Hypoglycemia In Diabetes

By

Prof. Nagy Shaaban
Endocrine & Diabetes Unit
Mansoura University
2006
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.

- **Iatrogenic 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
Children
Frequent yawning, episodic staring, bizarre 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 counterregulation

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.
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.
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.
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.
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”
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)
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 antecedent iatrogenic hypoglycemia.
- Hypoglycemia produces autonomic nervous system functional failure.
- Functional failure:
  1. Hypoglycemia unawareness.
  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 → Reduced Sympathoadrenal Responses to Hypoglycemia

Reduced Sympathetic Neural Responses → Hypoglycemia Unawareness

Reduced Epinephrine Responses → Defective Glucose Counterregulation → Recurrent Hypoglycemia

Antecedent Exercise
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.
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.
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

![Image showing a balance scale with Food and Insulin/Oral Meds on opposite sides]
Risk factor for hypoglycemia

**Common 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.
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
Less 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
Pharmacokinetics 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 hi )
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.
Regular 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.

Hypoglycemia late in the afternoon and in the middle of the night related to intermediate acting insulin frequently occur.
Insulin 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.

**Suitable for**

Patients with frequent nocturnal hypoglycemia and fasting hyperglycemia. Patients who do not wish to take or frequently forget the pre-lunch injection.
Insulin regimen consisting of injections of short-acting regular insulin and intermediate-acting insulin before breakfast, short-acting insulin before the evening meal and intermediate-acting insulin at bedtime.
Short acting insulin before each meal, intermediate acting insulin at bed time.

Advantages:

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 hypoglycemia 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

Basal-Bolus Therapy Using Glargine and Aspart or Lispro

Plasma Insulin (μU/mL)

Breakfast  Lunch  Dinner

Aspart or lispro  Aspart or lispro  Aspart or lispro

Glargine
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
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 hypoglycemia.
Important questions in management of hypoglycemia

- Time of occurrence of hypoglycemia
- Frequency of hypoglycemia
- Dietary habits of the patient
- Insulin type and regimen
- Insulin 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. It 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 exercising.
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.

planned 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 15-25% for afterơn morning exercise.
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)

Following High-Intensity Exercise
Following Extended Duration Activity
May Occur Up to 24 Hours After
Adjustments to food and insulin may be
Treatment of hypoglycemia

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

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

If 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