, this may contribute to noncompliance and poor glycaemic control. These concerns are being addressed through insulin delivery options that overcome the 'skin barrier'. Of all the options evaluated to date, pulmonary delivery of insulin appears as effective and well tolerated as rapid-acting injected insulin and, hence, appropriate for mealtime insulin therapy. The long-term safety of pulmonary insulin is currently being evaluated in ongoing extension trials.

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