REVIEW

Diabetes Management

Insulin aspart for the treatment of Type 2 diabetes

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Practice points

- Insulin aspart is a biosynthetic analog, homologous with and structurally identical to native human insulin except for the substitution of single proline amino acid with an aspartic acid residue.
- Insulin aspart possesses a faster onset of action and shorter duration of action than human insulin, enabling flexibility in dosing and results greater convenience for patients with an improved quality of life.
- Better control of postprandial excursions and HbA1c reduction with fewer hypoglycemic episodes and less weight gain is possible with insulin aspart.
- It is approved for use in Type 1, Type 2 and gestational diabetes mellitus and even in children above 2 years of age.
- In Type 1, insulin aspart can be used as a mealtime component in multiple-dose insulin regimens and also with continuous subcutaneous insulin infusion.
- In Type 2, it can be used flexibly in meal time administration – that is, either as sole insulin in supplementary insulin therapy or mealtime component with basal/premixed insulin.
- In pregnancy it provides a better postprandial glycemic control without any increase in maternal and fetal adverse outcomes.
- Insulin aspart is ideal for hospital setups to manage various acute complications ofdiabetes as well as comorbidities associated with diabetes by intravenous administration.
- It is compatible and well-tolerated for use in insulin pumps for continuous subcutaneous insulin infusion.
- For use in insulin pumps, insulin aspart is a more suitable insulin than human insulin or insulin lispro.
- It meets diverse needs in diabetes management in various delivery systems like vials, prefilled injectable pen devices and as cartridges.
- Of all available rapid-acting insulins, it is currently the most suitable.
- Insulin aspart is safer to use in renal and hepatic impairment patients.

SUMMARY Insulin aspart is a rapid-acting insulin analog and is approved for use in Type 1, Type 2 and gestational diabetes. Following the subcutaneous injection, it more closely mimics the physiological release of insulin in the human body with a faster onset and shorter duration of action. It also offers several advantages like flexibility in mealtime administration, better glycemic control in the form of superior control of postprandial glucose excursion and less nocturnal hypoglycemia as compared with regular human insulin. It is safe to use in patients with renal and hepatic impairment and is approved for use in pregnancy, in children above 2 years of age, in continuous subcutaneous infusion pumps and can be used intravenously in hospital settings.

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Diabetes mellitus is a heterogeneous group of metabolic disorders commonly characterized by hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both [1]. The diabetes disease burden in India is huge with an estimated 65.1 million people having the disease and around the world an estimated 382 million are living with diabetes. These figures are projected to rise by 55% by 2035 [2].

There is autoimmune destruction of β-cells in Type 1 diabetes and a progressive loss of β-cells in Type 2 diabetes, resulting in absolute or relative insulin deficiency. If untreated, this may result in acute and chronic hyperglycemia which can lead to various complications associated with diabetes.

In the pharmacotherapy of Type 1 diabetes, insulin is the only agent capable of controlling hyperglycemia and the only other drug approved for use along with insulin is pramlintide [3]. Glycemic control in Type 2 diabetes can be achieved with insulin and/or non-insulin-based therapies [4]. Though in T2DM most patients are initially managed with diet/exercise and oral hypoglycemic agents, many of them will eventually end up needing insulin for glycemic control due to the progressive nature of β-cell destruction. A multitude of studies prove that using insulin early in the disease does not only give a good and tight glycemic control but also significantly reduce the risk of diabetic complications [5,6].

Importance of glycemic control

Hyperglycemia in diabetes is associated with both microvascular and macrovascular complications. Landmark trials in diabetes have clearly shown that tight glycemic control reduces the risk of serious complications [7,8]. Both the DCCT and UKPDS showed that for each percentage reduction in HbA1c, there was a significant reduction in both microvascular as well as macrovascular complications [9,10].

The DCCT in Type 1 diabetes has suggested that postprandial hyperglycemia contributed to the onset of diabetes complications [11]. Further the study led by Monnier has also shown that in patients with HbA1c of <7.3%, the postprandial hyperglycemia had a significantly greater contribution to overall hyperglycemia than fasting hyperglycemia [12]. Besides available evidence specifically point toward postprandial hyperglycemia to be an independent risk factor for cardiovascular disease associated with diabetes [13] and reduction of postprandial glucose levels result in favorable cardiovascular outcomes [14]. Thus it is imperative to have both fasting and postprandial glucose under tight control to effectively manage diabetes [15]. Major landmark trials have also shown that intensive insulin therapy which includes a mealtime rapid-acting insulin provides better control and outcome when compared with conventional insulin therapy [7,8].

Need for analog insulin

Human insulin under physiological conditions exists in a monomeric form at concentrations ranging from 10^{-8} to 10^{-11} mol/l, forming dimers at higher concentrations and in the presence of zinc ions, three dimers assemble to form a hexamer. After subcutaneous injection, soluble human insulin self-associates into hexamers and then slowly dissociates to dimers and then monomers and get released into circulation [16]. This characteristic of soluble human insulin delays its onset of action and also prolongs the duration of action than ideally required and hence human insulin is recommended to be injected 30 min before meal; however, many patients take it closer to their meal [17]. As the soluble human insulin concentration rises slowly, it may result in postprandial peaks and may also result in hypoglycemia as the insulin may get released early or may persist after the post-meal hyperglycemia has passed. These are major limitations in the use of soluble human insulin and necessitate the need for better analogs that are devoid of the pharmacological limitations but retain the biological activity [18].

Insulin aspart pharmacokinetics & pharmacodynamics

Insulin aspart is a short acting, biosynthetic analog of human insulin. Insulin aspart is homologous with and structurally identical to native human insulin except for the substitution of single amino acid. In aspart, a single proline amino acid at position 28 of the B chain has been replaced with an aspartic acid residue [16].

Replacement of a proline amino acid residue by aspartic acid reduces the ability of insulin monomers to form dimers and hexamers. This also allows rapid dissociation of hexamers and dimers into monomers. But it does not affect the 3D structure or the biological activity [19]. These pharmacokinetic characteristics give

insulin aspart a faster action profile. When compared with human insulin, aspart has a faster onset of action and a shorter duration of action **(Table 1)** [20,21].

The insulin receptor binding affinity and rate of dissociation of insulin aspart are similar to that of human insulin [22] and the IGF-1 receptor binding affinity is also similar [23], suggesting that while retaining the efficacy and having a better pharmacokinetic profile, the safety in terms of mitogenicity of insulin aspart is comparable to that of human insulin.

Insulin aspart efficacy & safety

Insulin aspart gives a better postprandial glucose control in both Type 1 and Type 2 diabetic subjects. In Type 1 diabetic subjects insulin aspart has consistently shown a significantly better postprandial glucose control vis-à-vis soluble human insulin when compared alone [20], or in combination with neutral protamine Hagedorn [24] both in short- and long-term studies. This superior glycemic control with insulin aspart is also evident in Type 2 diabetes, as proven by various trials [25].

In comparison to soluble human insulin, insulin aspart could reduce HbA1c to a significantly lower level and could maintain better glycemic profile in both Type 1 [26] and Type 2 [27] diabetic subjects. Overall, the flexibility in dosing of aspart because of its pharmacokinetic properties and better glycemic control gives diabetic patient an improved quality of life.

On the safety aspect, various trials in both Type 1 and Type 2 diabetics, where insulin aspart was compared with soluble insulin head-to-head or in combination, have shown that insulin aspart was associated with far lesser overall and nocturnal hypoglycemia [28]. It also appears to be safe to use in patients with renal and hepatic impairment since the pharmacokinetics of aspart is not affected in these scenarios in a clinically significant manner [29].

Insulin aspart in clinical practice

Insulin aspart is used for the management of both Type 1 and Type 2 diabetes and could be considered over soluble human insulin due to its better efficacy and safety. In Type 1 diabetes it can be used as a mealtime component in multiple-dose insulin regimens and can also be used with continuous subcutaneous insulin infusion (CSII).

In Type 2 diabetes, management starts from diet/exercise and includes oral antidiabetic agents; a variety of options are available for starting and intensifying insulin therapy to achieve glycemic control. Accordingly, insulin aspart can be used as sole insulin in supplementary insulin therapy [30] or as the mealtime component in basal-plus, basal-bolus or premixed insulin regimens [31].

The safety of insulin aspart has been proven in both pregnancy in Type 1 diabetes [32] and gestational diabetes mellitus [33]. The use of aspart in pregnancy not only provides a better postprandial glycemic control, but also provides convenience in dosing without any increase in maternal and fetal outcomes **(Table 2)** [34].

Intravenous use of insulin aspart

Regulatory authorities like the US FDA have approved the intravenous use of insulin aspart. According to the FDA, it should be used at concentrations ranging from 0.05 U/ml to 1.0 U/ml in infusion systems with polypropylene infusion

Table 1. Comparison of regular human insulin vs insulin aspart.

Classification	Regular human insulin (conventional insulin)	Insulin aspart (insulin analog)
Structure	Unmodified human insulin in a buffer solution stabilized by a small amount of zinc	Single proline amino acid at B28 has been replaced with an aspartic acid residue in human insulin
Mechanism of action	In the injectable solution, self-aggregate to form hexamers around zinc ions. After sc. injection, insulin monomers are released gradually by dilution leading to slow absorption	Replacement of proline by aspartic acid removes interaction at monomer–monomer surface and repulsion between the charged aspartic acid and nearby glutamic acid B21 contributes to rapid dissociation into monomers
Onset of action (h)	0.5–1.0	<0.25
Peak action (h)	2–3	0.5–1.5
Duration of action (h)	6–8	3–5
Time of administration	30 min before meal	Just before the meal to 15 min after starting the meal
Use with 5% dextrose, ringer solution and normal saline	Compatible	Compatible

Table 2. Selected studies on insulin aspart.

Study (year)	No. of subjects	Subject population	Regimen used	Primary end point	Conclusion	Ref.
Cemeroglu *et al.* (2013)	13	Prepubertal children aged 4–11 years with T1DM ≥6 months	Basal-bolus	Mean BG, 2 h and 4 h postprandial BG excursion	Insulin aspart appears to be more effective than Insulin glulisine in controlling 2- and 4-h postprandial BG excursions in prepubertal children with T1DM	[35]
Dzygalo and Szypowska (2014)	56	Subjects aged 10–18 years with T1DM for at least 1 year, treated with CSII for at least 3 months with same insulin analog	CSII	PPG assessed 30, 60, 90, 120 and 180 min after meal bolus consumption (six-point glucose curve)	No statistically significant difference was found between GLU and ASP with regard to PPG after the consumption of a H-GI breakfast	[36]
van Bon *et al.* (2011)	256	Adult subjects with T1DM diabetes mellitus treated with insulin for at least 2 years and CSII for at least 6 months	CSII of lispro, aspart and glulisine (crossover)	Unexplained hyperglycemia and/or perceived infusion set occlusion	No significant difference was seen among the comparators in respect to primary outcome whereas nocturnal severe hypoglycemia was significantly lesser with aspart compared with glulisine or lispro	[37]
Rys *et al.* (2011)	Systematic Review	Patients with either T1DM or T2DM and with no restrictions on age	Include various MDI and CSII regimens of RHI and analogs (meta-analysis)	FPG, PPG and HbA1c	Treatment with IAsp in T1DM patients resulted in moderately better metabolic control and treatment satisfaction than RHI. In T2DM patients, meta-analysis showed improvement in PPG, but not in any other outcomes	[38]
Balaji *et al.* (2012)	323	Women aged ≥20 years and ≤30 years, 12–28 gestational weeks, body mass index ≤35 kg/m2 at first visit, and confirmation of GDM by 75 g oral glucose tolerance test response	BiAsp and BHI	The degree of neonatal macrosomia (neonatal birthweight >90th percentile)	BIAsp 30 was noninferior to BHI 30 and was well tolerated during pregnancy	[39]
Cucinotta *et al.* (2012)	4099	Patients using insulin ± metformin and received ≥2 injections of IAsp or SHI over a period of 3 months to 3 years	–	–	Patients using IAsp had a better clinical safety profile and a greater reduction in HbA1c compared with patients using SHI	[40]
Herrmann *et al.* (2013)	29	Patients with T2DM with a mean age of 59 years, treated with oral drugs for at least 6 months and a HbA1c >7.0%	Basal-bolus and three-times basal regimen	HbA1c levels	Insulin aspart in comparison to human regular insulin effectively decreased HbA1c levels without significant difference. BMI, lipids, waist circumference, HbA1c and adiponectin serum levels did not differ between the two groups	[41]

ASP: Aspart; BG: Blood glucose; BHI: Biphasic human insulin; BIAsp: Biphasic insulin aspart; CSII: Continuous subcutaneous insulin infusion; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; GLU: Glulisine; H-GI: High glysemic index; IAsp: Insulin aspart; MDI: Multidose insulin; PPG: Postprandial glucose; RHI: Regular human insulin; SHI: Soluble human insulin; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; Tmax: Time to maximum concentration.

Table 2. Selected studies on insulin aspart (cont.).

Study (year)	No. of subjects	Subject population	Regimen used	Primary end point	Conclusion	Ref.
Rathmann and Kostev (2013)	6308	Patients in both groups were on average 60 years old with a documented diabetes treatment period of about 2 years	Observational study	Compare incidence of recorded macro- and microvascular events in patients with T2DM with insulin aspart or regular human insulin in general practices	Risk of combined macrovascular outcomes was 15% lower for insulin aspart users ($p = 0.01$) than regular human insulin users	[42]
Nosek *et al.* (2013)	16	Healthy subjects	Pharmacokinetic and pharmacodynamic study	Late metabolic activity (4–12 and 6–12 h post-dosing) and duration of action (time to reach late half-maximal activity)	Late metabolic activity was lower for IAsp than RHI at all doses ($p < 0.05$) Also, IAsp had a shorter duration of action at all doses ($p < 0.01$)	[43]
Ando *et al.* (2012)	20	Patients with T2DM	Pharmacokinetic and pharmacodynamic study	T_{max}	Dose of insulin aspart (per bodyweight) was significantly correlated with both maximum concentration ($r^2 = 0.59$; $p < 0.01$) and area under the concentration–time curve for insulin aspart ($r^2 = 0.53$; $p < 0.01$)	[44]

ASP: Aspart; BG: Blood glucose; BHI: Biphasic human insulin; BIAsp: Biphasic insulin aspart; CSII: Continuous subcutaneous insulin infusion; FPG: Fasting plasma glucose; GDM: Gestational diabetes mellitus; GLU: Glulisine; H-GI: High glysemic index; IAsp: Insulin aspart; MDI: Multidose insulin; PPG: Postprandial glucose; RHI: Regular human insulin; SHI: Soluble human insulin; T1DM: Type 1 diabetes mellitus; T2DM: Type 2 diabetes mellitus; Tmax: Time to maximum concentration.

bags. It has been shown to be stable in infusion fluids like 0.9% sodium chloride. It can also be used along with 5% dextrose [45].

Udwadia *et al.* (2012) did an observational study and evaluated the intravenous use of insulin aspart in the Indian population in both ICU and non-ICU setting. It was observed that insulin aspart reduced the mean blood glucose levels in both the ICU (20.7–8.4 mmol/l; p = 0.0001) and non-ICU (17.7–8.9 mmol/l; p = 0.0001). A total of 0.6 and 2.8% patients experienced episodes of major and minor hypoglycemia, respectively. More than 98% physicians preferred to use insulin aspart in the future based on responses from a questionnaire [46].

A number of studies have shown that insulin aspart is compatible [47] and well tolerated for use in insulin pumps for CSII. It also has lesser tendency to crystallize and thus cause pump occlusion when compared with human insulin or insulin lispro [48], making it a more suitable insulin for use in insulin pumps.

Insulin aspart becomes a natural choice of short acting insulin in hospital setup since, when compared with human insulin, it has quick onset of action, better postprandial glucose reduction, better glycemic control, less hypoglycemia, safe for use in patients with kidney/liver impairment, safe for use in children above 2 years and has mealtime flexibility [29,49]. Insulin aspart is also approved for intravenous route and some of the indications for intravenous use are diabetic ketoacidosis, non-ketotic hyperosmolar state, critical care illness, myocardial infarction or cardiogenic shock, post-operative period following heart surgery, stroke, organ transplantation, total parenteral nutrition, labor and delivery and other acute illness requiring prompt glycemic control [45,50].

Co-formulations of insulin aspart

Insulin aspart in India is available in three co-formulations, namely, BiAsp 30, BiAsp 50 and the co-formulation of long-acting basal insulin degludec and aspart, IDegAsp, which has recently been approved by the Drug Controller General of India and will be available for use soon. BiAsp is a biphasic preparation of insulin aspart. BIAsp 30 contains 30% of soluble insulin aspart and 70% protaminated aspart. BiAsp 50 contains 50% of soluble insulin aspart and 50% protaminated aspart. Soluble insulin aspart is rapid-acting and protaminated aspart is intermediate-acting, so each injection provides insulin coverage for both prandial and basal insulin requirements [51]. BIAsp 30 may offer greater treat-to-target potential for pregnant women [39] though data are limited.

IDegAsp is the first soluble insulin co-formulation where a basal insulin analog is combined with a rapid-acting insulin analog in the same vial/penfill. The IDegAsp co-formulation contains 70% of basal insulin degludec and 30% soluble insulin aspart. Pharmacodynamic studies demonstrated its glucose-lowering effect which is characterized by a distinct peak action (from IAsp) and a basal action (from IDeg) which is stable for more than 24 h showing a closer approximation to physiological action than seen with current biphasic formulations [52].

Conclusion

Insulin aspart is a rapid-acting, biosynthetic insulin analog which has a faster onset of action and shorter duration of action when compared with human insulin. This enables flexibility in dosing aspart and gives greater convenience for patients. These properties also confer aspart the ability to achieve a better control of prandial excursions and HbA1c reduction while having fewer hypoglycemic episodes and less weight gain.

Insulin aspart is approved for use in Type 1, Type 2 and in the treatment of pregnant women with diabetes. It is used either as sole insulin at mealtimes or as the mealtime component along with basal/premixed insulin in various regimens. It can also be used intravenously thus making it an ideal insulin to use in hospital setups to manage various acute complications of diabetes as well as comorbidities associated with diabetes. Insulin aspart is pump compatible and can be used as preferred insulin in CSII. It is available in a range of delivery systems including vials, prefilled injectable pen devices and as cartridges. Thus it meets diverse needs in the management of diabetes and remains the ideal of all available rapid-acting insulins till date.

Disclaimer

In addition to the peer-review process, with the authors' consent, the manufacturer of the products discussed in this article was given the opportunity to review the manuscript for factual accuracy. Changes were made at the discretion of the authors and based on scientific or editorial merit only.

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- **Article highlighting the first combination of a basal and a rapid-acting analog.**