Hypoglycemia in Non-diabetic Patients

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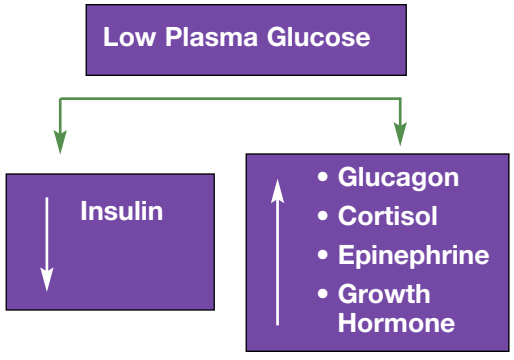
Table 1
Whipple's Triad:

1. Neuroglycopenic symptoms or signs of hypoglycemia
2. Low venous plasma glucose
3. Rapid resolution of symptoms/signs with carbohydrate intake

Figure 1
When Plasma Glucose Falls



Hypoglycemia in non-diabetics is extremely uncommon due to the effectiveness of the body's physiological defenses against falling plasma glucose concentrations. Euglycemia is maintained through a balance between glucose absorption, production (gluconeogenesis/glycogenolysis), and utilization. When plasma glucose levels fall, the body's first response is to decrease insulin production. This is followed by an increase in insulin counter regulatory hormones, including glucagon, cortisol, growth hormone, and catecholamines (Figure 1). Since hypoglycemia in non-diabetics is uncommon, a thorough evaluation of this population should be restricted only to patients with the Whipple's Triad (see Table 1).

Clinical Features

The clinical manifestations of hypoglycemia are divided into autonomic and neuroglycopenic symptoms. Autonomic symptoms include palpitations, hunger, nausea, sweating, tremours, and anxiety, and they are caused by sympathetic/vagal discharge in response to low plasma glucose. Neuroglycopenic symptoms, due to brain glucose deprivation, include blurry vision, behavioural changes, drowsiness, confusion, seizures, focal neurologic deficits, and coma. In most patients, autonomic and neuroglycopenic symptoms do not manifest until the plasma glucose drops below 2.8 to 3.0 mmol/L, although this varies between individual patients.

Diagnostic Approach

Hypoglycemia in non-diabetic patients is often divided into fasting or postprandial and well or unwell (Table 2). Fasting hypoglycemia (more than four to five hours after a meal) accounts for most cases of pathological hypoglycemia. Postprandial hypoglycemia (within four to five hours of a meal) occurs in patients after gastric surgery due to uncontrolled gastric emptying, which results in a rapid rise in plasma glucose and, therefore, an exaggerated insulin response. Patients with pancreatic beta cell disorders due to hypertrophy or hyperplasia (nesidioblastosis) can also develop postprandial hypoglycemia.

Table 2
Differential Diagnosis of Hypoglycemia in Non-diabetic Patients

Occurrence	Well	Unwell
Usually Occurs in Fasting State	1. Endogenous hyperinsulinism a. *Insulinoma b. *Autoimmune hypoglycemia	1. Critical illness – severe sepsis and severe hepatic, cardiac, and renal failure 2. Hormone deficiency – cortisol, glucagon, epinephrine 3. Non Islet cell tumours (IGF-2 secreting)
Usually Occurs in Post-prandial State	1. Endogenous hyperinsulinism c. Functional beta cell disorder *ie*.pancreatic islet cell hypertrophy, nesidioblastosis	
Usually Occurs in both Fasting and Post-prandial States	1. Endogenous hyperinsulinism d. */**Insulin secretagogues 2. Accidental, surreptitious or malingering a. */**Insulin/insulin secretagogues	4. */**Drugs/Insulin

Table 3
Common Drugs Established or Reported to Cause Hypoglycemia

Disorder Treated	Drugs
Diabetes mellitus	Insulin, insulin secretagogues, metformin
Infections	Quinine, pentamidine, sulphonamides, fluoroquinolones
Arrhythmias	Quinidine
Pain	ASA, indomethacin, acetaminophen

"Reactive hypoglycemia" describes a postprandial decrease in plasma glucose, and it occurs in 10 to 30% of patients undergoing oral glucose tolerance testing. This is not classified as "true" hypoglycemia, and only warrants further investigation if patients develop severe neuroglycopenic symptoms.

Patients who are unwell, hospitalized, or have comorbid medical conditions develop hypoglycemia most commonly due to medications (Table 3). Severe sepsis and severe hepatic, cardiac, or renal failure can cause hypoglycemia in critically ill patients. Hormonal deficiencies, such as adrenal insufficiency or hypopituitarism, are less common etiologies.

In a seemingly well individual, one must first exclude accidental, surreptitious, or even malingering causes of hypoglycemia. Medication errors, either in dispensing or administering medication, should be considered. Intentional use of insulin or insulin secretagogue is more likely in a patient with knowledge of hypoglycemia agents (*ie*., health care workers or patients with certain psychiatric illnesses). If the above causes of hypoglycemia are excluded, patients should be evaluated for endogenous hyperinsulinemia.

If a patient is euglycemic at the time of presentation, but the suspicion for pathological hypoglycemia is high, a 72 hour supervised fast in hospital should be performed to document hypoglycemia and evaluate for endogenous hyperinsulinemia. Venous plasma glucose, insulin, pro-insulin, ketones, and C-peptide levels should be drawn every six hours until hypoglycemia is documented. The complete 72 hour fast protocol is outlined in Table 4. Patients with endogenous hyperinsulinemia have elevated C-peptide and pro-insulin levels, which are insulin precursors. A rise in plasma glucose of greater than 1.4 mmol/L 30 minutes after a glucagon challenge (1 mg IV) also suggests endogenous hyperinsulinemia.

Table 5
Laboratory Findings in Patients with Hyperinsulinemic Hypoglycemia

Etiology	Insulin	Pro-insulin	C Peptide	Circulating Hypoglycemic Agent
Exogenous Insulin	↑	↓	↓	—
Oral hypoglycemic agent	↑	↑	↑	high
Insulinoma	↑	↑	↑	—

It is important to also measure oral hypoglycemic drug levels (*ie*., glyburide) to rule out accidental or surreptitious oral hypoglycemia use causing an increase in endogenous insulin secretion. Insulin antibodies should also be drawn to rule out autoimmune hypoglycemia, a disorder in which autoantibodies bind and subsequently release free insulin into the plasma. If free insulin is released at an inappropriate time, it results in hypoglycemia. The approach to interpreting laboratory results from a 72 hour fast is outlined in Table 5.

Insulinomas

Insulinomas are rare, neuroendocrine tumours that are benign in greater than 90% of cases. They should be suspected in patients with documented hyperinsulinemia, elevated plasma C peptide, and pro-insulin levels and in the absence of insulin secretagogue use. CT or MRI scan should be used to localize insulinomas, as the sensitivity of ultrasound is poor (less than 20%). Octreotide scintigraphy will detect 50 to 80% of insulinomas. Surgical resectioning is the treatment of choice, and it is curative in the majority of cases. To maintain euglycemia prior to surgical intervention, small frequent meals and oral diazoxide are used. If hypoglycemia persists, subcutaneous octreotide and an intravenous dextrose infusion may be required.

Take Home Points

- Evaluate all non diabetic patients with Whipple's Triad for pathological hypoglycemia
- Determine if the hypoglycemia is well or unwell and fasting or post-prandial

Table 4
72 Hour Fast Protocol

- Onset recorded as last food ingestion
- Calorie and caffeine-free beverages only
- Measure glucose, C peptide, insulin and pro-insulin every 6 hours
- Once blood glucose < 3.3mmol/L, measure every 1to 2 hours
- End fast once blood glucose < 2.5mmol/L and patient has signs or symptoms of hypoglycemia
- Measure insulin, C peptide, pro-insulin, and beta hydroxybutyrate at the end of fast
- Inject 1 mg glucagon IV, measure plasma glucose at 10, 20, and 30 minutes

- Drugs are the most common cause of hypoglycemia in non-diabetic patients
- If spontaneous hypoglycemia cannot be documented, a 72 hour fast should be performed (See Table 4)
- Measurement of insulin, C peptide, and pro-insulin levels are needed to document endogenous hyperinsulinemia in the workup for a possible insulinoma
- Over 90% of insulinomas are benign, and surgical resection is recommended

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For references, and resources please contact **cme@sta.ca**

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