

THE ROLE OF BASAL INSULIN IN COMPREHENSIVE DIABETES MANAGEMENT

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AGENDA

1

Physiology of Insulin

2

Modern Role of Basal Insulin

3

Types of Basal Insulin

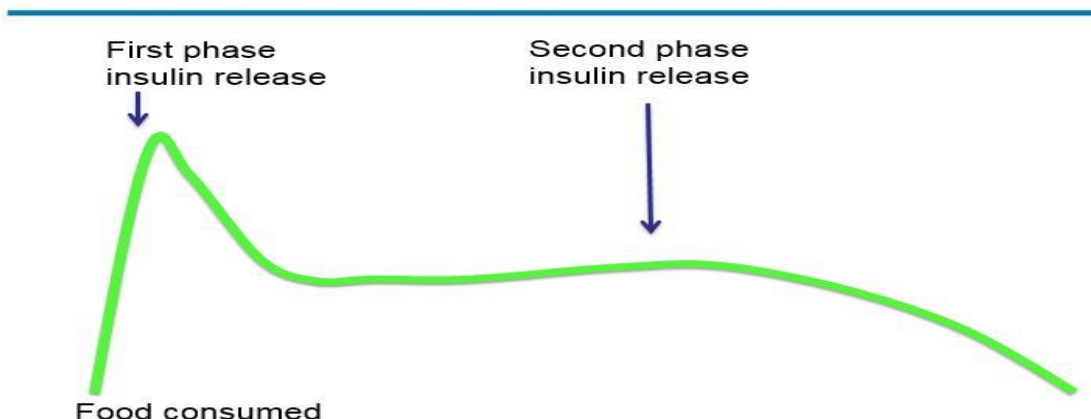
4

Indication, Titration and Monitoring

Physiology of Insulin

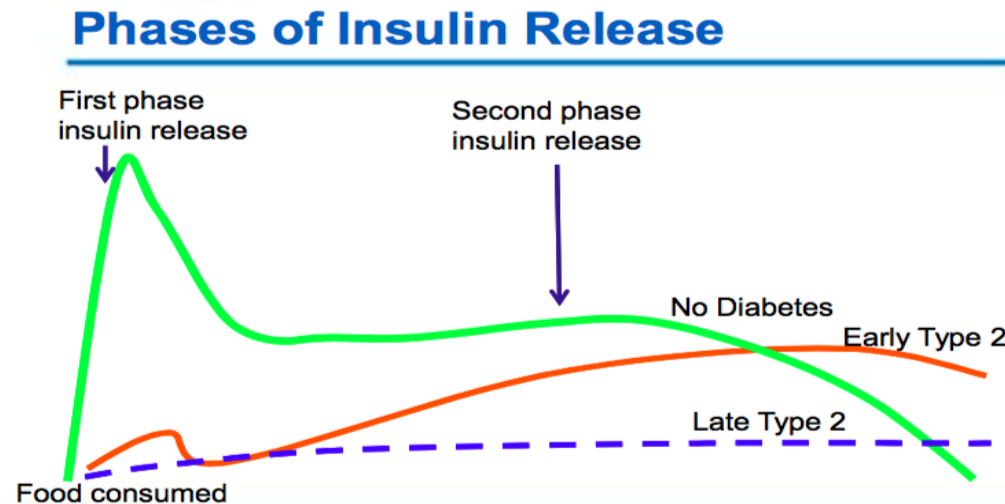
- ▶ Insulin is a hormone synthesized by pancreatic β -cells to regulate carbohydrate metabolism
- ▶ After meal ingestion, glucose concentrations in the circulation rise and stimulate insulin secretion. Increased delivery of insulin into the circulation causes further suppression of hepatic glucose release and increased stimulation of glucose uptake by insulin-sensitive tissues such as muscle to restore normoglycemia.

Phases of Insulin Release



Physiology of Insulin

- ▶ Diabetes mellitus with overt hyperglycemia is characterized by impaired pancreatic B-cell function; however, in noninsulin-dependent diabetic subjects, many aspects of insulin secretion are maintained by a compensatory increase in plasma glucose concentration.



Physiology of Insulin

- ▶ A shortcoming of current insulin regimens is that injected insulin immediately enters the systemic circulation, whereas endogenous insulin is secreted into the portal venous system.
- ▶ Thus, exogenous insulin administration exposes the liver to sub physiologic insulin levels, and requires achieving higher peripheral levels of insulin to restrain hepatic glucose production.
- ▶ No current insulin regimen reproduces the precise insulin secretory pattern of the pancreatic islet

Modern Role of Basal Insulin

Features of BI

- ▶ Mechanisms of action well established
- ▶ Research and clinical experience for >80 years
- ▶ Most efficacious and durable glucose-lowering treatment
- ▶ The only treatment with 100% of patients as responders (provided titration is appropriate)
- ▶ Most efficient removal of glucotoxicity (improved insulin secretion and action)
- ▶ Anti-inflammatory, antiatherogenic, vasodilator, and proendothelium effects

Modern Role of Basal Insulin

Features of BI

- ▶ Anabolic effects
- ▶ Limited contraindications
- ▶ Safe (natural hormone, not a synthetic drug)
- ▶ Can be titrated from (very) low to (very) high doses
- ▶ Can be used with any other diabetes treatment*
- ▶ Long-term protection of ASCVD/CKD risk in people in whom other therapies fail to maintain target HbA1c

Types of Basal Insulin

- ▶ Basal insulin :
 - Suppresses glucose production between meals and overnight
 - Nearly constant levels
 - 50% of daily needs

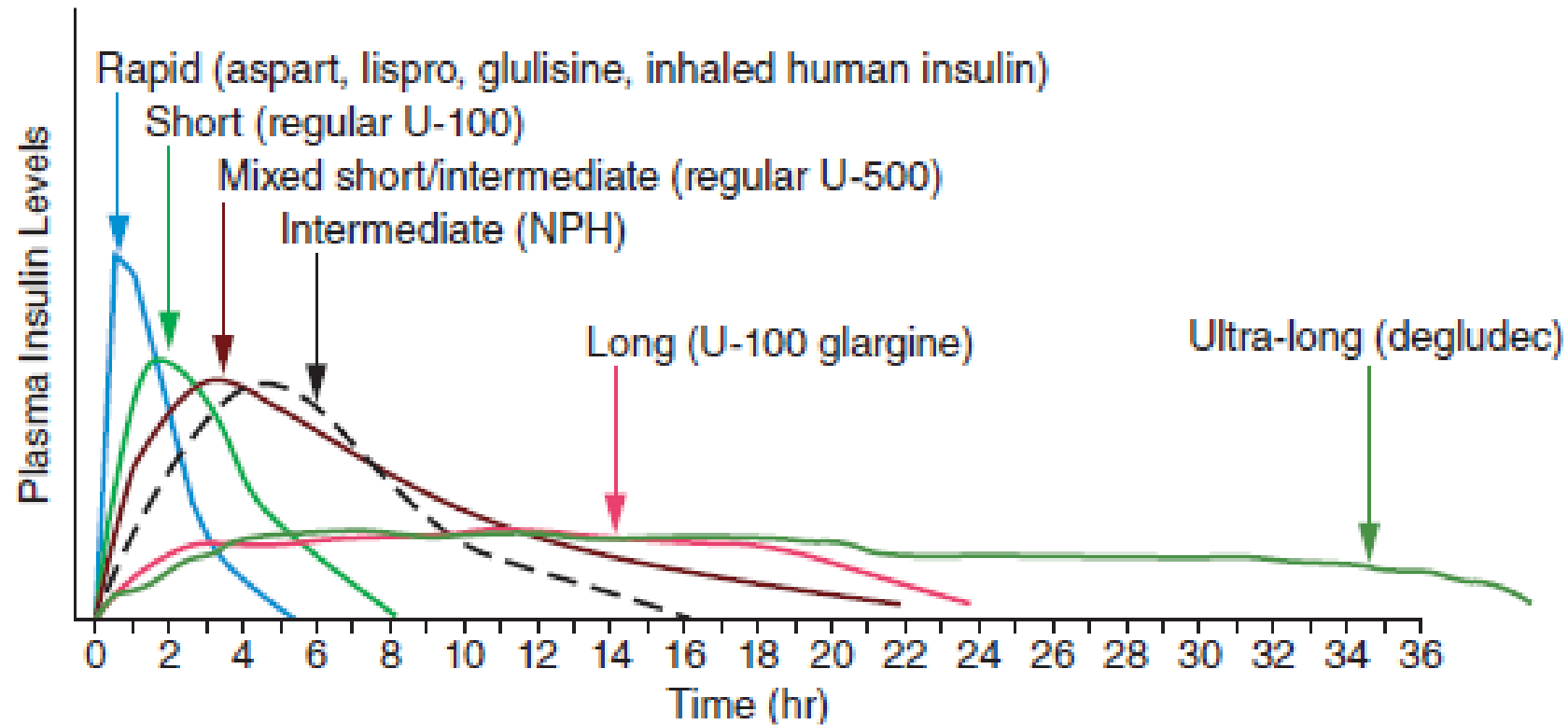
Types of Basal Insulin

- ▶ Basal insulin includes NPH insulin, long-acting insulin analogs
- ▶ Basal insulin analogs have longer duration of action with flatter, more constant and consistent plasma concentrations
- ▶ longer-acting basal analogs (U-300 glargine or degludec) may confer a lower hypoglycemia risk compared with U-100 glargine

Properties of Insulin Preparations

PREPARATION	TIME OF ACTION		
	ONSET, h	PEAK, h	EFFECTIVE DURATION, h
<i>Intermediate-acting, injected</i>			
NPH	2-4	4-10	10-16
<i>Long-acting or Ultralong-acting, injected</i>			
Degludec	1-9	-----	42
Glargine	2-4	-----	20-24
<i>Examples of insulin combinations</i>			
Combination of long-acting insulin and GLP-1RA			

Types of Basal Insulin



An
intermediate-
acting insulin
Administered
once or twice
daily

NPH

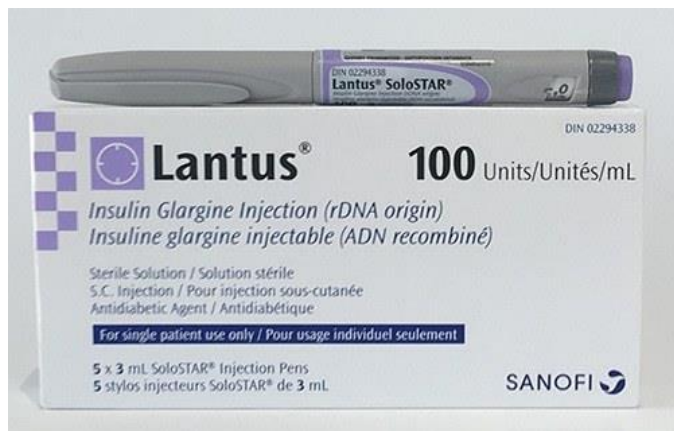
The onset
action is later,
the duration of
action is longer
(~24 h).
There is a less
pronounced
peak

Glargine

Longer-acting
basal analogs
convey a lower
nocturnal
hypoglycemia.
The duration of
action is longer
(~42 h)

Degludec

Types of Basal Insulin



Types of Basal Insulin



Indication, Titration and Monitoring

Table 2—Clinical scenarios in which starting BI may be preferred or not preferred in the era of the innovative medications, GLP-1RA and SGLT2i

Preferred

Metabolic emergencies (hyperosmolality, ketoacidosis)
Acute or variable hyperglycemia (sick days, steroid therapy, trauma, major surgery, stress)
Patient preference
Comorbidities (kidney and liver failure, cancer, chemotherapy)
Autoimmune pathogenesis (LADA)
Pregnancy
Lean, predominantly insulin-deficient T2DM

- including some elderly onset
- with excessive weight loss on other therapies

New-onset T2DM with marked hyperglycemia
HbA_{1c} not at target with other management
Intolerance of noninsulin therapies (including GLP-1RA, SGLT2i)
Possibility that patient may have T1DM

Not preferred

Specific indication for other medication (HF, CKD risk, acute CV protection)
Obesity
Nonpreference by the potential user*

HF, heart failure. *Nonpreferred as first choice, but BI may be added on later to other therapies to lower HbA_{1c}.

Indication, Titration and Monitoring

- ▶ Treatment with insulin often becomes necessary as type 2 DM enters the phase of relative insulin deficiency and is signaled by inadequate glycemic control with one or two oral glucose-lowering agents.
- ▶ Insulin alone or in combination should be used in patients who fail to reach glycemic targets

Indication, Titration and Monitoring

- ▶ In adults with type 2 diabetes, initiation of insulin should be considered regardless of background glucose lowering therapy or disease stage if symptoms of hyperglycemia are present [weight loss or ketonuria/ketosis and with acute glycemic dysregulation (e.g. during hospitalization, surgery or acute illness)] or when A1C or blood glucose levels are very high (A1C>10 % or blood glucose 300 mg/dL)

Indication, Titration and Monitoring

- ▶ The preferred way of initiating insulin in people with type 2 diabetes is to add basal insulin to the existing pharmacological therapy
- ▶ A single dose of long-acting insulin at bedtime is often effective in combination with metformin
- ▶ Basal insulins are typically administered before bedtime but, with newer analogues, more flexibility in the timing of insulin injection is possible (i.e. any time of the day).

Indication, Titration and Monitoring

- ▶ As endogenous insulin production falls further, multiple injections of long-acting insulin together with rapid-acting insulin are necessary to control postprandial glucose excursions
- ▶ The daily insulin dose required can become quite large (1–2 units/kg per day) as endogenous insulin production falls and insulin resistance persists, especially in the setting of weight gain.

Indication, Titration and Monitoring

- ▶ Once a basal-bolus insulin plan is initiated, dose titration is important, with adjustments made in both prandial and basal insulins based on blood glucose levels and an understanding of the pharmacodynamic profile of each formulation
- ▶ Twice-daily injections of glargine are sometimes required to provide optimal 24-h basal insulin coverage

Indication, Titration and Monitoring

- ▶ U-300 glargine and U-200 degludec are three and two times, respectively, as concentrated as their U-100 formulations and allow higher doses of basal insulin administration per volume used than U-100 glargine but modestly lower efficacy per unit administered
- ▶ Degludec and glargine have minimal peak activity. Duration is dose-dependent

Indication, Titration and Monitoring

- ▶ an initial dose reduction of 10–20% can be used for individuals in very tight management or at high risk for hypoglycemia and is typically needed when switching from insulin detemir or U-300 glargine to another insulin
- ▶ Weight gain and hypoglycemia are the major adverse effects of insulin therapy

Indication, Titration and Monitoring

- ▶ The addition of a GLP-1RA can limit this and reduce the dose of insulin needed
- ▶ Long-acting insulin/GLP-1RA combinations in fixed doses (degludec plus liraglutide or glargine plus lixisenatide) are effective and are associated with less weight gain

Indication, Titration and Monitoring

If injectable therapy is needed to reduce A1C¹

Consider GLP-1 RA or dual GIP and GLP-1 RA in most individuals prior to insulin²

INITIATION: Initiate appropriate starting dose for agent selected (varies within class)

TITRATION: Titrate to maintenance dose (varies within class)

Indication, Titration and Monitoring

If A1C is above goal

Considerations for adding basal insulin³

Choice of basal insulin should be based on person-specific considerations, including cost. Refer to **Table 9.4** for insulin cost information. Consider prescription of glucagon for emergent hypoglycemia.

Initiation and titration of basal analog or bedtime NPH insulin⁴

INITIATION: Start 10 units per day OR 0.1-0.2 units/kg per day

TITRATION:

- Set FPG goal (see Section 6, "Glycemic Goals and Hypoglycemia")
- Choose evidence-based titration algorithm, e.g., increase 2 units every 3 days to reach FPG goal without hypoglycemia
- For hypoglycemia: determine cause; if no clear reason, lower dose by 10-20%

Assess adequacy of insulin dose at every visit

Consider clinical signals to evaluate for overbasalization and need to consider adjunctive therapies (e.g., elevated bedtime-to-morning and/or postprandial-to-preprandial differential, hypoglycemia [aware or unaware], high glucose variability)

Indication, Titration and Monitoring

**If on bedtime NPH, consider converting
to twice-daily NPH plan**


























Conversion based on individual needs and current glycemic management. The following is one possible approach:

INITIATION:

- Total dose = 80% of current bedtime NPH dose
- 2/3 given in the morning
- 1/3 given at bedtime

TITRATION:

- Titrate based on individualized needs

	individual medications			combinations	
	BI	GLP-1RA	SGLT2i	BI + GLP-1RA	BI + SGLT2i
FPG					
Postprandial PG					
HbA _{1c}					
Weight					
Hypoglycemia					

Guidance on starting and titrating of BI in people with T2DM

Insulin dosing

Initial BI dose 0.1 or 0.2 units/kg/day (depending on high or low insulin sensitivity, respectively)

Target FPG 100–120 mg/dL (5.6–6.6 mmol/L) in absence of hypoglycemia

Algorithm of titration Titration 1–2 times/week*

Measure FPG every morning and consider the values from at least three consecutive days at 2–5 days after last dose change

Consider the median (the middle number) FPG value of the three consecutive days, as well as any unexplained low results (<80 mg/dL)

- >120 mg/dL and none <80 mg/dL: increase dose by 2 units/day
- 100–120 mg/dL: no dose change
- <100 mg/dL or any <80 mg/dL: decrease dose by 2 units/day

Cessation of titration

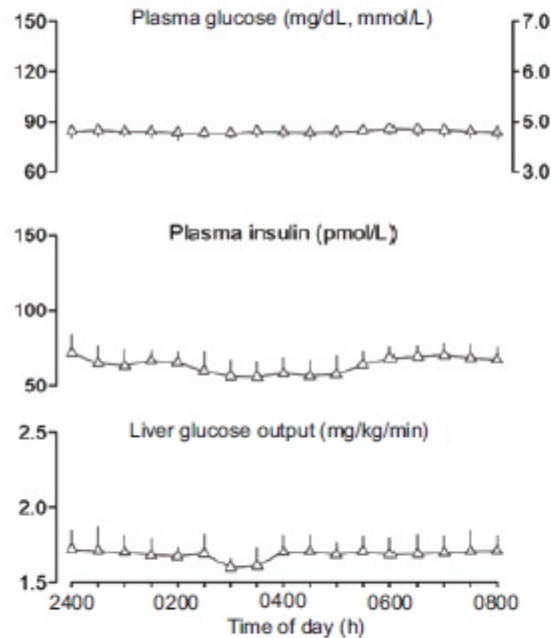
If median FPG is to target (continue BI)

If median FPG is above target and where there is unexplained confirmed (including biochemical) hypoglycemia (consider prandial insulin dosing)

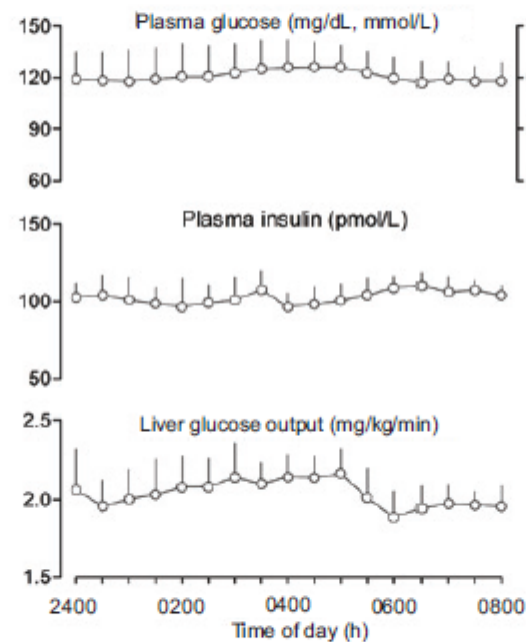
If median FPG is approaching target (<140 mg/dL) but postprandial excursions (>100 mg/dL) suggest that most glucotoxicity is meal related (consider prandial insulin dosing[s])

The Modern Role of Basal Insulin in Advancing Therapy in People With Type 2 Diabetes

Physiologically basal insulin controls plasma glucose by suppressing hepatic glucose production



In T2DM a 24-hour basal insulin normalizes glucose production and thus basal glucose control



Basal insulin can be used in a host of important useful clinical scenarios:

- At diagnosis, for symptom control or safety if so required
- After GLP-1RA/SGLT2i therapy if glucose control is inadequate or if there are problems with these
- In combination with these medications to improve glucose control while minimizing hypoglycemia and weight gain
- As part of a multiple injections regimen in times of metabolic stress
- As part of a multiple injections regimen when insulin secretion is or becomes very deficient

Use of basal insulin remains a cornerstone of continuing good control of T2DM, often after use or consideration of GLP-1RA/SGLT2i, or in combination with these

References

- ▶ ADA 2025
- ▶ EASD 2024
- ▶ Harrison 22e, 2025
- ▶ Williams 15e, 2024