
بسم الله الرحمن الرحيم

Hypoglycemia In Diabetes

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Introduction

- It is now well-established that glycemic control makes a difference for people with diabetes.
- Glycemic control over time prevents or delays micro vascular complications and may also reduce macro vascular events.
- **Iatrognic hypoglycemia** is the limiting factor in the glycemic management of diabetes.
- The effects of hypoglycemia on the brain are real and the glycemic management of diabetes in therefore complex and only partially successful.

Definition:

- **Biochemical:** plasma glucose < 70 mg/dl (<60 mg/dl) whole blood.
- Best to defined on the basis of biochemical and clinical picture **(Whipple's triad)**
  1. Presence of symptoms and/or signs compatible with low plasma glucose concentration.
  2. Presence of low plasma glucose concentration.
  3. Rapid resolution with restoration of plasma glucose concentration.

Hypoglycemia: Definitions

- "**Mild**": Adrenergic (BG<70)
- "**Moderate**": Cognitive (BG<50)
- "**Severe**": Unconscious (BG ???)

N.B.

- Patients with persistently high plasma glucose concentration may perceive symptoms of hypoglycemia at a higher glucose level (relative hypoglycemia).
- Patients with intensively controlled diabetes recognize hypoglycemia at lower than normal glycemic threshold.

Symptoms & signs hypoglycemia

- **Early adrenergic**

Shakiness, palpitation, tachycardia, anxiety, irritability, pallor, sweating, hunger.

- **Late neuroglycopenic**

Irritability, confusion, slurred speech, headache, fatigue, paresthesia, stupor, seizures, motor defects, coma

Cont.

- **Children**

Frequent yawning, espisodic staring, bizzare behaviour twitching, pallor, remoteness, paresthesias, visual disturbances, loss of concentration.

- **Newborn**

High-pitched cry, skin pallor or cyanosis, respiratory distress, apnea, irritability, hypotonia, intermittent twitching, occasionally grand mal seizures.

Glucose conterregulation

- **Decreasing plasma glucose concentration elicits a characteristic sequence of events.**
  1. **Decreased insulin secretion as glucose concentration decline within the physiologic range.**
  2. **Increased glucagon and epinephrine secretion and other neuro-endocrine responses as glucose concentrations fall just below the physiological range (65-70 mg/dl).**
  3. **Neurogenic and neuro-glycopenic symptoms and cognitive impairment at lower plasma glucose concentration.**

Glucose conterregulation (Cont.)

- The magnitude of the neuroendocrine responses to hypoglycemia is a function of the nadir plasma glucose concentration, not the rate of fall of plasma glucose.

- women exhibit a less vigorous response to a given level of hypoglycemia than men.

Glucose conterregulation (cont.)

- Decreased insulin secretion, which favors increased hepatic (and renal) glucose production and decreased glucose utilization by insulin-sensitive tissues such as muscle, is the initial defense against falling plasma glucose concentrations.
- Among the glucose counterregulatory factors, increased glucagon secretion, which stimulates hepatic glycogenolysis and favors hepatic gluconeogenesis, plays a primary role.

Cont.

- increased epinephrine secretion which stimulates hepatic glycogenolysis and gluconeogenesis (and renal gluconeogenesis)
- Glucagon and epinephrine act rapidly (within minutes) to raise plasma glucose concentrations.
- Increased secretion of cortisol and growth hormone, both of which limit glucose utilization by insulin-sensitive tissues and support glucose production over a longer time frame (hours)

Hypoglycemia counter-regulation in type 1 diabetes.

As plasma glucose levels decrease

1- Insulin levels are not decreased.

2- Glucagon production is lost after 5 years from the onset of type I diabetes.

3- Impaired epinephrine response in type I diabetic patients undergoing intensive treatment.

Type 1 diabetes patients with deficient glucagon and epinephrine response to hypoglycemia have ≥ 25 fold risk of hypoglycemia during intensive insulin therapy.

Hypoglycemia counter-regulation in type 2 diabetes.

- Severe hypoglycemia is much less common in type 2 diabetes because of insulin resistance and residual β-cell function.
- Insulin levels do not decrease as blood glucose levels fall because of the non-glucose dependent elevation of insulin secretion by sulfonylurea.
- Glucagon responses are lost late in the evolution of type 2 diabetes treated by insulin.

Hypoglycemia

"The Greatest Limiting Factor In Diabetes Management"

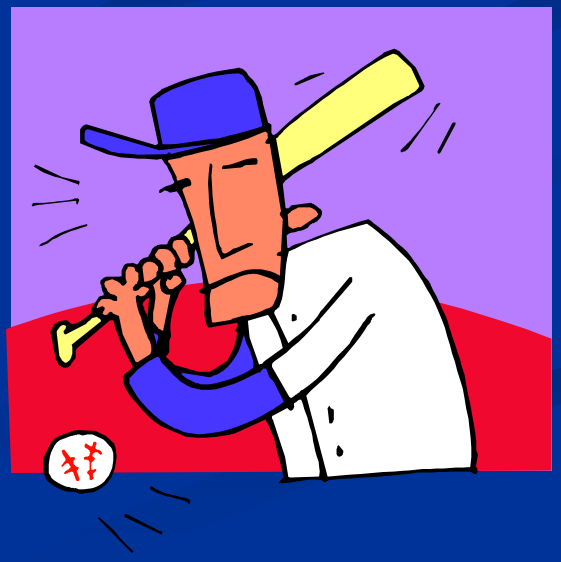
Hypoglycemia in Diabetes

Iatrogenic hypoglycemia is the limiting factor in the glycemic management of diabetes.

- It causes recurrent morbidity in most people with T1DM and many with advanced T2DM, and is sometimes fatal.
- It precludes maintenance of euglycemia over a lifetime of diabetes and, thus, full realization of the benefits of glycemic control.
- It impairs defenses against subsequent hypoglycemia.

The Great Limiting Factor

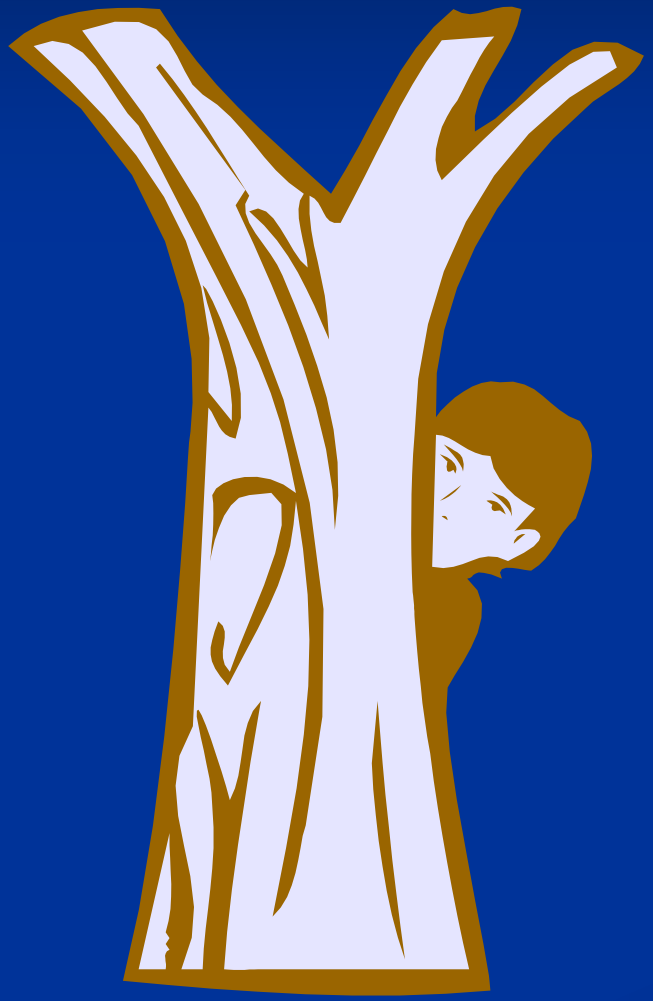
- Performance Impairment



The Great Limiting Factor

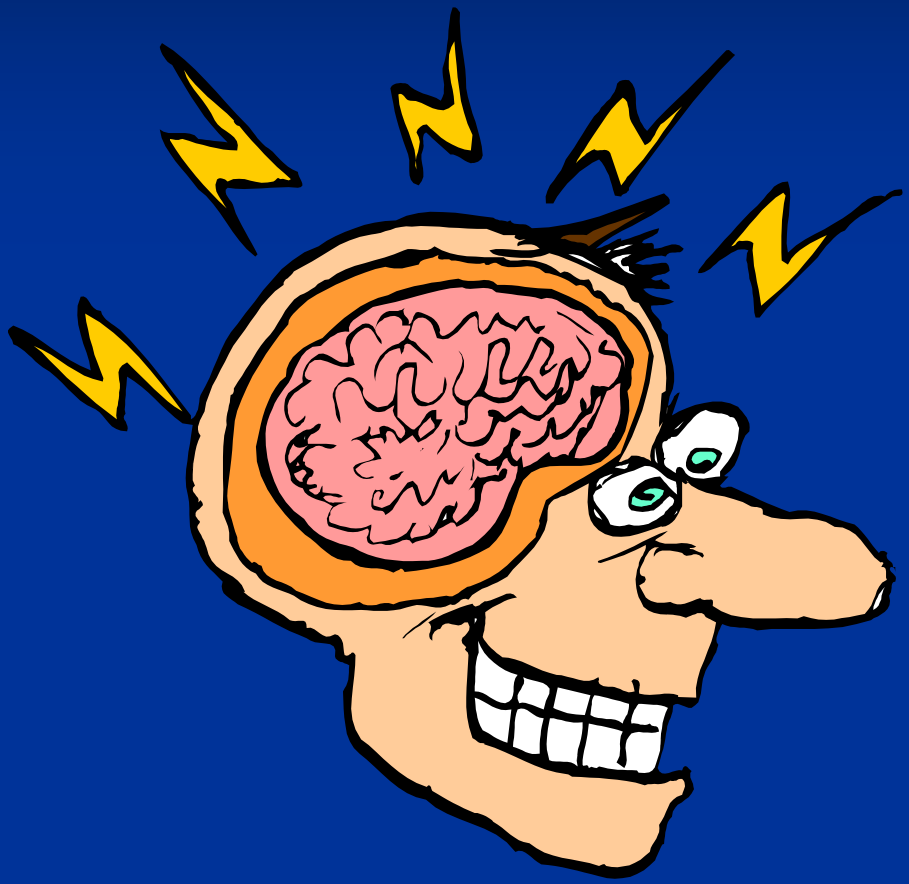
- Accident Risk

The Great Limiting Factor



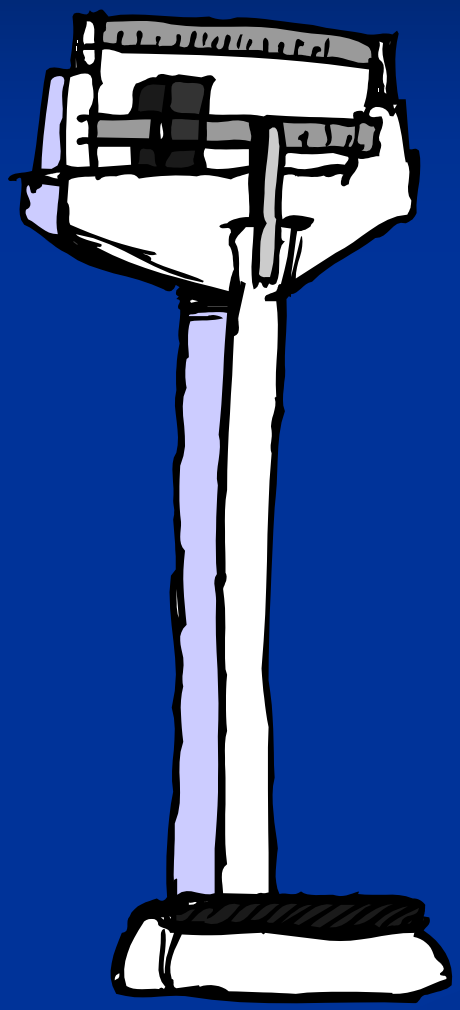
- Anxiety / Embarrassment

The Great Limiting Factor



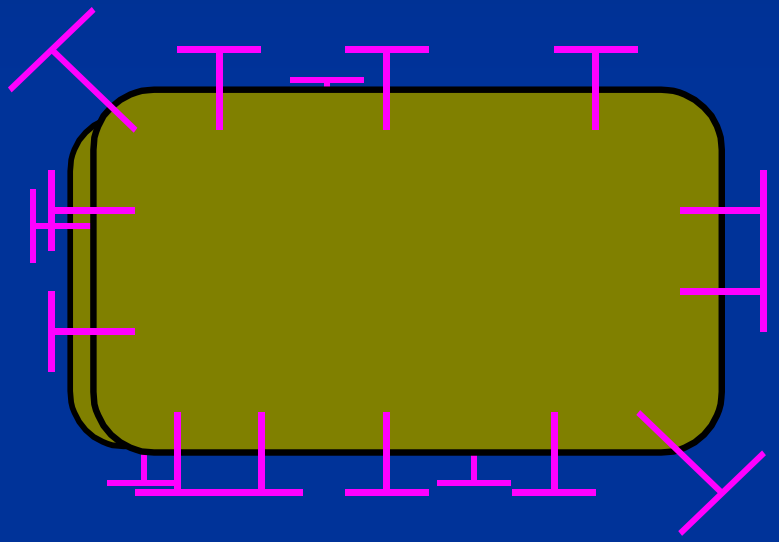
- Lasting Damage?

The Great Limiting Factor



- Weight Gain

The Great Limiting Factor



- Diminished Symptoms

  (Hypoglycemic Unawareness)

Hypoglycemia unawareness

- The clinical syndrome of **hypoglycemia unawareness** means loss of the warning, largely neurogenic symptoms of developing hypoglycemia.
- Because it compromises behavioral defenses against developing hypoglycemia (e.g., the ingestion of food), hypoglycemia unawareness is also associated with a **high frequency of severe iatrogenic hypoglycemia**
- Hypoglycemia unawareness is generally thought to be the **result of reduced sympathoadrenal responses** and the resultant reduced neurogenic symptom responses to a given level of hypoglycemia

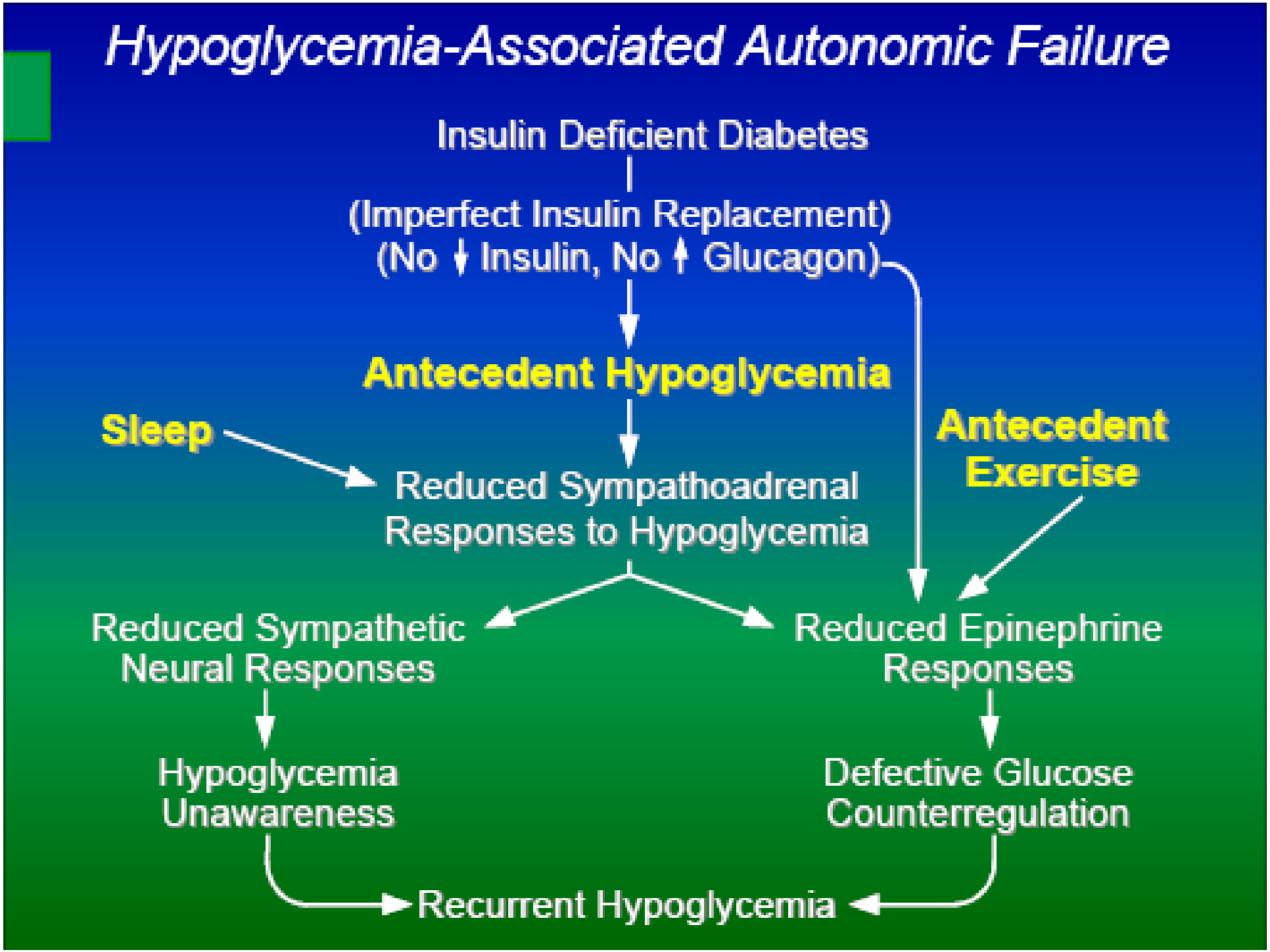
Hypoglycemia-Associated Autonomic Failure

- Results from antecedant iatrogenic hypoglycemia.
- Hypoglycemia produces autonomic nervous system fuctional failure.
- Fuctional failure:

  1- Hypoglycemia unawarness.

  2- Failure of glucose counter regulation.

Both produce further hypoglycemia and perpetuate the cycle


Hypoglycemia-Associated Autonomic Failure
Insulin Deficient Diabetes
(Imperfect Insulin Replacement)
(No ↓ Insulin, No ↑ Glucagon)
Antecedent Hypoglycemia
Sleep
Antecedent Exercise
Reduced Sympathoadrenal Responses to Hypoglycemia
Reduced Sympathetic Neural Responses
Reduced Epinephrine Responses
Hypoglycemia Unawareness
Defective Glucose Counterregulation
Recurrent Hypoglycemia

The clinical impact of HAAF

The clinical impact of HAAF is well established in T1DM. Recent antecedent hypoglycemia, even asymptomatic nocturnal hypoglycemia, reduces sympathoadrenal – epinephrine and neurogenic symptom – responses and cognitive dysfunction responses to subsequent hypoglycemia, glycemic defense against hyperinsulinemia, and detection of hypoglycemia in the clinical setting in T1DM.

The clinical impact of HAAF

Perhaps the most compelling support for the concept of HAAF is the finding, in three independent laboratories, that as little as 2-3 weeks of scrupulous avoidance of iatrogenic hypoglycemia reverses hypoglycemia unawareness and improves the reduced epinephrine component of defective glucose counterregulation in most affected patients.

HAAF in Advanced T2DM

advanced (insulin deficient) T2DM …

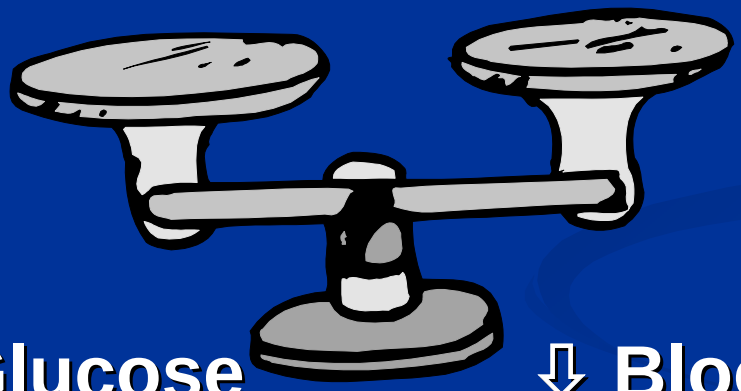
Glucagon responses to hypoglycemia are lost, as in T1DM.

Glycemic thresholds for epinephrine and neurogenic symptom responses (among other responses) are shifted to lower plasma glucose concentrations by recent antecedent hypoglycemia, as in T1DM.

Thus, people with advanced T2DM are also at

Hypoglycemia: Cause

- *Imbalance* **between factors raising and lowering blood glucose levels**



⇧ Blood Glucose	⇩ Blood Glucose
Food	Insulin/Oral Meds

Risk factor for hypoglycemia

ommon risk factors:

- Mismatch of insulin timing, amount or type for carbohydrate intake.
- Oral secretagogues without appropriate carbohydrate intake.
- History of severe hypoglycemia.
- General anesthesia or sedation → altered consciousness.

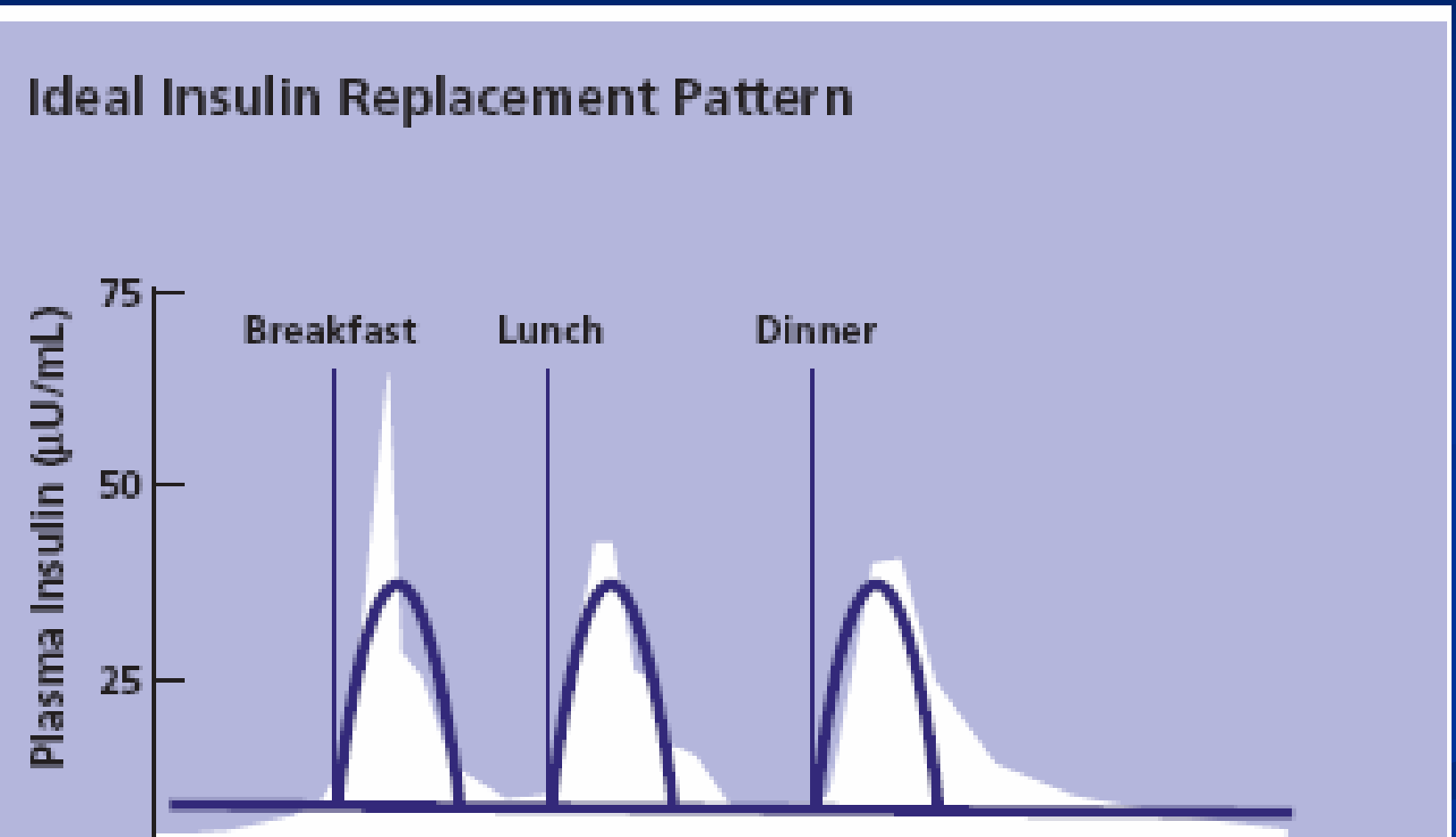
ont.

- Reduction of oral intake.
- New NPO status.
- Unexpected transport after injection of rapid or fast acting insulin
- Critical illness (hepatic, cardiac, renal failure, sepsis, severe trauma).
- Mismatch of exercise with insulin, insulin

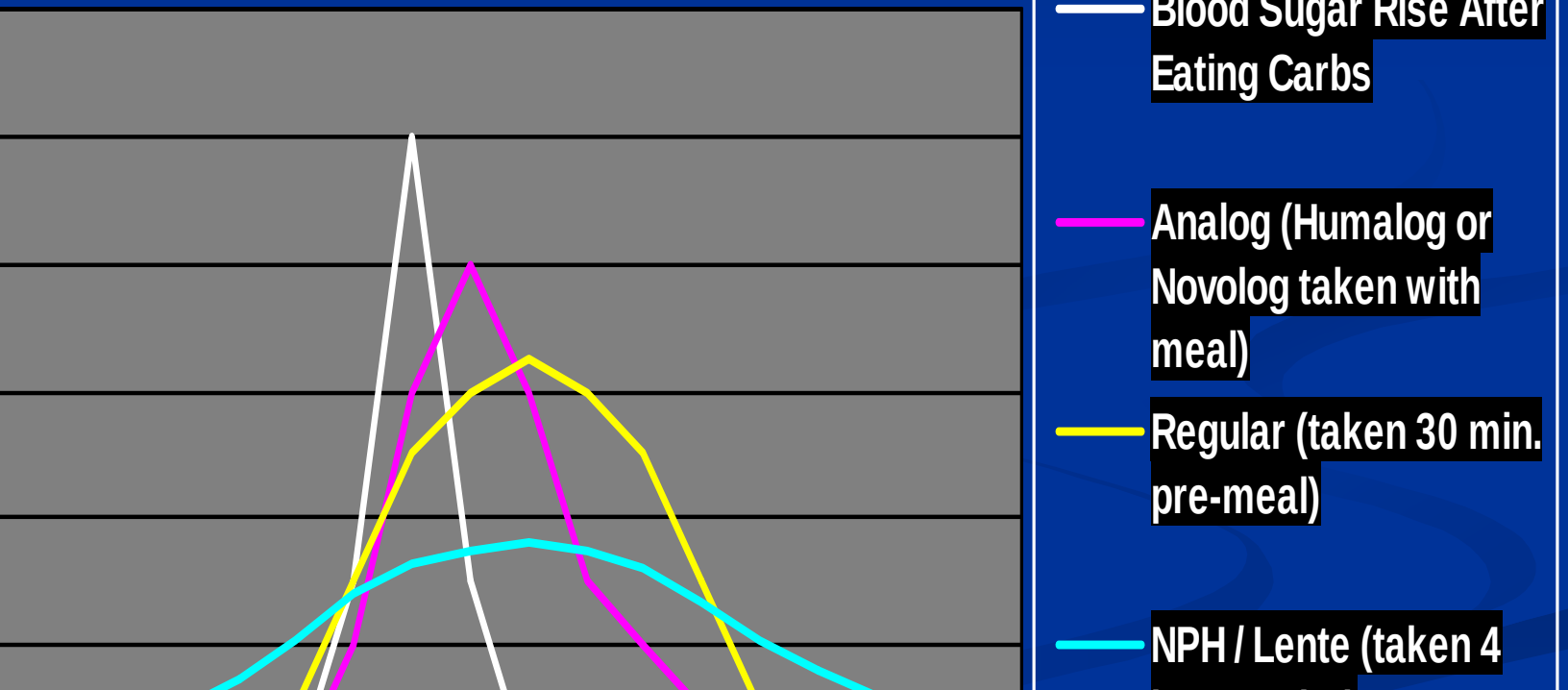
ess common risk factors

- Endocrine deficiencies (cortisol, growth hormone).
- Sudden reduction of corticosteroid dose.
- Emesis.
- Reduction of IV dextrose.
- Unexpected interruption of enteral feeding or parenteral nutrition.

Profile of ideal insulin replacement pattern



harmacokinetics of some currently available insulin preparations



Blood Sugar Rise After Eating Carbs

Analog (Humalog or Novolog taken with meal)

Regular (taken 30 min. pre-meal)

NPH / Lente (taken 4

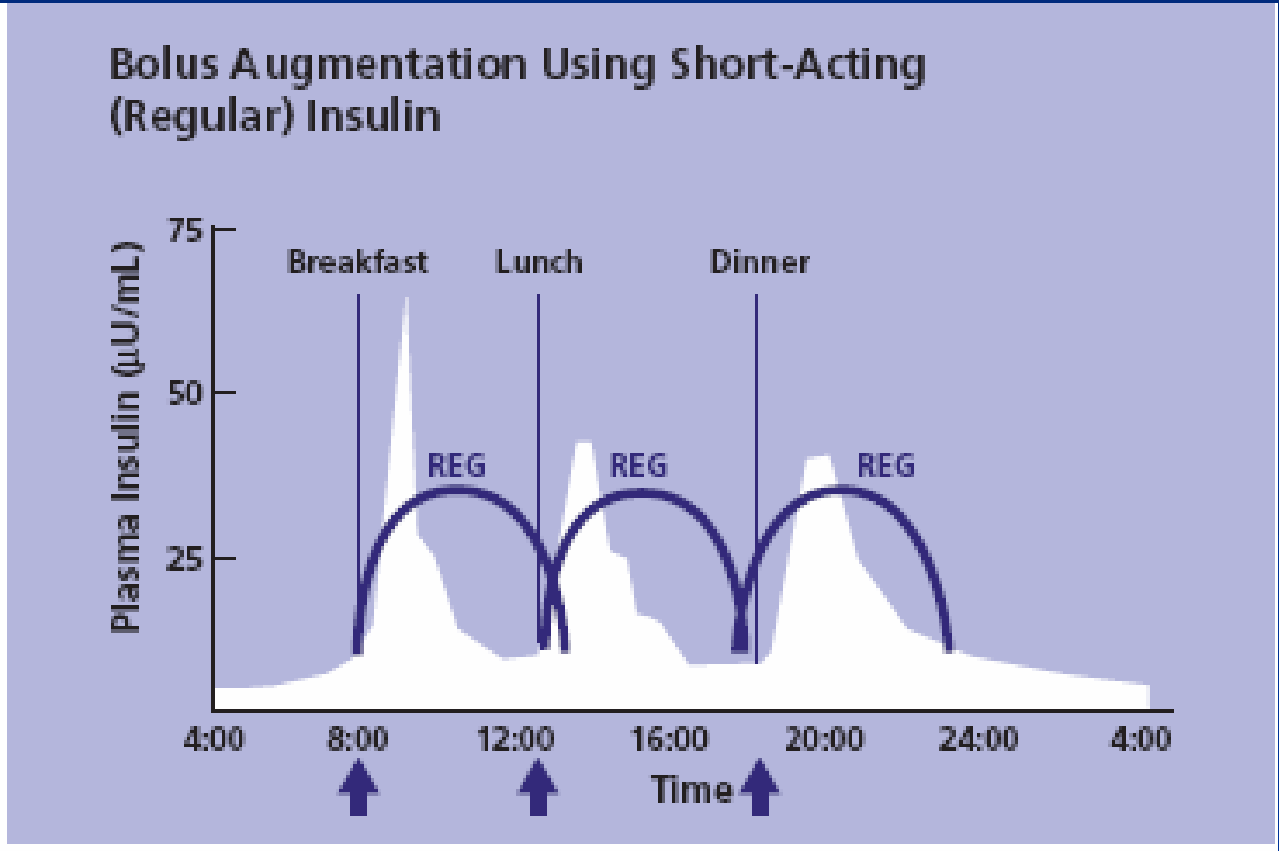
1- Short acting regular insulin:

Onset: 15 – 60 min → injection 30 min before meal.

Peak: 2 – 4 h → too late to control post mixed meal hyperglycemia.

Duration: 6 - 8 h → hypoglycemia may occur before the next meal.

egular insulin, mealtime insulin profile



2- short acting insulin analogues:

Onset: 10 – 15 min → injection just before meal.

High and short peak → 2 more efficient control of post mixed meal hyperglycemia.

Duration: 3 – 5 h →no occurrence of hypoglycemia before the next meal.

- Twice daily insulin injection (fixed combination)

Given as a combination of short or rapid acting insulin and intermediate acting insulin before breakfast and supper.

The fixed combination of short and intermediate acting insulin are not suitable for individual variation of the dose.

Hypogylycemia late in the afternoon and in the middle of the night related to intermediate acting

nsulin regimen consisting of two injections per day (arrows) of short-acting regular insulin and intermediate-acting insulin (NPH or Lente).

Mixture of short and intermediate acting insulin before breakfast, short acting insulin before supper, intermediate acting at bedtime

itable for

- Patients with frequent nocturnal hypoglycemia and fasting hyperglycemia.
- Patients who do not wish to take or frequently forget the pre-lunch injection.

sulin regimen consisting of injections of short-acting regular
sulin and intermediate-acting insulin before breakfast, short-
cting insulin before the evening meal and intermediate-acting
insulin at bedtime.

Short acting insulin before each meal, intermediate acting insulin at bed time.

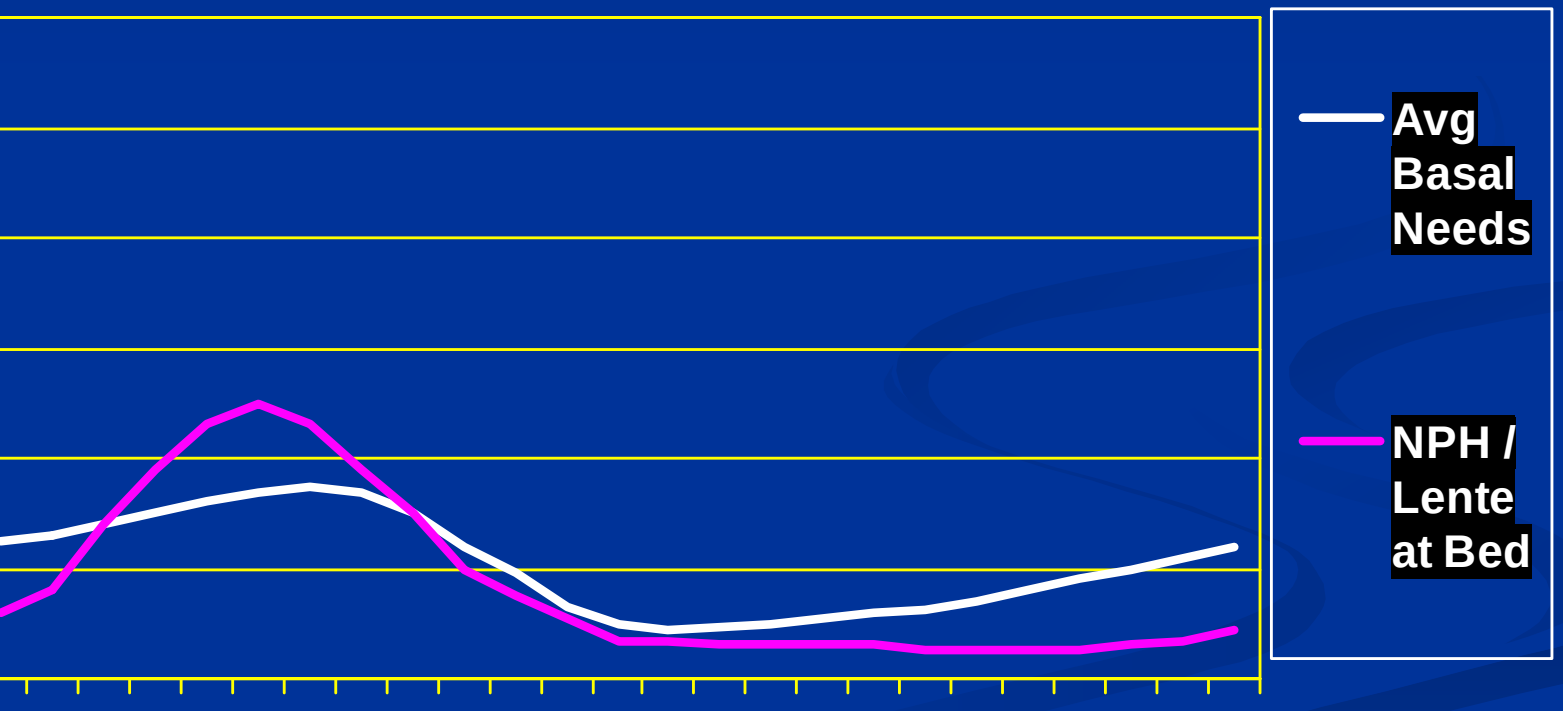
dvantages:

- Avoid peak afternoon hypoglycemia.
- Avoid nocturnal hypoglycemia.
- Avoid fasting hyperglycemia.

Basal insulin replacement and nocturnal hypoglycemia

- Intermediate – acting insulin is used for overnight insulin replacement.
- It has marked peak affect compared to non prandial pattern of insulin secretion from healthy pancreas.
- This will lead to nocturnal hypo-glycemia associated with next morning hyperglycemia

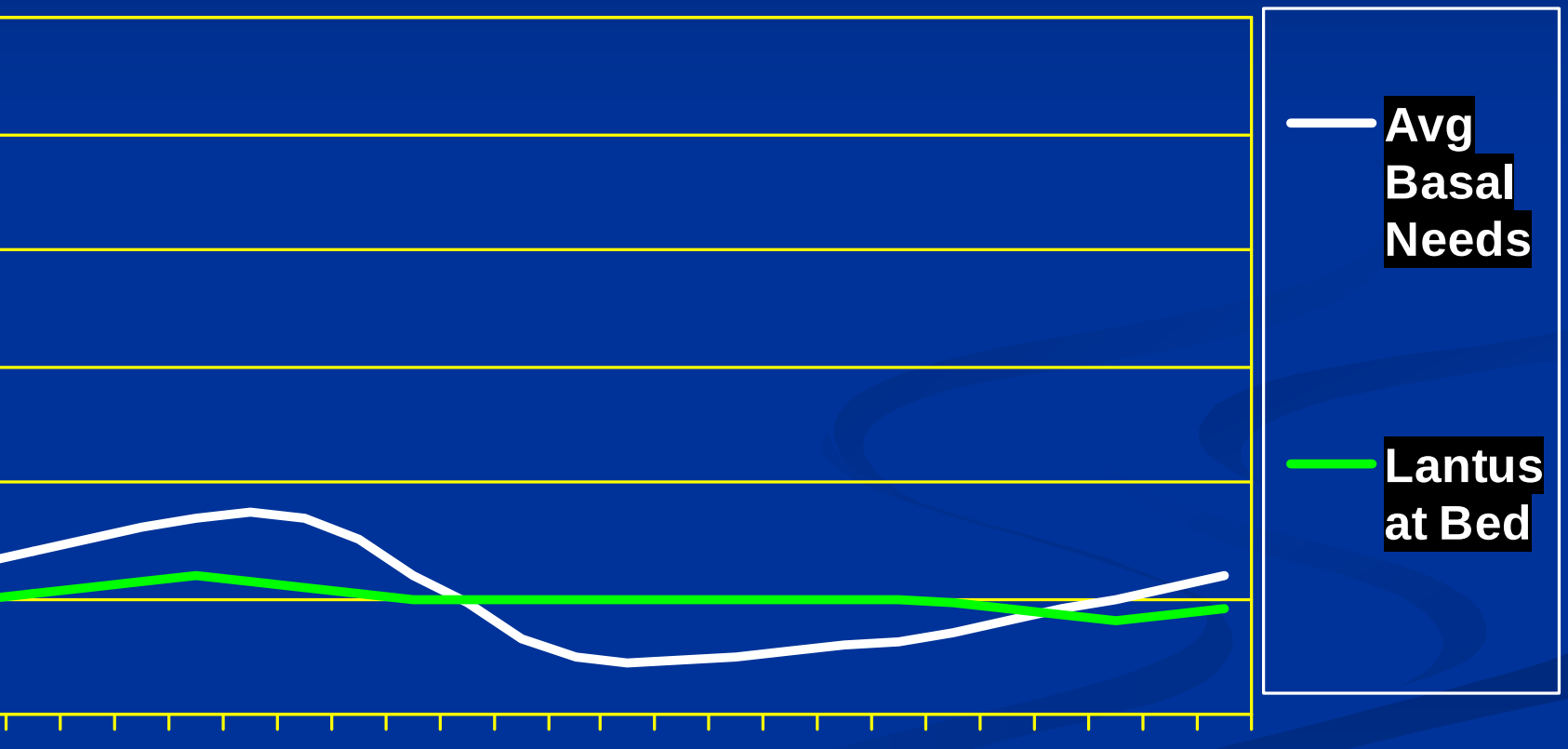
Basal insulin replacement and nocturnal hypoglycemia



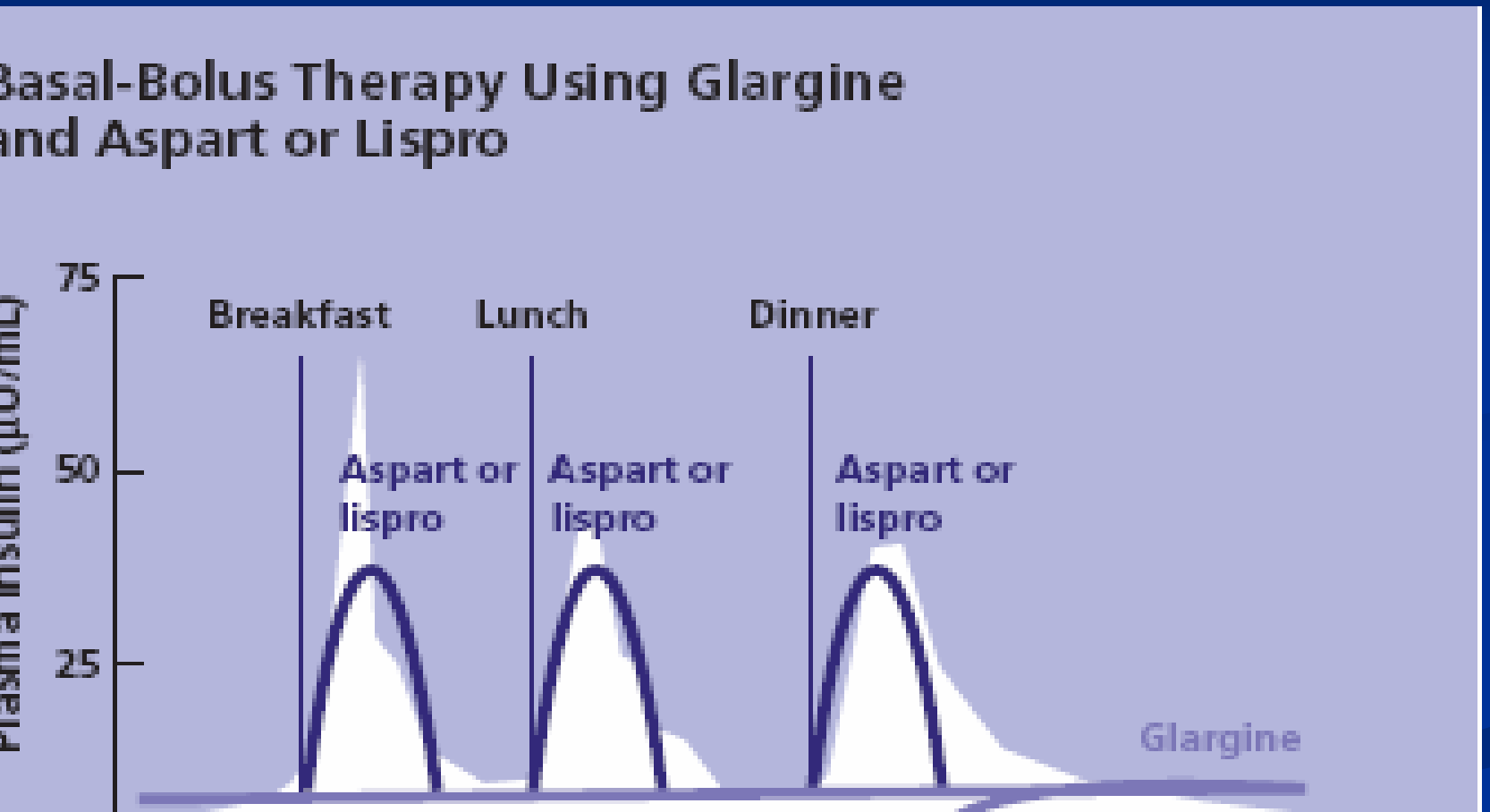
Treatment of hypoglycemia related to basal insulin replacement.

- Delay the administration of intermediate – acting insulin to bedtime.
- Basal insulin replacement is provided by twice-daily intermediate acting insulin rather than by one evening dose.
- Use insulin analogues which have a flat, more prolonged insulin action.

Treatment of hypoglycemia related to basal insulin replacement



Basal plus meal related regimen using glargine plus aspart or lispro



ypoglycemia & oral anti-diabetic agents

- Hypoglycemia is not common with the use of metformin, thiazolidinediones, or α-glucosidase inhibitors.
- The risk of hypoglycemia is highest with long-acting sulfonylureas.
- Glimepiride, a long-acting sulfonylurea, has a low risk of hypoglycemia as it has a low affinity for β-cell receptor and low insulin secretory capacity in both the

poglycemia & oral anti-diabetic agents (cont.)

A modified release preparation of gliclazide may have a lower risk of hypoglycemia.

Repaglinide and nateglinide are oral glucose prandial regulators, insulin secretagogues that have a rapid onset of action but do not stimulate insulin secretion in the fasting state and provoke

mportant questions in management of hypoglycemia

- Time of occurance of hypoglycemia
- Frequency of hypoglycemia.
- Dietary habits of the patient.
- nsulin type and regimen.
- nsulin syringe.
- Other drugs used by the patient.
- Other comorbid conditions.

Prevention of hypoglycemia

Recognition of precipitating factor

Delay in the timing of meals.

Errors in the dosage or timing of oral hypoglycemic drugs and / or insulin.

Presence of co-morbidity such as renal, adrenal or pituitary insufficiency which ↑ the risk of hypoglycemia.

Comorbidities that ↑ hypoglycemia risk e.g. anorexia, malabsorption, gastropa-

Scheduled insulin therapy.

Regular insulin sliding scale without basal insulin replacement remains a common method for control of hyperglycemia.

This regimen includes no basal insulin and prandial insulin is given only if pre-meal blood glucose is elevated.

t is ineffective and carry the risk of hyper

Inpatient use of oral agents

Oral agents should not be used by inpatients who are too ill to maintain adequate caloric intake or who are on NPO status because of illness or planned procedure.

These patients should be converted to SC or IV insulin regimen during hospitalization which provides a more flexible regimen to control blood glucose.

) Glucose monitoring:

Should be performed at least 4 times daily.

Reduce the dose of insulin in patients with persistent hypoglycemia.

Patient who require continuous tube feeding should have blood glucose checked every 6 hours.

Glucose monitoring (cont.):

- Before All Meals & Snacks
- Pre/Post Exercise
- Bedtime
- 3 a.m. (occasionally)

Exercise

General guidelines

- Check blood glucose level prior to exercise.
- Before initiating any activity, correct hypoglycemia with 15-30 gm carbohydrate and repeat treatment until blood glucose reading is > 100 mg/dl.
- Check blood glucose reading every 60-90 min during exercise and at the end of exercise
- Always carry source of carbohydrate while

Exercise (cont.)

- Drink fluids every hour, especially if exercising in warm temperatures.
- Avoid exercise at the expected peak of insulin activity.
- Adjust insulin and food intake to avoid delayed hypoglycemia that can occur many hours after exercise.
- A bedtime snack may be necessary if patient exercise in the evening.

Exercise (cont.)

planned exercise

- Ingest 15-30 gm of carbohydrate for every 30-45 min of moderate exercise.
- Ingest 1-2 protein exchanges prior to a period of sustained exercise.

anned exercise

- Decrease short acting insulin 25-50% prior to moderate exercise.
- Additional carbohydrate may be needed (15-30 gm) depending on the length and intensity of the activity.
- Reduce the dose of morning NPH insulin by 15-

) Exercise (cont.)

- ✓ Exercise, recreation, chores: all count!
- ✓ Reduce meal insulin (25%, 33%, 50%) for after-meal activity
- ✓ Snack prior to after/between meal activity
- ✓ Lower long-acting/basal insulin prior

) Exercise (cont.)

Watch Out for D'OH!

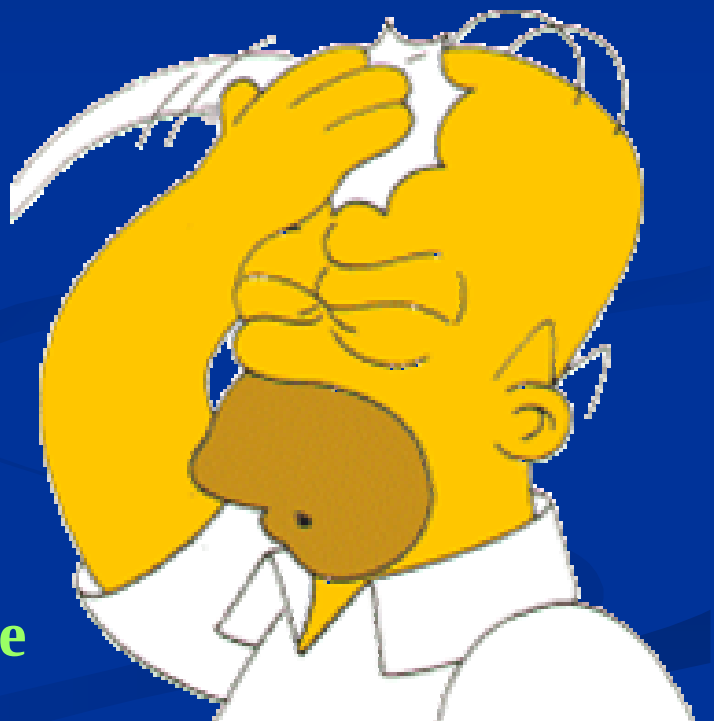
Delayed Onset Hypoglycemia)

llowing High-Intensity Exercise

llowing Extended Duration Activity

ay Occur Up to 24 Hours After

djustments to food and insulin may be



Treatment of hypoglycemia

f blood glucose is < 70 mg/dl, give 15-20 gm of quick acting carbohydrate (1-2 teaspoons of sugar or honey, ½ cup of egular soda, 5-6 pieces of hard candy.

Test blood glucose 15 min after treatment. If still <70 mg/dl, etreat with 15 gm of additional carbohydrate.

f blood glucose is not <70 mg/dl but at is > 1 hour until the next meal, have a snack with starch and protein.

For patients who are unconscious or unable to take oral carbohydrate → give 25 gm (50 ml) 50% dextrose (IV) or 100 ml

Hypoglycemia Treatment

Always Carry Rapid-Acting Carbs!


Thank
you