Observational Study

# Basal insulin supported oral therapy in type 2 diabetes

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**Early intensive glycemic control in type 2 diabetes reduces the risk of long-term complications, and often requires timely initiation and optimization of insulin therapy. While there are several patient and physician-related barriers to early insulin initiation, basal insulin supported oral antidiabetic therapy (BOT) offers an effective, more acceptable and safe way to transition to insulin therapy in type 2 diabetes. Basal insulin, when combined with oral antidiabetic medications with complementary mechanisms of action, targets multiple pathophysiological defects and results in better glycemic control. Another advantage is a reduced risk of side-effects such as hypoglycemia and weight gain, which are associated with more intensive insulin regimens. Basal insulin can be initiated once daily, at a dose of 0.1-0.2 units/kg and the dose can be further titrated based on fasting plasma glucose to achieve a target of 80-130 mg/dl. Oral therapy is individualized based on other factors such as baseline HbA1c, postprandial hyperglycemia, complications and comorbidities, socioeconomic considerations, lifestyle, patient preference and convenience. Further intensification of treatment may be required with addition of bolus insulin or GLP1 receptor agonist or switching to premixed insulin in individuals who are not able to maintain or sustain glycemic control on BOT regimen.**

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***Key words*** **: Basal insulin, type 2 diabetes, basal insulin supported oral antidiabetic therapy (BOT), early insulin initiation.**

Early intensive glycemic control in type 2 diabetes results in better metabolic 'karma' and significantly reduces the risk of long-term complications[1]. Due to a progressive decline in beta-cell function over time, many patients with type 2 diabetes require insulin to maintain adequate glycemic control. In fact, early insulin initiation can facilitate ß-cell rest by reducing glucotoxicity and improving insulin sensitivity, and therefore help preserve ß-cell mass and function in the long-run[2]. However, insulin initiation is significantly delayed due to several factors, both physician-related and patient-related[3], as outlined in Table 1.

## Basal Insulin Supported Oral Antidiabetic Therapy (BOT): Concept, Rationale and Benefits :

Basal insulin supported oral antidiabetic therapy (BOT) involves addition of once daily basal insulin, either NPH or basal insulin analogs such as U-100 glargine, detemir, degludec or U-300 glargine, while oral antidiabetic agents are continued. The pharmacokinetic profiles of various basal insulin formulations are enlisted in Table 2. Basal insulin can be combined with any of the oral antidiabetic agents including metformin, sulfonylureas, pioglitazone, DPP4 inhibitors, SGLT2 inhibitors or alpha-glucosidase inhibitors and also with injectable GLP1 receptor agonists. While basal insulin improves fasting and basal glycemic control by reducing hepatic glucose output and endogenous glucose production, it indirectly helps control postprandial glucose as well[4].

When basal insulin is combined with oral antidiabetic agents, it can help target multiple pathophysiological defects in type 2 diabetes. This leads to improved glycemic control and reduced risk of side effects such as hypoglycemia and weight gain, which are associated with more intensive insulin regimens[5]. Metformin and thiazolidinediones may reduce the insulin dose requirement by targeting insulin resistance, without undue increase in risk of hypoglycemia. While metformin can mitigate the weight gain associated with insulin use, pioglitazone may result in increased weight gain[6,7]. Sulfonylureas help increase endogenous insulin secretion, which results in improved glycemic control and reduced insulin dose requirement of exogenous insulin. However, the risk of hypoglycemia is increased when sulfonylureas are combined with insulin, and the dose of sulfonylureas may need to be reduced when adding basal insulin[6]. Alpha-glucosidase inhibitors target postprandial control and are useful adjuncts to basal insulin in patients who have high carbohydrate intake and/or are not attaining postprandial glucose targets[8]. DPP4 inhibitors and SGLT2 inhibitors offer the advantage of improved glycemic control and reduced insulin dose requirement and SGLT2 inhibitors may further

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Table 1 — *Barriers to insulin initiation: how early basal insulin can help overcome barriers*

| Barriers to Early Insulin Initiation | Basal Insulin Supported Oral Antidiabetic Therapy (BOT) as a Bridge to Early Insulin Initiation |
|---|---|
| Needle phobia and needle pain | Single injection associated with less pain, may reduce needle phobia when only one injection per day is started instead of multiple injections |
| Fear of hypoglycemia | Less risk of hypoglycemia with basal insulin alone as add-on to OADs. Risk further reduced with basal insulin analogs. |
| Fear of weight gain | BOT associated with less weight gain. Concomitant use of Metformin, DPP4 inhibitors, SGLT2 inhibitors or GLP1a can mitigate weight gain. |
| Complex treatment | Once daily insulin is easy to initiate and titrate. Patient can follow simple self-titration algorithm at home. |
| Lack of self-confidence to manage insulin | Simple dose-titration algorithm to be followed by patient gives him/her greater confidence and a sense of control over his treatment. |
| Frequent monitoring of blood glucose | BOT regimen is simpler, with daily monitoring of fasting glucose till dose titration is done, and later less frequent monitoring. Postprandial monitoring can be periodic only. |
| Frequent clinic visits | BOT requires less frequent patient-physician interaction, which can be further reduced after dose-titration phase. |
| Increased cost of treatment | BOT associated with less cost, reduced need for SMBG and less frequent clinic visits. Reduced risk of complications with early insulin initiation further reduces long-term cost. |
| Physical limitations – inability to self-inject | Basal insulin can be administered once daily at any time of the day, preferably same time every day, irrespective of meals. Hence, can be given by a caregiver easily. Longer acting analog degludec offers even greater flexibility of timing and can be administered at different times. |
| Healthcare resource limitations – educate about insulin, SMBG, insulin injection technique and hypoglycemia care | Once daily insulin is a simpler regimen and more acceptable to patients than multiple daily injections. Pen devices are easier to teach and use. BOT needs less frequent clinic visits and patients can be given a self-titration algorithm to follow at home. |
| Inadequate skills training of healthcare practitioner | Insulin initiation and dose titration in BOT can be done using simple algorithm and is easier to titrate and monitor, compared to complicated, multiple daily insulin injection regimens. |

mitigate insulin-associated weight gain[9,10]. Combination therapy should be individualized for each patient based on baseline HbA1c and glycemic profile, complications and comorbid conditions, patient lifestyle and socio-economic considerations, personal preference and patient convenience.

Basal insulin, when added early to oral antidiabetic therapy, compared to intensification of oral antidiabetic therapy alone, provides better glycemic control with greater number of patients achieving glycemic targets without any increase in the risk of hypoglycemia[11]. Early basal insulin therapy also results in more sustained glycemic control and offers the advantage of glycemic durability[4,12]. BOT can help bridge several barriers to early insulin initiation by providing a simpler once daily insulin regimen while oral antidiabetic agents, including insulin secretagogues, are continued. This is further highlighted in table 1. It may also help in easier and more acceptable transition to insulin therapy for most individuals.

## Basal Insulin Initiation in Type 2 Diabetes: Guidelines :

Most national and international guidelines support the use of basal insulin in type 2 diabetes at various stages of treatment intensification[13-16]. While it can be considered as second line agent if glycemic control is inadequate with metformin alone, it can be more appropriately added if 2 or 3 oral antidiabetic agents are unable to achieve or sustain glycemic targets. While the International Diabetes Federation 2017 guidelines recommend use of basal insulin if HbA1c targets are not sustained with at least 2 oral antidiabetic agents, the American Diabetes Association and the American Academy of Clinical Endocrinologists 2018 guidelines support its use even earlier as add-on to metformin or any other first line drug if entry HbA1c is >7.5%[13-15]. Basal insulin can be initiated at a dose of 10 units or 0.1-0.2 units/kg and the dose can be titrated in increments of 2-4 units once or twice a week to reach a target fasting plasma glucose of 80-130 mg/dl. The dose should be reduced by 2-4 units or 10-20% in case of hypoglycemia. Adequate patient education regard-

Table 2 — *Pharmacokinetic profiles of basal insulins*

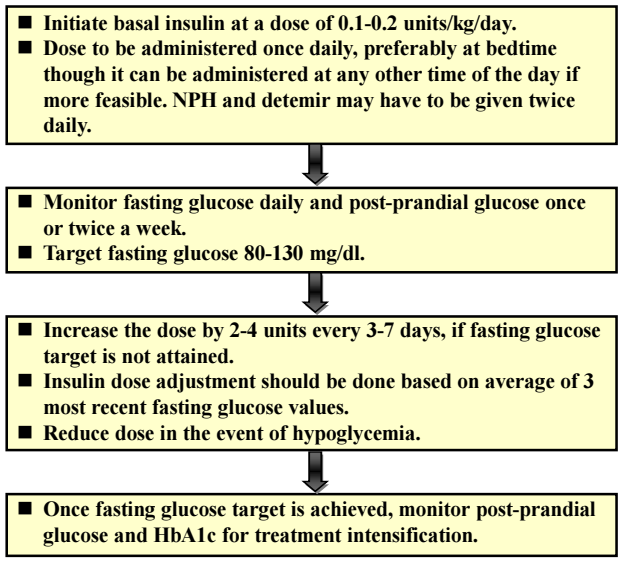
| Basal Insulin | Peak (hours) | Duration (hours) | Half-life (hours) | Variability (CV%) | Frequency |
|---|---|---|---|---|---|
| Neutral Protamine Hagedorn (NPH) | 4-6 | 12-16 | 4 | 68 | Once or twice daily |
| Glargine U 100 | Flat, some peak at 4-12 hours | ~24 | 12 | 32-82 | Once daily or (sometimes) twice daily |
| Detemir | Flat, some peak at 7-14 hours | 20-24 | 5-7 | 27 | Once daily or (often) twice daily |
| Degludec | Flat, no peak | >24 hours (up to 48 hours) | 25 | 20 | Once daily |
| Glargine U 300 | Flat, no peak | >24 hours (up to 36 hours) | 18 | 17-35 | Once daily |

ing self-monitoring of blood glucose (SMBG), insulin injection technique, site rotation, prevention and detection of lipohypertrophy and detection and management of hypoglycemia is essential[17].

Most guidelines recommend the use of long-acting basal analogs including U-100 glargine or detemir, as they are associated with lower risk of symptomatic and nocturnal hypoglycemia[13-16]. However, human insulin NPH can be considered safely in people without a history of hypoglycemia if there are cost constraints. The newer longer-acting analogs, U-300 glargine and degludec offer further reduced risk of hypoglycemia and should be considered in people at high risk of hypoglycemia, hypoglycemia unawareness or high glycemic variability[18,19]. Further intensification of treatment may require addition of other oral antidiabetic medications, addition of bolus insulin, switching to premixed insulin or addition of GLP1 receptor agonists, if adequate glycemic control is not maintained[5].

## Basal Insulin Supported OAD Therapy : Clinical Considerations :

- Consider use of basal insulin in patients who are unable to maintain glycemic goals with 2 or 3 oral antidiabetic drugs used in adequate doses. Basal insulin may also be initiated as second line agent after metformin if HbA1c is >9%. Use of basal insulin can be temporary if initiated early in the course to reverse glucotoxicity.
- Patient should be counselled about the benefits of early insulin initiation and its potential to improve long-term glycemic control and prevent long-term complications.
- Adequate patient education and training should precede insulin initiation. This should include advice regarding optimal lifestyle modification, self-monitoring of blood glucose, insulin injection technique, insulin storage and care during travel, injection site rotation to prevent lipohypertrophy and detection and management of hypoglycemia.
- Basal insulin can be initiated with NPH, U-100 glargine, detemir, degludec or U-300 glargine. Insulin analogs with peakless and more stable time-action profiles are preferred due to lower risk of nocturnal and symptomatic hypoglycemia. However, NPH can be considered in patients with no history of hypoglycemia if there are cost constraints. Ultra-long acting insulin analogs such as degludec and U-300 glargine should be considered in patients at high risk of hypoglycemia, severe hypoglycemia, recurrent hypoglycemia or high glycemic variability.
- Basal insulin is preferably injected once daily at bedtime. However, it can be injected at any time of the day if bedtime injection is not suitable due to socio-cultural factors, such as religious fasts, shift workers, or injection being administered by a caregiver. But the timing of insulin injection should be kept constant every day. Insulin degludec offers some flexibility as it can be taken at different times of the day. NPH and detemir may need to be taken twice daily in some individuals.
- It is important to identify the insulin delivery device that most suits the patient's needs. Insulin can be administered with insulin syringes or pen devices. The correct syringe (40 U or 100 U) should be used for vials of same strength. Incorrect syringe (eg 40 U syringe for a vial of 100 IU/ml strength) can lead to significant dosing error and hypoglycemia.
- Injection is administered in subcutaneous tissue. Correct injection technique and site rotation can prevent the occurrence of lipohypertrophy and other injection site reactions.
- Insulin is initiated at an initial dose of 10 units or 0.1-0.2 units/kg once daily and the dose titrated based on fasting plasma glucose.
- Fasting glucose should be monitored, preferably daily, by SMBG and the dose increased by 2-4 units every 3-7 days, to reach a FPG target of 80-130 mg/dl. Insulin initiation and dose titration of basal insulin is depicted in Fig 1.
- Simple-to-follow insulin titration algorithms can be handed to patients for self-titration of insulin. This would reduce clinic visits and impart a greater sense of control over their diabetes among the patients.
- Avoid daily manipulations of insulin doses. Increase




**Basal insulin analogs such as glargine and detemir are associated with lower risk of hypoglycemia and are preferred. Where cost is a constraint, NPH can be used. In individuals at high risk of hypoglycemia, longer-acting insulin analogs such as degludec or U-300 glargine should be considered.*

Fig 1 — Algorithm for Initiation and Titration of Basal Insulin in Basal Insulin Supported Oral Anti-Diabetic Therapy (BOT)

in dose should be based on average or last 3 readings and done once or twice a week. Fast daily titration of insulin can increase the risk of hypoglycemia.

- Patients should be educated about warning symptoms of hypoglycemia and the management and prevention of hypoglycemia.
- In the event of a hypoglycemia, the factors causing hypoglycemia should be identified and insulin dose reduced by 2-4 units.
- Once fasting glucose targets are attained, further treatment intensification should be based on postprandial glucose values, which should be monitored periodically and HbA1c value measured after 3 months.

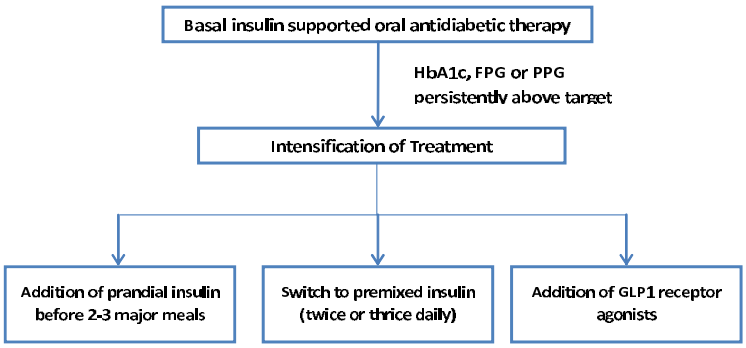



Fig 2 — Intensification of basal insulin supported oral antidiabetic therapy

## Limitations of Basal Insulin : When to Intensify :

The success of BOT depends on early initiation, optimal titration of oral antidiabetic medications and insulin dose and adherence to the treatment regimen. Physician and patient empowerment is needed to overcome the barriers to early optimal use of basal insulin in type 2 diabetes[20]. However, BOT may be unable to achieve or sustain adequate glycemic control in a significant proportion of patients due to progressive decline in ß-cell function[21]. Individuals with an HbA1c > 8.5% or significant postprandial hyperglycemia are more likely to demonstrate inadequate response to basal insulin[21-23]. Such individuals will require intensification of insulin regimen, as outlined in Fig 2. This can be done by adding prandial insulin or switching to premixed insulin[24,25]. Addition of GLP1 receptor agonists is another novel promising approach for treatment intensification of basal insulin based regimens in type 2 diabetes[26].

In addition, BOT regimens should not be considered for individuals with acute hyperglycemic emergencies such as diabetic ketoacidosis or hyperosmolar hyperglycemic state or in acute severe illness, where basal bolus therapy should be started initially. BOT may not be a suitable approach for those individuals with type 2 diabetes who have very high HbA1c and/ or significant postprandial hyperglycemia. More intensive regimens such as premixed insulin twice or thrice daily or basal bolus insulin therapy are required in such patients.

## Conclusion :

Basal insulin supported oral antidiabetic therapy targets multiple pathophysiological defects in type 2 diabetes and can help achieve early and sustained glycemic control. The success of BOT would depend on timely initiation of insulin, pragmatic titration and optimization of treatment and intensification with more intensive regimens in case of persistent inadequate glycemic control.

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