Artefactual hypoglycaemia

Adam Morton

CASE

A woman, aged 43 years, was brought to the emergency department (ED) because of hypertension and hypoglycaemia on point-of-care testing. The woman had measured her blood pressure because of headache, noting a reading of 210/127 mmHg. On arrival, paramedics measured her capillary glucose as 1.9 mmol/L, without adrenergic or neurogenic symptoms or signs of hypoglycaemia. Following glucose gel, capillary glucose rose to 2.9 mmol/L, but fell to 1.6 mmol/L on arrival at the ED. The woman's blood pressure settled without additional therapy. Systemic lupus erythematosus (SLE) complicated by lupus nephritis with hypertension, pancytopenia and arthralgias had been diagnosed two years earlier. The woman's medications were tacrolimus 5 mg bd, mycophenolate 500 mg bd, ramipril 10 mg mane and prednisone 5 mg mane. She denied medication non-adherence. Following further oral carbohydrate in the ED, venous glucose was 5.1 mmol/L. Serum creatinine was 120 mmol/L (normal 40–90 mmol/L), and serum cortisol at 10 pm (two hours after presentation) was 93 nmol/L.

QUESTION 1

What criteria are used to diagnose hypoglycaemia in non-diabetic individuals?

QUESTION 2

How accurate is point-of-care testing of capillary glucose?

QUESTION 3

What causes of hypoglycaemia should be considered?

QUESTION 4

In the absence of a clear cause, what further testing should be performed in the investigation of hypoglycaemia in non-diabetic individuals?

ANSWER 1

Hypoglycaemia is suggested by Whipple's triad: symptoms of hypoglycaemia, venous glucose <3.0 mmol/L and resolution of symptoms after the plasma glucose concentration is raised.[1] However, the glucose concentration that is diagnostic of hypoglycaemia is poorly defined. Various venous glucose levels ranging from <2.5 to <3.3 mmol/L have been used to define hypoglycaemia in non-diabetic subjects.[2] However, healthy women and children might have a venous glucose level as low as 2.2 mmol/L without symptoms during fasting.

ANSWER 2

Point-of-care testing of capillary glucose is associated with significant inaccuracy when referenced against venous glucose. The International Organization for Standardization states that if blood glucose if <5.6 mmol/L, then glucometer results must be ±0.84 mmol/L of the venous glucose.[3] In the US Food and Drug Administration (FDA) guidelines,[3] 95% of all capillary glucose results must be within ±15%, and 99% within ±20%, of the venous glucose.

ANSWER 3

Major causes of hypoglycaemia are summarised in Box 1.

ANSWER 4

The testing performed depends on the clinical scenario, in particular whether the patient is acutely symptomatic of hypoglycaemia and whether their conscious state is impaired (Box 2). In an individual in whom the suspicion for true hypoglycaemia is low, continuous interstitial glucose monitoring over a period of one to two weeks might be useful to document whether it is likely that hypoglycaemia is occurring, and whether this correlates with symptoms. If symptoms predominantly occur during fasting, a 72-hour fast as an inpatient

Box 1. Causes of hypoglycaemia in non-diabetic adults

- Insulinoma
- Reactive hypoglycaemia: after bariatric surgery
- Cortisol deficiency
- Non-islet cell tumour hypoglycaemia (mesenchymal, hepatocellular, lymphoma, colorectal tumours): usually mediated by elevated levels of 'big IGF2' acting on insulin receptors
- Non-insulinoma pancreatogenous hypoglycaemia/nesidioblastosis
- Factitious hypoglycaemia: surreptitious use of insulin or sulphonylureas
- Adulteration of complementary/herbal therapies with sulphonylureas or repaglinide
- Alcohol excess
- Medications (eg opioids, quinine, indomethacin, hydroxychloroquine, ACE inhibitors)
- Hepatic, renal or cardiac failure
- Sepsis
- Autoimmune: insulin antibodies, antibodies to insulin receptor
- Malnutrition
- Inborn errors of metabolism
- Artefactual hypoglycaemia

ACE, angiotensin-converting enzyme; big IGF2, high molecular weight forms of insulin-like growth factor 2.

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will usually be required to measure insulin, proinsulin, C-peptide, β-hydroxybutyrate and cortisol concentrations concurrent with venous hypoglycaemia, together with a sulphonylurea screen. In individuals with solely postprandial hypoglycaemia, testing should be performed following a mixed meal and not an oral glucose load. Following a glucose challenge, approximately 10% of the general population will have a plasma glucose concentration <2.6 mmol/L, and 68% of individuals who have undergone bariatric surgery will develop reactive hypoglycaemia.[4,5]

CASE CONTINUED

Pallor and coldness of the woman's hands were noted, and the patient confirmed Raynaud's syndrome. Subsequent continuous interstitial fluid glucose monitoring for two weeks did not demonstrate hypoglycaemia. Anti-insulin antibodies were negative.

QUESTION 5

What are the causes of artefactual hypoglycaemia on testing capillary and venous blood?

QUESTION 6

What further testing could be performed to confirm the suspicion of artefactual hypoglycaemia?

ANSWER 5

Sources of artefactual hypoglycaemia with capillary and venous blood are listed in Box 3. Reduced capillary flow with Raynaud's phenomenon is thought to result in increased tissue extraction of glucose.

ANSWER 6

Alternative methods of monitoring in the setting of suspected artefactual capillary hypoglycaemia include venous sampling, capillary sampling from ear lobes or interstitial fluid glucose monitoring.

Artefactual venous hypoglycaemia can be avoided through the collection of blood in a sodium fluoride, and not a lithium–heparin, tube. In individuals with an intact hypothalamic–pituitary–adrenal (HPA) axis, serum cortisol should be >500 nmol/L for at least two hours following significant hypoglycaemia.[6] A lower value is suggestive of either artefactual hypoglycaemia, or true hypoglycaemia with cortisol deficiency.

CASE CONTINUED

Further testing of serum cortisol by high performance liquid chromatography (to avoid interference from prednisone) revealed an intact HPA axis.

Box 2. Investigation of suspected hypoglycaemia

Scenario	Investigations
Not currently symptomatic or hypoglycaemic	• Collect blood for early morning cortisol, liver function, prothrombin time, renal function; sulphonylurea screen if factitious hypoglycaemia suspected • Consider continuous or flash glucose monitoring, documenting time of symptoms and response to glucose ingestion • Consider further investigation if Whipple's triad fulfilled: prolonged fast if fasting symptoms or mixed-meal test if postprandial symptoms
Acute hypoglycaemia, normal conscious state	• Collect venous blood[A] • **Then** treat hypoglycaemia (oral)
Acute hypoglycaemia, impaired conscious state	• Treat hypoglycaemia (intravenous dextrose, subcutaneous/intramuscular glucagon) • **Then** collect venous blood[A]
Prolonged fast	• Baseline blood samples for glucose, insulin, C-peptide • Capillary blood glucose 3-hourly • Blood samples 6-hourly for glucose, insulin, C-peptide • If plasma glucose <2.5 mmol/L or 72 h elapsed, take blood samples for glucose, insulin, C-peptide, β-hydroxybutyrate, proinsulin, sulphonylurea screen, insulin antibody levels
Mixed-meal testing[B]	• Blood specimens for glucose, insulin, C-peptide at baseline and 30, 60, 90, 120, 180, 240, 270 and 300 min after the mixed meal • If hypoglycaemic symptoms occur prior to 300 min, take blood samples for glucose, C-peptide, insulin, proinsulin, sulphonylurea screen and insulin antibodies; stop test if venous glucose confirmed <3 mmol/L

[A]Blood samples for venous glucose, cortisol, insulin, proinsulin, C-peptide, β-hydroxybutyrate, sulphonylurea screen, liver function, prothrombin time.

[B]An oral glucose tolerance test should not be performed.

Box 3. Sources of artefactual hypoglycaemia

Capillary glucose

- Reduced capillary flow: hypothermia, shock, Raynaud phenomenon, peripheral vascular disease, acrocyanosis, cryoglobulinaemia, Eisenmenger syndrome
- Analytical errors: expired strips, high oxygen levels, polycythaemia

Venous glucose

- Leucocytosis: leukaemia, reactive
- Reticulocytosis: sickle cell anaemia, polycythaemia rubra vera
- Hyperviscosity: Waldenstrom macroglobulinaemia
- Prolonged delay in analysis where a lithium–heparin tube is used

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Key points

- Hypoglycaemia in non-diabetic individuals should not be diagnosed on glucometer readings.
- The level of venous glucose defining hypoglycaemia is unclear but is likely <2.5 mmol/L.
- Artefactual hypoglycaemia might occur with testing of both capillary and venous blood.
- Investigation of possible hypoglycaemia with a 72-hour fast is laborious and carries significant financial cost to the health system, and potentially significant emotional cost to patients.
- Suspicion of hypoglycaemia in non-diabetic individuals and further investigation should be based on the presence of Whipple's triad.

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