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# Non-diabetic hypoglycaemia

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## Abstract

Hypoglycaemia is diagnosed by the presence of symptoms of hypoglycaemia, documented low plasma glucose (often less than 50 mg/dL) at the time of symptoms, and recovery of symptoms by correction of glucose. If plasma glucose is normal at the time of symptoms, causes other than hypoglycaemia should be considered. If hypoglycaemia has been documented, the cause of hypoglycaemia should be investigated. Only after documentation of spontaneous endogenous insulin secretion causing hypoglycaemia should we proceed with localization of the tumor. Surgery will cure hypoglycaemia in about 90% of patients with insulinoma. Dumping syndrome can cause postprandial symptoms in people who have had upper gastrointestinal (GI) surgery (and rarely without surgery). The symptom complex in dumping syndrome includes the ones caused by GI stretching and GI hormones, or hypoglycaemia, or both. Dumping syndrome often needs to be managed by dietary interventions with or without pharmacotherapy.

**Key words: hypoglycaemia**, dumping syndrome, insulinoma

## Introduction

Symptoms of hypoglycaemia can be classically divided into adrenergic and neurological (Table 1). In a person on anti-diabetic medications, clinical features or if in doubt, a glucometer or glucose sensor reading is sufficient for diagnosis and treatment of hypoglycaemia. However, in non-diabetic hypoglycaemia, capillary meter glucose or sensor interstitial glucose values are not sufficient to reach a diagnosis. In a person without diabetes (not known to be on diabetes medications) diagnosis of hypoglycaemia requires documentation of the Whipple's triad.(1)

## History and physical examination

### Precipitants

People who experience episodes of symptoms, often know what precipitates their symptoms. These may include:

*Precipitants suggestive of hypoglycaemia as a cause of symptoms*

- Fasting for longer periods of time (eg., delaying breakfast) is more likely to precipitate a symptomatic episode
- Physical activity
- Avoiding carbohydrates

*Precipitants suggestive of hypoglycaemia and/or other causes of symptoms*

- Postprandial symptoms (E.g., after Gastric Bypass, suggestive of dumping syndrome with or without hypoglycaemia). These are often associated with:
    - large meals
    - eating rapidly
    - eating refined carbohydrates
    - drinking with food (even water)
    - drinking fizzy drinks (carbonated drinks like Coca Cola, plain soda)
    - alcohol

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*Precipitants not indicating hypoglycaemia as a cause of symptoms*

- Postural symptoms caused by getting up too fast from lying or sitting posture (suggestive of postural hypotension as a cause of symptoms), including vasovagal episodes
- Changes in mood, stress level
- Changes in weather/temperature

**Prevention and self-treatment of the episodes**

Patients often already know how to prevent the symptomatic episodes. They may be avoiding the precipitants. They may be consuming sweets, sugar-containing drinks and bread to prevent the episodes from getting worse. Patients may get up past midnight to eat an extra meal to prevent early morning hypoglycaemia.

Dietary protein does not prevent or treat hypoglycaemia. Dietary fat delays the recovery from hypoglycaemia by delaying the motility and digestion of food and absorption of glucose.

Symptoms not relieved by fast acting carbohydrates (sugar or refined starch) but relieved by food containing predominantly protein and fat (e.g., meat, cheese, paneer, etc.) are likely not from hypoglycaemia. Symptoms relieved by consuming fast acting carbohydrates may be from hypoglycaemia. Usually, resolution of symptoms by consuming fast acting carbohydrates take about 10-15 minutes, though some symptoms may persist for the next hour or two. If symptoms take one hour or more to start improving, they are unlikely to be from hypoglycaemia.

## Differential diagnoses of spells suspected to be hypoglycaemia

Cardiovascular, neurologic, gastrointestinal and endocrine causes of symptoms can be confused with the symptoms of hypoglycaemia. Plasma glucose documented at the time of a typical spell guides the diagnosis.

If hypoglycaemia is suspected in a nondiabetic person, venous blood should be drawn before treatment if it can be safely accomplished.(2) Blood should not be drawn if the symptoms are only minimal; or after attempted correction. Venous blood glucose levels are not comparable to finger-prick capillary (or sensor interstitial) glucose levels. During a spell with pallor, finger-prick capillary blood glucose (and interstitial glucose by continuous glucose monitor (CGM)) may be low while plasma glucose is normal.

If the blood is drawn during a typical and severe episode and the plasma glucose is > 60 mg/dL, irrespective of whether the patient feels better after consuming food or drink, it can be concluded that hypoglycaemia is not the cause of the symptoms. Therefore other possible causes are entertained.

The diagnosis of hypoglycaemia is made with the confirmation of the Whipple's Triad; with typical symptoms, documented low plasma glucose (≤60 mg/dL, esp. if ≤50 mg/dL) and the improvement of symptoms and plasma glucose on taking carbohydrates.

**Table 1** - Symptoms and signs of hypoglycaemia

| Adrenergic | Neurological |
|---|---|
| Shakiness<br>Trembling<br>Anxiety<br>Nervousness<br>Palpitations, tachycardia<br>Clamminess/ Sweating<br>Dry mouth<br>Hunger<br>Pallor<br>Pupil dilation | Irritability<br>Paresthesia<br>Headaches<br>Difficulty in thinking/ speaking<br>Confusion, abnormal mentation<br>Slurred speech<br>Diplopia<br>Ataxia<br>Seizures<br>Stupor/ Coma |

**Differential Diagnoses of hypoglycaemia**

After a documented Whipple's Triad the cause of hypoglycaemia is investigated.(2)

*hypoglycaemia in a sick person*

hypoglycaemia in a hospitalized sick person is often caused by medications and comorbidities. Many medications have been associated with hypoglycaemia, especially with comorbidities (Table 2). Specific diseases have been associated with hypoglycaemia, especially with certain specific medications (Table 3).

***hypoglycaemia*** *in an otherwise healthy person*

If Whipple's triad is documented in an otherwise healthy person, further investigations are required; serum beta-hydroxybutyrate, plasma insulin, plasma C-peptide, plasma Proinsulin, and hypoglycaemia agent screen. These are performed on the same blood sample drawn during the symptomatic hypoglycemic episode. If possible, plasma glucose response to injection of glucagon (plasma glucose level at the baseline, 10, 20 and 30 minutes after glucagon) is documented (Figure 1).

**Table 2**- Medications (other than diabetes medications) associated with

| Medications known to cause hypoglycaemia |
|---|
| • Pentamidine, especially if used systemically |
| • Trimethoprim–sulfamethoxazole- in the presence of renal failure |
| • Propoxyphene (dextropropoxyphene) - in the presence of renal failure |
| • Quinine |
| • Quinidine |
| • Salicylates- in the presence of renal failure |

In the presence of hypoglycaemia (symptoms with a plasma glucose <60 mg/dL) if beta-hydroxybutyrate is elevated, and plasma glucose response to glucagon is poor (<25 mg/dL) hypoglycaemia is not being caused by insulin-like action. The causes include normal prolonged fasting, glycogen storage disorders (usually these people present during their childhood) and hypothalamic, pituitary and/ or adrenal insufficiency (Table 3).

If beta-hydroxybutyrate is suppressed and plasma glucose response to glucagon is robust (≥25 mg/dL) it implies insulin-like action causing hypoglycaemia. In such a situation, if plasma insulin is suppressed, the insulin-like action is not due to insulin. Possible causes include injection of insulin analogues and tumor derived Insulin like Growth Factor-2 (IGF-2).

If there is insulin-action and non-suppressed insulin, in the presence of suppressed C-peptide and proinsulin, it is implied that hypoglycaemia is not due
to endogenously secreted insulin; but due to insulin being injected.

**Table 3** - Medical conditions associated with

| |
|---|
| • Severe prolonged malnutrition |
| • End-stage liver disease (ESLD, esp. with ESRD, or with certain medications) |
| • End-stage kidney disease (ESRD, esp. with ESLD, or with certain medications) |
| • Panhypopituitarism (esp. if severe and involving Growth hormone and ACTH deficiency) |
| • Addison disease (esp. severe, or in Addisonian crisis) |
| • Septicaemia |
| • After stopping parenteral nutrition (esp. after overnight total parenteral nutrition) |
| • After stopping continuous enteral nutrition (esp. after overnight enteral feeding) |

If there is insulin-action, non-suppressed insulin, elevated levels of C-peptide and proinsulin, it indicates that endogenously secreted insulin is causing hypoglycaemia. hypoglycaemia agents (sulfonylureas or meglitinides) are therefore measured from that sample.

If hypoglycaemia is being caused by endogenously secreted insulin and hypoglycaemia agents screen is negative, spontaneous endogenous hyperinsulinemic hypoglycaemia is diagnosed and the source of insulin from the pancreas should be localized. The least invasive method; ultrasound or CT of the pancreas is used first. Then more invasive methods such as endoscopic ultrasound and gallium Ga 68-DOTATATE PET scan are used. Finally the most invasive method; selective pancreatic arterial calcium stimulation test may be used.(3)

## Postprandial Symptoms

Postprandial hypoglycaemia can be seen in about 25% of people with insulinoma. Postprandial symptoms are exclusively seen only in about 5%. Most people who experience postprandial episodic symptoms 0.5 to 3 hours after eating do not have insulinomas. These symptoms may also include some that are not characteristic of hypoglycaemia, called dumping syndrome.

Abnormal distension of small intestine and release of vasoactive agents: neurotensin, vasoactive intestinal

peptide (VIP), cholecystokinin, glucagon, incretins; glucose-dependent insulinotropic polypeptide, gastric inhibitory polypeptide (GIP), glucagon like peptide-1 (GLP-1) are thought to be responsible for the postprandial symptoms of dumping syndrome, often called gastrointestinal dumping. Rapid transit of food to the small intestine (pyloric sphincter incompetence, post gastric bypass surgery) can be associated with postprandial hyperglycemia followed by excessive insulin secretion causing hypoglycaemia. Normal postprandial insulin secretion is followed by ongoing delivery of food to the intestine by gastric emptying over the next 1-3 hours. However, in the presence of incompetent or absent pylorus there is no gradual delivery of food to the intestine. Therefore, excessive insulin secretion along with inadequate ongoing supply of carbohydrates from the meal lead to postprandial hypoglycaemia. This endocrine dumping is often precipitated by food containing easily digestible carbohydrates (esp. without protein), often with symptoms of gastrointestinal dumping.(4)

Therefore, the symptoms associated with the episodes of postprandial symptoms especially after Gastric Bypass surgery are multifactorial in origin and are derived from abnormal vasoactive hormones, gastrointestinal motility and glycemic excursion.

Postprandial symptoms (including postprandial hypoglycaemia) are typical and "normal" in a person who has dumping syndrome (eg., after gastric bypass) if a person consumes fast-acting carbohydrates (eg., sugar, glucose, etc.). Oral glucose tolerance test has no role in diagnosis or differential diagnoses of hypoglycaemia.

## Treatment of hypoglycaemia

### Prevention and Treatment of Hypoglycemic Episodes

Patients usually know how to prevent the onset, blunt the progression or reverse the symptoms of the hypoglycemic episodes. Patients should be directed to use rapid-acting carbohydrates (usually 15-20 g of the usual sugar, glucose, sugar containing drinks, juice, candy, sweets, etc.). Sometimes, treatment of the hypoglycemic episode with rapid acting carbohydrates needs to be followed by complex carbohydrates (bread, lentils, beans, rice, sandwich etc.) to prevent recurrence of hypoglycemic episodes over the next few hours.(5)

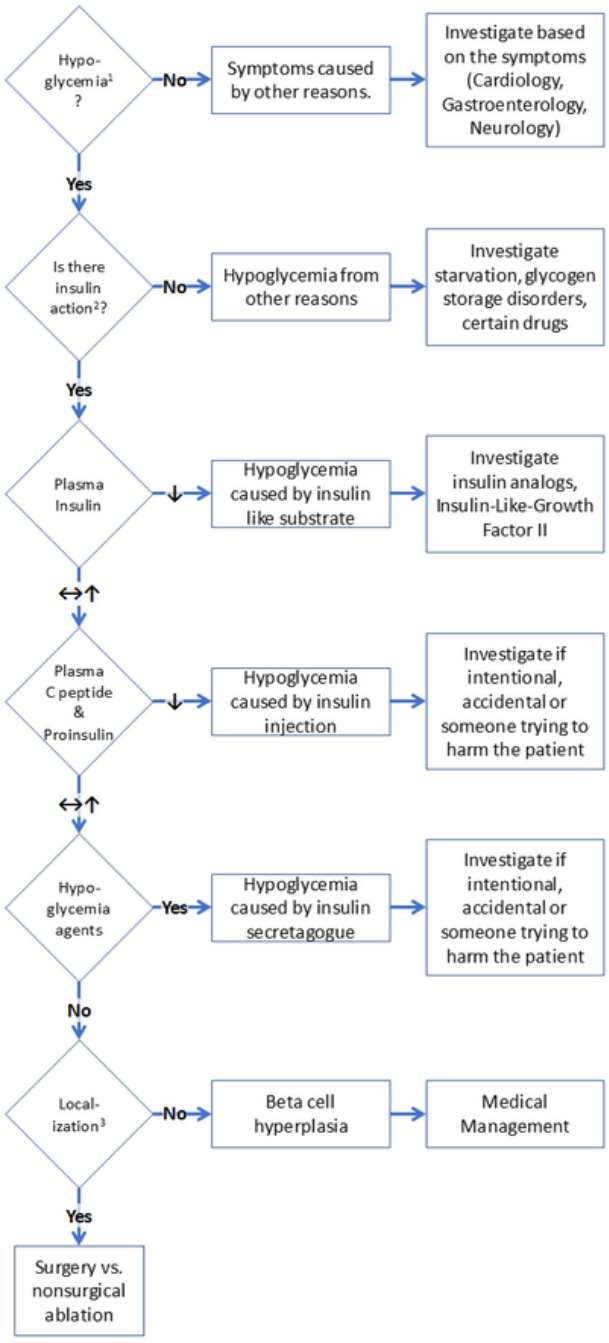


**Figure 1** - Investigative strategy in a person suspected to have hypoglycaemia.

[1]Whipple's Triad
[2]Suppressed beta hydroxybutyrate and a robust (delta >25 mg/dL) response to injection glucagon
[3]CT abdomen, Endoscopic Ultrasound, Dotatate PET scan, Selective Pancreatic Arterial Calcium Stimulation Test

↔↑: nonsuppressed or high; ↓: suppressed

Dietary protein and fat are not useful to prevent nor to treat hypoglycemic episodes.(6)

**Treatment of the cause of hypoglycaemia**

*Insulinoma*

Insulinoma is usually surgically treated. The type and extent of surgery depends on the malignant potential, size and location of the tumor in the pancreas, relationship to the pancreatic ducts and blood vessels, and patient's surgical risk. Other options for treatment include alcohol injection to the tumor (if safe), diazoxide (with some serious adverse effects), and somatostatin.(7)

Surgical treatment of benign insulinoma has a success rate of about 90%. About 10% have recurrence of the index tumor or another tumor.(8)

Management of malignant insulinoma requires surgical removal or debulking of the primary and metastatic disease followed by chemotherapy (including biological agents and inhibitors of mammalian target of rapamycin (mTOR) like everolimus), and resection of the metastatic disease. (9)

*Postprandial symptoms*

Avoidance of precipitants will reduce the frequency and severity of the episodes. Other measures include: agents that increase meal viscosity (guar gum, pectin), prevention of digestion of carbohydrates using acarbose or miglitol with meals (usually not well-tolerated), prevention of the release of hormones: vasoactive gastrointestinal hormones and insulin, using fast-acting somatostatin or insulin release alone using diazoxide (with significant adverse effects).

## Conclusions

Diagnosis of hypoglycaemia should precede determination of the cause. Localization of insulinoma should be sought after a diagnosis of spontaneous endogenous hyperinsulinemic hypoglycaemia. In the absence of insulinoma there is no surgical cure for episodic symptoms from hypoglycaemia or from other causes.

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