review article

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The pharmacokinetics and pharmacodynamics of rapid-acting insulin analogues and their clinical consequences

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Postprandial glucose excursions can inhibit achievement of good glycaemic control, and possibly have a specific effect on the risk of vascular comorbidities. Rapid-acting analogues control these excursions better than human insulin because their pharmacokinetic/pharmacodynamic (PK/PD) profile is closer to that of meal-time endogenous insulin secretion. Review of the findings of PK/PD studies and clinical trials suggests that the three marketed rapid-acting analogues—insulin lispro, insulin aspart and insulin glulisine—are equally efficacious and safe. In comparison with human insulin when using the same basal insulin, they provide comparable glycaemic control with a reduced risk of hypoglycaemia, although the combination of rapid-acting and basal analogues reduces glycated haemoglobin (HbA_{1c}) more than human meal-time insulin combined with neutral protamine Hagedorn (NPH) insulin. Some studies have suggested that insulin glulisine has a slightly faster onset of action compared with insulin lispro or insulin aspart, but this has not been translated into demonstrable clinical benefit. Treatment satisfaction in patients with diabetes has been higher when therapy with a rapid-acting analogue is used instead of human insulin, perhaps due to differences in advised timing of injection. The largest benefits in efficacy, hypoglycaemia incidence, treatment satisfaction and quality of life have occurred when patients receive an all-analogue meal-time plus basal regimen as compared with an all-human insulin regimen. No new safety issues have been identified with the marketed rapid-acting analogues, and their insulin-like growth factor 1receptor affinity and mitogenic activity are comparable to human insulin.
Keywords: diabetes, insulin analogue, insulin aspart, insulin glulisine, insulin lispro, pharmacodynamics, pharmacokinetics

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Introduction

Postprandial glycaemic excursions can prevent people with diabetes from achieving their desired overall glycated haemoglobin (HbA_{1c}) target [1], and thus possibly increases their risk of vascular comorbidities [2]. Rapid-acting insulin analogues were developed to better control these excursions by achieving a pharmacokinetic (PK) profile more similar to meal-time endogenous insulin than human unmodified insulin does. Clinical laboratory studies have confirmed that rapid-acting insulin analogues do indeed have a PK profile closer to that of the normal meal-time insulin excursion, with a faster rise in plasma concentration, higher peak concentration and shorter subcutaneous residence time than unmodified human insulin [3–5]. The pharmacodynamic (PD) profile of the rapid-acting insulin analogues is also more similar to the physiological effect of endogenous insulin than subcutaneous human insulin, with smaller postprandial glycaemic excursions. They also show less within-patient variability [3–6].

There are currently three rapid-acting analogues marketed in the USA and Europe: insulin lispro (Humalog®; Eli Lilly, Indianapolis, IN, USA), insulin aspart (Novolog®/NovoRapid®; Novo Nordisk, Bagsvaerd, Denmark) and insulin glulisine (Apidra®; Sanofi, Paris, France). Currently in clinical development is another injectable form of rapid-acting insulin known as Linjeta™, formerly called VIAject® (Biodel, Danbury, CT, USA). This pharmaceutical agent contains unmodified human insulin in a proprietary formulation that showed more rapid subcutaneous absorption and thus onset of action compared with unmodified human insulin in a small PK/PD study [7]. Evidence from larger trials or comparisons with available rapid-acting analogues has not been published. An inhaled form of human insulin, Technosphere® insulin (AFREZZA® or Afresa; MannKind, Valencia, CA, USA), is also under development, but few studies have been published. In a small PK/PD study with 11 non-diabetic volunteers, Technosphere® insulin had a more rapid onset and completion of absorption than subcutaneous injection of unmodified human insulin [8]. The limited volume of published data about rapid-acting products in development for oral and buccal delivery of insulin has been summarized elsewhere [9]. The most forward of these products appear to be the oral insulin analogue IN-105 (Biocon Limited, Bangalore, Karnataka, India) and an oral spray formulation of regular human insulin known as Oral-lyn™ (Generex Biotechnology Corporation, Toronto, ON, Canada), which is commercially available in India, Algeria, Lebanon and Ecuador.

In this review, the PK/PD profiles of insulin lispro, insulin aspart and insulin glulisine will be examined together with the results from clinical trials to determine if there is any clinically

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significant difference in efficacy, tolerability, safety or treatment satisfaction between them.

Methods

Data for this review were collected through systematic PubMed searches, covering the period from 2000 to 2010. Search terms included diabetes, human insulin, insulin analog/analogue, insulin aspart, insulin lispro, insulin glulisine, postprandial glucose, bolus and rapid-, fast- and short-acting insulin, pharmacodynamic and pharmacokinetic. References from retrieved publications provided additional material and were used to expand the period of time from which data were assembled. A total of 19 papers were identified with results of PK/PD studies for rapid-acting analogues: 11 for insulin lispro [10–20], 10 for insulin aspart [13–17,21–25] and 9 for insulin glulisine [11,18–20,23,24,26–28]. Some studies included more than one analogue. Six of the total were not euglycaemic glucose clamp studies [13,14,19,24,25,27]. The study population comprises people with type 1 diabetes in nine studies [10,13,15–17,20,21,26,27], healthy or obese non-diabetic people in eight studies [11,12,14,18,22,23,25,28] and obese people with type 2 diabetes in two studies [19,24]. Research activity in this area, clinical experience in helping people with all types of diabetes and involvement in diabetes guideline development aided analysis and interpretation of the findings.

Structure and PK/PD Profile of Rapid-acting Insulin Analogues

The molecular structures of insulin lispro, insulin aspart and insulin glulisine, which allow them to be absorbed more quickly than unmodified (regular) human insulin, differ only slightly from human insulin, with two amino acid changes for insulin lispro and insulin glulisine and one for insulin aspart (figure 1). The principal site of change is towards the end of the insulin B-chain, and these changes destabilize hexamerization. Accordingly after subcutaneous injection, dissociation to dimers and monomers occurs, and these are rapidly absorbed compared with human insulin whose hexamers dissociate relatively slowly [10,11,21,29].

The pharmaceutical formulation of the three analogues may have some effect upon their comparative PK/PD profile, as discussed below. The formulation of insulin lispro and insulin aspart is similar: each contains glycerin, metacresol, zinc and phenol. For insulin lispro and insulin aspart, the buffer is disodium hydrogen phosphate [30,31]. Glulisine, however, contains metacresol, tromethamine, sodium chloride and polysorbate 20, the latter to ensure its pharmaceutical stability in the absence of zinc [32].

Because clearance of insulin from plasma has a very short half-life (4–5 min), plasma insulin concentrations at any time closely follow and reflect the absorption rate from the subcutaneous depot. More rapid insulin absorption from the same subcutaneous insulin pool (dose) means that insulin concentrations rise more quickly and to a higher peak. As the subcutaneous pool is thus more quickly depleted, peak absorption rate is passed earlier and plasma concentrations accordingly fall rapidly in concert. Assuming that bioavailability is the same and thus nearly all of injected insulin—whether analogue or human—is absorbed into the circulation, the total area under the plasma concentration curves will be similar.

The results of PK studies (examples in figure 2) illustrate that, when tested in people with type 1 diabetes, the peak plasma concentration of rapid-acting analogue insulins is approximately double that of human insulin, and that their time to maximum concentration is approximately less than half that of human insulin [10,21,26]. Having passed peak levels, concentrations fall more rapidly, as expected, returning to levels <20% of peak concentrations at about 4 h, at a time when human insulin absorption is still continuing (figure 2).

The comparative area under the insulin concentration curve varies from study to study. A compounding problem here is standardization of insulin assays, which can have different immunospecificity for human insulin compared with the analogues. Overall, however, and despite a faster absorption rate, the total blood availability of the three analogues is comparable with human insulin because the absorption of human insulin and subsequent elimination through the insulin receptor takes place over a longer time period. Thus, both subcutaneous and whole-body residence time of a human insulin dose will be longer. In some insulin aspart studies, there appears to be significantly greater area under the insulin concentration time curve compared with human insulin [figure 2B: 71.0 ± 39.6 nmol/l/min vs. 52.9 ± 29.6 nmol/l/min (0–6 h); $p < 0.001$], but the control human insulin profiles appear unusually flat, and thus much of the area under the

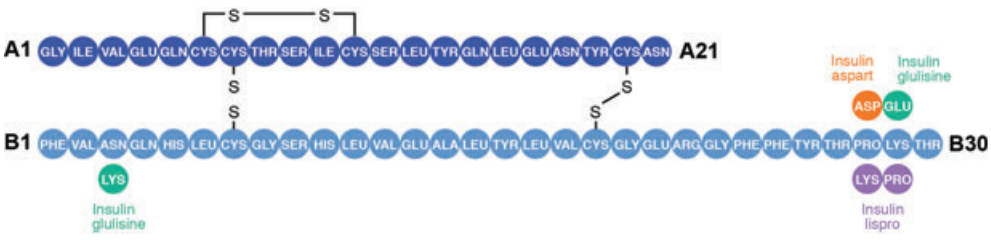

Figure 1. Molecular structures of insulin lispro, insulin aspart and insulin glulisine created by amino acid modifications of human insulin: for insulin lispro, proline and lysine at positions 28 and 29 on the B-chain of human insulin are reversed; for insulin aspart, proline at position 28 on the B-chain of human insulin is replaced with aspartic acid and for insulin glulisine, asparagine at position 3 on the B-chain is replaced with lysine, and lysine at position 29 on the B-chain is replaced with glutamic acid.

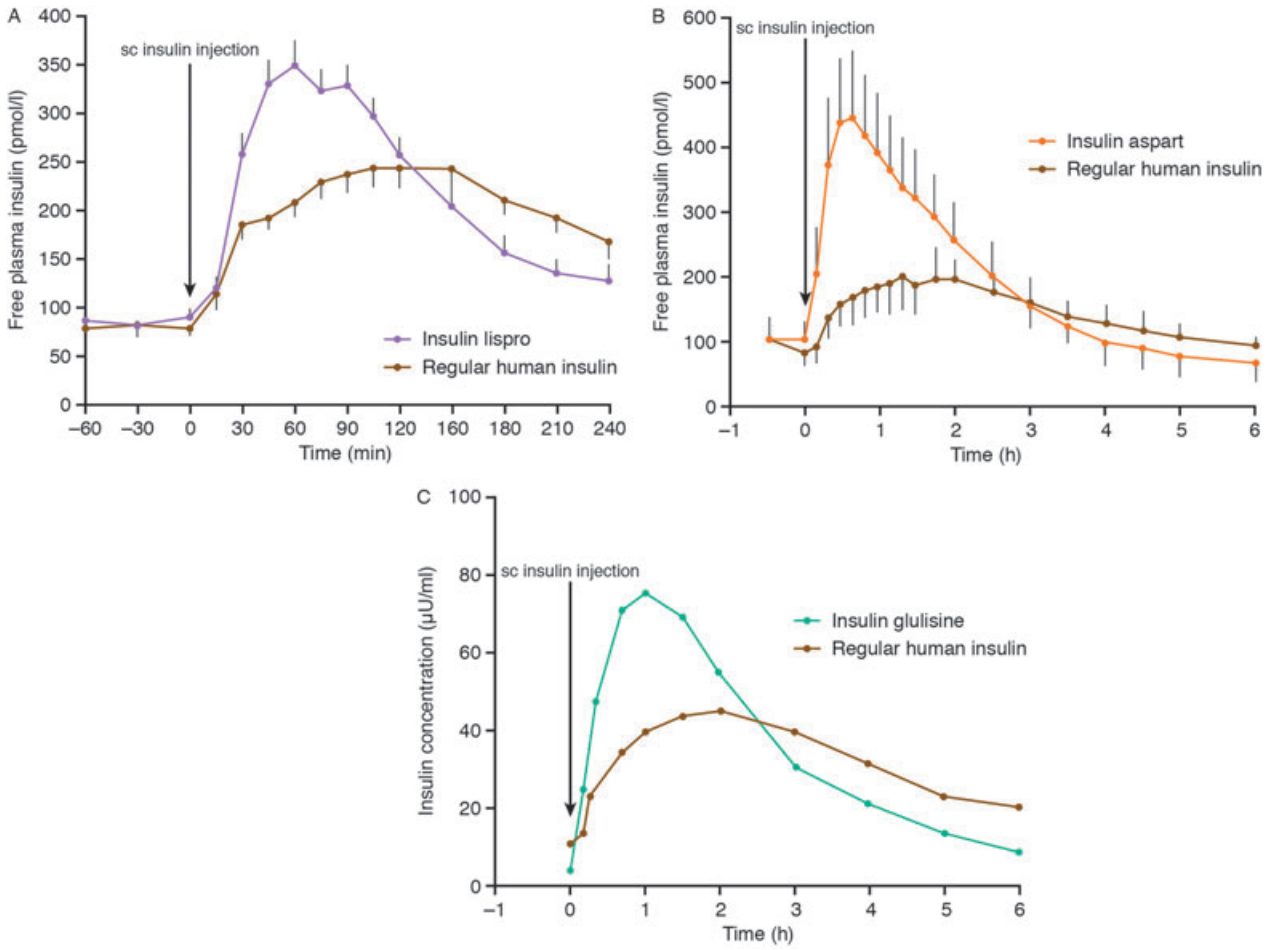

Figure 2. Pharmacokinetics (serum insulin levels) after subcutaneous (sc) injection of (A) insulin lispro (Adapted with permission from Ref. [10]), (B) insulin aspart (Adapted with permission from Ref. [21]) and (C) insulin glulisine (Adapted with permission from Ref. [26]), all versus human insulin in people with type 1 diabetes.

control curve is beyond the time span of the study. For insulin lispro and insulin glulisine administered simultaneously, the area under the absorption curves appears very similar to human insulin in the same study [figure 2: insulin lispro 52.9 ± 3.2 µmol/l × 240 min vs. −48.8 ± 3.3 µmol/l × 240 min, not significant (NS); insulin glulisine: 11.9 mU/l × min vs. 11.5 mU/l × min; statistical significance not reported] [10,21,26].

PD data, in terms of glucose excursions, are presented in Table 1 and show that rapid-acting analogues, when compared to human insulin administered at the same time (immediately before a meal), lead to a significantly lower peak postprandial glucose excursion, time to peak and total glucose excursion (area under curve) for the period 0–4 h, or 0–2 h in the case of insulin glulisine. However, when human insulin is administered 30 min before a meal, these differences are partly ameliorated [10,21,26].

It is this type of data that leads to the conclusion that the minor amino acid structural alterations of insulin analogues permit them to be administered immediately before a meal, when the recommendation for human insulin continues to be that it should ideally be given 30 min before a meal. However, it remains unknown whether administration of rapid-acting analogues 15–30 min before a meal would further ameliorate subsequent glucose excursions, albeit with a possibly enhanced risk of periprandial hypoglycaemia.

Because of the similarity in PK/PD profiles, directions for administering the rapid-acting analogues are virtually identical. In Europe, they should be injected shortly before a meal or soon thereafter [33–35], while in the USA, insulin lispro is recommended to be injected within 15 min before or after a meal, insulin aspart 5–10 min before a meal, and insulin glulisine 15 min before or 20 min after starting a meal [30–32].

The site of subcutaneous injection also has a significant influence upon the PK of rapid-acting insulins. Injections in the abdominal region produce the highest plasma insulin concentration at the earliest maximum time compared with injections in the arm, thigh or buttocks [12,22,36]. Overall blood glucose lowering, however, is not affected [12,22]. Consequently, abdominal-wall injections are usually advised when a rapid onset of effect and limited duration of action are desirable, as will usually be the case for prebreakfast injections in particular.

A single study, performed in elderly patients, suggests that avoiding skin affected by lipodystrophy (now rare) can improve

Table 1. Meal-time glucose excursions for insulin lispro, insulin aspart and insulin glulisine when compared separately in people with type 1 diabetes with unmodified human insulin.

Lispro study [10]		Aspart study [21]			Glulisine study [26]		
Insulin type and time of injection (min)							
Human (0 min)	Lispro (0 min)	Human (0 min)	Human (−30 min)	Aspart (0 min)	Human (0 min)	Human (−30 min)	Glulisine (0 min)
Baseline blood glucose concentration (mmol/l)							
6.7 ± 0.2	6.7 ± 0.2	5.0–8.0	5.0–8.0	5.0–8.0	6.7	6.7	6.6
Maximum glucose concentration (mmol/l)							
11.9 ± 2.8	9.9 ± 1.4*	16.4 ± 3.4	14.5 ± 3.5	13.5 ± 3.5†, ‡	4.9	3.6	3.6
Time to maximum glucose excursion (min)							
66 ± 37	41 ± 7*	105 (60–120)	105 (105–120)	60 (40–150)‡, §	70‖	115‖	48‖
Glucose excursion AUC (mmol/l × h)¶							
37.7 ± 11.3	29.3 ± 5.7**	21.9 ± 8.5	18.4 ± 9.5	14.9 ± 8.7††, ‡‡	18.6	14.5	15.5

Differences should only be assessed within study, as comparator (human insulin) findings vary between study due to study conditions such as meal administered, basal insulin supply and pharmacokinetic parameters measured. Data are mean ± standard deviation (where available) or median (95% confidence interval) unless marked otherwise. Values shown for insulin lispro and insulin glulisine represent total glucose concentration, while values for insulin aspart are baseline subtracted. AUC, area under the curve; NS, not significant.

*$p < 0.05$.

†$p < 0.001$.

‡NS compared to human at −30 min; p-values not available for the glulisine study.

§NS compared to human at 0 min.

‖Median.

¶0–4 h, except glulisine study 0–2 h.

**$p < 0.01$.

††$p < 0.0001$ compared to human at 0 min.

‡‡$p < 0.02$.

the metabolic effect of insulin glulisine as injections into lipodystrophic areas slow insulin absorption, leading to higher and more variable glucose values [27].

Comparison of PK/PD Activity Between Rapid-acting Insulin Analogues

In studies that have directly compared the absorption rate and glucose control of one rapid-acting insulin analogue with another, few PK/PD differences have been noted. Of five studies that compared insulin lispro and insulin aspart, only two detected a significant difference [13–17]. In one of them, a randomized, crossover trial in 14 people with type 1 diabetes, subcutaneous injection of insulin lispro reached maximum insulin concentration significantly earlier than insulin aspart ($p = 0.02$) and declined to 50% of the peak insulin concentration significantly earlier ($p = 0.02$) [13]. Maximum insulin concentrations were similar, however, and there was no difference in blood glucose profiles. With both analogues, the peak glucose excursion occurred 40 min after injection and the total area under the glucose curve was the same. The data from this study suggest that the two analogues are equally effective at controlling postprandial glucose levels. In the other study that reported a significant difference between insulin lispro and insulin aspart, which was also a randomized, crossover trial but with 20 healthy volunteers, maximal reduction of plasma glucose occurred at 50 min with insulin aspart and at 60 min with insulin lispro [14]. In addition, insulin aspart led to a higher maximal serum concentration of insulin than insulin lispro (24.6 ± 1.3 mU/l vs. 20.8 ± 1.1 mU/l, $p = 0.032$). However, since this study did not report total area under the glucose curve, it is impossible to determine whether there was any overall difference in blood glucose profiles. The other three studies concluded that the effect of insulin lispro and insulin aspart upon blood glucose is similar, and they did not detect a difference in time to maximum insulin concentration [15–17]. In one of these studies with 24 people with type 1 diabetes, the time to maximum insulin concentration was 46.7 ± 4.7 min with insulin lispro and 43.8 ± 3.9 min with insulin aspart ($p = 0.66$) [15]. The 50% decline from peak concentration was 116 ± 10 and 113 ± 9 min, respectively (NS).

In most published PK/PD studies comparing insulin glulisine with either insulin lispro or insulin aspart, insulin glulisine has appeared to have a faster onset of action than the two other analogues [11,18,19,23], especially in obese patients [body mass index (BMI) 30–40 kg/m^2] [19,24]. However, the overall plasma glucose profiles of insulin glulisine and the two other rapid-acting analogues in the published studies again appear to be similar [11,18–20,23,24].

In the largest of the studies comparing insulin glulisine with another rapid-acting analogue, 80 non-diabetic people, divided evenly into four groups according to BMI (<25, ≥25 to <30, ≥30 to <35 and ≥35 kg/m^2), were randomized to receive a single injection of 0.2 or 0.4 U/kg insulin glulisine or insulin lispro on four separate days while undergoing a glucose clamp [18]. At both dose levels, the 10-h total glucose requirement (0.2 U/kg: insulin glulisine vs. insulin lispro: 1.57 ± 0.52 g/kg vs. 1.54 ± 0.51 g/kg; 0.4 U/kg: 2.56 ± 0.81 g/kg vs. 2.46 ± 0.76 g/kg), maximum metabolic activity

(0.2 U/kg: 5.8 ± 2.1 vs. mg/kg/min 5.9 ± 2.6 mg/kg/min; 0.4 U/kg: 8.4 ± 2.9 mg/kg/min vs. 8.3 ± 3.0 mg/kg/min) and the time to maximum metabolic activity (0.2 U/kg: 190 ± 75 min vs. 171 ± 53 min; 0.4 U/kg: 196 ± 73 min vs. 198 ± 65 min) were similar. The only apparent difference between the analogues was a slightly more rapid onset of action with insulin glulisine, as it required a higher glucose infusion rate in the first hour than insulin lispro [0.2 U/kg: 102 ± 75 mg/kg vs. 83 ± 73 mg/kg ($p < 0.05$); 0.4 U/kg: 158 ± 100 mg/kg vs. 112 ± 71 mg/kg ($p < 0.001$)]. The faster onset of action of insulin glulisine was observed in all BMI groups in this study, but average glucose control was the same for both analogues over 10 h. A similar result was found when 12 healthy volunteers received 0.2 U/kg of insulin glulisine or insulin aspart under euglycaemic clamp conditions [23]. The glucose infusion rate area under the curve in the first 30 min was higher at 30.3 ± 26.4 mg/kg with insulin glulisine compared with 16.2 ± 18.4 mg/kg for insulin aspart ($p = 0.042$). The overall metabolic effect, however, was the same with similar total glucose infusion rate area under the curve results (2.17 ± 0.72 mg/kg vs. 2.26 ± 0.59 mg/kg, respectively; NS).

The authors of that study suggested that the zinc-free formulation of insulin glulisine is the reason for the faster onset of action compared with insulin lispro and aspart, as other authors have done [11,18,19,23]. For product stability between manufacture and therapeutic application, insulin lispro and insulin aspart are formulated with zinc to promote hexamer formation, whereas insulin glulisine is stabilized with polysorbate 20. The zinc may delay the absorption and action of insulin lispro and insulin aspart by slowing down their disassociation into monomers after injection, as has indeed been observed in a developmental study of insulin lispro [37]. It has also been suggested that the unique formulation of insulin glulisine may perform better among obese patients because a zinc-free analogue might more quickly penetrate subcutaneous fat [11]. While this is consistent with insulin glulisine showing faster onset of activity within the first hour compared with insulin lispro, and within the first 30 min compared with insulin aspart, as yet this has not been shown to produce differences in clinical efficacy [11,18,19,23].

Efficacy and Hypoglycaemia in Clinical Trials

The data from randomized-controlled clinical trials have, in general, substantiated the findings of the PK/PD studies with rapid-acting analogues. Thus, the faster absorption and quicker onset of glucose-lowering activity shown in the clinical laboratory studies have led to significantly lower postprandial glucose excursions when compared with meal-time human insulin in adults and children, and in type 1 and type 2 diabetes [4,38–48]. The decreased incidence of major hypoglycaemia requiring third-party assistance, in particular major nocturnal hypoglycaemia, which has been sometimes observed in clinical trials by comparison with unmodified human insulin, is the expected consequence of the shorter subcutaneous residence time of rapid-acting analogues [4,38,42,43,46].

Despite lowering postprandial glucose levels more than unmodified human insulin, the overall efficacy of rapid-acting analogues on HbA_{1c} has been found to be comparable to human insulin in the clinical trials, with modest but statistically significant superiority in some studies [38–40,47–50]. Meta-analyses have concluded that rapid-acting analogues confer either no additional benefit in glycaemic control, or a minor one, for the majority of people with diabetes compared with human insulin [51,52]. However, their use is recommended, especially when hypoglycaemia is an issue, due to a reduced risk of hypoglycaemia [53–55]. In people with type 1 diabetes, the median incidence of severe hypoglycaemia for rapid-acting analogues is 21.8 episodes per 100 person-years compared with 46.1 episodes for human insulin [52]. In people with type 2 diabetes, the median incidence is 0.3 episodes per 100 person-years for analogues compared with a median of 1.4 episodes per 100 person-years for human insulin [52].

When study participants have received an all-analogue basal–bolus therapy, in comparison with an all-human insulin or mixed analogue human insulin basal–bolus therapy, greater reductions in HbA_{1c} and hypoglycaemia have been reported [56–58]. In an analysis of 2923 people with type 1 or 2 diabetes participating in the observational, open-label Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE™) study, who switched to insulin detemir plus a rapid-acting insulin or human insulin from another basal–bolus therapy, the greatest improvement in HbA_{1c} was seen in people who received an all-analogue regimen after previously being treated with an all-human insulin regimen [56]. This group also experienced a large reduction in the mean incidence of hypoglycaemia from 42.4 to 20.3 episodes per patient-year for a mean difference of −22.1 episodes per patient-year ($p < 0.001$). The rate of nocturnal hypoglycaemia was also reduced from 11.8 to 2.1 episodes per patient-year for a mean difference of −9.9 episodes per person-year ($p < 0.001$) [56].

In a 32-week crossover study with just 56 participants, in which they were randomized to an all-analogue (insulin glargine plus insulin lispro) or all-human insulin basal–bolus therapy for 16 weeks before switching to the other regimen, HbA_{1c} was significantly lower with the all-analogue regimen compared with the human insulin regimen [7.5% vs. 8.0% (58 mmol/mol vs. 64 mmol/mol), $p < 0.001$] with a 15% lower postprandial glucose area under the curve ($p = 0.002$) [57]. Although the number of episodes of symptomatic hypoglycaemia was comparable between the treatments (1277 for analogue vs. 1327 for human), the monthly rate for nocturnal hypoglycaemia was reduced by 44% during analogue treatment (0.7 vs. 1.2 episodes/month respectively, $p < 0.001$) [57].

In comparisons of rapid-acting analogues and human insulin when administered in biphasic formulations, biphasic analogue insulins have provided a more physiological insulin profile, as expected, lowering postprandial glucose excursions more than biphasic human insulin [59–65]. In some of these studies, lower rates of nocturnal and major hypoglycaemia have also been reported [59–62,66]. For example, in a meta-analysis of nine randomized, parallel or crossover trials comparing biphasic insulin aspart and biphasic human insulin, no significant difference was found in HbA_{1c} between treatments.

However, biphasic analogue treatment was associated with reduced postprandial glucose levels averaged over breakfast, lunch and dinner [treatment difference, −0.31; 95% confidence interval (CI), −0.49 to −0.07 mmol/l; $p < 0.01$]. In addition, although rates of overall hypoglycaemia were not significantly different between treatments, with biphasic analogue treatments there were significantly lower rates for nocturnal hypoglycaemia (relative risk = 0.50; 95% CI, 0.38–0.67; $p < 0.01$) and major hypoglycaemic events (odds ratio = 0.45; 95% CI, 0.22–0.93; $p < 0.05$) [62].

Comparative Efficacy of Rapid-acting Analogues in Clinical Trials

In the few direct reported comparisons of rapid-acting analogues in clinical trials, they appear to show equivalent glycaemic control and frequency of hypoglycaemia [67–72]. During a 26-week study in which 672 people with type 1 diabetes were randomized to insulin lispro or insulin glulisine, the mean change in HbA_{1c} was −0.1% (1 mmol/mol) in both treatment groups, and there was no difference in reported hypoglycaemia [67]. In another randomized comparison of insulin lispro and insulin glulisine, mean HbA_{1c} increased by 0.1% (1 mmol/mol) in the glulisine group ($n = 132$) and by 0.0% (0 mmol/mol) in the insulin lispro group ($n = 135$) with a similar safety profile after 28 weeks [68]. Comparisons between insulin aspart, insulin lispro and insulin glulisine when delivered by continuous subcutaneous insulin infusion in adults and children with type 1 diabetes indicate that the rapid-acting analogues are equally effective at reducing blood glucose, and equally safe [69–73].

Treatment Satisfaction and Quality of Life

In addition to efficacy and safety, two other aspects of insulin therapy that should be considered when comparing rapid-acting analogues with human insulin are treatment satisfaction and quality of life, as these can play an important role in treatment adherence and clinical outcome [74]. When treatment satisfaction or quality of life have been measured, studies show that people respond more positively to treatment with rapid-acting analogues than human insulin. However, a caveat here is that the premeal timing of advice for rapid-acting analogues may result in a preference for them over inconvenient earlier administration of short-acting human insulin, and because of this timing difference most studies are open-label and new product bias becomes an unmeasurable possibility.

In a 3-month study of 423 people with type 1 diabetes who received meal-time insulin aspart or human insulin, HbA_{1c} was decreased 0.2% (2 mmol/mol) with insulin aspart ($p < 0.05$), with no difference in hypoglycaemia incidence. However, in responses to the Diabetes Treatment Satisfaction Questionnaire (DTSQ), people perceived therapy with insulin aspart to be more flexible ($p = 0.022$) and with a lower hypoglycaemia risk ($p = 0.005$) [40].

Other studies have noted a similar personal preference for rapid-acting analogues over human insulin where the efficacy and safety between treatments appeared to differ little [38,45,75], including studies in children [44,76]. In a 64-week study with 368 people with type 1 diabetes randomized to meal-time insulin aspart or human insulin, there were no significant differences in overall HbA_{1c}, hypoglycaemia or adverse events, although postprandial glucose was lower with insulin aspart. Nevertheless, at the end of the study, treatment satisfaction was significantly higher in the insulin aspart group ($p = 0.004$), despite high baseline DTSQ satisfaction scores (28 for both groups, on a scale of 0–36) [45].

When changes in health-related quality of life have been measured, the differences between analogue and human insulin treatment have been less apparent than the differences observed in treatment satisfaction [45,74]. A significant improvement in treatment appeared in the Diabetes-Specific Quality of Life Scale (DSQOLS) score on dietary restrictions ($p < 0.01$) during a 6-month study with 424 people with type 1 diabetes receiving either meal-time insulin aspart or human insulin. This study indicated that participants using the rapid-acting analogue felt less dietary restriction, which perhaps accounted for the reason why overall blood glucose control was not improved [74].

Overall health-related quality of life appears to be particularly improved with meal-time rapid-acting analogues when a long-acting basal insulin analogue is also used. In a crossover study, 56 patients with type 1 diabetes were randomized to insulin glargine in the evening plus insulin lispro at meals, or to NPH insulin once or twice a day plus human insulin at meals for 16 weeks before switching treatments [77]. After 32 weeks, the quality of life score, as measured by the Audit of Diabetes Dependent Quality of Life (ADDQoL) questionnaire, rose significantly during analogue treatment from a baseline of 1.3 to 1.6 points, while it remained the same with human insulin treatment for a between-treatment difference of 0.3 ($p = 0.014$). Treatment satisfaction was also greater in the analogue group with a DTSQ score difference between responses for analogue and human insulin regimens of 8.6.

Mitogenic Activity

Concerns over mitogenic activity of rapid-acting analogues arose in the 1990s after the finding that B10-Asp human insulin induced mammary tumours in rats [78]. Although this insulin showed increased mitogenic activity in some cell lines, it had a number of other unusual receptor-binding properties, of which the most problematic may have been its very slow insulin receptor dissociation rate [79]. However, interaction with the growth factor receptor and thus mitogenic activity is easier to conceptualize, leading to concentration on comparative analogue properties in this area, and controversy with regard to long-acting insulin analogues with di-basic amino acid extensions to the B-chain [80].

Laboratory studies of rapid-acting analogues, however, have shown that insulin lispro, insulin aspart and insulin glulisine produce molecular and biological effects similar to human insulin [81–83]. Thus, the rapid-acting analogues have an insulin-like growth factor 1 receptor affinity and ability to stimulate mitogenesis not different from human insulin. The results of clinical studies support these laboratory findings [81,82]. In an observational study of 127 031 people with diabetes who were treated with human insulin, insulin aspart, insulin lispro or insulin glargine, after a mean follow-up

time of 1.63 years, no increased cancer risk was observed with the rapid-acting analogues compared with human insulin [80]. Another retrospective observational study that examined the cancer risk of various glucose-lowering medications in 62 809 people with type 2 diabetes found no increased cancer risk for analogues in comparison to human insulin [84].

Conclusions

It is clear that rapid-acting analogues have a PK/PD profile that is superior to human insulin for controlling postprandial glycaemic excursions, and that in short- to medium-term clinical trials this translates into a reduced incidence of hypoglycaemia in people with type 1 diabetes. However, the gains for overall blood glucose control measured as HbA_{1c} have been more difficult to ascertain, perhaps because of amelioration of lower blood glucose levels during the night. When used in combination with long-acting analogues in people with type 1 diabetes, gains to either blood glucose control or to hypoglycaemia or both are clearer. Overall, the advantage in terms of treatment satisfaction and quality of life seems easily measurable, perhaps dominated by the convenience of immediate premeal or even postmeal injection.

The PK/PD profiles are similar between the three rapid-acting analogues, though with a faster onset of action for insulin glulisine. However, this has not been shown to be of clinical significance in terms of improved overall glucose control, hypoglycaemia or treatment satisfaction.

Rapid-acting analogues are thus recommended in evidence-based guidelines when used in people with type 1 diabetes in combination with long-acting analogues. In people with type 2 diabetes, rapid-acting analogues are still considered to pose less risk of hypoglycaemia than human insulin, and are therefore to be recommended for people in whom hypoglycaemia is a problem on human insulin preparations. It should be noted that the arguments around rapid-acting biphasic insulins are not addressed in this review.

The risk of other safety differences between rapid-acting analogues and human insulin appears to be low. Insulin lispro and insulin aspart, like human insulin, are rated category B for pregnancy use, which means that well-controlled trials in pregnant women are lacking, while insulin glulisine is category C, because only animal reproduction studies have been performed with it. To provide a more solid basis upon which to recommend the use of rapid-acting analogues, further study of their effect in pregnant women and in large populations over long time periods is advisable.

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Conflict of Interest

P. D. H. contributed in the design, conduct/data collection, analysis and writing of manuscript. P. D. H. has participated in advisory panels for Boehringer Ingelheim, BMS/AstraZeneca alliance, GlaxoSmithKline, Mannkind, Merck MSD, Novo Nordisk, Roche Diagnostics, Roche Pharma, Sanofi, Transpharma and Xoma. He has received research support from BSM/AstraZeneca alliance, Eli Lilly, GlaxoSmithKline, Johnson and Johnson, Novo Nordisk, Roche Pharma and Sanofi. He has lectured for BMS/AstraZeneca alliance, Eli Lilly, GlaxoSmithKline, Merck MSD, Novo Nordisk, Roche Diagnostics and Sanofi.

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