Hypoglycemia: Causes, clinical features and treatment

Hypoglycaemia is an abnormally low plasma glucose concentration with or without associated symptoms.

It is very common among patients with diabetes mellitus, usually secondary to insulin or certain oral hypoglycaemic agents such as sulphonylureas. Hypoglycaemia may also occur in patients without diabetes mellitus. In this situation, it is uncommon and may occur due to a range of abnormalities, some very rare.

Hypoglycaemia is clinically defined as an abnormally low blood glucose concentration (less than 4.0 mmol/L).

?Normal fasting range: 4.0-5.4 mmol/L

?Normal post-prandial range: 4.0-7.8 mmol/L (up to two hours after eating)Clinically significant hypoglycaemia is generally defined as less than 3.0 mmol/L.

At this level, hypoglycaemia can be associated with serious immediate and long-term consequences. A blood glucose concentration less than 3.0 mmol/L rarely occurs in the absence of diabetes mellitus.

Severe hypoglycaemia is a hypoglycaemic event whereby the affected patient requires assistance to restore blood glucose concentration.

Asymptomatic hypoglycaemia is a blood glucose concentration

Symptomatic hypoglycaemia is a blood glucose concentration

Pseudohypoglycaemia is a symptom of hypoglycaemia but blood glucose concentration is greater than or equal to ? 4.0 mmol/L. Usually due to long-standing poor glycemic control with symptoms when blood glucose concentration falls into physiological range.

What is a Whipple’s triad?

In clinical practice, there may be a discrepancy between plasma glucose concentration and symptoms.

A confident diagnosis of hypoglycaemia is therefore made on the basis of symptoms correlating with the episode of hypoglycaemia.

1. Low blood glucose concentration
2. Symptoms of hypoglycaemia
3. Reversal of symptoms when blood glucose concentration is restored to normal

In patients with diabetes mellitus, they may have reduced hypoglycaemic awareness due to reduced neurogenic symptom response. Therefore, Whipple's triad is more clinically relevant to further investigating patients without diabetes mellitus.

Physiology of blood glucose control

Activation of counter-regulatory mechanisms are vital to prevent or rapidly correct low plasma glucose concentration.

During a fasting state, when blood glucose concentrations fall, there is the activation of four main counterregulatory mechanisms:

- Decrease in insulin secretion
- Increase in glucagon secretion which in turn increases hepatic glucose production through glycogenolysis and gluconeogenesis. The threshold for glucagon secretion is 3.6-3.9 mmol/L. If there are poor hepatic stores of glycogen or hepatic impairment, this response is ineffective.
- Increases in adrenaline secretion which increases hepatic glucose production similar to glucagon. Inhibits insulin secretion. Inhibits glucose utilisation of peripheral tissues. The threshold for adrenaline secretion is 3.6-3.9 mmol/L. Similar to glucagon, an adequate response requires hepatic glycogen stores and normal functioning.
- Secretion of cortisol and growth hormone that is released if hypoglycaemia ongoing for hours. Decreases peripheral tissue utilisation of glucose and increases hepatic glucose production.

The fall in insulin secretion and increase in glucagon secretion are the main counter-regulatory mechanisms. Alongside these biochemical responses, hypoglycaemia (usually at levels less than 3.1 mmol/L) stimulates autonomic symptoms (e.g. anxiety, hunger), which triggers the ingestion of food to restore plasma glucose concentration.

Causes of hypoglycemia

Hypoglycaemia most commonly occurs in association with treatment for diabetes mellitus.Diabetes mellitus. Hypoglycaemia may occur in type 1, or less commonly, type 2 diabetes mellitus. This may be due to medication changes, concurrent illness, or dietary or activity changes.

Hypoglycaemia in T1DM is commonly due to an incorrect dosage of insulin and can occur during the day or night.

Patients with type 2 diabetes mellitus (T2DM) are much less likely to develop hypoglycaemia.

Classically, patients treated with insulin and sulphonylureas are at increased risk of hypoglycaemia. Other diabetic medications such as metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose co-transporter 2 (SGLT2) inhibitors do not usually cause hypoglycaemia.

There are numerous causes of hypoglycaemia in the absence of diabetes mellitus. There are different ways of classifying these causes, which include:

- Insulin-mediated versus non-insulin mediated
- Fasting versus post-prandial
- Clinically unwell versus clinically well.

The differentiation between unwell and well is felt to be the most practically useful and is discussed below.

Clinically unwell

- Medications: for example insulin, hypoglycaemic agents, quinolones, pentamidine, quinine, beta-blockers, angiotensin-converting enzyme inhibitors)
- Alcohol: as ethanol inhibits gluconeogenesis but not glycogenolysis, it can take several days of increased ethanol consumption for hypoglycaemia to develop with the exhaustion of glycogen stores
- Critical illness: sepsis, renal impairment, hepatic or cardiac failure
- Malnourishment: glycogen store depletion and limited substrates for gluconeogenesis
- Hormone deficiency: hypocortisolaemia from adrenal insufficiency
- Paraneoplastic syndrome: often from the secretion of insulin-like growth factor from non-islet cell tumours.

Clinically well

Among those who appear well, hypoglycaemia may be secondary to accidental or malicious use of diabetic medications (e.g. insulin, beta cell secretagogues) or endogenous hyperinsulinaemia. The use of beta cell secretagogues will lead to endogenous hyperinsulinaemia, so it occurs in both groups.

Causes of endogenous hyperinsulinaemia:

- Beta cell secretagogue ingestion (e.g. ingestion of a medication that stimulates insulin release from beta cells)
- Islet beta-cell tumour (e.g. insulinoma - discussed below)
- Functional beta cell disorder (e.g. high insulin secretion not due to an insulinoma)
- Insulin autoimmune hypoglycaemia (antibodies develop against insulin or its receptor)

InsulinomaAn insulinoma refers to a tumour of the beta cells within the islets of Langerhan of the pancreas.

Insulinomas are most commonly benign tumours that cause excess secretion of insulin. This leads to recurrent fasting hypoglycaemia due to an inappropriately high level of insulin for the blood glucose concentration. Insulinomas may occur de novo or occur in association with multiple endocrine neoplasias, an autosomal dominant inherited condition. See our notes on MEN syndromes.

The diagnosis is usually made through a combination of prolonged fasting over 72 hours, which shows an inappropriately high level of insulin during an induced or spontaneous episode of

hypoglycaemia, and imaging of the pancreas. The treatment of choice is surgical resection.

Signs and symptoms of hypoglycemia

Hypoglycaemia is characterised by the development of autonomic and neuroglycopenic symptoms.

Autonomic features

The onset of symptoms usually occurs when blood glucose concentration falls below 3 mmol/L.

- Tremor
- Palpitations
- Anxiety
- Sweating
- Hunger
- Paraesthesia

Neuroglycopaenic features

These are a collection of more severe symptoms that typically develop at a blood glucose concentration below 2.8 mmol/L

- Dizziness
- Weakness
- Drowsiness
- Confusion
- Altered mental status
- Seizure

It is important to note that patients with diabetes mellitus may lose their hypoglycaemic awareness. This may lead to reduced symptoms and presentation with severe hypoglycaemia.

It can occur in patients with type 1 diabetes and long-standing type 2 diabetes mellitus. It is usually a combination of defective glucose counter-regulatory mechanisms and hypoglycaemia awareness. Collectively, this leads to recurrent hypoglycaemia.

Diagnosis

The diagnosis of hypoglycaemia is based on capillary blood glucose or serum blood glucose measurements.

In patients with suspected hypoglycaemia, a capillary blood glucose measurement should be taken. This will confirm a blood glucose concentration of less than 4.0 mmol/L, which is consistent with hypoglycaemia.

Further investigations depend on the suspected diagnosis (diabetes mellitus versus no diabetes

mellitus), the likely precipitant (e.g. concurrent illness) and whether it is recurrent. In patients with diabetes, simple adjustments to insulin or medications may be all that is required.

Investigations

In patients without diabetes mellitus, further investigations may be warranted to determine the underlying cause.In patients with hypoglycaemia without diabetes mellitus, it is first important to document true hypoglycaemia based on Whipple’s triad.

There is unlikely to be an underlying hypoglycaemic disorder if the blood glucose concentration is greater than 2.2 mmol/l.Many cases of hypoglycaemia may occur transiently in an unwell patient (e.g. sepsis, alcohol consumption) and investigations should be guided by the suspected diagnosis (e.g. serum cortisol in adrenal insufficiency). Routine blood tests including full blood count, renal function and liver function are essential.

Hypoglycaemia work-up

In patients who appear well and have recurrent, significant hypoglycaemia, a series of investigations can be requested

- 72 hour fast
- Glucose
- Insulin: will be inappropriately high in endogenous hyperinsulinaemia
- C-peptide: short polypeptide that forms part of proinsulin. It is cleaved to form insulin. Inappropriately high in endogenous hyperinsulinaemia.
- Pro-insulin: prohormone precursor released by beta cells. Cleaved to form insulin and C-peptide.
- Sulfonylurea screen: used to detect accidental or malicious use of oral hypoglycaemic agents
- Beta-hydroxybutyrate (BHOB): a blood ketone.
- Levels should be low in the context of hyperinsulinaemia because of the anti-ketone effect of insulin.

72 hour fast

This test aims to provoke normal homeostatic responses to keep blood glucose concentration from failing. In normal individuals, a 72-hour fast should not lead to hypoglycaemia.

The test is stopped if:

- Plasma glucose concentration falls ?2.5 mmol/L
- The patient has clinical features of hypoglycaemia
- The 72 hours elapses
- Plasma glucose concentration falls below 3.0 mmol/L with previous documentation of Whipple's triad

At the end of the test, blood is taken for insulin, C-peptide, proinsulin, Beta-hydroxybutyrate, and

oral hypoglycaemic agents. Glucagon may be given intravenously the following venepuncture and the patient is able to eat.

These blood tests are then interpreted to determine the cause. In an insulinoma, there is an inappropriately elevated level of insulin and C-peptide despite the presence of hypoglycaemia.

Management

Hypoglycaemia may be mild with minimal symptoms or a medical emergency requiring urgent treatment.

The management of hypoglycaemia depends on whether the patients is alert or has reduced GCS.

Alert and hypoglycaemia

- Give an oral glucose load: for example 120 mls of lucozade, single dose of hypostop or glucogel orally.
- Give a more complex carbohydrate meal: oral glucose load will only last an hour
- Monitor capillary blood glucose: usually 1-2 hourly until stable
- Consider intravenous dextrose (5-10%): if persistent hypoglycaemia, whilst investigating suspected cause
- Determine underlying cause

Coma and hypoglycaemia

- ABCDE assessment: if any concerns, call senior help urgently
- Establish intravenous access
- Give an intravenous load of glucose: 50 mls 50% dextrose, 100 mls 20% dextrose or 200 mls 10% dextrose (often depends on stock available)
- Consider 1 mg glucagon (SC/IM/IV): particularly if difficult to establish access. Remember, unlikely to be effective if poor glycogen stores (e.g. malnourished, hepatic disease).
- Reassess: should see rapid improvement in symptoms (i.e. less than 10 minutes) if hypoglycaemia is the cause of low GCS.
- Consider starting intravenous glucose infusion: for example, 1 litre 10% dextrose.
- Continue monitoring: usually capillary blood glucose 1-2 hourly until stable
- Determine underlying cause