Engineering Basal Insulin—Clinical Evidence Translating to Clinical Experience

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Abstract

Type 2 diabetes mellitus is a progressive disorder demanding a dynamic approach in its management. The chronic complications related to diabetes mellitus can be reduced with strict glycaemic control. Not only in type 1 but also in type 2 diabetes the insulin therapy is an essential treatment option. The goal of exogenous insulin therapy is to mimic endogenous insulin secretion. The earlier human insulins had few shortcomings in terms of time action profile and variability leading to inconvenient injection timings and undesirable effects. To overcome these shortcomings and to match the physiological insulin secretion, minor alterations in the insulin structure led to the development of insulin analogues/modern insulins. Three varieties of modern insulins available in practice are rapid acting, long acting and the premixed analogues. The advent of basal modern insulins has made insulin therapy more convenient for people with diabetes. The basal insulin provides the background flat and continuous insulin supply at a low rate. The long acting basal analogues like insulin detemir and glargine have better safety profile and longer duration of action compared to NPH. These basal insulin analogues provide a long, peakless and protracted course of action permitting once daily administration. Both these modern basal insulins have comparable efficacy. However, the unique property of albumin binding of insulin detemir reduces the variability making it even more predictable. Also the weight neutrality observed with insulin detemir makes it an interesting treatment option for people where weight gain with antidiabetic therapy is a concern.

Diabetes mellitus (DM) is characterized by absent insulin secretion by pancreatic beta cells (type 1) and both or either of resistance to the action of insulin and/or impairment insulin secretion in peripheral tissues (type 2), resulting in dysregulation of blood glucose (BG) levels. The hyperglycemia itself, when it remains uncontrolled, impairs beta-cell secretory action and tissue sensitivity to insulin, a phenomenon called glucotoxicity, further compromising insulin secretion and action, thus setting up a vicious cycle.

The treatment of diabetes should always be based on specific target goals. The primary goal of treatment should be directed towards prolongation the life of patients with diabetes along with a secondary goal of improving their quality of life. The quantity and quality of life, of patients are mainly influenced by the micro and macrovascular complications of diabetes. It is well known from studies in both types of diabetes that lowering HbA1c can reduce the risk of both micro as well as macrovascular complications; however, the reduction in macrovascular complication is debated.

In type 1 diabetic patients specifically this trend was reported by Diabetes Control and Complications Trial (DCCT) (Figure 1). Another large observational study the United Kingdom Prospective Diabetes Study (UKPDS) in Type 2 diabetic patients showed that also in type 2 diabetes microvascular complications are directly related to HbA1c. However, in macrovascular diseases, there are other risk factors that are to be considered.
in addition to glucose, like lipid levels, blood pressure and clotting factors.\(^5\)

There are many options available for achieving glycemic control in type 2 diabetes such as insulin, oral antidiabetics and non insulin injectables. The rationale of use of insulin comes from the finding that impaired insulin secretion in type 2 diabetes is due to failing β-cell function in these patients.\(^4\) In this regard it needs a progressive adaptation of treatment. This has also been taken into account in the consensus guidelines issued by American Diabetes Association (ADA) and the European Association for the Study of Diabetes (eASD) (Figure 2). Consensus guideline advocates initiating insulin early in the course of management when Lifestyle modifications plus metformin fail to keep HbA1c ≤ 7%. Currently available oral antidiabetic drugs and even the newer drugs like GLP-1 analogues like exenatide have ability to reduce HbA1c by 1–1.5% at maximum doses. Insulin is the only drug which gives unlimited potential to titrate, and necessary to maintain the targeted HbA1c levels.\(^5\)

Insulin—Role in Diabetes

The discovery of insulin in the 1920's was a landmark in the history of diabetes. Later on, the physiological insulin secretion profile was elucidated, which consists of meal related rise in the insulin levels immediately at the beginning of the meal and then drop over 4-5 hours after the meal (Figure 3). Meal related insulin generally takes care of post prandial glucose. On the other hand there is a continuous background supply of basal insulin secretion. Basal insulin secretion is flat, low rate and is continuous over 24 hours. Basal insulin secretion takes care of hepatic glucose output and mainly affects fasting glucose levels.\(^6\)

Shortcomings of conventional human insulins

The older animal insulins paved the way for more advanced human insulins such as regular soluble insulin, neutral protamine hagedorn (NPH) and ultralente starting from early 1980's. However, when injected subcutaneously, the time-action profiles of these human insulins do not match the physiological insulin secretion pattern of the body (Figure 4). Regular insulin has a relatively slow onset of action (30-60 minutes) and acts for a long (6-8 hrs) in comparison to the endogenous insulin secretion pattern. An even bigger problem, is that there is significantly high intra- and inter individual variability observed due to inconsistent absorption profiles, particularly with intermediate acting insulins, like NPH. If NPH is given at bedtime to patients, then fasting glycaemia can be suppressed but it often causes nocturnal hypoglycaemia due to unpredictable insulin profiles. A disturbing side effect is that most of the insulins are associated with is weight gain, particularly when NPH is administered in type 2 patients as basal insulin, if the dose is titrated to high levels in the patient.\(^7\) Hence, we are often not able to achieve safe and tight glycemic control, which is expected from the exogenous administration of the natural human insulin. All these shortcomings led to the research on more efficient insulins with improved pharmacokinetic profile.

Insulin Analogues in Diabetes management

To address the shortcomings of conventional human insulins, modern insulins were developed with an ability to better mimic the physiologic insulin secretion profile of the body. These insulins differ in structure from the natural insulin at one or two amino acid positions only. The presently available insulin analogues are categorized into rapid acting, long-acting and premixed varieties.

The rapid acting analogues are insulin aspart (Novorapid\(^\text{®}\)), lispro (Humalog\(^\text{®}\)) and glulisine (Apidra\(^\text{®}\)) which provide postprandial glucose control. The premixed formulation contains a rapid acting analogue and the protaminated form of the same analogue in a single formulation, so as to provide prandial as well as the basal coverage in a single injection. Different mixtures are available, with different relative contributions of short versus protaminated formulation (e.g. 30% aspart and 70% protaminated aspart). The long acting insulin analogues, insulin glargine (Lantus\(^\text{®}\)) and insulin detemir (Levemir\(^\text{®}\)) provide a flat, peakless and 24 hour insulin coverage for basal insulin replacement.

It is important to choose a correct regimen of insulin therapy in type 2 diabetic patients for reaching the glycemic targets. Premix insulins are a good choice to start with as they provide both the prandial as well as basal coverage in a single formulation depending on the profile of the patient. The major function of basal insulin in type 2 diabetics, who fail oral antidiabetic therapy, is to suppress the hepatic glucose output during the night, thus controlling the fasting glucose.

Basal insulin analogues

The molecular structure of insulin glargine consists of modifications in both A as well as B chain of the insulin profile was elucidated, which consists of meal related rise in plasma insulin levels (Mean)
molecule. In the A chain, substitution was made by replacing asparagine with glycine and two arginine residues were added to the C-terminus of the B-chain. By this modification, the isoelectric point of glargine shifts from pH 5.4 to 6.7, making glargine completely soluble in an acidic solution. When injected subcutaneously, it precipitates under the skin’s physiological pH, resulting in a crystallized form. The unpredictable nature of the formation and redissolution of a precipitate might, however, introduce an important source of variability.

Insulin detemir is another unique molecule with modifications in the B chain of the insulin structure. Amino acid Threonine was deleted from the B30 position and in addition a C-14 fatty acid chain has been attached at B29 position. This modification gave it a unique protein binding property. It was found to bind reversibly to the most abundant protein in the body, albumin, and therefore, gets a protracted action. Levemir®, when injected subcutaneously, binds to albumin and other tissue proteins in the subcutaneous tissue. After moving to the bloodstream, it binds to albumin in the plasma, resulting in a second buffering stage. It even binds to albumin in the interstitial tissues in the muscle, liver or fatty tissues resulting in a very stable protracted profile.

Rationale for Using Basal Insulin Analogues

Given subcutaneously, long acting insulin analogues mimic the physiologic basal insulin and have shown their superiority over the conventional basal insulins due to various unique properties.

Basal insulin analogues: Duration of action

An isoglycaemic clamp study using continuous glucose monitoring system showed that once-daily dosing of both detemir and glargine provides comparable glycemic efficacy over a 24-hour period in Type 2 diabetic patients. Also, in a recent clamp study conducted in type 2 diabetic patients it was found that the time-action profiles of insulin detemir are identical to that of insulin glargine at clinically relevant doses. In a review article evaluating of glucose-clamp studies, Heise and Pieber concluded that the mean duration of action of insulin detemir and insulin glargine in the clinically relevant dose range is close to 24 h in type 1 diabetics and at least 24 h in patients with type 2 diabetes patients. These findings in controlled conditions are also consistent with observations in real patient settings and support routine once daily use with either analogue, particularly in people with type 2 diabetes. The German and European cohort of Predictive study used once daily Levemir in real life clinical practice. In this study 82% of type 2 diabetics in German cohort and 77% in European cohort achieved glycemic control with once daily Levemir. In an Indian study also Levemir once daily was used in all the study subjects in combination with an oral antidiabetic drug. In 131 insulin naïve type 2 diabetic subjects, it was concluded that adding once daily Levemir to OADs resulted in significant improvement in HbA1c, fasting as well as post prandial glucose profiles with a minimum weight gain. Basal insulin analogues: Predictability

Predictability reflects into intra-patient as well as inter-patient variability in action of a drug. More the predictability of the insulin, lesser will be the chance of hyperglycaemic as well as hypoglycaemic episodes. Insulin detemir was found to be more consistent with each injection and with a long and flat time-action profile. A clamp study in patients with type 2 diabetes comparing pharmacokinetics of insulin detemir and insulin glargine showed that detemir has a flat profile, similar to that of glargine and with a lower within-subject variability. In another recently published review of isoglycaemic clamp studies in type 1 and type 2 diabetes showed that both the basal analogues insulin glargine as well as insulin detemir show a gentle rise and fall in glucose-lowering action over time. Taking into consideration clinically relevant dose range of 0.35 – 0.8 units/kg, the duration of action is 24 h or more for both drugs in question. In comparison to NPH, both glargine and detemir appear flat and we should remember that they are not absolutely peakless.

Basal insulin analogues: Clinical Efficacy

A number of studies have investigated the efficacy and safety of insulin glargine in comparison with NPH. In a long-term study, insulin glargine was compared with NPH insulin, in combination with human regular insulin. Baseline to endpoint decrease in HbA1c was similar in both groups in this study, but the baseline to endpoint reduction in fasting plasma glucose was significantly greater with insulin glargine than with NPH insulin. The incidences of symptomatic, nocturnal or severe hypoglycaemia were significantly lower in the insulin glargine treatment group compared with NPH insulin treatment group.

Data taken from different phase 3 studies on Levemir in people suffering from type 1 diabetes were analysed on the basis of hypoglycaemic risk vs. HbA1c (Figure 7). According to the data collated from these studies, insulin Levemir showed lesser hypoglycaemic events when compared to NPH at similar HbA1c levels. In other words, the closer we reach the HbA1c targets with NPH higher is the risk of hypoglycaemia. Figure 5 shows that Levemir, in comparison to NPH, provides the same level of HbA1c reduction with less hypoglycaemia or with the same level of hypoglycaemia provides much better HbA1c reduction. The same was the result seen in patients suffering from type 2 diabetes.

14 week data from a large observational study PREDICTIVE study with more than 35,000 type 2 diabetics has shown significant improvements in HbA1c. Patients who switched from a basal–bolus regimen using NPH insulin or insulin glargine experienced a 0.5 and 0.4% drop in HbA1c and a 55 and 51% reduction in major hypoglycemia respectively (p<0.0001). Another group, who switched from a human insulin basal–bolus regimen to insulin detemir plus insulin aspart, had reductions of 55% and 0.6% in major hypoglycemia and in HbA1c, respectively (p<0.0001).
In a study conducted by Rosenstock et al. in type 2 diabetic patients, who were randomized into receiving Lantus® once-daily or Levemir® once or twice-daily along with oral antidiabetic drugs showed that in the duration of one year, the HbA1c levels were maintained at the required standards.18 There was no overall difference in the nocturnal hypoglycaemia. A weight gain difference of 1 kg was observed between the detemir- and glargine-treated patients. At the end of the study it was observed that 55% of the patients were switched by the investigators to twice-daily Levemir®. However, the shift of patients from Levemir® once-daily to twice-daily did not make a difference in HbA1c levels. However, in the once-daily Levemir® group the overall nocturnal hypoglycaemia and weight gain was found to be less as compared to twice-daily Levemir® group. Hence, addition of once daily Levemir® to other oral antidiabetic drugs can control fasting glycaemia and lower HbA1c levels to target as efficiently as other basal insulins, with the major asset of having lesser gain in weight.19 However, a critical appraisal of results of Rosenstock et al is required here. Glargine was used once daily as the prescribing information did not allow twice daily administration and had the same criterion which was used for titrating the detemir has been applied even for glargine, 87% of patients on glargine would have required twice daily injection vs 83% of patients on detemir.

Basal insulin analogues: Safety profile

Risk of hypoglycaemia is one of the major limiting factors for the intensive insulin therapy in diabetes management. However, many controlled clinical trials have confirmed the safety of basal insulin analogues as compared to NPH insulin. Many studies have shown that the treatment with insulin glargine was associated in significant improvement in the incidence of nocturnal hypoglycaemia as well as severe episodes of hypoglycaemia as compared to NPH insulin.17,20 Similar data are available for detemir. In a review, Home et al. (Figure 6) have compiled data from nearly 14 studies done on insulin detemir and conclude to a dramatic risk in hypoglycaemia risk in patients using detemir vs NPH.21

A recent large randomized trial comparing efficacy and tolerability of insulin detemir or insulin glargine in combination with insulin aspart was conducted for the duration of 26 weeks in type 1 diabetic patients. It was found that HbA1c reduction was similar in both groups, risk of severe hypoglycemia was 72% less and risk of nocturnal hypoglycaemia was 32% less in the insulin detemir group than insulin glargine group. Overall risk of hypoglycaemia was similar for both the groups.22

For insulin detemir, the binding to albumin has been shown to be independent of the binding of drugs in the two major binding pockets that are located in domains IIA and IIIA of the albumin molecule. Thus, insulin detemir is unlikely to be involved in clinically significant drug interactions at the albumin binding level.23 Moreover, considering the excessive abundance of albumin molecules compared to the small amounts of circulating detemir, even severe albumin losses or hypoalbuminæmia conditions do not affect the action profile and safety of detemir.

Basal insulin analogues in children and special situations

The studies of efficacy and safety of insulin glargine in children is scarce. The largest comparative study in type 1 diabetic children (n=349) compared insulin glargine (once daily) versus NPH (once or twice daily) over six months. The trial reported no difference between treatments in their effect on HbA1c, non significant reductions in severe hypoglycaemic and severe nocturnal hypoglycaemic episodes in the glargine group but fasting blood glucose decreased more in the insulin glargine than the NPH insulin group. Also, no differences in frequency of symptomatic hypoglycaemia were reported.24 Carefully conducted comparative studies of insulin detemir with NPH insulin have been carried out in paediatric patients with type 1 diabetes. A randomized, parallel-group, study compared once or twice-daily insulin detemir with NPH insulin in type 1 diabetic children. HbA1c values were similar in the two treatment groups after 26 weeks, but there were significant differences in within-patient variability in fasting plasma glucose, as well as fasting glucose, nocturnal hypoglycaemia (26% lower risk on detemir than on NPH insulin; p=0.041) and change in body mass index (BMI), all favouring insulin detemir.25 The data from another study suggests that insulin detemir can be used in children and adolescents with type 1 diabetes using titration guidelines similar to those used in adults. Moreover, insulin detemir may offer the advantage of greater predictability of response in comparison to NPH insulin due to lower total variability and a lesser degree of kinetic disparity across age-groups.26 Insulin detemir has been approved for use in the US in children over the age of six years.

Data of insulin glargine in patients with renal or hepatic impairment is again scarce whereas a study of insulin detemir in adult patients undergoing haemodialysis or having renal or hepatic impairment did not show any change in the pharmacokinetic profile as compared to the healthy volunteers.27

![Fig. 6: Evidence of Lesser Hypoglycemia with insulin detemir in comparison with NPH](image)

RR Levemir vs NPH

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| Table 1: Receptor Binding, Metabolic and Mitogenic Potency of Basal Insulin Analogues |
|---------------------------------|----------------|----------------|----------------|----------------|----------------|
| Insulin receptor affinity       | Metabolic potency | IGF-1 receptor affinity | IGF-IR/IR affinity | Mitogenic potency |
| Human Insulin                  | 100             | 100            | 100             | 1              | 100            |
| Insulin Glargine               | 86±3            | 60±3           | 641±51          | 7.5            | 783±13         |
| Insulin Detemir                | ~18.46          | ~27            | 16±1            | 0.9            | ~11            |
Basal insulin analogues and weight gain

Insulin is an anabolic hormone and there exists a positive correlation between weight gain and tight glycemic control. Concerns about increasing weight have been a barrier to initiation and particularly to intensification of insulin therapy. With the use of basal insulin analogues, especially with insulin detemir, this problem of weight gain is answered to a great extent. It has been reported in most clinical trials in patients with diabetes that therapy with insulin detemir results in significantly less weight gain than with NPH insulin or insulin glargine.10–20

Even recent studies of insulin detemir shows the same trends and defies the notion that weight gain with insulin therapy is inevitable.10,21

If we compare the results of two treat to target studies done by Riddle et al (Glargine vs NPH) and Hermansen et al (Detemir vs NPH) it was obvious from the studies that treatment with glargine as well as with detemir were better as far as the hypoglycaemic events were considered. However the weight gain with glargine was nearly one third with that of NPH whereas treatment with glargine did not show any benefit in this regard.20,21

Insulin Receptor Binding Kinetics of Basal Insulin Analogues

Mitogenic effects of insulin are primarily mediated via the insulin-like growth factor-1 (IGF-1). It is now an accepted fact that insulins with more affinity towards the IGF 1 receptor have more mitogenic potential. Insulin receptor binding kinetics of insulin detemir is similar to those of regular insulin, whereas as the affinity for IGF 1 receptor about 6 times less. However, insulin glargine appears to have a higher affinity for the IGF-1 receptor than regular human insulin (Table 1).21,22 Increased binding time at the insulin receptor or increased affinity for IGF-1 receptors may increase the mitogenic potential. In the case of insulin detemir, the ratio of insulin receptor affinity to IGF-1 receptor affinity is not increased relative to insulin receptor affinity, and this is reflected in a lower mitogenic potency of this molecule in human cancer cell line. The in vitro profile of insulin glargine thus raised safety concerns, while that of insulin detemir did not.23

Conclusion

Good glycemic control is the key in the management of diabetes, reducing the risk or progression of complications. While no treatment is at present able to perfectly reproduce a physiological insulin profile, several insulin analogues look promising. The modern basal insulins have achieved lower HbA1c levels in more patients with lesser hypoglycaemic events, hence helping patients to achieve the targets and improved quality of life. The modern basal insulin Levemir has the added advantage of weight neutrality and better predictability.

References


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