Basal Insulin in Type 2 Diabetes Mellitus

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INTRODUCTION

India is one of the largest and most diverse populations of people living with diabetes. Limitations in appropriate and timely use of insulin impede the achievement of good glycemic control. Epidemiological studies for India and international bodies have raised alarm on diabetes prevalence. Current global prevalence of diabetes is 415 million in which China rank first with 109.6 million and India gets second with 69.2 million.[1] More than 60 % of world population with diabetes comes from Asia. Estimates from a recent Indian Council of Medical Research -India Diabetes study indicates that in India, there are 62.4 million people with diabetes and 77.2 million with pre-diabetes condition.[2] Early intensive insulin therapy in newly diagnosed T2DM patients which gives favourable outcomes on recovery and maintenance of β-cell function.[3] It is also protracted glycaemic remission as compare to oral anti diabetic agents and improve both insulin sensitivity and insulin secretion. Short-term insulin treatment may have long-lasting effects when introduced in the early stages of T2DM.[4]

THE CONCEPT OF BASAL GLUCOSE – MEASURE AND ESTIMATE

It takes 3 days to estimate the basal blood sugar levels. Pre-meal glucose needs to be evaluated for 3 days with 2 hours post prandial and then followed by next pre-meal reading. It takes at least 3 blood sugar readings for 3 consecutive days to determine a pattern. The period of 3 days is important as high carbohydrate / high fat meal or an unexpected activity can cause blood sugar excursions and the 3-day period will determine whether the issue is consistent.

Basal rate testing is not done regularly unless a problem is suspected or there's been a shift in the regular routine. If the daily schedule, activity or eating habits change, a basal test may be required to match the changed need. A basal test requires refraining from consuming any carbohydrates during the entire testing period, which often means skipping a meal.

Overnight basal testing is often the first focus that is evaluated. The 4-hour window allows the carbohydrates to be digested and out of the bloodstream, for the most part, and the fast-acting insulin used to cover the food to also be out of the system. The night before the testing it is recommended to eat a low-carb meal for dinner, so that both the carbohydrates and the insulin have been utilised before the sleep. If a basal test is started before this 4-hour window has lapsed, there may be blood sugar fluctuations not related to basal insulin. Normally, the expected range should be between 70 and 250 mg/dl and if the follow up readings every 2-3 hours until breakfast are within 30 mg/dl, the basal rate is fine. If the readings vary more than that then the insulin dosage may need adjustment.

PATHOPHYSIOLOGY OF TYPE 2 DM

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. T2DM is a complex metabolic/cardiovascular disorder with multiple pathophysiologic abnormalities. Insulin resistance in muscle/liver and b-cell failure represent the core defects.[5,6]

This leads to a decrease in glucose transport into the liver, muscle cells, and fat cells. There is an increase in the breakdown of fat with hyperglycemia. The involvement of impaired alpha-cell function has recently been recognized in the pathophysiology of type 2 DM.[7] As a result of this dysfunction, glucagon and hepatic glucose levels that rise during fasting are not suppressed with a meal. Given inadequate levels of insulin and increased insulin resistance results in hyperglycemia. Collectively, the eight players comprise the "ominous octet" (Figure 1).

TYPES OF BASAL INSULIN

There are two types of basal insulin available,

1. Intermediate-acting insulin - Neutral Protamine Hagedorn (NPH)
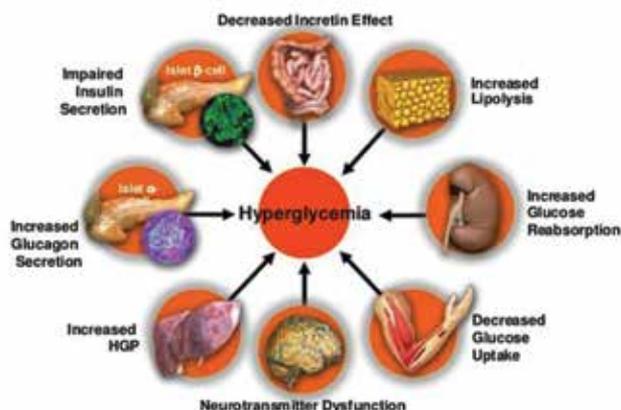
Fig. 1: The ominous octet depicting the mechanism based upon the pathophysiologic disturbances present in T2DM.

2. Long-acting insulin - detemir (Levemir), glargine (Lantus), degludec (Tresiba)

Neutral Protamine Hagedorn (NPH) insulin

NPH or isophane insulin is a crystalline suspension of insulin with protamine and zinc. This enhances its aggregation into dimers and hexamers after subcutaneous injection. A depot is formed after injection and insulin is released slowly, providing intermediate-acting insulin with a slow onset of action and a longer duration of action than regular insulin. The duration of action of NPH insulins is variable. Due to the variable absorption and peaks of NPH, side-effects such as early morning hypoglycaemia and fasting hyperglycaemic episodes are more likely, especially with higher doses. These limitations have been largely reduced by the introduction of basal insulin analogues like glargine and detemir.[8]

Insulin Glargine

Glargine is a recombinant human insulin analogue. It differs from human insulin in that after subcutaneous injection, the acidic solution is neutralized which leads to the formation of a precipitate within the depot from which glargine is slowly released. Pharmacokinetic and pharmacodynamics studies show that a single injection of insulin glargine leads to a smooth 24-hour time–action profile with no undesirable pronounced peaks of activity which also resembles basal insulin secretion of non-diabetic pancreatic beta cells.[9] A bedtime injection of insulin glargine produces a much lower frequency of nocturnal hypoglycemia, but similar glycemic control. Furthermore, for similar HbA1C reduction, glargine allowed significantly less weight gain than NPH Insulin. A potential major advantage of insulin glargine over NPH insulin is a lack of pronounced peaks in plasma insulin concentrations and a more constant delivery of insulin over a 24-hour period. The combination of glargine and oral agents resulted in a 56% reduction of nocturnal hypoglycemia and lower post-dinner plasma glucose levels than NPH plus oral agents.[20]

Insulin Detemir

Detemir is a normal analogue of human insulin in which a 14-carbon fatty acid is acrylates to the

detemir, and buffers against changes in absorption rate from the subcutaneous injection site. Fatty acid acylation enhances detemir insulin's affinity to albumin, enabling a longer duration of action via delayed absorption from the subcutaneous adipose tissue depot. Once in the bloodstream hexamers or dimers of detemir rapidly dissociate into monomers. This is a dynamic process. Detemir monomers sporadically disassociate only to reattach to other albumin. Albumin binding further protracts the action of detemir, and in addition, it may buffer against oscillations in the absorption rate from the injected site. Insulin detemir is soluble at neutral pH, which enables it to remain in a liquid form following subcutaneous injection, unlike NPH insulin and glargine. Compared with NPH, use of insulin detemir may be associated with a lower risk of hypoglycemia, especially

nocturnal hypoglycemia and the added clinical benefit of no appreciable bodyweight gain in patients with type 1 or type 2 diabetes.

Insulin Degludec

Insulin degludec is a new basal insulin that forms soluble multihexamer assemblies after subcutaneous injection, resulting in an ultra-long action profile. Degludec has an action duration of more than 24 hours. The protein sequence of Insulin Degludec was based on human insulin, modified by acyl ting DesB30 at the e-amino group of LysB29 with hexadecandioic acid via a c-L-glutamic acid linker. To date Insulin Degludec is the only insulin analogue to self-associate into multi-hexamers upon subcutaneous (SC) injection, resulting in a soluble depot from which Insulin Degludec is slowly and continuously absorbed into the circulation.[23] in the presence of phenol and zinc, the IDeg hexamers adopt a conformation where only one of the ends is available to interact with the side chain of another IDeg hexamer and thus forms stable di-hexamers. Upon diffusion of phenol following injection, the IDeg di-hexamers open at both ends and lead to the formation of multi-hexamers.[24] Insulin Degludec compared with first-generation basal insulin analogues like NPH, Insulin Glargine and Insulin Detemir, Insulin Degludec offers the possibility for a simple titration algorithm and the potential for a more flexible dosing interval to accommodate varying patient lifestyles. This could help improve adherence and ultimately contribute towards improved glycemic control in patients with diabetes.[10]

BASAL INSULIN IN CLINICAL PRACTICE

Basal insulin requirements are provided by long-acting (NPH insulin, insulin glargine, or insulin detemir) insulin formulations. These are usually prescribed with short acting insulin to mimic physiologic insulin release with meals. Although mixing of NPH and short-acting insulin formulations is common practice, this mixing may alter the insulin absorption profile (especially the short-acting insulins). For example, lispro absorption is delayed by mixing with NPH. The alteration in insulin absorption when the patient mixes different insulin formulations should not prevent mixing insulins. However, the following guidelines should be followed:

1. mix the different insulin formulations in the syringe immediately before injection (inject within 2 min after mixing)

2. do not store insulin as a mixture

3. follow the same routine in terms of insulin mixing and administration to standardize the physiologic response to injected insulin; and

4. do not mix insulin glargine or detemir with other insulins. The miscibility of some insulins allows to produce combination insulins that contain 70% NPH and 30% regular (70/30), or equal mixtures of NPH and regular (50/50).

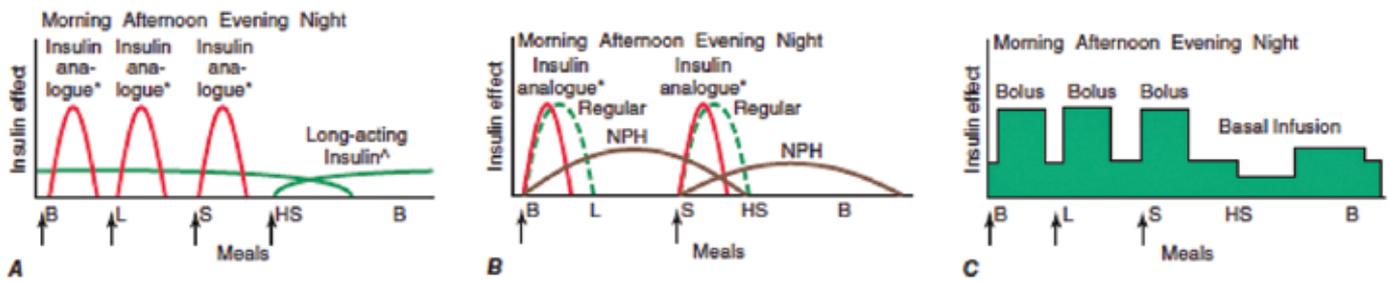A. Multiple-component insulin regimen consisting of

Fig. 2: Representative insulin regimens for the treatment of diabetes. For each panel, the y-axis shows the amount of insulin effect and the x-axis shows the time of day. B, breakfast; HS, bedtime; L, lunch; S, supper. *Lispro, glulisine, or insulin aspart can be used. The time of insulin injection is shown with a vertical arrow. The type of insulin is noted above each insulin curve
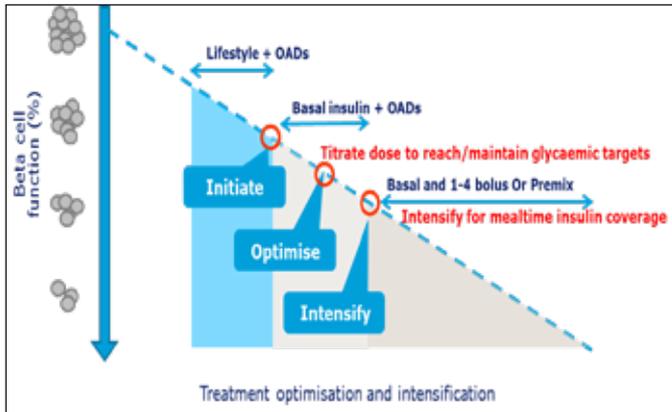

Fig. 3: Insulin initiation and intensification with beta-cell function

long-acting insulin (glargine or detemir) to provide basal insulin coverage and three shots of glulisine, lispro, or insulin aspart to provide glycemic coverage for each meal.

B. Injection of two shots of long-acting insulin (NPH) and short-acting insulin analogue (glulisine, lispro, insulin aspart [solid red line], or regular insulin [green dashed line]). Only one formulation of short-acting insulin is used.

C. Insulin administration by insulin infusion device is shown with the basal insulin and a bolus injection at each meal. The basal insulin rate is decreased during the evening and increased slightly prior to the patient awakening in the morning. Glulisine, lispro, or insulin aspart is used in the insulin pump.

If the pre-meal blood sugar starts within 'goal range' (70-130 mg/dl) and the 2-hour post-meal blood sugar is greater than 180 mg/dl, then the bolus ratio is likely responsible for the hyperglycemia. If the blood sugar is spiking more than 2 hours after a meal or climbs back up by the next meal, then the basal rate is the target.

BASAL INSULIN INITITION, OPTIMIZATION, INTENSIFICATION

Rational for Early Basal Insulin Initiation

Timely initiation of insulin therapy is an important component of diabetes management. Early initiation followed by timely intensification can help reverse glucotoxicity, reduce insulin resistance and preserve

Table 1: Initiation, Optimization and Titration Schedule for Patients Using Basal and/or Prandial Insulin Therapy		
Fasting plasma glucose Levels	Blood glucose levels for 3 consecutive Days, mmol/L (mg/dL)	Preprandial or bedtime glucose levels
Adjustment of basal insulin dose, U		Adjustment of Rapid-acting insulin dose, U/ injection
8#	≥9.90 (>180)	3
6	8.80 to 9.90 (160 to 180)	2
4	7.70 to 8.75 (140 to 159)	2
2	6.60 to 7.65 (120 to 139)	1
1	5.50 to 6.55 (100 to 119)	Maintain dose
Maintain dose	4.40 to 5.45 (80 to 99)	-1
-2	3.30 to 4.35 (60 to 79)	-2
-4	<3.30 (<60) *	-4

#Fasting glucose levels for 3 consecutive Days: >9.90 (180) mmol/L (mg/dL)

beta-cell function for longer than is possible with OADs alone. Insulin therapy may also slow or even halt diabetes progression. The ORIGIN trial has demonstrated that insulin slows disease progression in type 2 diabetes. In addition, the UKPDS showed that early addition of insulin to oral therapy reduced the risk of complications.

Dose optimization of basal insulin

Evidence from several large RCTs that self-titration of insulin based on SMBG, can improve HbA_{1C} control, can improve reductions in FBG and does not increase risk of hypoglycemia. [11] Basal Insulin Intensification

The stepwise addition of prandial insulin has been investigated in several clinical trials. The addition of a single prandial insulin injection to the existing basal regimen before breakfast or the main meal, or before the meal consistently with the highest postprandial

glucose, is referred to as a 'basal-plus' strategy. Rapid-acting prandial insulin analogues, such as insulin glulisine, insulin aspart, and insulin lispro, have a more rapid onset, earlier peak, and shorter duration of action than regular human insulin, thereby allowing greater convenience in timing injections and a reduced risk of postprandial hypoglycemia. This basal-plus strategy has been identified as effective when intensifying insulin therapy, before a full basal–bolus regimen is considered

Initiation:

• Maintain oral glucose lowering drugs

• Start on 10-20 units of insulin glargine (according to body weight and BG)

Optimization:

• Adapt dosage every 3 to 5 days according to FBG

• Goal: FBG < 100 mg/dl

ADVERSE EVENTS

Hypoglycemia, weight gain, Bronchitis, allergic reaction, Peripheral edema, sinusitis, back pain, infection, cataracts.

CONCLUSION

Insulin is an important component of diabetes treatment management. Addition of basal insulin to previous therapy is considered the most effective and simplest way to initiate insulin therapy. However, due to progressive nature of dabetes proactive escalation of the existing insulin therapy is eminent as it minimizes patients' exposure to chronic hyperglycaemia and weight gain, and reduces patients' risk of hypoglycaemia, while achieving individualized glycaemic targets.

As Per the ADA EASD 2015 guidelines, basal insulin is the most convenient insulin to start with due to long action, single daily dose and low risk of hypoglycemia.

Addition of prandial as a basal plus after fixing the fasting first can provide precise and flexible prandial coverage. Tailoring the insulin requirement to suit the needs of the patients will increase the success of therapy and in achievements of glycaemic goals.

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