

## Basal Insulin Analogues — Where are We Now?

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Insulin is a polypeptide secreted by the beta cells of pancreas and consists of 51 amino acids (AA). It has two polypeptide chains, the A Chain (21AA residues) and B Chain (30 AA residues) linked by two disulphide bridges as shown in Figure 1.

The first insulins introduced in the market in 1923 were an impure mix (with proinsulin, pancreatic proteins and insulin derivatives as contaminants) of bovine and porcine insulin. These impurities were upto 10000 parts per million (ppm) and were therefore highly antigenic. In 1970s, improved techniques for purification of insulin like gel filtration and ion exchange chromatography became available. By these techniques, impurities in the conventional insulin were reduced to less than 20 ppm and therefore the insulin became much less antigenic. These were the only insulins available for nearly 60 years. It was only in 1980's that the technology to produce human insulin biosynthetically by genetic

engineering called recombinant DNA (rDNA) technology became available.

Human insulins were synthesized by introducing human preproinsulin gene into *Escherichia coli* bacteria, which produced proinsulin. Proinsulin was then converted to insulin and c-peptide by enzymatic conversion<sup>1</sup>.

### Physiology of Insulin Secretion

In a normal person, blood glucose is maintained between 80-120 mg/dl. Insulin secretion is tightly matched to the prevailing blood glucose concentrations in order to maintain perfect euglycemia.

About half of the daily secretion of insulin occurs in the basal state and this helps to modulate the hepatic glucose output and peripheral glucose uptake in between meals and during the night (approximately 50%

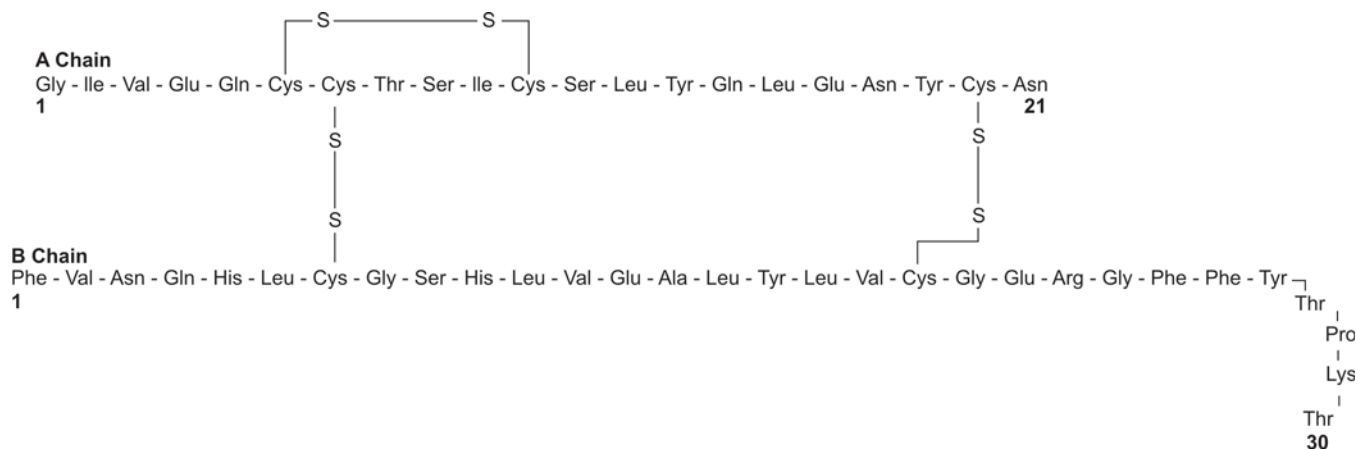


Fig. 1: The human insulin molecule

of the insulin is secreted in the basal condition). In addition, insulin secretion is augmented intermittently by a burst of secretion in response to food. This increased postprandial secretion is in turn, proportional to the extracellular glucose concentration. This pattern of insulin secretion maintains euglycemia throughout the day and night.

### Insulin Secretion in Type 1 and Type 2 Diabetes

In type 1 diabetes, there is near total loss of beta cell mass and hence there is little or no secretion of insulin. If this condition is untreated, it ultimately leads to hyperglycemia, ketoacidosis and death and hence there is a need for exogenous insulin to maintain life and health.

In type 2 diabetes, there is a gradual but progressive beta cell dysfunction and a reduction in beta cell mass occurs as the disease progresses. This leads to abnormal insulin secretory profiles, during basal and postprandial states, which predisposes to late complications. In type 2 diabetes, initially the glycemia is maintained with non-pharmacological measures. Thereafter, starting with one oral hypoglycemic agent, progressively a combination of two or three different agents are needed to maintain euglycemia as the disease progresses. Finally, many patients require exogenous insulin to obtain glycemic control.

### Historical Development of Basal Insulins

In 1923, regular conventional insulin was first used in clinical practice for treatment of diabetes. Since regular insulin has a short duration of action, multiple injections are needed and they still cannot suppress the inter-prandial, nocturnal and fasting hyperglycemia. Moreover this pattern of insulin administration was nowhere near the physiological pattern of insulin secretion. It was thus clear that pharmacological modification of insulin was needed to match the basal profile of insulin secretion<sup>2</sup>.

Protamine and excess zinc were added to the regular insulin to prolong the action of insulin and thus protamine zinc insulin (long acting) was introduced in the 1930's and this was a long acting insulin. In the 1940's, addition of crystalline complex of protamine to regular insulin resulted in NPH (Neutral Protamine Hagedorn) or isophane insulin which is an intermediate acting insulin. Addition of either long acting or intermediate acting insulin with short acting insulin was used to try to match the physiological pattern of insulin secretion. The major limitation to the use of traditional

basal insulins were their unpredictable action profile, because of the substantial day to day variability in absorption which resulted in peaked and prolonged action after subcutaneous injection<sup>3</sup>.

### Insulin Analogues

Insulin analogues are the preparations synthesized to offer different time action profiles. Analogues are produced by means of genetic engineering by changing the amino acid (AA) sequence of insulin molecule or by adding a molecule which slightly differs from that of human insulin (Fig. 2)<sup>4</sup>.

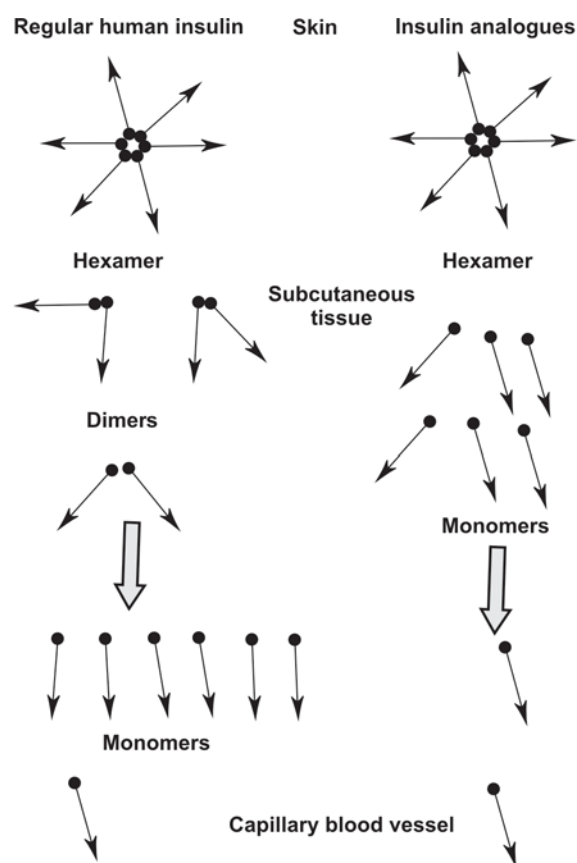


Fig. 2: Difference in degradation of regular human insulin and insulin analogues

By changing the AA sequence, the insulin hexamer can be rapidly dissociated to monomer for a rapid absorption or by delaying the dissociation of hexamer to monomer for slow absorption. The amino acid (AA) changes in analogues were done outside the areas of ligand receptor interaction in such a way that pharmacokinetic action of molecule could be changed without affecting the hormonal action.

### Classification of Insulin Analogues

Insulin analogues can be broadly classified as short acting or long acting as shown in Figure 3.

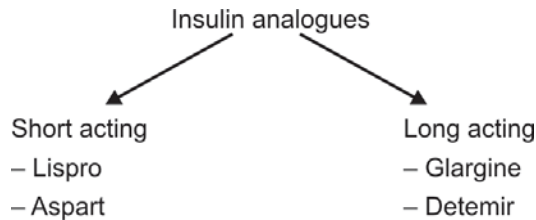


Fig. 3: Insulin analogues

### Mode of Action of Long Acting Analogue

Basal insulin analogues are designed in such a way to protract their absorption from the injected site either by shifting the isoelectric point of the insulin molecule to a neutral pH (glargine) or by attaching fatty acid which can bind to albumin thereby increasing the self association of the insulin molecule (detemir).

### INSULIN GLARGINE

This is a human insulin analogue which is designed to have a low solubility at neutral pH. Asparagine at A21 position has been replaced with glycine and two arginine molecules are added to the C terminus of the B chain (Fig. 4).

Addition of 2 molecules at B chain shifts the isoelectric point of insulin from 5.4 to 7.4 thus making glargine insoluble at physiological pH and thereby delaying the absorption and prolonging its duration of action.

### Pharmacodynamics and Pharmacokinetics

Glargine is completely soluble at the acid pH of the glargine injection solution. After subcutaneous administration, the solution is neutralized, leading to formation of microprecipitates from which small amounts of insulin glargine are continuously released, providing a smooth, peakless profile and a prolonged duration of action. After entering into blood stream, insulin glargine is very similar to human insulin with respect to insulin receptor binding kinetics.

The once daily administration of the glargine insulin is achieved because of its longer duration of action and it is directly related to its slower rate of absorption from the subcutaneous tissue. However, the time course of glargine may vary considerably in different individuals or within the same individual. Because of this, approximately 80% of patients need once daily injection while approximately 20% of patients need twice daily administration of glargine insulin. It takes 2-4 days to reach steady state levels after the first dose of glargine injection<sup>5</sup>.

### Administration

Glargine should be administered once daily at any time of the day irrespective of the meal but at the same time each day subcutaneously. It should be individually adjusted according to the patients need from 2-100 IU once daily. Close monitoring is needed during transition from other insulin to glargine. The dosage of glargine could be reduced approximately by 20% for the first week, when transferring from once daily NPH or ultralente insulin and the dose should be adjusted according to the blood sugar levels thereafter.

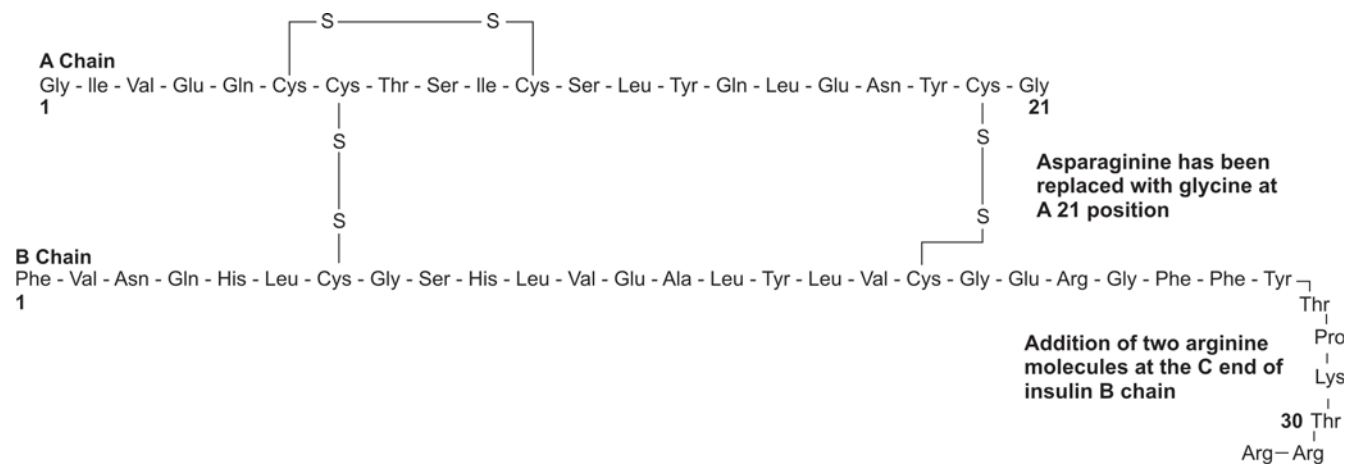


Fig. 4: The insulin glargine molecule

### Advantages of Glargine

1. Basal peakless insulin
2. Once a day dose
3. Flexible - can be given at any time of the day but should be administered at the same time each day.
4. Less hypoglycemic episodes.

### Disadvantages

1. Expensive
2. Cannot be mixed with regular insulin and hence multiple injections are required.
3. Cannot be used in children less than 6 years of age.
4. Not yet approved for use in pregnancy.
5. Vials have to be used within 28 days. Hence only ideal for patients requiring at least 36 units/day.

### The “Treat to Target” Trial

This study comparing insulin glargine with human NPH insulin in type 2 diabetes mellitus, confirmed that insulin glargine given once daily reduces the risk of hypoglycemia compared with NPH insulin and thus facilitates more aggressive insulin treatment to reach the target of  $HbA_{1c} \leq 7\%$  in patients with type 2 diabetes mellitus<sup>6</sup>.

### DETEMIR

Detemir is a peakless, long acting, insulin analogue. Here the amino acid (AA) threonine at B30 position on the human insulin chain is lacking and a 14 carbon fatty acid (tetradecanoic acid or myristic acid) is attached to lysine at B29 (Fig. 5).

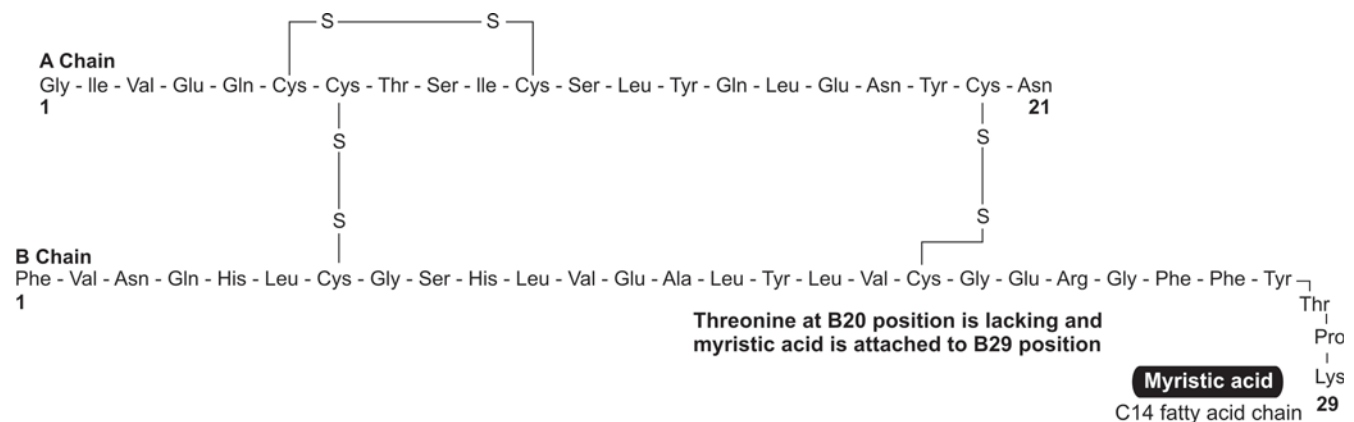


Fig. 5: The insulin detemir molecule

### Pharmacodynamic and Pharmacokinetic Properties

After injecting into the subcutaneous tissue, insulin detemir forms a liquid depot which does not precipitate. Insulin detemir exists as a hexamer like human insulin at a higher concentration in the presence of zinc. Following absorption from the depot, insulin detemir binds to albumin with the help of myristic acid in the plasma and forms a complex which delays dissociation and hence prolongs the action of insulin detemir. This allows for a steady, protracted, peakless action profile of insulin detemir without hypoglycemia.

### Dosage and Administration

Dosage of detemir ranges between 0.2 to 0.5 U/kg/day according to patients' needs. It can be given once or twice daily depending on the dose and the patient. There is a lack of clinical safety data to use in children less than 6 years of age and in pregnancy and lactating women. Approximately 80% of patients need twice daily administration while 20% of patients need only once daily administration of detemir insulin.

### Advantages

1. Basal insulin.
2. Less hypoglycemic episodes.
3. Less weight gain.
4. Less intra-patient variability compared to NPH and glargine (more pre-diabetic action).

### Disadvantages

1. Expensive.

**Table 1:** Classification of insulins based on duration of action

Type	Onset of action	Peak of action (hrs)	Duration of action (hrs)
<b>Rapid acting analogues</b> (Aspart, Lispro)	10 - 30 min	1-3	3 - 4
<b>Short acting insulin</b> (Regular)	30 - 60 min	2 - 4	6 - 8
<b>Intermediate acting insulin</b> (NPH or Isophane, Insulin)	60 - 120 min	4 - 7	8 - 16
Zinc Suspension (Lente)	60 - 120 min	8 - 10	20 - 24
<b>Long acting insulin</b> (Extended insulin zinc suspension (Ultralente))	4 - 6 hours	14 - 18	24 - 36
Long acting analogues (Glargine, Detemir)	2 - 4 hours	Peakless	Upto 24
	2 - 4 hours	Peakless	12-16

2. Cannot be mixed with regular insulin, multiple insulin injections needed.

3. Twice daily injection in most patients.

Data from the German cohort of the Predictive study support that insulin detemir improves glycemic control, reduces the incidence of hypoglycemia and maintain weight neutrally in clinical practice<sup>7</sup>. Another study showed that subjects with Type 1 DM treated for 6 months with detemir + human soluble insulin experienced comparable glycemic control but significantly lower within subject variability and lower glucose excursions compared to subjects treated with NPH and human soluble insulin<sup>8</sup>. Table 1 summarizes the action profiles of the various insulin available today.

## CONCLUSIONS

Basal insulins have a definite role in the treatment of diabetes. In many patients with type 2 diabetes requiring insulin, addition of a single basal insulin would probably suffice. Basal insulins help to control fasting hyperglycemia and to control interprandial blood sugar levels. The advent of glargine and detemir have added a new dimension to the use of basal insulin in therapy of diabetes. The only limiting factor is the cost of these insulin which make them unaffordable to a section of the society.

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