BMJ Best Practice

# Non-diabetic hypoglycaemia

Straight to the point of care

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# Summary

Non-diabetic hypoglycaemia may commonly present with symptoms such as nausea, confusion, tremor, sweating, palpitations, or hunger. Patients may present with a non-specific clinical history.

Documentation of a blood glucose <3.3 mmol/L (<60 mg/dL) with accompanying symptoms is crucial to diagnosing clinically significant hypoglycaemia.

Important causes to consider are iatrogenic or factitious hypoglycaemia secondary to insulin or sulfonylurea use. Another common cause may be physiological reactive hypoglycaemia. However, the most worrisome causes are insulinoma and tumour-related hypoglycaemia.

Preferred treatment for an insulinoma is surgical excision.

# Definition

Hypoglycaemia is a clinical syndrome present when the blood glucose concentration falls below the normal fasting glucose range, generally <3.3 mmol/L (<60 mg/dL). When glucose values drop below the normal fasting range, glucose meters are not accurate and laboratory serum or plasma testing is useful to confirm the actual blood sugar value.[1] Whipple's triad should be present in cases of true hypoglycaemia: hypoglycaemic symptoms, accompanying low blood glucose concentration, and resolution of symptoms after raising the blood glucose concentration to normal.[2]

This topic covers non-diabetic hypoglycaemia in adults.

# Epidemiology

Hyperinsulinaemic hypoglycaemia is rare in the general population, while iatrogenic or factitious hypoglycaemia is a far more common occurrence among those with access to glucose-lowering agents. The incidence of insulinoma is estimated to be between 0.7 and 4 cases per million per year.[6] One large cohort study found the median age at time of surgery for an insulinoma to be 47 years, with 59% female preponderance. Males and females had no variation with respect to age at time of diagnosis or surgery.[7] People undergoing gastric bypass surgery have been noted to have an increased incidence of hypoglycaemia due to inappropriate insulin response in the setting of altered gastric and jejunal emptying.[8]

# Aetiology

Hypoglycaemia is due to excessive amounts of insulin, exogenous or endogenous. Presence of a sulfonylurea, a meglitinide, or synthetic insulin indicates iatrogenic hypoglycaemia. Growth hormone deficiency and adrenal insufficiency, due to either hypopituitarism or Addison's disease, may lead to hypoglycaemia by causing a failure in the response to low glucose levels. This tends to cause significant hypoglycaemia only in the paediatric population, although there are case reports of hypoglycaemia in adults with these conditions.

Postprandial hypoglycaemia has been documented in malnourished individuals who eat unripened ackee fruit.[9] Many cases of postprandial symptoms are not confirmed to be true hypoglycaemia upon evaluation.[10] Alcohol-use disorder and malnutrition are commonly associated with a hypoglycaemic episode.[11]

Endogenous excess of insulin or substances with insulin-like action, for example, insulin-like growth factor (IGF)-II, can be the result of several rare disorders. An insulinoma typically arises from pancreatic ductal and acinar cells rather than islet cells, although the mechanism behind the unregulated/excessive excretion of insulin is not clear.[7] Similarly to an insulinoma, large mesenchymal tumours can secrete enough unregulated IGF-II to disturb glucose homeostasis. IGF-II acts directly on insulin receptors and thereby has insulin-like effects. It also induces dysregulation of glucagon and growth hormone resulting in perpetuation of hypoglycaemia. Tumours that have been reported to secrete IGF-II include sarcomas, fibromas, fibrosarcomas, and renal cell carcinoma. Large tumours in the liver may disturb gluconeogenesis and/or cause hypoglycaemia due to excess consumption of glucose to fuel high metabolic rate of the tumour cells.

Nesidioblastosis and islet hypertrophy result from genetic mutations, most often autosomal recessive although sporadic and autosomal-dominant inheritance are possible. These mutations of the adenosine triphosphate-dependent potassium channel of beta cells lead to cell membrane depolarisation and calcium ion influx. This results in insulin release despite low blood glucose concentrations.[12] Rarely, islet hypertrophy is discovered following bariatric surgery.[8] [13]

Iatrogenic hypoglycaemia is an expected consequence of glucose-lowering agents, but reduction of blood glucose concentration by other drugs is also reported. Examples include fluoroquinolone antibiotics, beta-blockers, heparin, proton pump inhibitors (e.g., pantoprazole), and tramadol.[3] [4] [5] [14]

Critical illness involving multi-organ failure can cause hypoglycaemia by reducing endogenous glucose production while increasing metabolic stress and glucose utilisation.[13]

# Pathophysiology

Sympathoadrenal symptoms are the result of increased secretion of glucagon, epinephrine (adrenaline), cortisol, and growth hormone in an effort to elevate blood sugar levels:

- Typically begin when blood glucose concentrations fall below 3.0 mmol/L (55 mg/dL)
- Glucagon and epinephrine (adrenaline) secretion are triggered by glucose concentrations below 3.6 mmol/L (65 mg/dL)
- Growth hormone and cortisol secretion increase when glucose concentrations fall below 3.3 mmol/L (60 mg/dL)
- Symptoms may include sweating, anxiety, nausea, tremor, hunger, generalised tingling, and palpitations.

Neuroglycopenic symptoms result from insufficient glucose supply to the brain despite the sympathoadrenal attempts to raise blood sugar:[15]

- Typically occur with glucose concentrations <2.8 mmol/L (<50 mg/dL)
- Symptoms may include blurred vision, dizziness, confusion, dysarthria, and somnolence
- At the extreme end of the spectrum, convulsion, coma, and death may occur.

# Classification

## Aetiologies of non-diabetic hypoglycaemia

Factitious

- Surreptitious use of insulin

Endocrine

- Adrenal insufficiency, most often in children
- Growth hormone deficiency, most often in children
- Hypopituitarism, may also occur in adults
- Hyperthyroidism, early reactive hypoglycaemia can occur

Tumours

- Large tumours of mesenchymal origin: may secret insulin-like compounds (e.g., IGF-II); may be metabolically active enough to cause hypoglycaemia
- Neuroendocrine tumours, especially insulinoma

Iatrogenic

- Insulin
- Aspirin
- Fluoroquinolones
- Quinine
- Haloperidol
- Disopyramide
- Sulfonylurea
- Beta-adrenergic blockers
- Tramadol
- Proton pump inhibitors (e.g., pantoprazole) have been found to have a glucose-lowering effect; however, further research is required[3]

- Heparin: there is limited evidence that heparin causes hypoglycaemia.[4] [5]

Neonatal

- Nesidioblastosis (also called “persistent hyperinsulinemia hypoglycemia of infancy”)
- Pancreatic islet hypertrophy
- Newborn of a diabetic mother (transient)

Toxins

- Alcohol-use disorder, especially with starvation
- Ackee fruit (hypoglycin)

Congenital

- Glycogen storage disorders

Miscellaneous

- Early pregnancy (late reactive hypoglycaemia can occur during pregnancy)
- Hypoglycaemia of inanition (terminal cancer)
- Acute or chronic liver disease
- Chronic renal failure
- Congestive heart failure
- Autoimmune: insulin receptor abnormalities
- Following gastric surgery: gastric bypass, vagotomy with pyloroplasty, subtotal or total gastrectomy. Early reactive hypoglycaemia can occur after gastric surgery.

# Case history

## Case history #1

A 45-year-old woman presents with sweating, nausea, and headache. She does not have any significant prior medical illnesses. The symptoms typically occur when she has skipped a meal or not had anything to eat for several hours, although they have rarely occurred within a couple hours of a meal as well. She does not snack between meals and reports that her weight has been stable. She has never lost consciousness, but has become very confused and distractible. If she does not eat soon after, she begins to feel nauseated and sweaty. She has found that the symptoms quickly resolve after eating.

## Other presentations

Patients may also present with seizure or loss of consciousness without premonitory symptoms. Late reactive hypoglycaemia can occur within 3-5 hours after a meal in some patients with prediabetes or impaired glucose tolerance, and during pregnancy.

# Approach

The diagnosis of clinically significant hypoglycaemia in adults is made when serum glucose concentration is low (<3.3 mmol/L [60 mg/dL]) and either sympathoadrenal or neuroglycopenic symptoms are present. This is confirmed by establishing the Whipple's triad, which consists of hypoglycaemic symptoms, accompanying low-serum glucose concentration, and resolution of symptoms after raising the serum glucose concentration to normal.[13] [18] Glucose levels below normal range indicate either failure to regulate insulin levels, excessive circulating insulin-like compound, a failure of counter-regulatory mechanisms, lack of enzymes needed for glucose production, lack of substrate required for gluconeogenesis, or severe derangement of function of organs required for glucose production, for example, liver, kidney.

## Clinical presentation

The patient presenting with hypoglycaemia should be able to describe either:

Sympathoadrenal symptoms:

- Sweating
- Anxiety
- Nausea
- Tremor
- Hunger
- Generalised tingling
- Palpitations.

Or neuroglycopenic symptoms:

- Blurred vision
- Dizziness
- Confusion
- Dysarthria
- Somnolence
- Seizures
- Focal neurological deficits also possible.

There need not be a progression from sympathoadrenal symptoms to neuroglycopenia. The temporal relationship between symptom's onset and diet, meal time, or medication administration should be elicited. The timing of symptoms of hypoglycaemia in relationship to a meal or its occurrence during a fasting state may offer clues as to the presence of certain disorders. If the symptoms occur after the patient begins a new medication or is known to take an insulin secretagogue, such as a sulfonylurea, then iatrogenic cause is strongly suspected. Symptoms occurring while the patient is in a fasting state suggest an insulinoma, insulin-like growth factor (IGF)-II hypersecretion, or a disturbance of the hypothalamic-pituitary axis or its target organs. Symptoms occurring soon after a meal raise the possibility of islet cell hypertrophy or nesidioblastosis.

Late reactive hypoglycaemia can occur within 3-5 hours after a meal in some patients with prediabetes or impaired glucose tolerance, and during pregnancy.

## Hypoglycaemia at presentation, initial testing

If the patient is exhibiting symptoms of hypoglycaemia on presentation, or at any point of the evaluation, the serum or plasma glucose concentration should be assessed promptly. Serum and plasma glucose



 

measurements are for practical purposes equivalent, but glucometers are inaccurate below normal range, so laboratory evaluation is necessary.[37]

If blood sugar is <2.8 mmol/L (<50 mg/dL), additional tests should immediately be collected, including serum insulin, C-peptide, proinsulin, ethanol, beta-hydroxybutyrate, liver and kidney function tests, and levels of insulin secretagogues (sulfonylureas). In a patient with chronic low energy, unexplained weight changes, hyperpigmentation, or other suspicion of pituitary or other endocrine dysfunction, consideration should also be given to assess serum cortisol, human growth hormone (HGH), thyroid-stimulating hormone, and adrenocorticotropic hormone (ACTH) levels.

## No hypoglycaemia at presentation, inpatient fast

In the presence of hypoglycaemic symptoms but with a blood glucose concentration >2.8 mmol/L (>50 mg/dL), the patient might not have clinically significant hypoglycaemia. If symptoms are mild and non-specific, further investigation may be deferred until the presence of hypoglycaemia is confirmed by additional blood sugar readings, or if the symptoms are very typical or severe, the patient may be admitted for a 48- to 72-hour fast.

There has been some debate as to whether a 48-hour fast under observation is adequate in rendering a diagnosis, and the full 72-hour fast under observation has been found to identify individuals with an insulinoma not identified by 48-hour fast.[38] During the fast, the patient may drink non-caloric and caffeine-free beverages and is encouraged to be active. Blood glucose levels are checked every 6 hours. Once the blood sugar concentration by a finger stick is <3.3 mmol/L (<60 mg/dL), blood glucose levels should be checked every hour, along with serum proinsulin, C-peptide, and insulin levels. The test ends upon any of the following occurrences: onset of sympathoadrenal or neuroglycopenic symptoms, blood glucose levels <2.8 mmol/L (<50 mg/dL), or conclusion of full 72 hours of fasting under observation.

In the event of hypoglycaemic symptoms accompanied by a blood glucose concentration <2.8 mmol/L (<50 mg/dL), the following additional tests should be performed: serum sulfonylurea and beta-hydroxybutyrate, cortisol, HGH, and ACTH levels. Next, the patient is given glucagon 1 mg intramuscularly. Glucose level is checked 30 minutes later and the patient is then allowed to eat.[39]

An oral glucose tolerance test should be performed to rule out diabetes mellitus, as late reactive hypoglycaemia occurring within 3-5 hours after a meal can occur in some patients with prediabetes or impaired glucose tolerance, and during pregnancy.

## No hypoglycaemia at presentation, insulin suppression test

Alternatively, an insulin suppression test may be done. Insulin 0.4 to 0.6 unit/kg is administered intravenously after an overnight fast. Blood sugar is assessed with a finger stick every 5 minutes. The blood glucose concentration should decline to <3.3 mmol/L (<60 mg/dL) within 15 to 25 minutes. At this time and in 5-minute intervals for 3 additional times, blood is drawn for serum glucose, C-peptide, cortisol, and HGH levels. The patient is given 50 mL of 50% dextrose intravenously to aid in recovery at the end of the test.

## Further testing for elevated C-peptide

Inappropriate elevation of C-peptide, proinsulin, and insulin suggest either insulinoma or sulfonylurea use.[34]

- These results should lead to serum sulfonylurea testing, and if that is negative, imaging to detect an insulinoma.
- Imaging begins with computed tomography (CT) of the abdomen and pelvis, with and without intravenous contrast. If this fails to detect a suspected insulinoma, transabdominal ultrasound is employed, and if that also fails to locate the insulinoma, endoscopic ultrasound may be used. Octreotide nuclear scanning may be employed if the suspected insulinoma still has not been localised.[40]

### Further testing for low C-peptide

A low beta-hydroxybutyrate and a rapid rise above 1.4 mmol/L (25 mg/dL) in serum glucose within 30 minutes of glucagon administration suggest the presence of excessive exogenous insulin or IGF-II.

- Low C-peptide, proinsulin, and insulin levels suggest excess IGF-II, which should lead to imaging to detect mesenchymal tumour. Characteristics following 72-hour fast under observation: low insulin level, low beta-hydroxybutyrate, a >1.4 mmol/L (>25 mg/dL) increase in glucose in response to glucagons, and elevated serum IGF-II levels.
- Imaging begins with CT of the abdomen and pelvis, with and without intravenous contrast. As the tumours are generally large when they cause clinically significant hypoglycaemia, they may also be detectable on physical examination.
- Insulin levels are high but both proinsulin and C-peptide levels are low in the case of surreptitious insulin injection.
- Serum insulin antibodies will confirm surreptitious insulin injection as the cause of hypoglycaemia.

## History and exam

### Key diagnostic factors

#### diaphoresis (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

#### anxiety (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

#### tremor (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

#### hunger (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

#### generalised tingling (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]



 

### nausea (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

### palpitations (common)

- Possible sympathoadrenal symptom of hypoglycaemia, although constellation of several symptoms is more specific than any one symptom alone.[15]

### confusion (common)

- Possible neuroglycopenic symptom; the constellation of several symptoms is more specific than any one symptom alone.

### irritability (common)

- Possible neuroglycopenic symptom; the constellation of several symptoms is more specific than any one symptom alone.

### blurred vision (common)

- Possible neuroglycopenic symptom; the constellation of several symptoms is more specific than any one symptom alone.

### drowsiness (common)

- Possible neuroglycopenic symptom; the constellation of several symptoms is more specific than any one symptom alone.

## Other diagnostic factors

### unexplained weight gain (uncommon)

- When present with hypoglycaemic symptoms, may suggest insulinoma.[7]

### unexplained weight loss (uncommon)

- May suggest adrenal insufficiency.
- Lack of a cortisol response to low serum glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[26]

### hyperpigmentation (uncommon)

- Typically, in folds and scars and includes areas not exposed to sun.
- May suggest adrenal insufficiency.
- Lack of a cortisol response to low serum glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[26]

### hypotension (uncommon)

- Frank hypotension or orthostatic hypotension.
- May suggest adrenal insufficiency.
- Lack of a cortisol response to low serum glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[26]

### short stature (uncommon)

- Possible growth hormone deficiency; may also be asymptomatic.
- Lack of a growth hormone response to low serum glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[26]

# Risk factors

## Strong

### middle age

- True hypoglycaemia (i.e., fulfills Whipple's triad) in people without diabetes mellitus more commonly affects those who are middle-aged.[16] In one retrospective cohort of inpatients outside of critical care, non-diabetic hypoglycaemia was found to be more common in people aged over 65 years.[17]

### insulinoma

- Neuroendocrine tumour that secretes insulin in an unregulated fashion.[7]

### exogenous insulin

- Incorrect dosage of insulin, intentional overdose of insulin, or correct dosage of insulin but decreased food intake may cause hypoglycaemia.[31]

## Weak

### female sex

- True hypoglycaemia in people without diabetes mellitus has a slight female predominance.[16] [18]

### ethanol consumption

- Heavy alcohol consumption decreases hepatic production of glucose.[19] In one study, alcohol-use disorder was the most common cause of non-diabetic hypoglycaemia requiring emergency medical services.[11]

### bariatric surgery

- Bariatric surgery causes abnormalities in stomach emptying (e.g., rapid transit of carbohydrates), which can lead to hypoglycaemia.[20] [21] Nesidioblastosis/islet hypertrophy has been reported after bariatric surgery.[8]

### liver failure

- Hepatic failure may result in depleted glycogen stores and impaired gluconeogenesis.[22]

### renal failure

- Renal failure may impair gluconeogenesis.[23]

### intense exercise

- Exercise induces glucose uptake independent of insulin receptors and if intense enough can lead to hypoglycaemia.[24]

### fibromas

- Large tumours of mesenchymal origin can secrete insulin-like growth factor-II, an insulin-like compound, in an unregulated fashion and result in hypoglycaemia.

### sarcomas

- Large tumours of mesenchymal origin can secrete insulin-like growth factor-II, an insulin-like compound, in an unregulated fashion and result in hypoglycaemia.

### fibrosarcomas

- Large tumours of mesenchymal origin can secrete insulin-like growth factor-II, an insulin-like compound, in an unregulated fashion and result in hypoglycaemia.

### adrenal insufficiency

- Lack of a cortisol response to low blood glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[25]

### growth hormone deficiency

- Lack of a growth hormone response to low blood glucose levels may lead to failure to counteract hypoglycaemia. Typically, only a significant component of hypoglycaemia in paediatric cases.[26]

### hypopituitarism

- Failure of the hypothalamic-pituitary axis may lead to deficient growth hormone and adrenocorticotropic hormone secretion.[25]

### sepsis

- End-organ damage and a heightened metabolic demand may predispose to hypoglycaemia.[27]

### glycogen storage diseases

- Lack of stored glycogen hinders production of glucose to counteract hypoglycaemia.[28]

### anorexia nervosa

- Chronic malnourishment results in paucity of glycogen stores needed to counteract hypoglycaemia.[29] [30]

### malnutrition

- Chronic malnourishment results in paucity of glycogen stores needed to counteract hypoglycaemia.[30]

### ackee fruit ingestion

- Ingestion of unripened ackee fruit in a malnourished individual can cause hypoglycaemia due to the effects of hypoglycin toxins on gluconeogenesis.[9]

### haloperidol exposure

- Known to weakly cause alpha-adrenergic blockade, thus possibly contributing to hypoglycaemia.[32]

### quinine exposure

- Quinine or fluoroquinolone may cause excess secretion of insulin. Mechanism is poorly understood.[33]

### fluoroquinolone exposure

- Quinine or fluoroquinolone may cause excess secretion of insulin. Mechanism is poorly understood.[33]

### sulfonylurea exposure

- Directly stimulates secretion of insulin regardless of blood glucose levels.[34]

### disopyramide exposure

- Mechanism causing hypoglycaemia is not understood.[35]

### beta-adrenergic-blocking agent exposure

- Causes adrenergic blockade, which may sustain existing hypoglycaemia.[35]

### salicylate exposure

- Overdose of salicylates may cause an increase in the insulin response.[4]

### tramadol exposure

- Tramadol therapy is associated with an increased risk of hypoglycaemia, sometimes requiring hospitalisation.[14] [36]

### proton pump inhibitor exposure

- Proton pump inhibitors (e.g., pantoprazole) have been found to have a glucose-lowering effect; however, further research is required.[3]

# Investigations

## 1st test to order

| Test | Result |
|---|---|
| **serum glucose**<br>• Measured when symptoms present or at the end of 72-hour fast, every 6 hours or at the onset of symptoms of hypoglycaemia confirmed by finger stick blood sugar of <50 mg/dL.<br>• After glucagon administration at the end of 72-hour fast, glucose increase >1.4 mmol/L (>25 mg/dL) is consistent with insulinoma or insulin-like growth factor-II secretion. | **<2.8 mmol/L (<50 mg/dL)** |
| **liver function testing**<br>• Ordered as a screening test once patient presents complaining of hypoglycaemic symptoms, to rule out hepatic causes (e.g., acute hepatitis, hepatic cirrhosis, hepatorenal syndrome). | **normal; abnormal when liver disease is the cause** |
| **renal function testing**<br>• Ordered as a screening test once patient presents complaining of hypoglycaemic symptoms, to rule out renal causes (e.g., congestive heart failure, chronic renal failure, hepatorenal syndrome). | **normal; abnormal when renal disease is the cause** |
| **serum insulin**<br>• Measured when glucose <3.3 mmol/L (<60 mg/dL) or at the end of 72-hour fast. Should be undetectable.<br>• Elevated value is consistent with factitious hypoglycaemia or insulinoma.<br>• Inappropriate elevation of C-peptide, proinsulin, and insulin suggest either insulinoma or sulfonylurea use.[34] | **>21 picomol/L (>3 microunits/mL)** |
| **serum C-peptide**<br>• Measured when glucose level <3.3 mmol/L (<60 mg/dL) or at the end of 72-hour fast.<br>• Elevated if insulin is endogenous. Inappropriate elevation of C-peptide, proinsulin, and insulin suggest either insulinoma or sulfonylurea use.[34] | **>200 picomol/L** |
| **serum beta-hydroxybutyrate**<br>• Measured at the time of hypoglycaemic symptoms or at the end of 72-hour fast.<br>• Excessive insulin or insulin-like growth factor-II inhibits ketogenesis and lowers beta-hydroxybutyrate.<br>• Therefore, low beta-hydroxybutyrate would support diagnosis of mesenchymal tumour. | **<2.7 mmol/L** |
| **serum sulfonylurea**<br>• Presence indicates iatrogenic hypoglycaemia. Test assays chlorpropamide, tolazamide, tolbutamide, glipizide, glyburide, acetohexamide, glimepiride, or gliclazide.<br>• In the UK sulfonylurea screening is usually done on urine rather than serum, and both are valid options. | **positive** |
| **thyroid-stimulating hormone levels**<br>• To rule out thyroid function disorders. | **normal; abnormal if thyroid dysfunction** |

| Test | Result |
| --- | --- |
| **serum cortisol**<br>• Low level would indicate adrenal glands (primary) or hypopituitarism as source of adrenal insufficiency. To be confirmed by an adrenocorticotropic hormone stimulation test. | **may be below normal** |

## Other tests to consider

| Test | Result |
|---|---|
| **48- to 72-hour fast under observation**<br>• Indicated in adults if presence of hypoglycaemic symptoms but blood glucose >2.8 mmol/L (>50 mg/dL).<br>• Blood glucose levels are checked every 6 hours. Once the blood sugar concentration by a finger stick is <3.3 mmol/L (<60 mg/dL), blood glucose levels should be checked every hour, along with serum proinsulin, C-peptide, and insulin levels.<br>• The test ends upon any of the following occurrences: onset of sympathoadrenal or neuroglycopenic symptoms, blood glucose levels <2.8 mmol/L (<50 mg/dL), or conclusion of full 72 hours of fasting under observation. | **hypoglycaemia or sympathoadrenal or neuroglycopenic symptoms** |
| **oral glucose tolerance test**<br>• It should be performed to rule out diabetes mellitus, as late reactive hypoglycaemia occurring within 3-5 hours after a meal can occur in some patients with prediabetes or impaired glucose tolerance, and during pregnancy. | **normal or low; 2-hour plasma glucose ≥11.1 mmol/L( ≥200 mg/dL) if diabetes mellitus** |
| **serum insulin-like growth factor (IGF)-II**<br>• Used to confirm IGF-II hypersecretion if suspicion is raised by results of 72-hour fasting test. Patient need not be fasting.[41] | **>157 nanomol/L (1200 ng/mL)** |
| **serum adrenocorticotropic hormone**<br>• Low level would suggest secondary or tertiary cause for adrenal insufficiency. | **below normal range** |
| **serum human growth factor (HGH)**<br>• Low level suggests pituitary disorder. | **below normal** |
| **insulin suppression test**<br>• Indicated in adults if presence of hypoglycaemic symptoms but blood glucose >2.8 mmol/L (>50 mg/dL).<br>• Insulin 0.4 to 0.6 unit/kg is administered intravenously after an overnight fast. Blood sugar is assessed with a finger stick every 5 minutes. The blood glucose concentration should decline to <3.3 mmol/L (<60 mg/dL) within 15 to 25 minutes. At this time and in 5-minute intervals for 3 additional times, blood is drawn for serum glucose, C-peptide, cortisol, and HGH levels.<br>• The patient is given 50 mL of 50% dextrose intravenously to aid in recovery at the end of the test. | **blood sugar decline** |
| **serum proinsulin**<br>• Measured when glucose level <3.3 mmol/L (<60 mg/dL) or at the end of 72-hour fast.<br>• Elevated if insulin is endogenous, especially with insulinoma. Inappropriate elevation of C-peptide, proinsulin, and insulin suggest either insulinoma or sulfonylurea use.[34] | **>5.0 picomol/L** |
| **CT scan abdomen and pelvis with and without intravenous contrast**<br>• Order after non-factitious hypoglycaemia has been diagnosed. Imaging is sought to look for small islet cell tumours that could be responsible for an insulinoma or large tumours that may be producing IGF-II.[42] | **islet cell tumour** |

| Test | Result |
|---|---|
| **transabdominal ultrasound**<br>• Order after non-factitious hypoglycaemia has been diagnosed and no tumours identified on CT scan. The ultrasound may be useful for detecting small islet cell tumours not seen on CT scan. | **islet cell tumour** |
| **endoscopic ultrasound**<br>• This test should be ordered when both the CT scan and transabdominal ultrasound failed to identify the site of an insulinoma.[43] | **islet cell tumour** |
| **nuclear imaging with octreotide scan**<br>• Corroborative test to identify a neuroendocrine tumour. | **positive** |

# Differentials

| Condition | Differentiating signs / symptoms | Differentiating tests |
|---|---|---|
| **Idiopathic postprandial syndrome (pseudohypoglycaemia)** | • Clinical history of hypoglycaemic symptoms after ingesting a carbohydrate-rich meal. | • Glucose level >3.3 mmol/L (>60 mg/dL) in presence of symptoms.<br>• A 5-hour mixed meal test may also be used, although the sensitivity is poor.[44] |
| **Insulin autoimmune hypoglycaemia** | • Extremely rare condition that usually spontaneously resolves. | • Can assay for insulin antibodies as well as antibodies to insulin receptors.[44] [45] |
| **Diabetic hypoglycemia** | • History of diabetes mellitus. It is otherwise difficult to clinically distinguish diabetic hypoglycaemia from non-diabetic hypoglycaemia because the patient typically presents in a similar manner, with typical neuroglycopenic symptoms that improve quickly with administration of glucose. | • Oral glucose tolerance test: 2-hour plasma glucose ≥11.1 mmol/L (≥200 mg/dL) if diabetes mellitus. |

# Criteria

## Whipple's triad[2]

Present in cases of true hypoglycaemia: hypoglycaemic symptoms, accompanying low serum glucose concentration, and resolution of symptoms after raising the serum glucose concentration to normal.[2]



 

# Approach

All adult patients may require supportive care with glucose and/or glucagon while awaiting definitive therapy for the underlying condition, whether that is surgery, for example, for insulinoma and insulin-like growth factor (IGF)-II-secreting tumour; medical management of renal and liver failure; antibiotics, and supportive care for sepsis; or waiting for an inciting medicine to be cleared from the system.[17] [18] [46] Patients with reactive hypoglycaemia are often treated successfully with dietary changes.[44]

## Exposure to medicine, toxin, or ethanol

Hypoglycaemia should resolve as toxin or medicine is metabolised. The patient may require inpatient monitoring and glucose infusion until the effects of the toxin, medicine, or exogenous insulin/sulfonylurea diminish, the time course for which is widely variable and may be further prolonged if there is concomitant hepatic and/or renal dysfunction.

If intentional overdosing of salicylates, ethanol, insulin, or sulfonylureas is suspected, the patient should be screened to determine whether referral to a psychiatric speciality is warranted. If suicidality is present, involuntary commitment may be necessary.

## Bariatric surgery, anorexia, malnutrition, ackee fruit ingestion

In addition to correcting the glucose deficiency, referral or consultation with endocrinology, eating disorders, toxicology, or gastrointestinal disease specialists may be necessary in these patients.

## Insulinoma

Surgical excision is indicated for insulinoma.

- Until surgery the patient should be instructed to be alert for hypoglycaemic symptoms. Should such symptoms occur and the patient is unable to tolerate oral intake to raise glucose levels, he or she may be taught to self-administer glucagon injections.
- If the patient continues to have hypoglycaemic events after surgery, then it is possible that a metastatic lesion was missed or the primary tumour was not fully excised. Consideration should be given to repeating surgery.[7]
- Focal embolisation or chemotherapy may be required for metastatic disease in the presence of rare malignant insulinoma.[47]

## Inoperable insulinoma

For patients who are not surgical candidates or in whom surgery was unsuccessful, pharmacological therapy may offer a degree of control over the hypoglycaemia. There is limited evidence to suggest superiority of one agent over another, and each carries significant risks:[47] [48] [49] [50]

Diazoxide:

- Can control hypoglycaemia by inhibition of insulin secretion
- May cause oedema and hirsutism
- Monitor for lowering of blood pressure if also taking calcium-channel blockers.

Octreotide:

- High doses inhibit insulin secretion
- Thyroid-stimulating hormone, growth hormone, and glucagon are also inhibited.

Streptozocin:

- May destroy the tumour
- Can lead to hyperglycaemia or diabetes mellitus because it will destroy normal islets as well.

## IGF-II-secreting tumour

The patient with IGF-II hypersecretion should be referred to a surgeon for excision of the offending mass.

- While awaiting surgery, glucose levels may need to be supported with intermittent glucose infusion or glucagon administration.
- Therapies that reduce tumour burden (e.g., chemotherapy, radiotherapy) may help to relieve symptoms in some cases.[44]

## Renal failure, liver failure, sepsis, or other endocrinopathy

Treatment should focus on management of underlying organ dysfunction. Support with glucose infusion may be necessary until the condition resolves, especially if the patient cannot tolerate oral intake.

# Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

| Acute ( summary ) | | |
|---|---|---|
| **reactive hypoglycaemia** | | |
| | 1st | dietary changes |
| **exposure/overdose medication, toxin, ethanol** | | |
| | 1st | supportive care ± psychiatric evaluation and treatment |
| **bariatric surgery, anorexia, malnutrition, ackee fruit ingestion** | | |
| | 1st | supportive care ± referral to specialist |
| **insulinoma** | | |
| | 1st | surgical excision |
| | plus | supportive care |
| | 2nd | medical therapy |
| | plus | supportive care |
| ■ metastatic disease | plus | focal embolisation or chemotherapy |
| **IGF-II-secreting tumour** | | |
| | 1st | surgical excision ± chemotherapy/ radiotherapy |
| | plus | supportive care |
| **renal failure, liver failure, sepsis, or other endocrinopathy** | | |
| | 1st | management of underlying condition |
| | plus | supportive care |

# Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

## Acute

### reactive hypoglycaemia

**1st** **dietary changes**

» Reactive hypoglycaemia (RH) is often successfully treated with dietary changes.[44] The diet should be high in proteins and low in carbohydrates, with frequent but smaller feeds to avoid the big fluctuations in the insulin secretion from the pancreas.[51] [52] [53] A high-fibre diet or fibre supplementation is also recommended to prevent RH.[54]

### exposure/overdose medication, toxin, ethanol

**1st** **supportive care ± psychiatric evaluation and treatment**

» All patients may require supportive care with glucose and/or glucagon. Those exposed to offending medication/toxin or exogenous insulin/sulfonylurea may require inpatient monitoring and glucose infusion until the effects diminish; timeframe is variable.

» Options include D10 or D50 infusion or glycogen infusion or injection, closely monitored with frequent blood glucose checks or, as glucose stabilises in the normal range, glucometer readings. The aim is to monitor for sustained hypoglycaemia and prompt correction.

» If intentional overdosing of salicylates, ethanol, insulin, or sulfonylureas is suspected, the patient should be screened to determine whether referral to a psychiatric speciality is warranted.

» If suicidality is present, involuntary commitment may be necessary.

### bariatric surgery, anorexia, malnutrition, ackee fruit ingestion

**1st** **supportive care ± referral to specialist**

» In addition to correcting the glucose deficiency by supportive care with glucose and/or glucagon, referral or consultation with endocrinology, toxicology, or gastrointestinal disease specialists may be necessary in these patients.

### insulinoma

## Acute

**1st** **surgical excision**

» If hypoglycaemic events continue after surgery, consideration should be given to repeating surgery to look for incomplete excision of primary tumour or rare malignant transformation with metastases.[7]

**plus** **supportive care**

Treatment recommended for ALL patients in selected patient group

» Supportive care while awaiting surgery may include self-administered glucagon injections.

**2nd** **medical therapy**

**Primary options**

» diazoxide: 3-8 mg/kg/day orally given in 2-3 divided doses

**OR**

» octreotide: 50 micrograms subcutaneously twice to three times daily

**OR**

» streptozocin: refer to consultant for guidance on dosage

» For those who fail surgery or who are not surgical candidates, these pharmacological agents may be used to control hypoglycaemia for a period of time.

**plus** **supportive care**

Treatment recommended for ALL patients in selected patient group

» All patients may require supportive care to maintain their blood glucose levels while awaiting definitive therapy.[46] Options include D10 or D50 infusion or glycogen infusion or injection, closely monitored with frequent blood glucose checks or, as glucose stabilises in the normal range, glucometer readings. The aim is to monitor for sustained hypoglycaemia and prompt correction.

**metastatic disease** **plus** **focal embolisation or chemotherapy**

Treatment recommended for ALL patients in selected patient group

» If hypoglycaemic events continue after surgery, one possibility is rare malignant transformation with metastases.[7]

## Acute

| | | |
|---|---|---|
| | | » Focal embolisation or chemotherapy may be required for metastatic disease.[47] |
| **IGF-II-secreting tumour** | | |
| | **1st** | **surgical excision ± chemotherapy/ radiotherapy**<br>» The patient with insulin-like growth factor (IGF)-II hypersecretion should be referred to a surgeon for excision of the offending mass.<br>» Therapies that reduce tumour burden (e.g., chemotherapy, radiotherapy) may help to relieve symptoms in some cases.[44] |
| | **plus** | **supportive care**<br>Treatment recommended for ALL patients in selected patient group<br>» While awaiting surgery, glucose levels may need to be supported with intermittent glucose infusion or glucagon administration. |
| **renal failure, liver failure, sepsis, or other endocrinopathy** | | |
| | **1st** | **management of underlying condition**<br>» Mainstay of therapy in these aetiologies of hypoglycaemia is management of the underlying condition, with supportive therapies to maintain adequate blood glucose level. |
| | **plus** | **supportive care**<br>Treatment recommended for ALL patients in selected patient group<br>» Support with glucose infusion may be necessary until the condition resolves, especially if the patient cannot tolerate oral intake. |

# Emerging

## Verapamil

May inhibit insulin secretion at high doses, but evidence to support use in hypoglycaemia is limited.

## Phenytoin

May inhibit insulin secretion at high doses, but evidence to support use in hypoglycaemia is limited.

## Corticosteroids

In non-operable insulin-like growth factor-II-secreting tumours, there are case reports of successful control of hypoglycaemic symptoms by using an oral glucocorticoid.[55]

# Patient discussions

Patients should be advised that if they have recurrence of their hypoglycaemia symptoms, they should seek prompt medical assessment.

# Monitoring

## Monitoring

Following surgery for insulinoma or tumour removal the patient will require follow-up for healing of wounds and potential postoperative complications per the discretion of the surgeon. Frequent medical follow-up for an inoperable lesion may be required for titration of medications until a suitable regimen is established and hypoglycaemic symptoms resolve.

# Complications

| Complications | Timeframe | Likelihood |
|---|---|---|
| **seizure** | **short term** | **low** |
| When acutely presenting with clinically significant hypoglycaemia, glucose levels may be low enough to cause central nervous system manifestations such as seizures. The seizures should resolve with correction of glucose levels and not recur so long as hypoglycaemia is avoided. | | |
| **coma** | **short term** | **low** |
| At the extreme spectrum of hypoglycaemic complications is coma due to lack of glucose availability to the brain. The coma should resolve with correction of glucose levels and not recur so long as extreme hypoglycaemia is avoided. Permanent neurological sequelae are possible: for example, focal neurological deficits, memory loss. | | |
| **diabetes mellitus** | **long term** | **low** |
| There are limited follow-up data available regarding patients with true hypoglycaemic disorders. Diabetes mellitus has been reported after repeat surgery for insulinoma.[7] | | |

# Prognosis

## Post-surgical

Following successful surgery and if all tumours were excised, most patients with an insulinoma or tumour secreting insulin-like growth factor (IGF)-II are cured of their disease. A small portion of individuals may have re-growth of a partially excised tumour or growth of a metastasis and subsequently require repeat surgery, chronic medical therapy, or directed therapy for malignant disease.[7]

## Medically managed insulinoma

The medical options for the management of an insulinoma are limited and not as effective as surgical resection. Of the available medications diazoxide has been the most effective agent, although complications are common.[47] [48] [49] [50]

 

## Inoperable IGF-II-secreting tumours

For the patient with an IGF-II-hypersecreting tumour who is not an operable candidate, there is a strong possibility of becoming refractory to the use of glucagon to support glucose levels. Few studies exist on other alternatives, although oral glucocorticoid administration has worked well in some case studies.[55]

## Exposure-related hypoglycaemia

Patients with factitious or drug exposure-induced hypoglycaemia have a favourable outlook. Symptoms should not recur so long as surreptitious use of insulin and offending medications are avoided.

# Diagnostic guidelines

## United Kingdom

**Society for Endocrinology guidelines for the diagnosis and management of post-bariatric hypoglycaemia (https://ec.bioscientifica.com/view/journals/ec/13/5/EC-23-0285.xml)**

**Published by:** Society for Endocrinology **Last published:** 2024

## Europe

**ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors (https://www.enets.org/guidelines.html)**

**Published by:** European Neuroendocrine Tumor Society **Last published:** 2016

## North America

**Laboratory endocrine testing guidelines: hypoglycemia (https://actt.albertadoctors.org/cpgs/all-cpgs)**

**Published by:** Toward Optimized Practice Program, Alberta, Canada **Last published:** 2014

# Treatment guidelines

## Europe

**ENETS consensus guidelines update for the management of patients with functional pancreatic neuroendocrine tumors and non-functional pancreatic neuroendocrine tumors (https://www.enets.org/guidelines.html)**

**Published by:** European Neuroendocrine Tumor Society **Last published:** 2016

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Please note that recommended formulations and doses may differ between drug databases drug names and brands, drug formularies, or locations. A local drug formulary should always be consulted for full prescribing information.

Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.



### Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

**Figure 1 – BMJ Best Practice Numeral Style**

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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