Insulin aspart for the treatment of Type 2 diabetes

V Seshiah*,1, Sanjay Kalra2, Vijayam Balaji1 & Madhuri Balaji1

1Dr V Seshiah & Dr Balaji Diabetes Research Institute, Chennai, India
2Bharti Hospital & BRIDE, Karnal, India
*Author for correspondence: vseshiah@gmail.com

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.
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
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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

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

<table>
<thead>
<tr>
<th>Classification</th>
<th>Regular human insulin (conventional insulin)</th>
<th>Insulin aspart (insulin analog)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Unmodified human insulin in a buffer solution stabilized by a small amount of zinc</td>
<td>Single proline amino acid at B28 has been replaced with an aspartic acid residue in human insulin</td>
</tr>
<tr>
<td>Mechanism of action</td>
<td>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</td>
<td>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</td>
</tr>
<tr>
<td>Onset of action (h)</td>
<td>0.5–1.0</td>
<td>&lt;0.25</td>
</tr>
<tr>
<td>Peak action (h)</td>
<td>2–3</td>
<td>0.5–1.5</td>
</tr>
<tr>
<td>Duration of action (h)</td>
<td>6–8</td>
<td>3–5</td>
</tr>
<tr>
<td>Time of administration</td>
<td>30 min before meal</td>
<td>Just before the meal to 15 min after starting the meal</td>
</tr>
<tr>
<td>Use with 5% dextrose, ringer solution and normal saline</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Study (year)</td>
<td>No. of subjects</td>
<td>Subject population</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Cemeroglu et al. (2013)</td>
<td>13</td>
<td>Prepubertal children aged 4–11 years, with T1DM ≥6 months</td>
</tr>
<tr>
<td>Dzygalo and Szypowska (2014)</td>
<td>56</td>
<td>Subjects aged 10–18 years with T1DM for at least 1 year, treated with CSII for at least 3 months with same insulin analog</td>
</tr>
<tr>
<td>van Bon et al. (2011)</td>
<td>256</td>
<td>Adult subjects with T1DM diabetes mellitus treated with insulin for at least 3 months with same insulin analog</td>
</tr>
<tr>
<td>Rys et al. (2011)</td>
<td>Systematic Review</td>
<td>Patients with either T1DM or T2DM and with no restrictions on age</td>
</tr>
<tr>
<td>Balaji et al. (2012)</td>
<td>323</td>
<td>Women aged ≥20 years and ≤30 years, 12–28 gestational weeks, body mass index ≥5 kg/m² at first visit, and confirmation of GDM by 75 g oral glucose tolerance test response</td>
</tr>
<tr>
<td>Cucinotta et al. (2012)</td>
<td>4999</td>
<td>Patients using insulin ± metformin and received ≥2 injections of IAsp or SHI over a period of 3 months to 3 years</td>
</tr>
<tr>
<td>Herrmann et al. (2013)</td>
<td>29</td>
<td>Women aged ≥20 years and ≤30 years, 12–28 gestational weeks, body mass index ≥5 kg/m² at first visit, and confirmation of GDM by 75 g oral glucose tolerance test response</td>
</tr>
</tbody>
</table>

ASP: Aspart; BG: Blood glucose; BHI: Biphasic human insulin; BiAsp: Biphasic insulin aspart; CSII: Continuous subcutaneous insulin infusion; FPG: Fasting plasma glucose; 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.
### Table 2. Selected studies on insulin aspart (cont.).

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

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; GI: Glycemic 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.
Insulin aspart is rapid-acting and protaminated aspart and 50% protaminated aspart. Soluble BiAsp 50 contains 50% of soluble insulin aspart and 70% protaminated aspart. Soon. BiAsp is a biphasic preparation of insulin degludec and aspart, IDegAsp, which has the co-formulation of long-acting basal insulin and aspart, 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.

A number of studies have shown that insulin aspart is compatible 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, 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. 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.

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. BiAsp 30 may offer greater treat-to-target potential for pregnant women though data are limited.

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.

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

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• of interest


• Emphasizes the importance of initiating insulin early and how that helps preserving β-cells.

29 Holmes G, Gallit L, Hu P, Lyness W. Pharmacokinetics of insulin aspart in obesity,


• This study proves better efficacy and safety of aspart when compared with regular human insulin in gestational diabetes mellitus.


• Provides evidence for better efficacy and safety of aspart compared with human insulin in both Type 1 and Type 2 diabetic subjects.


• Evidence for better cardiovascular outcome with aspart vis-à-vis regular human insulin.


45 US FDA. Highlights of prescribing information. www.fda.gov/downloads


• Delineates intravenous use of aspart and advantages of aspart in managing inpatient hyperglycemia.


• Evidence for superiority of aspart for use in continuous subcutaneous insulin infusion in comparison to other rapid-acting analogs.


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