

Rapid Acting Analogues in Diabetes Mellitus Management



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Abstract

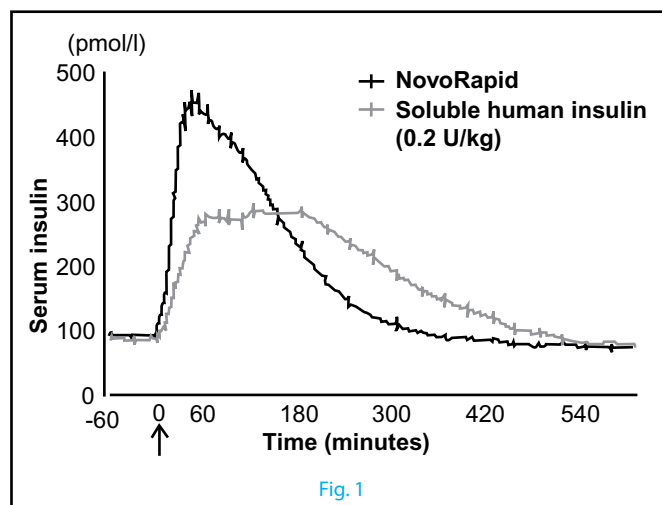
Rapid-acting human insulin analogues, provide more rapid absorption than regular human insulin after subcutaneous administration. The limitations of regular human insulin like variation in absorption kinetics, slow absorption rate, inappropriate prandial control and injection timing were addressed by these modern insulins. Studies have shown strong evidence of better glycaemic control, without an increased risk of hypoglycaemia, together with evidence supporting improved convenience and flexibility of insulin aspart compared with regular human insulin in adult diabetic subjects. These analogues have been associated with improved hospital outcomes with or without critical illness and managing emergencies like DKA. Insulin aspart has unaltered pharmacokinetics in renal failure as well, making it to be modern insulin of choice in emergencies. Insulin aspart and lispro have been approved to be used in GDM by the USFDA and have shown to provide better maternal and foetal outcomes than regular human insulin. Insulin aspart, lispro and glulisine have been used in insulin pumps and studies have shown them to provide better glycaemic control and stability than MDI.

The standard preparation of insulin aspart has the potential to better mimic the physiological response to meals than regular human insulin. Overall, there is a good body of evidence to support the efficacy, tolerability and ease of administration of insulin aspart in patients with type 1 and type 2 diabetes. In general, the extensive clinical data with these rapid acting modern insulins is well accepted and that they help to improve diabetes management significantly.

Introduction

The diabetes mellitus especially type 2 diabetes mellitus, a non communicable metabolic disorder gaining an epidemic stature in the present century with a prevalence of 177 million individuals worldwide in the year 2000. It is predicted to rise to at least 300 million individuals by 2025.¹ In the history of diabetes the discovery of insulin is considered as one of the greatest medical breakthroughs of the 20th century.² However; subcutaneous injection therapy has not succeeded in normalizing glycemic control despite the efforts to improve the insulin preparations and injection regimens. Animal origin insulin obtained by extraction and purification from pancreas of cows and pigs (bovine and porcine insulin's) ruled the diabetes treatment till 1980s even though associated with high incidences of allergic reactions and variable efficacy. The introduction of recombinant DNA technology derived insulins i.e., monocomponent human insulins was applauded and was thought as ultimate solution. This technology has enabled large-scale production of human insulin. These insulins too had their limitations as pancreatic hormone was not suitable for extraneous supplementation. In the later part of 20th century 'monomeric analogues of insulin (e.g. insulin lispro, aspart or glulisine) were invented with the help of DNA and protein engineering techniques. Here the amino acid sequence of insulin was altered to produce insulins that are more rapidly absorbed from the injection site providing flexibility & lesser hypoglycemia³.

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Limitations of Conventional Insulin

The inherent property of regular human (soluble) insulin (RHI) that it polymerizes to hexameric forms in the insulin vial/pens due to high concentration rendering it to be absorbed slowly into bloodstream from the injection site. These hexameric forms have to be converted to monomers and dimers before absorption. This leads on to variation in absorption kinetics resulting in non predictable responses. Further one has to wait for 30 to 45 minutes after the injection to start the meal. The RHI absorption is delayed by 30 min reaching its peak of action around 120 min. (Fig 1). To circumvent this slow absorption rate thereby to

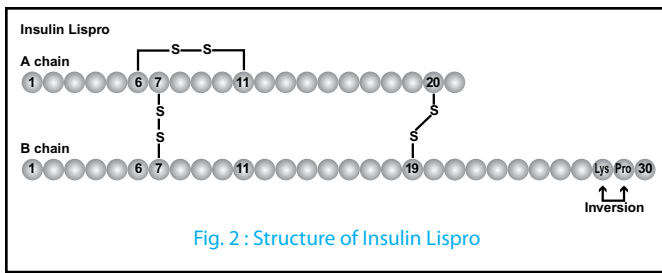


Fig. 2: Structure of Insulin Lispro

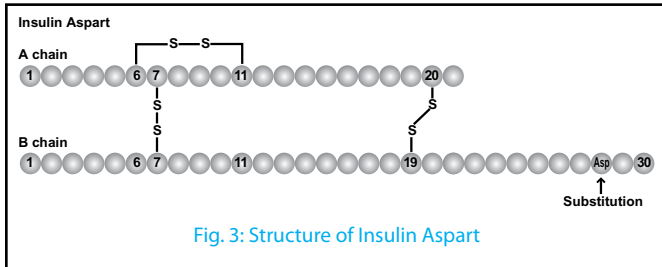


Fig. 3: Structure of Insulin Aspart

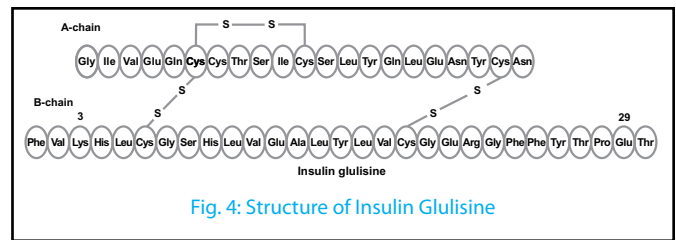


Fig. 4: Structure of Insulin Glulisine

Table 1 : Duration of action of rapid acting analogues:

Insulin Analogues	Onset of Action	Peak Action	Effective Duration
Lispro	5-15 min	30-90 min	4-6 hr
Aspart	5-15 min	30-90 min	4-6 hr
Glulisine	10-20 min	30-90 min	4-6 hr

Rapid Acting Analogues Addressing Unmet Needs

Analogue insulin structure resembles the HI but except that its composition altered to gain advantages over standard human insulin, while retaining the same biological effect. Insulin lispro, insulin aspart and insulin glulisine are the three available ultra short acting analogue insulins. These rapid-acting insulin analogues mimic the physiological profile as compared to RHI, thus improving postprandial glycemic control. These agents are short acting and hence a shorter duration of action, they do not contribute much to between-meal insulin level. These rapid acting analogues can be given immediately before the meals or even immediately after and is preferred by patients as well as health care professionals.

The amino acid changes that have been brought in each of these preparations result in weakly associated hexameric forms, the rapid dissociation of which results in a rapid onset and peak along with shorter duration of action, compared to RHI. Compared with standard soluble insulin, rapid acting insulin analogues may produce a modest but significant reduction in HbA1c after subcutaneous injection with in 3-6 months of initiation of treatment.^{12,13,14}

Insulin lispro, the rapidly acting analogue, differs from regular insulin by virtue of its capacity to dissociate rapidly into monomers in subcutaneous tissue. It was formulated on the premise that insulin-like growth factor 1 (IGF-1), which is structurally similar to insulin, does not tend to self-associate probably because of differences between the C-terminal portion of the B chain of IGF-1 and that of insulin. Inversion of the lysine of B29 and the proline of B28 (Fig 2) of human insulin confers a conformational change that results in a shift in the normal binding of the C-terminal portion of the B chain, which in turn reduces the formation of dimers and hexamers.

The immunogenic profile of insulin lispro is similar to that of recombinant insulin. Even before exposure to insulin lispro, there is an increase in cross-reactive antibodies (i.e., serum reacts with both insulin lispro and human insulin) but not in insulin-specific or lispro-specific antibody levels.¹⁵ These antibodies decrease over time and have no clinical consequences.^{15,16}

Insulin aspart is a novel rapid-acting analogue that was introduced in 1996 in the US and in the later half of 2003 in India. Insulin aspart was developed by replacing proline at B28 with aspartic acid. (Fig 3)

Studies have shown that insulin aspart has twice as rapid onset of action and reaches a higher peak than soluble human

avoid postprandial hyperglycemia, RHI is recommended to be injected 30–60 minutes before a meal, a recommendation that was inconvenient and difficult to comply with; nonetheless there was risk of hypoglycemia if the meal is missed or delayed. This was always a shortcoming.⁴ This necessity led to lack of compliance to timing of injection in relation to the meal and the consequent rise in postprandial blood glucose levels amongst the patients. Moreover, the loss of first phase of insulin secretion, the hallmark of type 2 DM is not addressed well with RHI. Because of this kind of Pharmacokinetics of RHI it has increased chances of pre meal hyperinsulinemia leading to increased mid meal snacking.⁴ Due to these limitations in most patients it was virtually impossible to obtain HbA1c values close to target (DCCT, 1993;^{5,6,7})

Another concern with this insulin due to its relatively long duration of action a huge day to-day variation in glycemic level among the recipients (inter individual) and with in an individual (intra individual)^{5,6} This limiting feature of RHI frequently lead to hypoglycemia. As a result there was invoking interest to produce safer insulins that more closely mimic the physiological endogenous insulin secretion and action and yielded insulin analogues. These are characterized by action profiles that afford more flexible treatment regimens with a lower risk of the development of hypoglycemia.

It is important to understand here that the single most significant factor that has prevented us from establishing good glycemic control is this fear of hypoglycemia and the modern analogue surely help us alleviate this.

Rapid acting insulin analogues or popularly known as rapid acting modern insulins provide an improved glycemic control both pre-prandial as well as postprandial in patients with diabetes mellitus.⁸

As regards to inter-individual variation, Rapid acting analogues due to the virtue of very short duration of action have significantly less variation than that observed with RHI.⁹ In a study of insulin aspart in which a dose of 0.2 unit per kilogram of body weight was used, the time to peak insulin action was 94±46 minutes for insulin aspart, as compared with 173±62 minutes for regular insulin (P<0.001).¹⁰ Use of these rapidly acting analogues also results in less variability in absorption at the injection site and possibly in less variation between and within patients.¹¹

Table 2 : Composition of rapid acting analogues

Ingredient	insulin aspart	insulin lispro	insulin glulisine
Sodium phos. (mM)	7.0	7.0	-
Tromethamine (mg/ml)	-	-	6.0
Meta-cresol (mg/ml)	1.72	3.15	3.15
Phenol (mg/ml)	1.50	"trace"	-
Glycerol (mg/ml)	16.0	16.0	-
NaCl (mg/ml)	0.58	-	5.0
Zinc (µg/ml)	19.6	19.7	-
Polysorbate 20 (mg/ml)	-	-	0.01
Formulation pH	7.2 - 7.6	7.0 - 7.8	≈7.3
Isoelectric point (pI)	5.1	5.65	5.1

insulin in a shorter span of time (See Fig). Therefore it provides better PPG control with low risk of hypoglycemia. The action of insulin aspart like other rapid-acting analogues lasts for only 3-5 hours unlike soluble human insulin whose action lasts up to 8 hours after injection into the subcutaneous tissue.

Insulin glulisine: Insulin glulisine was developed by replacing lysine at B29 with glutamic acid and B3 aspartic acid with lysine. (Fig-4) It contains polysorbate 20 as stabilizer instead of zinc (which is the stabilizer in aspart and lispro insulins).

A detail of the insulin analogues as regards to its onset of action, peak action and duration of all the three short acting analogues are outlined in the Table 1.

"Composition of Rapid Acting Analogues"

It is not only the structure of the modern insulins that is different but there are also differences in the composition of marketed preparations (Table 2). Insulin Lispro and Aspart have Zinc as stabilizing agent where as glulisine has Polysorbate 20 as stabilizing agent. These agents has been shown to increase the stability of insulin formulations and addition of it significantly increases the physico-chemical stability of the insulin molecule.^{17,18} Reduction in the hexameric form increases Physical and chemical instability i.e., increasing the risk of insulin fibrillation. Clinical consequence of physico-chemical instability might be increased risk of pump occlusion, antigenicity and potency. It is unclear if there is any clinical relevance to this.

Clinical Efficacy Profile of Rapid Acting Modern Insulins:

Clinical Advantages of Rapid acting Analogs over RHI are many fold viz.,

- better post prandial blood glucose control,
- good HbA1c control,
- less chance of hypoglycemia and
- meal time flexibility.

Post Prandial Glucose control: As the rapid acting analogues have onset of action less than 20 min and peak of action between 30-90 min it is very well understandable that they control the post prandial blood glucose/first phase insulin secretion very aptly. When compared to RHI which has an onset of action beyond 30 min and peak of action around 90-120 min, the analogue insulins match with the prandial glucose peak and

thus control the prandial glucose increments. This rapidity in absorption, earlier peak with short duration of action imparts the rapid acting analogue insulins a more physiological prandial insulin profile.^{19,20,21}

Euglycemic clamp study in healthy volunteers showed that insulin aspart has 'twice as rapid onset and as high peak' than soluble human insulin²² (Fig-1). Raskin et al showed, analogues like Insulin aspart provide superior postprandial glycemic control in comparison to HI after 6 and 12 months without any increased risk of hypoglycemia.¹⁴ Better glycemic control, as assessed by measurement of serum glucose excursions over 4 and 6 hours was achieved with insulin aspart administered immediately or 30 minutes before a meal than with regular insulin administered immediately or 30 minutes before a meal in both type 1 and 2 diabetes.^{23,24} Postprandial glycemic control was more effective with insulin aspart than with regular insulin in randomized, non blind comparisons in patients with type 1 diabetes. Postprandial glucose levels were generally significantly lower in patients receiving insulin aspart than in regular insulin recipient in all trials.^{12,13,14,15}

HbA1c: At higher HbA1c levels ~ 10 and above the contribution of prandial glucose is more to HbA1c, where as the HbA1c reaches the normal values the contribution of fasting blood glucose is more. However, both FPG and PPG contribute to the HbA1c.²⁵ Since short acting insulins analogue control the PPG well, it is logical that they control HbA1c better than RHI. All the three short acting analogues viz., Insulin aspart, lispro and glulisine are better than RHI in this aspect.^{26,27}

Home et al, recorded a significantly lower mean HbA1c levels with insulin aspart than with HI-treated patients at 6 months.²¹ This reduction in HbA1c was maintained for up to 3 years, in a 30 month extension of the study.²⁸ Bretzel et al concluded the same result in patients with type 2 diabetes. Insulin aspart treatment resulted in improved HbA1c and postprandial blood glucose with lower incidences of hypoglycemic episodes in a 6 month study.²⁹

Hypoglycemia: The more rapid pharmacodynamic effects of insulin lispro, insulin glulisine and insulin aspart make postabsorptive hypoglycemia less of a problem with these analogues than with regular insulin.^{19,30-34}

A large meta-analysis that represented more than 1400 patient-years reported a 25 percent reduction in the frequency of severe hypoglycemia with the use of insulin lispro, as compared with regular insulin.³⁵ Insulin lispro had an overall 47% lower incidence of nocturnal severe hypoglycemia.³⁶

Similar study profile done by Heller et al, with insulin aspart and compared with RHI in Type 1 diabetes showed when injected immediately before meals as part of intensive insulin therapy the rate of major nocturnal hypoglycemic episodes was 72% lower with insulin aspart than with human insulin.³⁷

Meal time Flexibility: The meal time flexibility of analogue insulins is highlighted by various studies. Brunner et al. reported that mean plasma glucose excursions were not statistically different for insulin aspart (0 min, +15 min) and HI (-15 min), (11.9, 14.2, 13.6 mmol.l-1.h, respectively). The plasma glucose excursion for HI (0 min) was 17.9 mmol.l-1.h. (p < 0.05 versus other treatments). Mean time to maximum concentration of plasma glucose for insulin aspart was (0 min, +15 min) and HI (-15 min, 0 min), was 75, 80, 99, 94min, respectively.³⁸

Lispro insulin can be given 0-15 minutes before meals, or even immediately following a meal. Administering lispro insulin

before or immediately following meals is one of the proposed advantages of using lispro over regular insulin³⁹

Use of Short Acting Modern Insulins in Special Situation

Critical Care

It is proven beyond doubts that improved glycemic control has been associated with improved hospital outcomes in patients with or without critical illness. Current practice guidelines recommend maintaining the blood glucose at <180 mg/dL in hospitalized patients.

A protocol developed by a Munoz et al is based on the observations by Umpierrez et al. that a rapid-acting insulin analogue such as aspart, given subcutaneously (SC) every 2 h can mimic the efficacy of a continuous i.v. insulin infusion with far less technical complexity.

The protocol provides a chart to calculate an initial dose of SC insulin aspart based on patient weight and presenting blood glucose (BG). If the initial BG \geq 400 mg/dL the insulin aspart was used at 0.2 U/Kg, if BG between 300-399 mg/dL – 0.15 U/Kg and if BG 200-999 mg/dL – 0.1 U/Kg of insulin aspart was used. In the insulin aspart group, mean BG declined from 333 \pm 104 mg/dL on admission to 158 \pm 68 mg/dL on discharge. In the RHI group, mean BG decline was significantly less, from 322 \pm 126 mg/dL on admission to 242 \pm 79 mg/dL on discharge (p < 0.001).^{40,41} This study concluded that using SC insulin aspart controls the blood sugars better than RHI with less technical complexities.

The advantage of SC analogue insulins is proven unequivocally superior to RHI. In hospital and ICU settings we commonly switch between SC and IV routes. It is definitely more user friendly to use the same insulin when used SC or in IV route. This approach does it lead to some additional advantage if the same modern insulin is used in SC and IV route needs further evaluation.

Diabetic Keto Acidosis:

In a prospective, randomized, open trial, to compare the efficacy and safety of aspart insulin given subcutaneously at different time intervals to a standard low-dose intravenous (IV) infusion protocol of regular insulin in patients with uncomplicated diabetic ketoacidosis (DKA) it was evident that the use of subcutaneous insulin aspart every 1 or 2 h was safe and effective alternative to the use of intravenous regular insulin⁴⁰

In a prospective, randomized, open trial, efficacy and safety of hourly subcutaneous (SC) insulin lispro administration was compared with intravenous (IV) RHI treatment in the treatment of diabetic ketoacidosis (DKA). The researchers concluded that, the treatment of mild and moderate DKA with SC insulin lispro is equally effective and safe in comparison with IV regular insulin.⁴²

Long term efficacy

There are not many studies on advantages of rapid acting analogue insulins in long duration. A comparison between Insulin aspart and RHI in NICE (Nippon ultrarapid Insulin and diabetic Complication Evaluation) study after a median follow-up of 4.5 years (range 3.5-5.0) where in hazard ratios were calculated reported that treatment with rapid-acting insulin analogue showed an improvement in PPG and a reduction in the risk of CV events. The results may be mediated not only by

the improvement in PPG but also by unknown mechanisms of the rapid-acting insulin analogue.⁴³

Analogues in Renal failure:

Insulin is 80% metabolized in liver and 20% kidneys. RHI is known to cause sacking effect in renally impaired patients. Insulin glulisine kinetics is affected in moderate to severe renal failure and the up to 40% increase in the serum concentration of this is also found.⁴⁴ Insulin aspart in renal impaired patients has shown unaltered pharmacokinetics and safety profile was comparable among persons with diabetes with various degrees of renal dysfunction⁴⁵. The prescribing information of lispro reads the dosage to be reduced in advanced renal compromise⁴⁶.

Rapid acting Insulin analogues and GDM

IAsp seems to be the right analogue for GDM because of better control of PPG due to its rapid onset, more flexible regimen because it can be given pre-prandial as well as postprandial, less hypoglycemia and safe for both mother and fetus. Jovanovic et al did a study where he compared the metabolic effects of Insulin aspart with Human Insulin in basal bolus s.c. regimens for patients with GDM that emphasized postprandial glycemic control. The results confirmed that Insulin aspart to be safe and effective and comparable to human insulin in pregnant women.⁴⁷ Recently in one of the largest RCT in diabetic pregnancy it as reported that The fetal outcome using IAsp was comparable with HI with a tendency toward fewer fetal losses and preterm deliveries and IAsp is at least as safe and effective as HI when used in basal-bolus therapy with NPH insulin in pregnant women with type 1 diabetes and may potentially offer some benefits in terms of postprandial glucose control and preventing severe hypoglycemia.^{48,49} Lispro (category B drug) has also been approved in pregnancy based on experience.⁴⁴

Analogues in Insulin Pumps

Replicating endogenous insulin production is the goal of treatment for diabetes mellitus (DM) and is necessary to minimize the risk of vascular complications. The 2 main methods of achieving this goal are continuous subcutaneous insulin infusion (CSII) and multiple daily injections (MDIs) comprising basal and prandial injections.

Hanaire et al, concluded, that when used with external pumps, lispro provides better glycemic control and stability with much lower doses of insulin compared MDI and does not increase the frequency of hypoglycemic episodes.⁵⁰ In patients with type 1 DM, CSII using the rapid-acting insulin analogue insulin aspart has been reported to improve glycemic control in clinical trials compared to MDI therapy using NPH plus insulin aspart (Basal Prandial). In patients with type 2 DM, the CSII and MDI regimens offered similar efficacy and tolerability. Although the efficacy of insulin aspart in CSII was comparable to other rapid-acting insulins, the frequency of hypoglycemia was shown to be significantly lower with insulin aspart compared with human insulin or insulin lispro in patients with type 1 DM.⁵⁰

The compatibility of insulin aspart and insulin lispro for use in CSII pumps was compared in an 8-week, double-blind, 2-period, crossover study of patients with type 1 DM. The overall adverse-effect score was significantly lower (P<0.005) with insulin aspart than with insulin lispro. Furthermore, a stability study reported on the suitability of insulin aspart for use in CSII pumps.⁵¹

A comparison of Insulin aspart CSII vs. insulin glulisine CSII shows comparable Glycaemic control between two treatment groups at comparable Insulin doses. Rate of catheter occlusion

Table 3 : Summary comparison of Glulisine, Lispro, and Aspart

Parameter	Glulisine	Lispro	Aspart
Meal Time Flexibility	Pre as well as post prandial administration	Pre as well as post prandial administration	Pre as well as post prandial administration
Blood glucose control	Similar control in comparison with Lispro	Similar to Glulisine	More than 10 mg/dl reduction as compared to Lispro
Hypoglycemia	Maximum reduction in Nocturnal Hypoglycemia up to 60% vs HI	Maximum reduction in Nocturnal Hypoglycemia up to 68% vs HI	Maximum reduction in Nocturnal Hypoglycemia up to 72% vs HI
Renal Impairment	Conc. increases with moderate to severe renal dysfunction - up to 40%	Dose reduction required	Remains unaffected
Storage	Temp , 30 C	Up to 30 C	Upto 30 C
Shelf Life	24 months	27 Months	30 months

similar between glulisine than aspart with frequency of catheter change of 2.1 ± 0.3 days and 2.0 ± 0.2 respectively. The incidences of nocturnal hypoglycemias were 69% and 50% respectively between Glulisine and Aspart.⁵¹ There was a lesser precipitation with aspart than glulisine leading on to less pump occlusion.⁵²

Mitogenic potential of Insulin analogues

Changes in the structure of the insulin molecule relative to human insulin may affect receptor interaction in unexpected ways. An increased residence time at the insulin receptor or an increased affinity for IGF-I receptors may increase the mitogenic potential of the analogue hormone; such pharmacological effects were associated with carcinogenicity in rodents with the prototype insulin analogue, Asp B10. This was the world's first insulin analogue but the development was stopped due to the unprecedented mitogenic potential. Thus, concerns about the risk of cancer and retinopathy have been debated when insulin analogues have increased insulin receptor residence times or act as IGF-I receptor agonists.

Insulin aspart binds to insulin receptor with similar affinity to human insulin, and to the IGF-1 receptor with slightly lower affinity. Insulin lispro binds to the IGF-1 receptor with affinity 1.5 x greater than human insulin.⁵³

Summary

Limitations of conventional insulin led to the evolution of rapid acting insulin analogues. Insulin analogues are genetically engineered, state of the art, modified or designer insulin's that have changed insulin treatment and improved glycemic control. Several clinical studies have shown that rapid acting analogues under various clinical situations provide superior glycemic control with more convenience and flexibility making them a patient friendly option. In spite of the structural change in modern ultra short acting insulins especially insulin aspart has not shown increase in immunogenic response and mitogenic potential when compared to human insulin. By virtue of reduced risk of hypoglycemia and better pharmacokinetic profile, modern insulins like insulin aspart and lispro are now preferred over RHI for management of diabetes in pregnancy. Although, these three rapid acting insulins are now available for clinical practice use in India, the long term usage and its impact on outcomes is been evaluated with insulin aspart. On the other hand insulin glulisine is a very new entrant and it would be interesting to have more clinical evidence before using it in regular clinical practice especially in situations like children, renally impaired patients, and other special situations. In general, the extensive clinical data with these rapid acting modern insulins it is now well accepted that they help to improve diabetes management significantly.

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