Once regarded as a single disease entity, diabetes mellitus (DM) is now seen, as a heterogeneous group of diseases characterized by chronic hyperglycemia, from whatever cause leading to complications involving cardiovascular, renal, neurological and ophthalmic systems.

Over the years, prevalence of diabetes continuously increased; and according to recent estimates, around 143 million people worldwide are affected with DM. The number is expected to reach 300 million mark by the year 2025. In India, the prevalence ranges from 2.4% to 11.6% with a higher prevalence in urban areas.[1]

The goal of treatment of DM is maintenance of long term near normoglycemia to prevent the onset and/or progression of long-term complications. Pharmacotherapy plays a crucial role in this regard. For type 1 DM, this goal can be achieved with the use of different available models of insulin replacement therapy that mimic physiologic insulin secretion, and in case of type 2 DM, oral hypoglycemic agents alone, or in combination with insulin are used.[2]

Presently, insulin plays a pivotal role in the management of DM. Different types of insulins are available for therapeutic use and are shown in Table 1.

Presently practised regimens in the intensive management are
• Split Mixed regimen- twice daily injections of mixture of regular and intermediate acting insulin.
• Multiple Component insulin regimen- two shots of ultralente, one at breakfast and one at supper along with three shots of lispro, one each before the major meals.
• CSII (Continues subcutaneous insulin infusion) with infusion pump device adjusting a basal supply and then providing the bolus at breakfast, lunch and supper. This regimen is taken as the gold standard.

Though these regimens are commonly used, there are few drawbacks like
• Intermediate and long acting insulin preparations do not give a smooth and steady concentration of insulin
• They all show a peak at some point in their duration of action, which carries a potential chance of precipitating hypoglycemia and also increase the need for mid morning, afternoon or evening snack resulting in weight gain.
• Multiple injections reducing patient adherence
• Though CSII may offer better control, it requires lot of

The current approach in the treatment of DM consists of intensive management with the help of insulin replacement therapy and has two components
1. Basal supply of insulin to mimic physiologic insulin secretion, which is provided with longer-acting insulin preparations.
2. Rapid acting insulin to normalize the postprandial hyperglycemia

**ABSTRACT**
The main goal of treatment of diabetes mellitus (DM) is to maintain long term near normoglycemia. Insulin therapy plays a pivotal role in the management of DM. Most insulin preparations and insulin delivery systems, do not mimic the physiological insulin secretion in the body, leading to impaired metabolic control and increased hypoglycemic attacks. Insulin glargine is newer, long acting insulin analog with duration of action of 24 hr. It practically does not show any peak over its duration of action. In various clinical trials, it has shown comparable/better efficacy than the currently used insulin replacement therapies with no increased side effects. In the current scenario, though it is difficult to achieve an ideal insulin replacement therapy, insulin glargine is definitely a positive step in that direction.

**KEY WORDS:** Diabetes mellitus, newer insulin, peak less insulin

**Table 1: Different insulin preparations with their time action profile**

<table>
<thead>
<tr>
<th>Type</th>
<th>Insulin preparation</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Effective duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid acting</td>
<td>Lispro, Aspart, Glulisine</td>
<td>&lt;0.25</td>
<td>0.5-1.5</td>
<td>3-4</td>
</tr>
<tr>
<td>Short acting</td>
<td>Regular</td>
<td>0.5-1</td>
<td>2-3</td>
<td>4-6</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td>NPH</td>
<td>2-4</td>
<td>6-10</td>
<td>10-16</td>
</tr>
<tr>
<td>Lente</td>
<td></td>
<td>3-4</td>
<td>6-12</td>
<td>12-18</td>
</tr>
<tr>
<td>Long acting</td>
<td>Ultralente, Insulin glargine*</td>
<td>6-10</td>
<td>10-12</td>
<td>18-20</td>
</tr>
</tbody>
</table>

*Glargine has no peak activity.*
patient education and motivation.

CSII is not a very cost effective option for a vast majority of the population.\[2,3\]

Hence, there is a need for better insulin preparation that can overcome these shortcomings, and mimic physiological insulin secretion.

Insulin glargine is a human insulin analog, with a duration of action of 24 hrs with no peak and gives good glycemic control. Though it doesn’t address all the above problems, it is definitely a remarkable step towards the goal.

**Salient features**\[4-6\]

Insulin glargine is a long acting human insulin analog produced by DNA recombinant technology.

- Aspargine is replaced by glycine at 21 position in A.A. chain, and two arginine residues are added to the C- terminus of the B chain of normal insulin to produce insulin glargine.
- This is a clear solution at lower pH (pH=4) but forms amorphous micro-precipitates at normal body pH, when given subcutaneously.
- From these micro precipitates, insulin is slowly and steadily released in the circulation for about 24 hr.
- It has no pronounced peak effect.
- Has lesser incidence of nocturnal hypoglycemia.

**Pharmacokinetic**

**Absorption**

The rate of absorption of insulin glargine is very slow with a significant residual activity at 24 hrs compared to NPH. There is also little or no difference in the rate of absorption of insulin glargine among the main subcutaneous injection sites.\[7\]

In the study conducted by Lepore et al to compare the pharmacokinetics/dynamics of insulin glargine with NPH, Ultralente and CSII of insulin Lispro, 20 patients of type 1 diabetes were studied on four occasions, by using an isoglycemic 24hr clamp technique.

Patients received SC injection of either 0.3 U/kg glargine or NPH insulin. On two subsequent occasions, they received either a SC injection of Ultralente or CSII (0.3U/kg/24hr). After SC insulin injection or CSII, intravenous insulin was tapered, and glucose was infused to clamp plasma glucose at 130 mg/dl for 24 hr. More than 50% reduction in IV insulin was taken as onset of action and an increase in plasma glucose above 150 mg/dl was considered the end of action of insulin preparation.

Figure 1a and 1b illustrate that - NPH and Ultralente both show a peak activity. Duration of action of Ultralente is greater, but inter-subject variability is more than that of NPH. Glargine is peak-less insulin, its duration of actin is almost 24 hr, it has lower inter-subject variability than NPH and Ultralente, and it closely mimics CSII, the gold standard of basal insulin replacement therapy.\[8\]

**Biotransformation**

Insulin glargine is metabolized by sequential cleavage at the carboxy terminus of the B chain, to yield products M1 and M2, both of which are structurally similar to human insulin. Studies also suggest that metabolism of insulin glargine is initiated at the injection site and continues within the circulatory system.\[9\]

Not many trials are done regarding its pharmacokinetics in case of pregnant women, lactating mothers and paediatric age group below 6 years of age. In case of hepatic and renal disease, dose reduction is recommended.\[10\]

**Pharmacodynamics**\[6,11-15\]

- Activation and deactivation kinetics of EGO (endogenous
glucose output) peripheral glucose utilization and absolute disposal rate are similar to human insulin.
• Symptomatic and counter regulatory hormone responses during hypoglycemia are similar to human insulin.
• It has a favorable effect on lipid profile by reducing plasma levels of fatty acids through inhibition of lipolysis.
• In type 2 DM patients it has shown to improve endothelial dependent and endothelial independent vasodilatation.
• It has 6-8 times more affinity for insulin receptors as compared to human insulin and has more mitogenic potential.

**Comparative clinical trials**

**Type 1 diabetes mellitus**

An open labeled parallel group trial with 32 type 1 DM patients comparing CSII of insulin lispro and Insulin glargine with pre-meal lispro has shown that both CSII and MDI of Lispro+glargine equally improves metabolic control (improvement in HBA\(_1c\), levels, fasting plasma glucose, and triglycerides) and reduce episodes of sever hypoglycemia in type 1 DM patients that are unsatisfactorily controlled on MDIs using NPH as basal insulin.\[16\] A study recently published has also shown that the MDI with a glargine based regimen was less expensive by $5000 annually with similar efficacy to CSII.\[17\]

In another study, the effects of insulin glargine bedtime or dinnertime and NPH insulin (17 patients in each group) were studied for 3 months. Insulin glargine had not shown any significant improvement in plasma glucose levels but was more effective in reducing HBA\(_1c\) levels and hypoglycemic attacks. There was no significant difference in bedtime or dinnertime insulin glargine.\[18\] It is also been documented that glargine can be given anytime of the day with similar glycemic control.\[17,19\]

Large open labeled controlled randomized trials for 16 weeks (619 subjects) and 4 weeks (comparing two preparations of insulin glargine) where NPH was compared with insulin glargine, showed that basal insulin therapy with insulin glargine is at least as safe as NPH, and as effective as NPH insulin twice a day in maintaining glycemic control in type 1 DM patients.\[20,21\]

In five different studies where insulin glargine was compared with NPH in children and adolescent age group (controlled randomized clinical trials. sample size 114,37,25, 361 and 349), three studies suggest that insulin glargine gives better or at least comparable glycemic control (in one study glycemic control was not a study objective). Four studies also show that incidence of sever hypoglycemic attack is reduced in case of glargine, when compared with NPH. Three of those studies have also shown that insulin glargine significantly reduces incidence of nocturnal hypoglycemia without jeopardizing glycemic control.\[22-24\]

**Type 2 diabetes mellitus**

In three studies done with patients of type 2 diabetes mellitus who are on oral hypoglycemic agents, effects of insulin glargine were compared with NPH. All these studies have shown that insulin glargine is as safe as NPH insulin when given with the oral hypoglycemic treatment. Insulin glargine has shown better glycemic control and fewer incidences of hypoglycemias, especially nocturnal hypoglycemias, as compared to NPH insulin. Similar effects were found in a study where 518 patients with type 2 DM, who were previously treated with insulin alone.\[25-28\]

**Adverse reactions**\[29\]

• It can cause hypoglycemia if the dose is not properly determined.
• Weight gain is a common problem of insulin replacement therapy; in case of insulin glargine, there is mixed type of information with insulin found in different studies. But when compared with NPH insulin, no difference in weight gain was observed.
• Insulin glargine has shown more injection site reactions like redness, hives, and itching, as compared to NPH insulin.
• Immunological reaction to insulin glargine may occur due to its slight structural difference with that of regular human insulin.
• Rarely, convulsions or unconsciousness may develop as a consequence of hypoglycemia.
• Initially, it was thought that its high binding affinity with IGF-1 receptors may have an adverse effect on progression of retinopathy in diabetic patients. But further studies done in this regard don’t show much significant relation of insulin glargine therapy and progression of retinopathy.
• Overall, insulin glargine is well tolerated.

**Drug interactions**

No specific interaction has been reported regarding the pharmacokinetic profile.

Only the drugs like beta-blockers, ACE inhibitors, clonidine, alcohol and glucose lowering antimicrobials, which can alter blood glucose metabolism, should be cautiously used when given concomitantly.\[29\]

**Dosage and administration**

Dose of insulin glargine should be individualized after due consideration to patient’s previous insulin therapy and concomitant oral antidiabetic therapy.

While switching from single dose NPH to glargine, dose of insulin can be kept same, but when there is multiple daily dose schedule of NPH that is to be switched to glargine, initial dose should be 80% of the previous dose and then depending upon the blood sugar levels, dose should be titrated.

During administration, Insulin glargine should not be mixed with any other insulin preparation.

It can be given at any time of day without any problem of
safety and efficacy.

It can be given safely at any of the commonly used subcutaneous sites like arm, thigh or abdomen.

The site of injection should be regularly rotated.

Presently, Lantus is the only brand available in India as well as in the international market, costs approximately 2500 Rs/ 50$ for 1 vial of 10 ml (100 units/ml).16,29

Current status of insulin glargine in management of diabetes

Good glycemic control is the key in management of diabetes. DCCT (Diabetes control and complication trial) and UKPDS (United Kingdom prospective diabetes study) have shown that improved glycemic control reduces the risk or progression of complications.

Given subcutaneously, insulin glargine mimics the physiologic basal insulin secretion, which is a very important aspect in the management of DM.

Various studies have shown that it gives better glycemic control than NPH insulin. It also reduces the incidence of hypoglycemias induced by intensive management with insulin.

In one randomized controlled clinical trial; insulin glargine had significantly improved patient treatment satisfaction, together with lower perceived frequency of hyperglycemia as well as hypoglycemia, compared to NPH insulin.

In accordance with this, National Institute Of Clinical Excellence, UK has recommended that it could be prescribed to:

- Any patient with type 1 DM.
- Type 2 DM patients who
  - Require assistance from a caregiver or healthcare professional for taking insulin.
  - Whose lifestyle is significantly restricted because of recurrent symptomatic hypoglycemia.
  - Who would otherwise need twice daily basal insulin injections in combination with oral hypoglycemic drugs.

For an ideal insulin replacement therapy, we still have to go a long way, and insulin glargine definitely appears to be a remarkable step in that direction.

References