Biochemical investigation of hypoglycaemia in adults without diabetes mellitus

Evaluation and management of hypoglycaemia should **only** be undertaken in patients in whom Whipple's triad is observed:

- Symptoms, signs, or both consistent with hypoglycaemia
- Low plasma glucose concentration (<3 mmol/L laboratory result)
- Documented resolution of those symptoms or signs after the plasma glucose concentration is raised

Review the history, physical findings, and all available laboratory data seeking clues to specific disorders (Table 1)

- Drugs (Table 2)
- Critical illnesses
- Hormone deficiencies
- Non-islet cell tumours.

When the cause of the hypoglycaemic disorder is not evident during an episode of spontaneous hypoglycaemia, these steps will distinguish hypoglycaemia caused by endogenous (or exogenous) insulin from that caused by other mechanisms:

- Plasma glucose (laboratory analysis)
- Insulin
- C-peptide
- Proinsulin
- ß-hydroxybutyrate
- Screen for oral hypoglycaemic agents
- Insulin antibodies
- Observe and record the plasma glucose response to iv injection of 1.0 mg glucagon.

For sample requirements please see table 3

When a spontaneous hypoglycaemic episode cannot be observed, formally recreate the circumstances in which symptomatic hypoglycaemia is likely to occur, *i.e.* during a fast of up to 72 h or after a mixed meal. **The use of oral glucose tolerance tests is not recommended due to the high false positive rate with this test (Cryer et al. 2009).** The findings of symptoms, signs, or both with plasma concentrations of the following indicate hypoglycaemia caused by insulin or an Insulin Growth Factor:

- Glucose (laboratory) less than 3.0 mmol/L
- Insulin of at least 18 mIU/L
- C-peptide of at least 200 pmol/L)
- Proinsulin of at least 5.0 pmol/L
- ß-hydroxybutyrate ≤ 2.7 mmol/L
- Increase in plasma glucose of at least 1.4 mmol/L after iv glucagon

In a patient with documented fasting or postprandial endogenous hyperinsulinaemic hypoglycaemia, negative screening for oral hypoglycaemic agents, and no circulating insulin antibodies, conduct procedures for localizing an insulinoma. These may include computed tomography or magnetic resonance imaging (MRI), transabdominal and endoscopic ultrasonography, and, if necessary, selective pancreatic arterial calcium injections with measurements of hepatic venous insulin concentration.

References:

Cryer, Philip E. et al. 2009. "Evaluation and Management of Adult Hypoglycemic Disorders: An Endocrine Society Clinical Practice Guideline." *Journal of Clinical Endocrinology and Metabolism* 94(3): 709–28.

Hojan, Michael, F John Service, Frank W Sharbrough, and John E Gerich. 1983. "Oral Glucose Tolerance Test Compared with a Mixed Meal in the Diagnosis of Reactive Hypoglycaemia. A Caveat on Stimulation." *Mayo Clinic Proceedings* 58: 491–96.

Table 1: Causes of hypoglycaemia in adults.

Ill or medicated individual

1. Drugs
    - Insulin or insulin secretagogue
    - Alcohol
    - Others (Table 2)
2. Critical illnesses
    - Hepatic, renal, or cardiac failure
    - Sepsis (including malaria)
    - Starvation
3. Hormone deficiency
    - Cortisol
    - Glucagon and epinephrine (in insulin-deficient diabetes mellitus)
4. Nonislet cell tumour

Seemingly well individual

5. Endogenous hyperinsulinism
    - Insulinoma
    - Functional -cell disorders (nesidioblastosis)
        - Noninsulinoma pancreatogenous hypoglycaemia
        - Postgastric bypass hypoglycaemia
    - Insulin autoimmune hypoglycaemia
        - Antibody to insulin
        - Antibody to insulin receptor
        - Insulin secretagogue
    - Other
6. Accidental, surreptitious, or malicious hypoglycaemia

Table 2: Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycaemia

Moderate quality of evidence
- Cibenzoline
- Gatifloxacin
- Pentamidine
- Quinine
- Indomethacin
- Glucagon (during endoscopy)

Low quality of evidence
- Chloroquineoxaline sulfonamide
- Artesunate/artemisin/artemether
- IGF-I
- Lithium
- Propoxyphene/dextropropoxyphene

Very low quality of evidence

Drugs with >25 cases of hypoglycaemia identified
- Angiotensin converting enzyme inhibitors
- Angiotensin receptor antagonists
- ß-Adrenergic receptor antagonists
- Levofloxacin
- Mifepristone
- Disopyramide
- Trimethoprim-sulfamethoxazole
- Heparin
- 6-Mercaptopurine

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Table 3: Testing rationale and sample requirements

Test	Rationale	Blood Tube
Plasma glucose (laboratory analysis)	To prove hypoglycaemia	Grey top (Fluoride Oxalate)
Insulin	To detect excess insulin	2 X Red top (no anticoagulant)
C-peptide	To detect endogenous production	
Proinsulin	To check for production of proinsulin which may be in excess in some cases. Proinsulin has a insulin activity (1/10 that of insulin). It is produced exclusively in the pancreas and gives rise to equimolar amounts of insulin and C-peptide	
ß-hydroxybutyrate	To determine if the patient is ketotic	
Screen for oral hypoglycaemic agents	To rule out use of hypoglycaemic agents	
Insulin antibodies	To rule out presence of insulin antibodies	