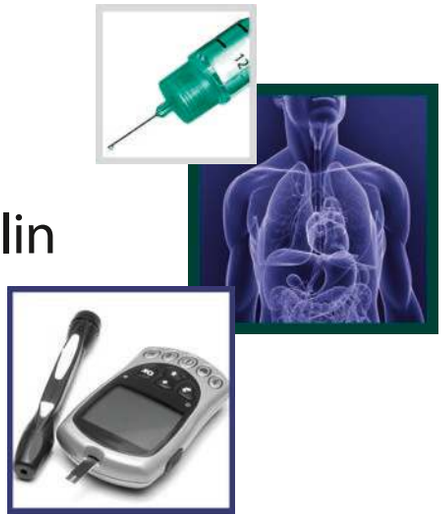
REVIEW

New developments to optimize postprandial glucose control with insulin in patients with diabetes



Bastiaan E de Galan*

Practice Points

- Postprandial hyperglycemia is an important factor that contributes to suboptimal glucose control in patients with diabetes, and is also an independent cardiovascular risk factor.
- Current rapid-acting insulin analogs are not rapid enough to sufficiently curtail postprandial hyperglycemia.
- The solidity of the subcutaneous interstitium and the tendency of insulin to self-assemble to hexamers are the rate-limiting factors for the absorption of subcutaneous insulin.
- The absorption of subcutaneous (rapid-acting) insulin can be enhanced and advanced by techniques including administration by jet injection, local skin warming, coadministration of hyaluronidase and the addition of compounds that inhibit hexamer formation.
- Pulmonary, oral and buccal insulin and insulin injected by microneedles are being developed as alternatives for subcutaneous rapid-acting insulin with a faster onset of action.
- Expansion of the arsenal of therapeutic rapid-acting insulin will enable individualized insulin treatment for patients with diabetes.

SUMMARY Many patients with Type 1 or insulin-requiring Type 2 diabetes fail to achieve the widely recommended glycemic target of HbA1c below 7%. Insufficient control of postprandial glucose excursion plays an important role in this failure. The pharmacological profile of rapid-acting insulin analogs is still far from mimicking the physiological profile of endogenous insulin secretion. Several products are under development that aim to bring this goal closer. These developments include the use of jet injectors for insulin administration, coadministration of hyaluronidase, insulin agents that are resistant to hexamer formation, and insulin products that use an alternative route of administration. This review provides an overview of recent developments and discusses potential benefits with respect to postprandial glucose control.

Background

Most guidelines have defined HbA1c levels below 7% as the target for glucose control in patients with Type 1 or 2 diabetes [1], however, few patients with Type 1 or insulin-treated Type 2 diabetes are able to achieve this target. For HbA1c levels below 8.5%, postprandial glucose excursions contribute more to overall

*Department of General Internal Medicine, 463, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB, Nijmegen, The Netherlands; Tel.: +31 24 36 18 819; Fax: +31 24 35 41 734; b.degalan@aig.umcn.nl

Future Medicine part of fsg

glycemic control than fasting glucose levels [2]. It is therefore imperative to limit postprandial glucose excursions when one wants to achieve optimal glucose control. In addition, there are strong suggestions that postprandial hyperglycemia independently predicts mortality and cardiovascular disease, at least in individuals with Type 2 diabetes and in those without diabetes [3,4]. Guideline recommendations from several organizations have thus set the postprandial glucose target at glucose values ranging from 7.8 to 10.0 mmol/l (i.e., in the high–normal region) [1,5].

Optimal postprandial glucose control can be best achieved using a therapeutic insulin that closely mimics the time–action profile of endogenous insulin release. Current rapid-acting insulin analogs have been developed for this purpose. However, although better than regular insulin, the pharmacokinetics and pharmacodynamics of rapid-acting insulin analogs are still far from approaching the time–action profile of endogenous insulin secretion. Indeed, the time-to-peak insulin levels vary between 45 and 90 min after subcutaneous injection, and the time to the maximal glucose-lowering effect varies between 85 and 198 min after injection **(Table 1)**. Consequently, postprandial hyperglycemia and (late) postprandial hypoglycemia remain relatively common, despite the use of rapid-acting analogs. Indeed, a Cochrane review revealed that treatment with rapid-acting analogs, rather than regular insulin, was associated with only a modest (0.2%) lower HbA1c level in patients with Type 1 diabetes, whereas there was no such benefit in patients with Type 2 diabetes. In neither patient group did the use of rapid-acting analogs reduce the risk of hypoglycemia [6].

Two factors determine the rate of insulin absorption from the subcutaneous area into the circulation. First, the extracellular matrix of the subcutaneous tissue consists of numerous structural macromolecules that limit the rate by which a certain volume of drug permeates the interstitium before it can be absorbed. The second factor is the tendency of most therapeutic insulins to self-assemble into hexamers in the presence of zinc. The degree and strength of hexamer formation is the rate-limiting step for the absorption of regular human insulin, but also affects the absorption of both the lispro and aspart insulins, which contain zinc as a stabilizing ligand [7,8]. However, the fact that the pharmacological profile of glulisine, which does not contain zinc, is very similar to that of lispro and aspart insulin indicates that the tendency for hexamer formation is not a major issue for any of the rapid-acting analogs. In addition, it should be acknowledged that subcutaneous insulin differs from endogenous insulin in that the latter reaches the liver first, where it is already degraded by ~50% before entering the circulation.

The need for developing more physiological insulin treatments that are better at approaching the profile of endogenous insulin secretion has gradually been recognized. A number of approaches are now in various stages of development. These approaches are aimed at either developing methods to improve absorption of subcutaneous insulin or at developing alternative routes for insulin administration. This review will examine the potential benefits and limitations of these developments for the treatment of diabetes with specific respect to postprandial glucose control.

Methods to enhance absorption of subcutaneous insulin

Various methods are under development that are aimed at promoting the absorption of subcutaneous insulin, either by facilitating subcutaneous tissue dispersion or tissue perfusion, or by limiting hexamer formation. These approaches include the use of jet injection or a heated patch for administration of currently available insulin products, and the development of novel, so-called ultrafast, insulins that contain the extracellular matrix degrading substance hyaluronidase or the hexamer destabilizing factors EDTA and citric acid. **Table 1** summarizes the main findings with respect to the pharmacokinetics and pharmacodynamics of these products in comparison with those of the rapid-acting insulin analogs, lispro or aspart.

■ Jet injection

The concept of jet injection for insulin administration was first introduced in the 1960s as a needle-free alternative, primarily for patients with needle-phobia or unwillingness to initiate conventional insulin therapy [9]. Current jet injectors use a high-velocity jet (typically >100 m/s) that ensures >90% delivery of injected insulin into the subcutaneous tissue, without penetration of the underlying muscle. A loaded spring mechanism that only releases the insulin after appropriate pressure has been applied to the skin

Table 1. Pharmacokinetics and pharmacodynamics of various novel methods to deliver postprandial insulin.

Modality	Comparator	Population	n	$T\text{-}INS_{max}$ (min)		Difference (%)	$T\text{-}GIR_{max}$ (min)		Difference (%)	Ref.
				Investigational product	Comparator		Investigational product	Comparator		
Jet injection	Lispro	Healthy controls	4	41 ± 15	85 ± 14[†]	-52	131 ± 95	181 ± 49	-28	[16]
	Aspart	Healthy controls	18	31 ± 13	64 ± 26[‡]	-52	51 ± 13	105 ± 47	-51	[17]
Heated patch	Lispro	T1DM patients	17	45 ± 28	78 ± 35	-42	-	-	-	[19]
Hyaluronidase	Lispro	Healthy controls	26	48.0 ± 8.0	97.5 ± 35.9	-51	114.0 ± 43.0	193 ± 58.2	-41	[21]
	Lispro	T1DM patients	22	30.0	49.0	-39	-	-	-	[22]
	Lispro	T2DM patients	21	43 ± 16	74 ± 36	-42	-	-	-	[23]
Linjeta	Lispro	Healthy controls	10	60.0 ± 43.0	66 ± 34	-9	136 ± 56	152 ± 30	-11	[26]
	Lispro	T1DM patients	43	31.6 ± 15.7	57.1 ± 21.8	-45	99.3 ± 53.9	118.0 ± 49.5	-16	[28]
Technosphere insulin	Regular	Healthy controls	5	14 ± 6	39 ± 36[§]	-64	-	-	-	[34]
	Regular	T2DM patients	13	17 ± 6	135 ± 68	-87	79 ± 47	293 ± 83	-73	[35]
Oral insulin	Regular	T2DM patients	16	100	220	-55	280	280	0	[41]
Buccal insulin	Lispro	Healthy controls	7	23.3 ± 5.2	83.3 ± 42.2	-72	44.2 ± 8.6	100.0 ± 35.6	-56	[47]
	Lispro	T1DM patients	6	26.7 ± 7.4	142.5 ± 73.2	-81	45.8 ± 22.7	145.0 ± 43.7	-68	[45]
Microneedle (1.5 mm)	Lispro	Healthy controls	10	40.6 ± 6.0	64.3 ± 18.0	-37	107.6 ± 11.4	130.0 ± 18.7	-17	[49]
	Lispro	T1DM patients	29	30.0	57.4	-48	-	-	-	[50]
Microneedle (0.9 mm)	Lispro	T1DM patients	5	27 ± 13	57 ± 20	-53	-	-	-	[51]

Data are shown as mean ± standard deviation.
[†]Syringe.
[‡]Insulin pen.
[§]Intravenous regular insulin.
T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; $T\text{-}GIR_{max}$: Time until maximal exogenous glucose infusion rate; $T\text{-}INS_{max}$: Time until maximal plasma insulin concentration.

prevents bruises and wet injections, in which the jet does not penetrate the skin. Jet injection results in a typical spray-like dispersion pattern in the subcutaneous area that differs from the drop-like pattern seen after injection with a syringe. The resultant larger surface area and increased permeation of the subcutaneous tissue both facilitate absorption of insulin into the circulation.

Early studies have already suggested that the absorption of neutral protamine Hagedorn or regular human insulin occurred faster when these insulins were administered using a jet injection rather than using a syringe [10–15]. Two studies have been published that investigated the use of jet injection for the administration of rapid-acting insulin analogs. A small study among four subjects showed that 30 units of lispro insulin were absorbed approximately twice as fast using jet injection compared with injection using a syringe [16]. In a larger study among 18 subjects, it was recently shown that jet injection advanced both pharmacokinetics and pharmacodynamics of a standardized dose of aspart insulin, using an insulin pen as a comparator [17]. Peak insulin levels were achieved after 31 min with jet injection versus 64 min after conventional pen injection ($p < 0.0001$). The maximal glucose-lowering effect, as derived from the glucose infusion rate needed to maintain euglycemia, was reached after 51 and 105 min, respectively **(Figure 1)**.

Injecting insulin with a jet injector has not been shown to be less painful than when an insulin pen is used. The pressure of the device on the skin may even be experienced as more inconvenient than the prick of a small needle. Sufficient training is required with the injection procedure to prevent wet injections and bruises. However, when trained properly, there is no indication that local complications are more frequent with jet injections than with conventional injections. An advantage of using jet injectors is that they can be applied for all insulins, although from a pharmacological point of view they appear to be appropriate for short-acting insulin (analogs).

■ Local heating of the skin

In daily practice, many patients with insulin-treated diabetes report advanced insulin action when the ambient temperature is elevated, such as in the summer, in tropical areas or during sauna visits [18]. Elevations of skin temperature typically result in vasodilation and increased tissue perfusion, which may promote absorption of subcutaneously injected insulin. This concept has been applied for the development of a heating pad attached to an insulin pump system that elevates skin temperature to 38.5°C for 30 min after an insulin bolus has been given. The device was recently tested in 17 pump-treated patients with Type 1 diabetes, who injected a standardized dose of their own rapid-acting insulin analog (either lispro or aspart) directly before a liquid meal. Local heating was reported to improve the pharmacokinetic profile of the insulin bolus with the time until maximal insulin concentration (T_{max}) being reduced by 42%. In addition, heating the skin resulted in a more shallow increase of postprandial glucose levels, a lower glucose peak and a significant reduction in postprandial glucose burden, as reflected by the 3-h area under the glucose curve [19]. The device and the heating were well tolerated by the patients. Studies that combine the heating pad to conventional insulin injections have not been published. Although there is no reason to believe that the concept of local heating would not promote insulin absorption to a similar degree when injected by pens or syringes, the practical execution appears rather cumbersome.

■ Coadministration of hyaluronidase

Hyaluronan is the main component contributing to the solidity of the extracellular matrix by transforming it into a gel-like substance that creates a barrier to large fluid flow. Recombinant human hyaluronidase (rHuPH20) is a soluble, neutral pH-activated substance that degrades hyaluronan and other glycosaminoglycans under physiologic conditions, thus promoting the permeation and absorption of subcutaneously injected drugs, including insulin [20]. In healthy volunteers, coadministration of rHuPH20 to regular or lispro insulin reduced the time to peak plasma insulin levels by ~50% **(Table 1)** [21]. Subsequent meal studies among patients with Type 1 [22] and Type 2 diabetes [23] confirmed the faster pharmacokinetics of both insulins when coadministered with rHuPH20. Coadministration with hyaluronidase was also associated with a lower area under the hyperglycemia excursion curves and – at least in patients with Type 2 diabetes – a reduced tendency towards hypoglycemia [23]. A remarkable, yet somewhat unexpected, finding was that coadministration of hyaluronidase reduced the intra- and inter-subject variability of pharmacokinetic and pharmacodynamic

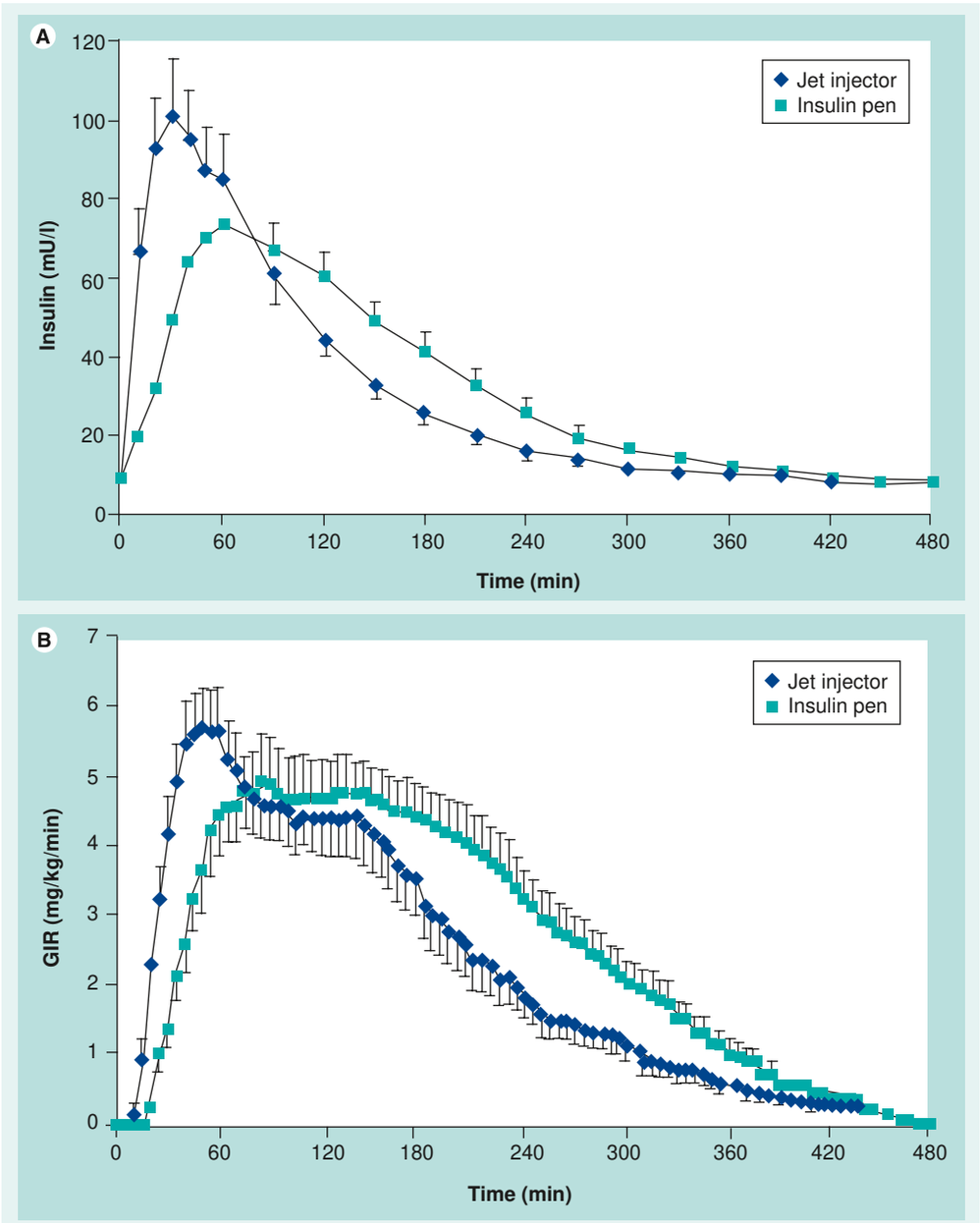


Figure 1. Pharmacokinetic and pharmacodynamic profile of aspart insulin. (A) Pharmacokinetic and **(B)** pharmacodynamic profile of aspart insulin injected by jet injector or a conventional insulin pen.
Reproduced from [17] with permission from the American Diabetes Association.

parameters [24]. Although no dose–response relationships were investigated, these findings suggest that disrupting the interstitial integrity may combat the concentration-related impediment of absorption of larger doses of insulin. Longer-term studies on the effect of adding rHuPH20 to the treatment with rapid-acting insulin analogs in patients with Type 1 or 2 diabetes are ongoing [25]. As with all new pharmacological treatments, extensive testing in randomized controlled trials of sufficient size is required to establish its efficacy and safety, so that the marketing of such a product cannot be expected in the next few years.

■ Addition of EDTA & citric acid

A different approach for faster insulin absorption is acheived by adding EDTA and citric

acid to regular human insulin, a formulation formerly known as VIAject™, but recently renamed Linjeta™. EDTA is a chelator of zinc, which may destabilize insulin hexamer formation by pulling out the zinc ions, whereas citric acid masks surface charges so that monomerization of insulin and subsequent absorption is facilitated. In a proof-of-concept study among ten healthy subjects, Linjeta was absorbed twice as fast as human soluble insulin and slightly faster than lispro insulin **(Table 1)**. After an injection of Linjeta, maximal glucose-lowering action was also reached faster than after regular insulin or lispro insulin [26]. In a meal study, use of Linjeta resulted in slightly flatter postprandial glucose excursions than did the use of regular or lispro insulin [27]. Injection site pain and irritation reported by participants were thought to be caused by the acidity of the product (pH ~4.0). The product was, therefore, recently reformulated to a neutral pH, which was shown to be bioequivalent to the original. Nevertheless, the frequency of injection site discomfort did not differ between the two formulations and was still higher in comparison to lispro insulin [28].

Alternative routes of insulin administration

■ Inhaled insulin

In 1925, Gaensslen envisaged delivering insulin through inhalation rather than by injection [29]. The large surface area (~140 m^2), rich perfusion and highly permeable monolayer of epithelium (0.1–0.2 µm) of the alveoli, combined with the absence of peptidases and proteolytic enzymes and the general immunotolerance of the lungs all facilitate the absorption of small peptides such as insulin [30].

Exubera® was the first – and thus far the only – inhaled insulin to have acquired approval from the US FDA and EMEA for the treatment of diabetes. The pharmacokinetic profile of Exubera was very similar to that of rapid-acting insulin analogs, except that the duration of hyperinsulinemia lasted longer with Exubera. The bioavailability of Exubera was only ~10% [31]. In clinical trials among patients with Type 1 or 2 diabetes, the use of Exubera, in conjunction with long-acting subcutaneous insulin if necessary, was about as effective as rapid-acting insulin analogs in maintaining glycemic control. However, a meta-analysis calculated a small but significantly lower HbA1c with subcutaneous insulin [32]. In 2008, Exubera was withdrawn from the market because sales were hugely lagging behind expectations [33]. Shortly thereafter, most other companies stopped their inhaled insulin development programs, supposedly for the same reason.

Technosphere® insulin (Afrezza®) is currently the only inhaled insulin product still under development and is awaiting approval by the FDA. Technosphere insulin is a dry powder, in which the inhaled insulin is encapsulated in microparticles. These microparticles rapidly dissolve after entering the alveolar space to release the insulin. The bioavailability of Technosphere insulin is approximately threefold greater than that of Exubera, and the absorption occurs much faster. Under euglycemic clamp conditions, the time-to-peak insulin concentration after inhalation was approximately 15 min and the time to maximal glucose-lowering effect was 39 min [34,35]. Technosphere insulin three-times daily in combination with glargine was equivalent to premixed insulin (bi-aspart) twice daily with respect to glycemic control in patients with Type 2 diabetes, but at lower risk of severe hypoglycemia and weight gain [36]. In a recent study of 130 patients with Type 1 diabetes who used glargine as basal insulin, 16 weeks of Technosphere insulin was as effective as lispro insulin in lowering HbA1c levels at a slightly lower risk of moderate hypoglycemia [37]. Technosphere is inhaled through a specifically designed breath-activated handheld inhaler, which is smaller than an insulin pen. Apart from a dry cough after inhalation that usually abates after weeks to months and an initial small decline in pulmonary function, Technosphere insulin is generally well tolerated [38]. Although studies of intermediate duration have not revealed an increased risk of pulmonary malignancies, inhaled insulin cannot be prescribed to smokers because of this concern.

■ Oral insulin

Oral insulin has the potential advantage over subcutaneous administration and other routes of insulin delivery in that it is absorbed in the gut and transferred to the liver in much the same way as endogenously released insulin. In the liver, insulin stimulates storage of glucose entering the liver through the same route, so that no more than ~50% of insulin is released into the circulation. Due to this first-pass hepatic insulin extraction, peripheral hyperinsulinemia will

be substantially lower after oral administration compared with after parenteral administration. Several obstacles limiting the oral route include the acidic environment of the stomach, the presence of peptidases in the upper GI tract, the tight barrier of epithelial cells lining the gut wall and the thick mucus layer in which mucins tend to bind the insulin protein [39]. These obstacles are overcome, in part, by using enteric coating on the tablets and conjugation with absorption enhancers so that the portal vein can be accessed. Nevertheless, the biopotency (i.e., pharmacodynamic action) is only ~5% [40] so large doses are required to obtain a clinically meaningful glucose-lowering effect. It has been reported that peak insulin levels can be reached ~20 min after ingestion and the subsequent maximal fall in glucose occurs after ~40 min [39]. However, most studies have reported much slower onset of glucose-lowering action, comparable to that of subcutaneous regular insulin [41–44], questioning the applicability of current oral insulin's pharmacology. A more extensive review on oral insulin is provided elsewhere [39].

■ Buccal insulin

The buccal mucosa is highly vascularized, has low enzymatic activity, can easily be accessed and has a neutral, relatively stable pH, all of which enable drug absorption. However, the continuous flow of saliva and the great variation in permeability of the different oral mucosal areas make buccal insulin delivery a challenging undertaking. The relatively large particle size of buccal insulin causes it to jam in the upper airways when accidently inhaled. When buccal insulin is inadvertently swallowed, it is rapidly degraded in the stomach [39]. Oral-lyn™ is the only buccal insulin under development that has been tested in humans. Each puff contains 10 units of insulin, which corresponds to ~1 unit of subcutaneous insulin (bioavailability of ~10%). Oral-lyn is more rapidly absorbed than a subcutaneous injection of regular insulin or a rapid-acting insulin analog, with plasma insulin levels typically peaking after 25–40 min and returning to baseline values in as early as 90 min [45–47]. A second round of puffs may therefore be required to achieve a long-lasting glucose-lowering effect. Oral-lyn has already been marketed in a number of countries, including India and Ecuador, even though sufficiently large clinical studies to establish its efficacy and safety have not been conducted [39].

■ Microneedles

Transdermal delivery of insulin by microneedles is a promising new method of insulin administration. The dermis is highly vascularized and contains a dense network of lymph vessels. The regional capillaries also have thinner vessel walls and reduced endothelial barrier function, both of which promote absorption of small proteins, such as insulin [48]. Microneedles of various lengths with a diameter of 260 µm were all found to increase the rate of absorption of lispro insulin in human volunteers, as evidenced by reductions in the T_{max} of 28–44% in comparison to subcutaneous injection. Similarly, the time until maximal glucose-lowering effect was reduced by 14–18% when employing the microneedle technique [49]. Similar results have been obtained in patients with Type 1 diabetes [50,51]. In animals, the pharmacokinetic profiles of lispro and regular human insulin were almost superimposable when injected by microneedles [48], but this could not be reproduced in humans [50]. Whether microneedles are less painful than conventional subcutaneous injections by syringes or pens has not been fully elucidated.

Conclusion

Current insulin treatment falls short in achieving widely recommended glucose targets in the majority of patients with Type 1 and 2 diabetes. An important reason for this failure is the inability of current rapid-acting insulin analogs to control postprandial glucose excursions. Several products are currently under investigation for their ability to afford a more physiological time–action profile of prandial insulin. Although the techniques to achieve this goal differ widely, early pharmacokinetic and pharmacodynamic studies show promising data with respect to the rate of insulin absorption and insulin action. However, there are still many issues that remain to be investigated. First, data on longer-term efficacy of these products on parameters of glucose control, such as HbA1c, 24 h glucose variability and hypoglycemic events are largely unavailable, the only exception being inhaled insulin. This is important, because a more physiological time–action profile does not automatically translate to better glucose control and lower risk of hypoglycemia [6]. A second important issue concerns safety. This is especially relevant for products that use an alternative route of

administration, such as inhaled, oral or buccal insulin and for products with specific additives to promote faster absorption of subcutaneous insulin. Third, the reproducibility is an often overlooked but important issue for any new insulin entering the market. A product meant for administration several times a day for many years needs to have a reliable and predictable pharmacologic effect. Finally, the patient's perspective should not be forgotten. Ease-of-use and acceptability of the insulin product or device with which the insulin is administered greatly contributes to the success or failure of that product in daily practice.

Future perspective

Around 15 years ago, rapid-acting insulin analogs were introduced and rapidly conquered the insulin world. Good marketing by pharmaceutical companies apparently convinced many care providers that the quest for seeking the optimal formulation of prandial insulin replacement was over. Few realized that rapid-acting insulin analogs, although clearly the best available at the time, were still not very good at mimicking the physiological profile of endogenous insulin. Results from the aforementioned Cochrane review and patient experiences of not reaching target glycemia levels despite use of analogs have gradually persuaded clinicians and scientists that faster (i.e., more physiologic) insulin products are needed. As a consequence, many products are still in such an early stage of development that marketing cannot be expected in the next couple of years, if at all. It is doubtful whether the medical world is ready to welcome insulin products that use alternative routes of administration, as painfully illustrated by the Exubera story. Indeed, although Technosphere inhaled insulin is quite different from Exubera in many aspects, the FDA has still not approved it for the treatment of diabetes. The reason for this conservative point of view may be that subcutaneous insulin, despite its many shortcomings, has been proven to be highly effective and safe, even when used for a lifetime of diabetes. Therefore, improvements to the administration of subcutaneous insulin are the most likely candidates to obtain a sizable market share in the near future. As such, both Linjeta and coadministration of hyaluronidase to insulin are attractive concepts that, when proven to be safe, could advance the treatment of patients with diabetes. Jet injectors hold a similar promise for improving postprandial glucose control and can already be prescribed to patients, at least in Europe. As a consequence, more tailor-made individualized insulin treatments will become available for patients with Type 1 or insulin-requiring Type 2 diabetes in the near future.

Financial & competing interests disclosure

The author is the principal investigator of studies on insulin administration by jet injection. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 American Diabetes Association. Standards of medical care in diabetes – 2011. *Diabetes Care* 34(Suppl. 1), S11–S61 (2011).

2 Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of Type 2 diabetic patients: variations with increasing levels of HbA(1c). *Diabetes Care* 26, 881–885 (2003).

3 Cavalot F, Pagliarino A, Valle M *et al.* Postprandial blood glucose predicts cardiovascular events and all-cause mortality in Type 2 diabetes in a 14-year follow-up: lessons from the San Luigi Gonzaga Diabetes Study. *Diabetes Care* 34, 2237–2243 (2011).

4 Ceriello A, Hanefeld M, Leiter L *et al.* Postprandial glucose regulation and diabetic complications. *Arch. Intern. Med.* 164, 2090–2095 (2004).

5 Rodbard HW, Jellinger PS, Davidson JA *et al.* Statement by an American Association of Clinical Endocrinologists/American College of Endocrinology consensus panel on Type 2 diabetes mellitus: an algorithm for glycemic control. *Endocr. Pract.* 15, 540–559 (2009).

6 Siebenhofer A, Plank J, Berghold A *et al.* Short acting insulin analogues versus regular human insulin in patients with diabetes mellitus. *Cochrane Database Syst. Rev.* 2, CD003287 (2006).

▪▪ **Elegant comprehensive systematic review showing that combination insulin analog treatment was only marginally better than regular insulin treatment. The paper is often neglected because it invalidates the common belief that analogs provide better glycemic control.**

7 Howey DC, Bowsher RR, Brunelle RL, Woodworth JR. [Lys(B28), Pro(B29)]-human insulin. A rapidly absorbed analogue of human insulin. *Diabetes* 43, 396–402 (1994).

8 Heinemann L, Heise T, Jorgensen LN, Starke AA. Action profile of the rapid acting insulin analogue: human insulin B28Asp. *Diabet. Med.* 10, 535–539 (1993).

9 Mitragotri S. Current status and future prospects of needle-free liquid jet injectors. *Nat. Rev. Drug Discov.* 5, 543–548 (2006).

■ **Well written overview on the pros and cons of jet injection for parenteral drug administration.**

10 Taylor R, Home PD, Alberti KG. Plasma free insulin profiles after administration of insulin by jet and conventional syringe injection. *Diabetes Care* 4, 377–379 (1981).

11 Pehling GB, Gerich JE. Comparison of plasma insulin profiles after subcutaneous administration of insulin by jet spray and conventional needle injection in patients with insulin-dependent diabetes mellitus. *Mayo Clin. Proc.* 59, 751–754 (1984).

12 Halle JP, Lambert J, Lindmayer I *et al.* Twice-daily mixed regular and NPH insulin injections with new jet injector versus conventional syringes: pharmacokinetics of insulin absorption. *Diabetes Care* 9, 279–282 (1986).

13 Malone JI, Lowitt S, Grove NP, Shah SC. Comparison of insulin levels after injection by jet stream and disposable insulin syringe. *Diabetes Care* 9, 637–640 (1986).

14 Kerum G, Profozic V, Granic M, Skrabalo Z. Blood glucose and free insulin levels after the administration of insulin by conventional syringe or jet injector in insulin treated Type 2 diabetics. *Horm. Metab. Res.* 19, 422–425 (1987).

15 Lucas A, Ribas L, Salinas I, Audi L, Sanmarti A, Foz M. Insulin levels after injection by jet stream and disposable syringe. *Diabetes Care* 11, 298–299 (1988).

16 Sarno MJ, Bell J, Edelman SV. Pharmacokinetics and glucodynamics of rapid-, short-, and intermediate-acting insulins: comparison of jet injection to needle syringe. *Diabetes Technol. Ther.* 4, 863–866 (2002).

17 Engwerda EE, Abbink EJ, Tack CJ, de Galan BE. Improved pharmacokinetic and pharmacodynamic profile of rapid-acting insulin using needle-free jet injection technology. *Diabetes Care* 34, 1804–1808 (2011).

18 Koivisto VA. Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *Br. Med. J.* 280, 1411–1413 (1980).

■ **Original study determining the stimulating effect of skin warming on the absorption of subcutaneous insulin.**

19 Raz I, Weiss R, Yegorchikov Y, Bitton G, Nagar R, Pesach B. Effect of a local heating device on insulin and glucose pharmacokinetic profiles in an open-label, randomized, two-period, one-way crossover study in patients with Type 1 diabetes using continuous subcutaneous insulin infusion. *Clin. Ther.* 31, 980–987 (2009).

20 Muchmore DB, Vaughn DE. Review of the mechanism of action and clinical efficacy of recombinant human hyaluronidase coadministration with current prandial insulin formulations. *J. Diabetes Sci. Technol.* 4, 419–428 (2010).

■ **Provides a good overview on the concept of hyaluronidase to enhance insulin absorption.**

21 Vaughn DE, Yocum RC, Muchmore DB *et al.* Accelerated pharmacokinetics and glucodynamics of prandial insulins injected with recombinant human hyaluronidase. *Diabetes Technol. Ther.* 11, 345–352 (2009).

22 Hompesch M, Muchmore DB, Morrow L, Vaughn DE. Accelerated insulin pharmacokinetics and improved postprandial glycemic control in patients with Type 1 diabetes after coadministration of prandial insulins with hyaluronidase. *Diabetes Care* 34, 666–668 (2011).

23 Hompesch M, Muchmore DB, Morrow L, Ludington E, Vaughn DE. Improved postprandial glycemic control in patients with Type 2 diabetes from subcutaneous injection of insulin lispro with hyaluronidase. *Diabetes Technol. Ther.* 14(3), 218–224 (2012).

24 Morrow L, Muchmore DB, Ludington EA, Vaughn DE, Hompesch M. Reduction in intrasubject variability in the pharmacokinetic response to insulin after subcutaneous co-administration with recombinant human hyaluronidase in healthy volunteers. *Diabetes Technol. Ther.* 13, 1039–1045 (2011).

25 Vaughn DE, Muchmore DB. Use of recombinant human hyaluronidase to accelerate rapid insulin analog absorption: experience with subcutaneous injection and continuous infusion. *Endocr. Pract.* 17(6), 914–921 (2011).

26 Steiner S, Hompesch M, Pohl R *et al.* A novel insulin formulation with a more rapid onset of action. *Diabetologia* 51, 1602–1606 (2008).

27 Heinemann L, Hompesch M, Flacke F *et al.* Reduction of postprandial glycemic excursions in patients with Type 1 diabetes: a novel human insulin formulation versus a rapid-acting insulin analog and regular human insulin. *J. Diabetes Sci. Technol.* 5, 681–686 (2011).

28 Heinemann L, Nosek L, Flacke F *et al.* U-100, pH-neutral formulation of VIAject®: faster onset of action than insulin lispro in patients with Type 1 diabetes. *Diabetes Obes. Metab.* 14(3), 222–227 (2011).

29 Gaensslen M. Ueber inhalation von insulin. *Klin. Wochenschr.* 2, 71–72 (1925).

30 Owens DR. New horizons – alternative routes for insulin therapy. *Nat. Rev. Drug Discov.* 1, 529–540 (2002).

31 Rave K, Bott S, Heinemann L *et al.* Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. *Diabetes Care* 28, 1077–1082 (2005).

32 Ceglia L, Lau J, Pittas AG. Meta-analysis: efficacy and safety of inhaled insulin therapy in adults with diabetes mellitus. *Ann. Intern. Med.* 145, 665–675 (2006).

33 de Galan BE. Can inhaled insulin be used for the treatment of diabetes mellitus? *Expert Rev. Pharmacoecon. Outcomes Res.* 8, 33–42 (2008).

34 Steiner S, Pfutzner A, Wilson BR, Harzer O, Heinemann L, Rave K. Technosphere/ insulin – proof of concept study with a new insulin formulation for pulmonary delivery. *Exp. Clin. Endocrinol. Diabetes* 110, 17–21 (2002).

35 Rave K, Heise T, Heinemann L, Boss AH. Inhaled Technosphere insulin in comparison to subcutaneous regular human insulin: time action profile and variability in subjects with Type 2 diabetes. *J. Diabetes Sci. Technol.* 2, 205–212 (2008).

36 Rosenstock J, Lorber DL, Gnudi L *et al.* Prandial inhaled insulin plus basal insulin glargine versus twice daily biaspart insulin for Type 2 diabetes: a multicentre randomised trial. *Lancet* 375, 2244–2253 (2010).

37 Garg S, McGill JB, Rosenstock J *et al.* Technosphere® Insulin vs insulin lispro in patients with Type 1 diabetes using multiple daily injections. *Diabetes* 56(Suppl. 1), A917 (2011).

38 Raskin P, Heller S, Honka M *et al.* Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere insulin or usual antidiabetes treatment: a randomized trial. *Diabetes Obes. Metab.* 14(2), 163–173 (2011).

39 Heinemann L, Jacques Y. Oral insulin and buccal insulin: a critical reappraisal. *J. Diabetes Sci. Technol.* 3, 568–584 (2009).

■ **Provides a comprehensive state-of-the-art on oral and buccal insulin for the treatment of diabetes.**

40 Kapitza C, Zijlstra E, Heinemann L, Castelli MC, Riley G, Heise T. Oral insulin: a comparison with subcutaneous regular human insulin in patients with Type 2 diabetes. *Diabetes Care* 33, 1288–1290 (2010).

41 Luzio SD, Dunseath G, Lockett A, Broke-Smith TP, New RR, Owens DR.

The glucose lowering effect of an oral insulin (Capsulin) during an isoglycaemic clamp study in persons with Type 2 diabetes. *Diabetes Obes. Metab.* 12, 82–87 (2010).

42 Eldor R, Kidron M, Arbit E. Open-label study to assess the safety and pharmacodynamics of five oral insulin formulations in healthy subjects. *Diabetes Obes. Metab.* 12, 219–223 (2010).

43 Eldor R, Arbit E, Miteva Y, Freier R, Kidron M. Oral Insulin: Type I diabetes (T1DM) patient response upon pre-prandial administration. *Diabetes* 59(Suppl. 1), A141 2010.

44 Kipnes M, Dandona P, Tripathy D, Still JG, Kosutic G. Control of postprandial plasma glucose by an oral insulin product (HIM2) in patients with Type 2 diabetes. *Diabetes Care* 26, 421–426 (2003).

45 Cernea S, Kidron M, Wohlgelernter J, Raz I. Dose-response relationship of an oral insulin spray in six patients with Type 1 diabetes: a single-center, randomized, single-blind, 5-way crossover study. *Clin. Ther.* 27, 1562–1570 (2005).

46 Cernea S, Kidron M, Wohlgelernter J, Modi P, Raz I. Dose-response relationship of oral insulin spray in healthy subjects. *Diabetes Care* 28, 1353–1357 (2005).

47 Cernea S, Kidron M, Wohlgelernter J, Modi P, Raz I. Comparison of pharmacokinetic and pharmacodynamic properties of single-dose oral insulin spray and subcutaneous insulin injection in healthy subjects using the euglycemic clamp technique. *Clin. Ther.* 26, 2084–2091 (2004).

48 Harvey AJ, Kaestner SA, Sutter DE, Harvey NG, Mikszta JA, Pettis RJ. Microneedle-based intradermal delivery enables rapid lymphatic uptake and distribution of protein drugs. *Pharm. Res.* 28, 107–116 (2011).

49 Pettis RJ, Ginsberg B, Hirsch L *et al.* Intradermal microneedle delivery of insulin lispro achieves faster insulin absorption and insulin action than subcutaneous injection. *Diabetes Technol. Ther.* 13, 435–442 (2011).

50 Pettis RJ, Hirsch L, Kapitza C *et al.* Microneedle-based intradermal versus subcutaneous administration of regular human insulin or insulin lispro: pharmacokinetics and postprandial glycemic excursions in patients with Type 1 diabetes. *Diabetes Technol. Ther.* 13, 443–450 (2011).

51 Gupta J, Felner EI, Prausnitz MR. Rapid pharmacokinetics of intradermal insulin administered using microneedles in Type 1 diabetes subjects. *Diabetes Technol. Ther.* 13, 451–456 (2011).