Insulin aspart revisited: new and clinical differential aspects versus other rapid-acting insulin analogs

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Abstract

The gradual deterioration of the pancreatic β -cell function in type 2 diabetes mellitus (T2DM) patients prompts the progressive introduction of more complex treatments, including the initiation of insulin in many patients. Rapid-acting insulin analogs (aspart, lispro, and glulisine) show advantages over human regular insulin due to their rapid absorption, short duration, and higher maximum insulin peaks. We reviewed the differential aspects of insulin aspart, its potential role in various strategies for intensifying insulin treatment in T2DM and its use in special situations such as older patients, pregnant women with diabetes, and treatment of hyperglycemic crises.

keywords: Type 2 diabetes mellitus, hyperglycemia, rapid-acting insulin analogs, aspart, basal-bolus therapy, stepwise therapy

Introduction

Diabetes mellitus, especially type 2 diabetes mellitus (T2DM), remains an important public health problem given its worldwide prevalence and the associated morbidity and mortality. Progressive deterioration of pancreatic β -cell function over time necessitates initiation of insulin treatment in a significant proportion of patients with T2DM for achieving or maintaining glycemic control targets.

Health care professionals who deal with T2DM patients are faced with the important task of adapting the glycemic control to individual targets, implementing new advances in treatment, and fighting against therapeutic inertia. The introduction of insulin analogs and development of new strategies for initiating and, particularly, intensifying insulin treatment, are among these new advances to be implemented. However, both patients and health professionals have some difficulties when initiating insulin treatment partly due to barriers raised from a lack of proper information regarding insulinization [1]. In this article, we will review some of the new and differential aspects of insulin aspart, a rapid-acting insulin analog (RAIA), its potential role in various strategies for insulin intensification, and its use in special situations such as the treatment of older patients, diabetic pregnant women or patients suffering from hyperglycemic episodes.

Rapid-acting insulin analogs vs. regular human insulin

RAIAs were developed to overcome some of the limitations of human regular insulin (HRI). In contrast to the physiological secretion of insulin induced by meal

ingestion, HRI shows a slow initiation of action (15–60 minutes after injection), which requires administration 30–45 minutes before meals, a late peak-effect at 2–4 hours, and a prolonged duration of action (5–8 hours) [2]. As a result, HRI administration is accompanied by postprandial hyperglycemia and an increased risk of late hypoglycemia before the next meal. Therefore, HRI should be administered 30–45 minutes before meals, a requirement that many patients do not meet [3].

As previously shown with insulin aspart in adolescents with Type 1 diabetes mellitus (T1DM) [4], the dose of RAIAs should be adjusted in patients ingesting a high fat meal to maintain postprandial normoglycemia.

Unlike HRI, which forms dimers and, upon aggregation, hexamers, RAIAs are monomeric insulin even at high concentration, which enables an improved absorption process. Their greater capacity for *in situ* dissociation and diffusion into the capillaries gives them a characteristic pharmacokinetic profile with a rapid increase in plasma insulin concentrations shortly after injection [5]. In general, the various RAIAs (aspart, lispro, and glulisine) exhibit similar pharmacokinetic and pharmacodynamic properties [6–9]. An injection of a RAIA results in a higher maximum insulin peak in half the time when compared with that of HRI [10]. When compared with HRI, RAIAs are more effective in reducing postprandial glycemic excursions (the difference between preprandial glycemia and postprandial glycemia at 1.5–2 hours) and the incidence of late postprandial hypoglycemia [10]. Furthermore, these advantages of RAIA allow for an administration just immediately before a meal or even after ingestion,

Table 1. Recommendations for glycemic control from the American Diabetes Association (2012).

A1C	< 7.0%
	<ul style="list-style-type: none"> In selected patients, stricter control may be reasonable (for example, < 6.5%) if it is possible to achieve this without the appearance of significant hypoglycemia or other adverse effects. A less strict target may also be appropriate (for example, <8%) for patients with antecedents of severe hypoglycemia, limited life expectancy, advanced macro- or microvascular complications, significant comorbidities, and patients with long-term diabetes for whom it is difficult to achieve general targets despite receiving proper attention.
Preprandial capillary plasma glycemia	70-130 mg/dL (3.9-7.2 mmol/L)
Postprandial capillary plasma glycemia (1-2 h)	< 180 mg/dL
The targets should be individualized based on <ul style="list-style-type: none"> Duration of the diabetes Age/life expectancy Comorbidity Known cardiovascular disease or advanced microvascular complications Hypoglycemia unawareness Individual patient considerations 	
If A1C targets are not reached despite having achieved those for preprandial glycemia, the targets should be focused on postprandial glycemia.	

Adapted from the American Diabetes Association (2012) [1].

which is an aspect particularly appreciated by patients. Additionally, unlike HRI, the duration of action does not increase significantly with increasing dose of insulin aspart or glulisine [9,11]. Finally, the patient's perception of the RAI is another important element to consider. In an observational study involving 66,726 patients with T2DM, the use of insulin analogs was also associated with an improvement in the quality of life [12].

Differential aspects of insulin aspart compared with other insulin

Although few comparative studies have been conducted among these types of insulin, a review of the results of the various randomized clinical trials indicates that all three RAIs present similar effectiveness and safety [13]. However, some differences in physicochemical stability among them could be clinically relevant in some situations, as in continuous subcutaneous infusion of insulin (CSII or insulin pumps). In our setting, this is a treatment reserved almost exclusively for patients with T1DM. Insulin molecules are known to suffer structural changes and molecular aggregation during the process of production, storage, and later use. These changes can result in the formation of fibrils, insulin precipitation, and possibly catheter occlusions under CSII therapy [14].

All three RAIs have demonstrated a greater stability than HRI. However, studies have shown that insulin aspart is the insulin with the least tendency to precipitate under adverse conditions, both *in vitro* and *in vivo*, being the insulin that offers the least risk of occlusion when used with insulin pumps, especially in comparison with glulisine [14].

Furthermore, the results of a single-center, randomized, double-blind, cross-over trial in 20 patients with T1DM on CSII also indicate the possible advantages of aspart in comparison with lispro in terms of patient tolerance and satisfaction [15].

Insulin aspart in various clinical situations Stepwise approach for insulinization in type 2 diabetes: role of insulin aspart

Treatment of T2DM usually begins with medical nutrition therapy and physical exercise, unless the patients consult with obvious hyperglycemia [16]. The *American Diabetes Association* (ADA) and the *European Association for the Study of Diabetes* (EASD) recommend adding metformin from the onset of the disease because of its beneficial effects on glycemic and weight control, its reduced cost, and the low incidence of side effects [17]. However, treatment with oral glucose-lowering drugs by monotherapy or in combination, although initially effective, is insufficient over time to achieve or maintain the target for glycemic control [16].

Targets for glycemic control

(Table 1) Currently, the ADA recommends to achieve/maintain glycated hemoglobin (A1C) less than 7% for most patients with diabetes [18]. Additionally, the *American Academy of Clinical Endocrinologists* and the *American College of Endocrinology* both recommend a goal of less than 6.5%, which is even more demanding [19]. Nevertheless, this goal should be individualized based on the characteristics of each patient (Table 1). Thus, the *Spanish Diabetes Society*

(SDS) along with other national scientific societies, including the semFyC (*Spanish Society of Family and Community Medicine*) and the SEMERGEN (*Spanish Society For Rural and General Medicine*), recommends an A1C of less than 7% as a general target, but a stringent requirement (less than 6.5%) is recommended for young, recently diagnosed patients without complications. Alternatively, in patients with advanced chronic complications such as those over 70 years of age or those who have a longer disease duration, a less rigorous glycemic goal (*i.e.*, less than 7.5%) is recommended [20].

Initiation of insulin treatment

When necessary, treatment with insulin usually begins with the introduction of basal insulin (detemir, glargine, or neutral protamine Hagedorn [NPH]). Less often, treatment is initiated with the administration of prandial insulin (that is, an RAIA or HRI) before the principal meals or with premixed insulin (a combination with fixed doses of a prandial insulin and a basal insulin).

The 4T study (*Treating to Target in Type 2 Diabetes*) was designed to evaluate which of the three options was the best for initiating treatment with insulin in patients with T2DM. In this open-label clinical trial, 708 T2DM patients who presented with inadequate levels of A1C (7-10%) despite treatment with maximum doses of metformin and sulfonyl ureas were randomized to receive treatment with biphasic insulin, aspart 3 times a day or insulin detemir 1 or 2 times a day for the first year, optimizing, if necessary, with additional injections of either detemir or aspart insulin for up to three years [21]. At 52 weeks, the A1C levels were similar in patients who received biphasic insulin or prandial

insulin (7.3% vs. 7.2%, respectively; $p=0.08$), although the levels were higher in those receiving basal insulin (7.6%; $p<0.001$ for the two comparisons). However, the frequency of hypoglycemia and weight gain were significantly reduced in the basal insulin group [21]. Conversely, after 3 years, all three groups achieved similar levels of A1C with a reduced frequency of hypoglycemia and weight gain in the basal insulin group [22].

The 4T study indicated that the choice of insulin for initiating treatment is not relevant because in the ensuing months/years, most patients will require an intensification of their insulin treatment to achieve/maintain the same degree of glycemic control. Consequently, initiating insulinization with basal insulin (detemir) appears to be a good option due to the smaller number of required injections, reduced risk of hypoglycemia, and lower weight gain. This procedure has also been recommended by a consensus of the ADA and EASD [17].

Intensification of insulin treatment

An intensification of the insulin treatment may be necessary if the target for glycemic control is not achieved despite adequate titration of basal insulin. Intensification could be achieved with two or three shots of premixed insulin or, as recently demonstrated, with the introduction of increasing prandial insulin doses or basal-bolus therapy if necessary. In the past, premixed insulin has been frequently used for insulin intensification. However, although it is effective in reducing hyperglycemia, this treatment is often associated with an increased risk of hypoglycemia and weight gain. Furthermore, the use of premixed insulin is a therapeutic scheme with little flexibility that frequently requires rigid

meal schedules [23]. Conversely, a basal-bolus therapy continues to be the most effective strategy of insulin treatment even in patients with T2DM [23]. Thus, to help adaptation of the patient to a progressive intensification of insulin treatment, other options have been proposed, such as the stepped addition of prandial insulin before meals. This strategy consists in a progressive introduction of increasing doses of prandial insulin, beginning with the main perceived meal or, alternatively, the meal with the greatest impact on postprandial glucose values while continuing treatment with basal insulin and oral agents (metformin) (Figure 1).

A 6-month, randomized, open-label clinical trial that evaluated the addition of a dose of insulin glulisine at the main meal in 106 patients with T2DM confirmed this approach as an effective strategy for insulin intensification [24]. Later trials involving the stepped addition of prandial insulin indicated that this strategy is also effective independent of both, the meal (breakfast or the meal with the highest glucose excursion) for which the prandial insulin (glulisine) is added [25], and the method used to adjust the dose [26]. In some studies, this therapeutic option seems to be similarly effective when compared with basal-bolus therapy [27,28].

In the STEP-wise study, which included 296 T2DM patients, the sequential addition of 1, 2, or 3 insulin aspart injections to a regimen of insulin detemir, previously optimized during a 12-week pre-inclusion period, was evaluated using a 48-week, randomized, open-label design. Insulin aspart was added using one of the following strategies: (a) adding it to the principal meal and adjusting the dose based on the premeal glucose values ("SimpleSTEP") or (b) adding it to the meal with the largest increase in postprandial glucose and adjusting the dose as a function of the postmeal glucose value ("ExtraSTEP"). The number of injections was increased with both strategies in the case of insufficient therapeutic effect ($A1C \geq 7\%$) [29]. The second and third administrations of aspart were performed at intervals of 12 weeks. The analysis at the conclusion of the study indicated that after 48 weeks of treatment, the two methods for intensifying the insulin treatment were equally effective. The A1C level was reduced by 1.2%, and no differences were detected between the strategies in episodes of hypoglycemia or increase in weight. At the end of the treatment period, more than 75% of the patients received the 3 injections of aspart. In clinical practice, the strategy of evaluating glycemia before ingestion may be easier for the patient and is actually the most often used in our country.

In summary, these studies indicate that the progressive introduction of prandial insulin, when added to a regime of basal insulin in combination with oral agents, is overall a good option for the transition to basal-bolus therapy. This strategy presents an adequate risk-benefit ratio and can facilitate the acceptance by the patient to increasingly complex therapeutic regimens.

Other relevant clinical situations

Transference from basal or premixed insulin to a basal-bolus strategy

To make the transference possible, one should initially calculate the patient's total daily dose requirements [30]. Generally, the daily insulin dose represents the total previous daily basal insulin dose (approximately 0.5 IU/kg/day) or the sum of the total daily dose if the patient has received premixed insulin. Next, the total daily dose is distributed to approximately 50% of basal insulin and 50% of prandial insulin, dividing the total amount by thirds for each meal (or between 10% and 20%). Finally, one should calculate a complementary correction scale with rapid-acting insulin. The correction factor estimates the reduction in plasma glucose per unit of insulin, as applied in accordance with the desired values of preprandial glucose and those actually presented by the patient. An empirical rule has been proposed in which the correction factor (the reduction of glycemia with 1 IU of insulin) can be calculated by dividing 1800 by the total daily dosage of insulin if RAIs are used or by dividing 1500 by the total daily dosage if HRIs are used. In this example, if the patient is treated with detemir 0-0-32 IU and aspart 4-6-5, the sensitivity factor will be as follows: $1800 \div (32+15) = 38$ (1 IU aspart reduces glycemia to ~40 mg/dL).

In addition, adjustments in the insulin dose should be continuous over time. Doses of basal insulin need to be titrated based on the fasting glucose levels (and before the meal in the case of 2 doses of basal insulin), whereas prandial insulin doses should be adjusted based on preprandial or postprandial glycemia according to the selected adjustment strategy.

Insulinization in older patients

Initiation of insulin therapy in older patients with diabetes is even more difficult than in young adults. These patients frequently exhibit cognitive problems, visual disorders or are living alone. In such cases, outpatient intensification of insulin treatment is complicated and sometimes impossible [31]. Furthermore, aged diabetic patients are more prone to the deleterious effects of hypoglycemia, which may be associated with other problems such as falls or other complications [31]. Nevertheless, age should not be an obstacle for beginning an insulin treatment that is considered necessary according to the glycemic control targets and the clinical situation of the patient [32]. However, goals for glycemic control should be less strict in older patients, especially in those with a limited life expectancy, [20].

Due to its simplicity, starting with basal insulin before bedtime, or even in the morning, is the best method to initiate insulin treatment in aged diabetic patients [32]. Long acting insulin analogs such as detemir or glargine allow improved adaptation to the physiological needs with a more predictable and consistent glycemic control

and a reduced risk of hypoglycemia [31].

As in younger adults, the addition of prandial insulin in older patients may be necessary for the control of excessive hyperglycemia when basal insulin alone is not enough. In most cases, RAIAs also offer a better physiological action profile when compared with HRI. Aspart has demonstrated a consistent pharmacokinetic profile in older people with diabetes, which is similar to that observed in younger adults in a randomized, double-blind, cross-over clinical trial in 19 patients with T2DM [33]. In addition, for those patients with renal insufficiency, PK/PD characteristics of aspart do not appear to vary significantly in the clinic according to the results of a small, phase I, pharmacokinetic study [34]. Furthermore, RAIAs offer an additional advantage in aged people due to a greater flexibility of administration with meals, especially for seniors who are institutionalized or for whom ingestion of foods may be unpredictable or occasionally compromised.

Incidental hyperglycemia at the outpatient clinic

Acute complications of diabetes include both hypoglycemia and hyperglycemic decompensations such as diabetic ketoacidosis or the hyperglycemic hyperosmolar state.

Diabetic ketoacidosis is a complication induced by an acute deficiency of insulin [35]. Precipitating factors in the development of diabetic ketoacidosis include infection, pancreatitis, myocardial infarction, cerebrovascular accidents, and drugs [36]. Although it occurs almost exclusively in T1DM patients, diabetic ketoacidosis may also appear in T2DM patients. If the patient presents with signs or symptoms of diabetic ketoacidosis, he/she should be sent urgently for treatment to the hospital. However, an early intervention using intravenous fluid therapy such as saline solution and treatment with rapid-acting insulin may be helpful; these, particularly, are evaluated first in a primary care setting [37]. Although intravenous administration of insulin is preferred in these patients, RAIAs may also be administered intramuscularly or subcutaneously if intravenous administration remains impossible.

A hyperosmolar hyperglycemic state is characterized by excessive hyperglycemia, extreme dehydration, and an increase in plasma osmolarity. This state occurs in patients with T2DM in whom a remaining persistent insulin secretion is able to prevent ketone production and the development of ketoacidosis [35]. However, mortality is high in these clinical situations, especially in patients of advanced age. The main clinical findings are serious dehydration and changes in mental status, which range from confusion to deep coma. Except for serious situations, treatment outside of the hospital should take place slowly, beginning with a saline solution infusion and administration of an individualized dose of rapid insulin by the intravenous (approximately 0.10-0.15 IU/kg) or subcutaneous route (approximately 12-16 IU) [37].

Although the general recommendation for treatment

of these hyperglycemic crises is the use of HRI, RAIAs are also an effective alternative [36]. In the case of insulin aspart, its use in acute situations has been evaluated in two randomized, open-label clinical trials in comparison with regular insulin in 45 patients admitted with diabetic ketoacidosis [38] and in 176 patients with T2DM and hyperglycemia seen at the emergency department [39]. In both cases, aspart demonstrated similar efficacy and tolerability when compared with HRI.

Finally, although making an appropriate diagnosis and selecting the most convenient therapeutic action against a hyperglycemic crisis is obviously more complex than previously described, interested readers are invited to review the latest recommendations of the ADA on this topic [36].

Diabetes and pregnancy

Among the types of prandial insulin, in addition to regular human insulin, both aspart and lispro have been evaluated specifically for this clinical situation (risk category B: no risks have been described for humans, with their use accepted during pregnancy) [40,41]. Thus, in a randomized, open-label trial conducted in 322 women with T1DM who were pregnant or planning to be pregnant, insulin aspart was at least as effective as HRI for glycemic control and seemed to offer some advantages over HRI for postprandial glucose control and preventing severe hypoglycemia [40]. In a randomized, open-label trial in 33 pregnant women with T1DM, insulin lispro provided similar glycemic control when compared with HRI [41]. Concerning basal insulin, only NPH insulin and insulin detemir have been studied in specific randomized clinical trials [42] and were therefore also recently included in the risk category B for pregnancy. In this non-inferiority, randomized clinical trial conducted in 310 pregnant women with T1DM, insulin detemir was non-inferior regarding glycemic control but resulted in lower fasting plasma glucose compared with insulin NPH [42]. Given that the information available regarding glargine use in pregnancy corresponds only to isolated clinical cases or small case studies, this long-acting insulin analog continues to be listed in the risk category C for pregnancy (fetal risk cannot be excluded when evaluating risk/benefit).

Conclusions

The gradual deterioration of the pancreatic β -cell function in T2DM patients prompts to the progressive introduction of more complex treatments, which make the introduction of insulin necessary for a large proportion of these patients. Usually, adding basal insulin is the first step in starting insulinization, advancing, if needed, to a progressive addition of prandial insulin, and finally, if necessary, to administration of prandial insulin at every meal (basal-bolus). At present, the latter strategy is considered the best in reproducing the physiological insulin secretion in healthy individuals.

Currently, RAIAs (aspart, lispro, and glulisine) offer

some advantages as prandial insulin due to their rapid absorption, short duration, and increased insulin peak in comparison with RHI [13]. These aspects result in a greater flexibility in relation to the meals, more effective reduction in postprandial hyperglycemia, and reduced incidence of late postprandial hypoglycemia [13]. Among RAIs, aspart has demonstrated the best physicochemical stability, which translates into targeted clinical benefits for some groups of patients such as those (largely T1DM patients) who use a continuous subcutaneous infusion of insulin [14]. This insulin has also been evaluated with success for new insulinization strategies such as the stepped addition of prandial insulin that have been developed to facilitate the transition to more complex therapies including basal-bolus therapy [29]. In addition, aspart has been evaluated in various patient populations and clinical contexts, such as in aged diabetic patients [33], in those with renal insufficiency [34], during pregnancy [40] and for treatment of hyperglycemic episodes [38]. In these situations, aspart has proven to be effective, safe, and consistent in maintaining its pharmacokinetic advantages.

Competing interests

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Authors' contributions

Ampudia-Blasco was responsible for the conception of this review and prepared an outline, drafted the manuscript and approved the final version; Rico-Villademoros revised the outline, drafted the manuscript and approved the final version; Cos-Claramunt and Orozco Beltran revised the outline, revised the manuscript critically and approved the final version.

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