Role of ultrafast-acting insulin analogues in the management of diabetes

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ABSTRACT

To control both fasting and prandial plasma glucose levels in people with diabetes, insulin therapy must mimic "normal" physiological insulin secretion as much as possible. This is achieved with a long-acting insulin injected once or twice daily and a bolus of insulin injected before every meal. Prandial (bolus) insulin can either be regular human insulin (RHI) or a rapid-acting insulin analogue (RAIA). Although the efficacy of RHI has been established over approximately 35 years of clinical use, RAIs offer several clinical advantages over RHI, namely that they have been engineered with a reduced tendency to aggregate as hexamers, which allows for rapid dissociation and absorption after a subcutaneous injection. Conventional RAIs include insulin lispro, insulin aspart, and insulin glulisine. The more recently developed fast-acting insulin aspart (faster aspart) is an ultrafast-acting mealtime insulin that contains the conventional insulin aspart in a new formulation with the excipients niacinamide and L-arginine to achieve faster insulin absorption than RHI and the conventional insulin aspart formulation. This article reviews the clinical evidence supporting the use of RAIs as part of a basal–bolus regimen in patients with diabetes, with a focus on new formulations whose pharmacological profiles more closely mimic the endogenous prandial insulin secretion pattern that is seen in individuals without diabetes. This review also provides a clinical perspective to help guide health care professionals in the use of RAIs.

Keywords: Aspart; diabetes; insulin; mealtime; prandial.

Introduction

The prevalence of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) has been increasing in the United States, with approximately 23.2 million people (7.3% of the US population) in 2016 compared with 21.1 million people (7.0%) in 2010; approximately 5% are estimated to have T1DM (Bullard et al., 2018; Center for Disease Control, 2019). Diabetes contributes to the development and progression of microvascular and macrovascular complications that cause significant morbidity and mortality (Fowler, 2008). Intensive insulin therapy improves glycemic control, which reduces the risk of diabetes-related complications (Nathan et al., 2005; Stratton et al., 2000; The Diabetes Control and Complications Trial Research Group, 1996). Evidence suggests that regimens must lower both fasting and postprandial hyperglycemia to achieve therapeutic goals (Garg, Ellis, & Ulrich, 2005). Thus, guidelines recommend that treatment plans be individualized and aim to achieve near-normalization of plasma glucose levels with target HbA1c values, including target goals for both fasting plasma glucose (FPG) and postprandial glucose (PPG) (American Association of Clinical Endocrinologists and American College of Endocrinology, 2015; American Diabetes Association, 2019; International Diabetes Federation Guideline Development Group, 2014). Despite these treatment targets and the wealth of evidence supporting a glucose-lowering regimen, an analysis of 2007–2010 data from the National Health and Nutrition Examination Surveys showed that almost half of patients with diabetes did not achieve target HbA1c <7.0% (<53 mmol/mol) (Stark Casagrande, Fradkin, Saydah, Rust, & Cowie, 2013); similar results have been reported in other developed countries (de Pablos Velasco et al., 2009; Schmieder et al., 2018; Yokoyama et al., 2016).

In individuals without diabetes, insulin and glucagon are secreted at a near-constant rate during the fasting state. This maintains a stable blood glucose profile at nighttime and before meals. At meal times, elevated blood glucose levels promote secretion of presynthesized insulin from the pancreatic β-cells, followed by a
slower secretion of newly synthesized insulin (Rorsman & Renstrom, 2003). Individuals with T1DM have an absolute insulin deficiency in which there is little or no endogenous insulin secretory capacity due to destruction of insulin-producing β cells (Home, 2015). Meanwhile, results from animal models suggest that during the early stages of T2DM, there is loss of the first-phase insulin response (that should occur with onset of ingested calories) as a result of impaired β-cell function, which may occur due to age and/or obesity. Individuals with T2DM may also have overall reduced insulin secretory capacity, insulin resistance, and β-cell fatigue, all of which will eventually affect both fasting and PPG levels (Del Prato & Tiengo, 2001; Rorsman & Renstrom, 2003).

Individuals with T1DM must manage blood glucose with exogenous insulin, with mealtime insulin representing an important approach to maintaining PPG in T1DM. Although there are several therapeutic options available for management of blood glucose levels in individuals with T2DM, the progressive nature of this disease means that many patients may ultimately require bolus insulin injections to control PPG.

The aim of insulin therapy was to mimic physiological insulin secretion, thereby controlling FPG and PPG levels, with a long-acting basal insulin injected once or twice daily and a bolus of insulin injected before every meal (Levich, 2011). Basal insulin may be either neutral protamine Hagedorn insulin or a long-acting insulin analogue, whereas prandial (bolus) insulin can either be a regular human insulin (RHI) or a rapid-acting insulin analogue (RAIA) (Home, 2015). Alternatively, insulin pumps can infuse RAIA as a bolus and continuously in very small amounts to provide basal coverage, obviating the need for a long-acting insulin component. The efficacy of RHI has been established over approximately 35 years of clinical use, but RAIA offers several clinical advantages over RHI (Home, 2015). The purpose of this review was to summarize the clinical evidence supporting the use of RAIA as part of a basal–bolus regimen in patients with diabetes, with a focus on new formulations whose pharmacological profiles more closely mimic the endogenous prandial insulin secretion pattern that is seen in individuals without diabetes. Because initiation and intensification of insulin regimens are often delayed in the face of inadequate glycemic control (Khunti et al., 2018), this review also provides a clinical perspective on the use of RAIA to help guide health care professionals, in particular nurse practitioners (NPs) who have a unique and crucial role in the clinical care paradigm for individuals with diabetes.

Development of conventional and fast-acting insulin analogues

Recombinant engineering of insulin has facilitated the development of RAIA with faster insulin absorption kinetics compared with RHI. These RAIA promote earlier and higher insulin levels in peripheral tissues, enhancing peripheral glucose uptake by skeletal muscle and fat. Consequently, there is more immediate suppression of hepatic glucose production and peripheral uptake that, in turn, help to reduce PPG excursions (Basu et al., 2018; Bruttomesso et al., 1999).

Conventional RAIA include insulin lispro, insulin aspart, and insulin glulisine; these molecules have been engineered with a reduced tendency to aggregate as hexamers, thereby allowing rapid dissociation and absorption after a subcutaneous injection (Pandya-ajan & Weiss, 2012). Furthermore, insulin lispro, conventional insulin aspart, and insulin glulisine contain amino acid substitutions that have resulted in faster pharmacokinetics (as discussed in greater detail in the next section) compared with RHI (Sanlioglu, Altunbas, Balci, Griffith, & Sanlioglu, 2013).

The more recently developed fast-acting insulin aspart (faster aspart) is an ultrafast-acting mealtime insulin that comprises conventional insulin aspart in a new formulation with the excipients niacinamide and L-arginine to achieve faster absorption than the conventional insulin aspart molecule (Heise et al., 2015; Home, 2015). Niacinamide promotes a more rapid absorption of faster aspart by accelerating dissociation of insulin aspart hexamers into monomers and, thus, leading to an increased permeation rate of conventional insulin aspart compared with conventional insulin aspart-L-Arginine, a naturally occurring amino acid, acts as a stabilizing agent (Heise, Pieber, Danne, Erichsen, & Haahr, 2017). Other ultrafast-acting injectable formulations (e.g., Biochaperone lispro, treprostinil lispro) currently in development and inhaled formulations (e.g., Afrezza) are not covered in this review.

Pharmacological profile of prandial insulins

Insulin analogues have modified molecular structures that offer several clinical advantages over RHI, based on differences in their pharmacokinetic and pharmacodynamic profiles. Differences between individual insulin formulations may be categorized according to a number of key parameters, including onset of action, peak of action, and duration of action.

Regular human insulin injected subcutaneously shows peak plasma insulin concentration 2–3 hours after injection (Edelman, Dailey, Flood, Kuritzky, & Renda, 2007) (Figure 1). This slow rise to peak insulin concentration does not reflect physiological temporal insulin profiles and may account for postprandial hyperglycemia that is observed in RHI-treated individuals (Zinman, 1989). Because duration of action of RHI is approximately 3–6 hours, there is a risk of late postabsorptive hypoglycemic episodes (Edelman et al., 2007).

Rapid-acting insulin analogues (e.g., insulin lispro, insulin aspart, and insulin glulisine) display a lower
tendency toward self-association than RHI whose molecules associate into hexamers that diffuse slowly into the circulation. This ability of RAIAs to dissociate into monomers in the subcutaneous depot results in a quicker absorption and shorter time to peak plasma concentrations (Hirsch, 2005). Peak plasma concentration is approximately twice as high and is achieved within approximately half the time compared with RHI (Figure 1). Additionally, the RAIAs have a more rapid tailing-off activity compared with RHI (Howey, Bowsher, Brunelle, & Woodworth, 1994; Kang et al., 1991).

In clinical outcomes, RAIAs are more effective in lowering PPG levels and have improved tolerability profiles because of a lower risk of late postprandial hypoglycemia (Rossetti et al., 2008). Rapid-acting insulin analogues also require less restrictive mealtime planning compared with RHI. Although RHI should be administered at least 30 minutes before meals, insulin aspart may be injected within 5–10 minutes before a meal (NovoLog prescribing information), insulin lispro within 15 minutes before a meal or immediately after a meal (Humalog [insulin lispro injection USP [rDNA origin], 2017] prescribing information), insulin glulisine within 15 minutes before a meal.

| Insulin name | Onset          | Peak           | Duration        |
|--------------|----------------|----------------|-----------------|
| RHI          | 30–60 min      | 2–3 hours      | 3–6 hours       |
| RAIAs        |                |                |                 |
| Lispro       | 5–15 min       | 0.5–1.5 hours  | 2–4 hours       |
| Aspart       | 5–15 min       | 0.5–1.5 hours  | 2–4 hours       |
| Glulisine     | 5–15 min       | 0.5–1.5 hours  | 2–4 hours       |
| Faster aspart| <5 min         | ~1 hour        | 2–4 hours       |

Figure 1. Pharmacological properties of RHI and conventional RAIAs (Edelman et al., 2007; Heise et al., 2017; Hirsch, 2005). Some data from the figure have been extracted and adapted from Hirsch, I. B. (2005). Insulin analogues. New England Journal of Medicine, 352, 174–183 (Hirsch, 2005). Table adapted from Edelman, S., Dailey, G., Flood, T., Kuritzky, L., Renda, S. (2007). A practical approach for implementation of a basal-prandial insulin therapy regimen in patients with type 2 diabetes. Osteopathic Medicine and Primary Care, 20, 9, under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0); and Heise, T., Pieber, T.R., Danne, T., Erichsen, L., Haahr, H. (2017). A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clinical Pharmacokinetics, 56, 551–559, under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/). Adaptations are themselves works protected by copyright. So in order to publish this adaptation, authorization must be obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation. Faster aspart = fast-acting insulin aspart; RAIAs = rapid-acting insulin analogues; RHI = regular human insulin; T1D = type 1 diabetes.
meal or within 20 minutes after starting a meal [APIDRA (insulin glulisine [rDNA origin] injection) prescribing information), and faster aspart may be administered at the start of a meal or within 20 minutes after starting a meal (Fiasp [faster aspart] prescribing information, 2018). The advantages offered by RAIAs have a positive impact on patient satisfaction, which may in turn help to promote treatment adherence; reasons for improved patient satisfaction include greater meal flexibility (analogue may be injected immediately before/after food intake), decreased frequency of prandial and nocturnal hypoglycemia, and more flexibility to schedule injections according to lifestyle (Hartman, 2008). However, conventional RAIAs still have shortcomings in their time-onset profile, which do not yet mimic that of physiological prandial insulin secretion.

Compared with conventional RAIAs, faster aspart has a pharmacological profile that more closely mimics the endogenous prandial insulin secretion pattern observed in individuals without diabetes according to results of a pooled analysis of six clinical studies using subcutaneous injection in adults with T1DM (Heise et al., 2017). In this analysis, the pharmacokinetic and pharmacodynamic profiles were left-shifted for faster aspart compared with insulin aspart (Figure 2). The left-shift in mean concentration–time profiles for serum insulin aspart indicates a more rapid onset and greater early insulin exposure with faster aspart than with conventional insulin aspart (Figure 2A, B). Meanwhile, the left-shift in the mean glucose infusion rate profiles, as measured using a euglycemic clamp, also indicates a quicker onset and greater early glucose-lowering effect with faster aspart than insulin aspart (Figure 2C, D). The differences between the pharmacokinetic and pharmacodynamic profiles of faster aspart and conventional insulin aspart translated into an approximately 5-minute earlier onset of appearance. Furthermore, within the first 30 minutes, a two-fold higher early insulin exposure and a 74% greater glucose-lowering effect was observed with faster aspart compared with insulin aspart. The offset of exposure and glucose-lowering effect occurred 12–14 minutes earlier with faster aspart than with insulin aspart. As a result, greater early insulin exposure and early glucose-lowering effect were consistently observed with faster aspart versus insulin aspart across individual trials comparing them both (Heise et al., 2017). The findings in children and adolescents also demonstrated that the onset of appearance occurred approximately twice as fast (5–7 minutes earlier), and early exposure (0–30 minutes) was statistically significantly greater by 78–98% for faster aspart compared with insulin aspart (p < .05 for both children and adolescents) (Fath et al., 2017). The profile of faster aspart better mimics the physiological first-phase insulin response to ingested calories and improves control over postprandial glycemic excursions.

Clinical trial data for conventional and ultrafast rapid-acting insulin analogues

In glycemic outcomes, clinical studies with RAIAs in T1DM and T2DM have shown similar or superior decreases in HbA1c and greater efficacy in reducing PPG excursions when compared with RHI, without increasing hypoglycemia (Anderson et al., 1997; Dailey, Rosenstock, Moses, & Ways, 2004; Garg et al., 1999; Home, Lindholm, Hylleberg, & Round, 1998; Ross, Zinman, Campos, & Strack, 2001). More recently, results of a systematic review in adults with T1DM reported moderately improved control of HbA1c with RAIAs compared with RHI and suggested that there was no significant difference in hypoglycemia; however, the analysis concluded that long-term data are needed (Fullerton et al., 2016). Results of a systematic review in patients with T2DM reported better control of HbA1c and PPG with RAIAs than RHI, without any significant reduction of the risk of severe hypoglycemia (Mannucci, Monami, & Marchionni, 2009).

Faster aspart has been evaluated in the onset clinical program in people with T1DM (Buse et al., 2018; Mathieu et al., 2018; Russell-Jones et al., 2017) and T2DM (Bowering et al., 2017; Rodbard et al., 2017) (Table 1). As part of a basal–bolus regimen in individuals with T1DM, faster aspart was observed to be noninferior compared with insulin aspart in HbA1c reduction. It also demonstrated improved control of PPG excursions, without a higher likelihood of overall severe or blood glucose-confirmed hypoglycemia (Buse et al., 2018; Russell-Jones et al., 2017). Similar findings were reported in individuals with T2DM (Bowering et al., 2017). Exploratory analyses reported statistically significant differences in meal-related hypoglycemia in patients with T1DM (onset 1 and 8) and T2DM (onset 2). In onset 8, significantly fewer hypoglycemic episodes were observed 3–4 hours after meals, with mealtime faster aspart than insulin aspart (rate ratio [95% confidence interval] 0.72 [0.54–0.96]; p = .024) (Buse et al., 2018). In onset 1, however, the rate of hypoglycemic episodes during the first hour after a meal was statistically significantly higher for mealtime faster aspart than for insulin aspart (rate ratio faster aspart/insulin aspart 1.48 [1.11–1.96]; p = .0073), although these represented only a small fraction (approximately 1 of 40) of all severe or blood glucose-confirmed hypoglycemic episodes reported for mealtime faster aspart in the trial (Russell-Jones et al., 2017). In onset 2, hypoglycemia rates up to 2 hours after a meal were also higher with faster aspart compared with insulin aspart (1.60 [1.13–2.27]) (Bowering et al., 2017). The differences observed between these trials are likely to reflect the pharmacological differences between faster aspart and conventional insulin aspart. The safety profile of faster aspart is comparable with that of insulin aspart in T1DM and T2DM (Bowering et al., 2017; Russell-Jones et al., 2017). Similar with other insulin therapies, adverse
reactions observed with faster aspart include hypoglycemia, injection site reactions, and weight gain (Fiasp [faster aspart] prescribing information).

The onset program also assessed the compatibility of faster aspart in an insulin pump in a 2-week crossover study in T1DM (onset 4; NCT01999322). No new safety issues were found when faster aspart was administered using an insulin pump (Zijlstra et al., 2018). The recently completed onset 5 clinical trial assessed the use of faster aspart with continuous subcutaneous insulin infusion (Klonoff et al., 2018); however, faster aspart is not currently indicated for use in pumps and thus, will not be a topic for this review.

Practical aspects of starting, switching, titrating, and intensifying rapid-acting insulin analogues

Nurse practitioners have a pivotal role in tailoring treatment toward individual patient needs. American Diabetes Association treatment guidelines advocate that most people with T1DM are treated with multiple daily injections of prandial insulin and basal insulin or continuous subcutaneous insulin infusion, with RAIAs being used to reduce hypoglycemia risk. Similarly, for patients with T2DM who are not achieving glycemic goals, drug intensification, including consideration of insulin therapy, should not be delayed (American Diabetes Association, 2019). However, results from epidemiological studies and from a recent systematic review in patients with T2DM have reported long delays in the initiation and intensification of insulin therapy, for which there are a number of proposed reasons, including fear of injection pain, potential side effects (hypoglycemia and weight gain), and reduced quality of life, in addition to concerns about adherence to treatment (Khunti et al., 2018; Yacoub, 2017).

Figure 2. Key pharmacokinetic and pharmacodynamic properties of faster aspart. Mean concentration–time profiles for faster aspart and insulin aspart from a) 0–300 minutes and b) 0–120 minutes (early phase). Glucose-lowering effect (raw mean glucose infusion rate profiles) of faster aspart and insulin aspart from c) 0–300 minutes and d) 0–120 minutes (early phase). Adapted from Heise, T., Pieber, T.R., Danne, T., Erichsen, L., Haahr, H. (2017). A pooled analysis of clinical pharmacology trials investigating the pharmacokinetic and pharmacodynamic characteristics of fast-acting insulin aspart in adults with type 1 diabetes. Clinical Pharmacokinetics, 56, 551–559, under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (http://creativecommons.org/licenses/by-nc/4.0/). Shaded bands indicate standard error of the mean.
| Trial Name (ClinicalTrials.gov Identifier) | Description | Duration | N | Population | Interventions | Outcomes |
|------------------------------------------|-------------|----------|---|------------|---------------|----------|
| Onset 1 (NCT01831765) (Russell-Jones et al., 2017) | Randomized, double-blind, basal–bolus, treat-to-target, phase 3a trial | 26 weeks | 1143 Adults with T1DM | Mealtime faster aspart (n = 381), IAsp (n = 380), or open-label postmeal faster aspart (n = 382), each with insulin detemir | • Non-inferiority to IAsp for both mealtime and postmeal faster aspart in HbA1c change (ETD [95% CI] faster aspart–IAsp, mealtime, −0.15% [−0.23; −0.07]; −1.62 mmol/mol [−2.50; −0.73]); and postmeal, 0.04% [−0.04; 0.12]), 0.47 mmol/mol [−0.41; 1.36]; p < .0001 for noninferiority) • Mealtime faster aspart statistically significantly reduced HbA1c vs. IAsp (p = .0003) • Compared with IAsp, faster aspart provided superior mealtime PPG control • No difference in overall rate of severe or BG-conﬁrmed hypoglycemia |
| Onset 1 additional treatment period (Mathieu et al., 2018) | Randomized, double-blind, multicenter, treat-to-target, phase 3 trial | 52 weeks | 761 Adults with T1DM | Mealtime faster aspart or IAsp, each with once- or twice-daily insulin detemir | • Mean changes from baseline in HbA1c levels were −0.08% (faster aspart) and +0.01% (IAsp); (ETD [95% CI] faster aspart–IAsp, −0.10% [−0.19; −0.00]; −1.04 mmol/mol [−2.05; −0.04]; p = .0424) • Changes from baseline in 1-hour PPG increment signiﬁcantly favored faster aspart (faster aspart −1.05 mmol/L; IAsp −0.14 mmol/L; (ETD [95% CI] −0.91 mmol/L [−1.40; −0.43]; −16.48 mg/dl [−25.17; −7.80]; p = .0002) • No difference in overall severe or blood glucose-conﬁrmed hypoglycemic episodes | (continued)
| Trial Name (ClinicalTrials.gov Identifier) | Description | Duration | N | Population | Interventions | Outcomes |
|------------------------------------------|-------------|----------|---|------------|---------------|----------|
| Onset 8 (NCT02500706) (Buse et al., 2018) | Randomized double-blind treat-to-target phase 3b trial | 26 weeks | 1025 | Adults with T1DM | Faster aspart ($n = 342$), IAsp ($n = 342$), or open-label postmeal faster aspart ($n = 341$), each with insulin degludec | Noninferiority was observed for the change from baseline in HbA1c with mealtime and postmeal faster aspart vs. IAsp (mealtime ETD [95% CI] $-0.02\% [-0.11; 0.07]$; $-0.24$ mmol/mol $[-1.24; 0.76]$; and postmeal $0.10\% [0.004; 0.19]$; $1.04$ mmol/mol $[0.04; 2.04]$; $p = .0001$ for noninferiority)  
Mealtime faster aspart was superior to IAsp for 1-hour PPG increment using a meal test (ETD $-0.90$ mmol/L $[-1.36; -0.45]$; $-16.24$ mg/dl $[-24.42; -8.05]$; $p < .001$)  
Overall rate of severe or BG-conﬁrmed hypoglycemia was similar between treatments, but signiﬁcantly less hypoglycemia was seen 3–4 hours after meals with mealtime faster aspart |
| Onset 2 (NCT01819129) (Bowering et al., 2017) | Randomized, double-blind, basal–bolus, treat-to-target, phase 3a trial | 26 weeks | 689 | Adults with T2DM | Mealtime faster aspart ($n = 345$) or IAsp ($n = 344$), plus insulin glargine and metformin | HbA1c change was $-1.38\% (-15.1$ mmol/mol; faster aspart) and $-1.36\% (-14.9$ mmol/mol; IAsp)  
Faster aspart noninferior vs. IAsp in reducing HbA1c (ETD [95% CI] $-0.02\% [-0.15; 0.10]$; $-0.24$ mmol/mol $[-1.60; 1.11]$; $p < .0001$ for noninferiority)  
PPG increment (liquid meal test) was statistically signiﬁcant in favor of faster aspart after 1 hour (ETD [95% CI] $-0.59$ mmol/L $[-1.09; 0.09]; -10.63$ mg/dl $[-19.56; -1.69]$; $p = .0198$) but not after 2–4 hours  
Overall rate of severe or BG-conﬁrmed hypoglycemia was not statistically different between treatments (treatment rate ratio 1.09 [95% CI: 0.88; 1.36])  
Postmeal hypoglycemia rates (0–2 hours) were 2.27 (faster aspart) and 1.69 (IAsp) per patient-year of exposure (RR [95% CI] 1.60 [1.13; 2.27]; $p = .0082$) |

(continued)
| Trial Name (ClinicalTrials.gov Identifier) | Description | Duration | N  | Population | Interventions | Outcomes |
|------------------------------------------|-------------|----------|----|------------|--------------|----------|
| Onset 3 (NCT01850615) (Rodbard et al., 2017) | Randomized, open-label, basal–bolus vs. basal trial | 18 weeks | 236 | Adults with T2DM | basal–bolus regimen with faster aspart (n = 116) or continuation of once-daily basal insulin (n = 120), both with metformin | • Change in HbA1c from baseline was −1.2% (−12.7 mmol/mol) in the faster aspart + basal group vs. −0.2% (−2.4 mmol/mol) in the basal group after 18 weeks of treatment (ETD [95% CI]: −0.94% [−1.17; −0.72]; −10.3 mmol/mol [−12.8; −7.8]; p < .0001 for superiority)  
• Reductions from baseline in overall mean 2-hour PPG and overall PPG increment for all meals (self-measured plasma glucose profiles) were statistically significant in favor of basal–bolus treatment (p < .0001)  
• Severe/BG-confirmed hypoglycemia rate (12.8 vs. 2.0 episodes per patient-years of exposure) and weight gain (1.8 vs. 0.2 kg) were greater with basal–bolus than basal-only |

BG = blood glucose; ETD = estimated treatment difference; IAsp = insulin aspart; PPG = postprandial glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
American Diabetes Association recommends a step-wise approach for individuals with T2DM receiving basal insulin who are starting on prandial insulin (American Diabetes Association, 2019). Rapid-acting insulin analogues should be initially administered before the largest meal or the meal with the greatest PPG excursion, with a suggested starting dose of mealtime insulin of 4 units per day or 10% of the basal dose. If HbA1c is <8.0% (64 mmol/mol) when starting mealtime bolus insulin, consideration should be given to decreasing the basal insulin dose by 4 units per day or 10% of the basal dose. If HbA1c levels are not controlled, the mealtime dose should be adjusted by 1–2 units or 10–15% twice weekly until self-measured blood glucose target is reached. For those individuals whose HbA1c levels remain uncontrolled, there should be a stepwise addition of prandial insulin to...
two and then three meals, if necessary, using the same mealtime dose and adjustment as outlined above. In cases where postprandial hypoglycemia is experienced, the cause (e.g., dose relevant to food intake and timing) should be determined and addressed. If no clear etiology is identified, the premeal dose should be reduced by 10–20%.

Educating individuals on calculating premeal insulin dose based on carbohydrate intake, blood glucose levels, and anticipated physical activity is also an important aspect of managing patients with prandial insulins (American Diabetes Association, 2019). Specific information regarding how to initiate faster aspart and transfer patients from conventional RAIAs to faster aspart is provided in Figure 3.

Faster aspart may be clinically beneficial for all patients who require insulin therapy as its rapid onset of action provides greater flexibility in mealtime dosing than conventional RAIAs, and this may result in greater treatment satisfaction and patient adherence. Nonetheless, patients who may particularly benefit from the use of faster aspart include patients with questionable appetites and dosing during or after completion of meal, patients exhibiting a high degree of glucose variability (e.g., continuous glucose monitoring [CGM] data) around meal times, and patients with very unpredictable meal schedules.

As with any change to insulin therapy, due care and continuous monitoring are needed after starting patients on faster aspart. Furthermore, as patients are typically accustomed to timing mealtime insulin 5–15 minutes (RAIA) to 30 minutes (RHI) before meals, it is important to emphasize that faster aspart should be dosed just before eating, or within 20 minutes after starting a meal. Because hypoglycemia is the most common adverse reaction with all insulin therapies, patients should be advised on self-management procedures including glucose monitoring, proper injection technique, recognition of symptoms and proper management of both hypoglycemia and hyperglycemia—especially at initiation of therapy.

Case study
Martha is a 36-year-old health care worker with T1DM, who is being managed using a basal–bolus regimen with insulin aspart and insulin detemir. Martha uses a CGM to monitor her blood glucose levels. Analysis of her CGM data shows an increase in postprandial glycemic excursions across recent visits.

Martha admits that she has not been good at taking her prandial insulin in advance of meals. She is reminded by the NP that premeal injection of prandial insulin will reduce the likelihood of postprandial glycemic excursions. She tells the NP that the nature of her shift work, and the need to fit in meals when time permits, makes it difficult to inject 15–20 minutes before a meal. She explains, “I don’t always have the ability to plan the actual timing of when I start to eat. When I have attempted to take my mealtime insulin that far in advance, things have often come up and I do not always get to eat as I planned, or often I am not able to even finish my meal. This has caused me to have low blood sugars and that scares me. I cannot have low blood sugars while I am at work.”

Martha’s NP discusses the possibility of switching her to an alternative fast-acting formulation called faster aspart, which may be more beneficial with her unpredictable meal schedules. The key information is outlined to help Martha make an informed decision about whether it may be the best option for her. Faster aspart offers a more flexible prandial insulin option, with less restrictive mealtime planning than conventional RAIAs. The pharmacokinetic profile of faster aspart is more similar, compared with conventional RAIAs, to endogenous insulin in individuals without diabetes. Results in T1DM show an approximately 5-minute earlier onset of appearance, a two-fold higher early insulin exposure, and a 74% greater glucose-lowering effect with faster aspart compared with insulin aspart (Heise et al., 2017). Patients using a different fast-acting mealtime insulin (insulin lispro, insulin aspart, and insulin glulisine) can transfer to faster aspart on a unit-to-unit basis.

Martha agrees that a fast-acting insulin may better suit her needs. The NP provides information regarding how to initiate faster aspart and reminds her of the need for continuous monitoring. On Martha’s return visit, the NP notices an improvement in her CGM data, with fewer postprandial glycemic excursions than previously observed.

Discussion/Conclusion
Basal–bolus insulin therapy aims to mimic both basal and prandial physiological hormone secretion to achieve normal physiological glycemia (Levich, 2011). There has been an unmet need in diabetes management to replicate the physiological prandial insulin secretion profile of individuals without diabetes. Although RAIAs show improved pharmacokinetic and pharmacodynamic profiles compared with RHI, their relatively slow absorption is not typical of that observed with normal physiological insulin. A new generation of ultrafast RAIAs is emerging, with pharmacological profiles that more closely mimic endogenous prandial insulin secretion, compared with conventional RAIAs and RHI (Heise et al., 2017).

Faster aspart, whose formulation has been optimized to achieve faster insulin absorption than RHI and conventional RAIAs, has shown promising results in clinical trials (Bowering et al., 2017; Buse et al., 2018; Mathieu et al., 2018; Rodbard et al., 2017; Russell-Jones et al., 2017; Zijlstra et al., 2018). Although faster aspart is a new formulation of insulin aspart, NPs and patients can feel assured by the well-established efficacy and safety profile of insulin.
aspart, and the two US Food and Drug Administration, 2008 (FDA)-approved additional excipients, L-arginine and niacinamide (FDA, 2008). Nevertheless, patient education and careful monitoring when starting faster aspart is recommended to ensure patient is dosing appropriately. The timing of meals must match the faster insulin action profile to maximize glycemic benefits and minimize risk of postprandial hypoglycemia. The rapid onset of action of faster aspart provides greater flexibility than conventional RAIAs for patients in mealtime dosing, which may lead to greater treatment satisfaction and patient adherence that in turn may help to curtail prandial excursions and improve overall glycemic control.

Nurse practitioners have a key role in educating patients and ensuring that treatment is tailored toward individual patient needs.

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