Hypoglycaemia in nondiabetic patients

An evidence based approach

Background
Hypoglycaemia can have serious consequences for patients. Hypoglycaemia in nondiabetic patients is not a common condition, and is often a diagnostic challenge for general practitioners.

Objective
To search for evidence based guidelines on diagnosis and management of hypoglycaemia in nondiabetic adult patients and to see how these guidelines can be applied in general practice.

Discussion
The Endocrine Society clinical practice guideline 2009 recommends evaluation and management of hypoglycaemia only in patients in whom Whipple’s triad is documented: symptoms and/or signs of hypoglycaemia; low plasma glucose; and resolution of symptoms and/or signs after plasma glucose returns to normal. The first step in evaluation is to pursue clinical clues to specific aetiologies, i.e. drugs, critical illnesses, hormone deficiencies and nonislet cell tumours. In a seemingly well individual, the differential diagnosis of hypoglycaemic disorder narrows to drug induced hypoglycaemia; accidental, surreptitious, or malicious hypoglycaemia; endogenous hyperinsulinism; and idiopathic postprandial hypoglycaemia. When a spontaneous hypoglycaemic episode cannot be observed, patients should be referred for a prolonged fasting test or a mixed meal test.

Keywords: hypoglycaemia

Case study
Mr N is a retired businessman; he is 68 years of age and in good health. He had breakfast at 7 am. At 10 am he had sudden onset sweating, palpitations and tremor. His wife gave him a piece of bread and the symptoms subsided within a few minutes. He attends a clinic on the same afternoon and his physical examination is normal. Recent routine fasting blood glucose and renal function tests were normal. The working diagnosis is hypoglycaemia. Mr N asks, ‘Doctor, my wife is a diabetic, and she suffers from hypoglycaemia occasionally. But I’m not a diabetic and take no antidiabetic medications, how come I have hypoglycaemia?’
Classification of hypoglycaemic disorders in adults

Traditionally hypoglycaemic disorders in nondiabetics are classified as:

- postabsorptive (fasting) hypoglycaemia, or
- postprandial (reactive) hypoglycaemia (ie. hypoglycaemia that occurs within 4 hours after food ingestion).13

This classification has been criticised for being unhelpful diagnostically.8 For instance, some causes of hypoglycaemia can present with both postabsorptive and postprandial hypoglycaemia (eg. insulinoma). Other disorders can present with erratically occurring symptoms independent of food ingestion (eg. factitious hypoglycaemia).8

A more useful approach for clinicians is a classification based on clinical characteristics7–10 (Table 1). People who appear healthy are likely to have different hypoglycaemic disorders from those who are ill. Accidental, surreptitious, or malicious hypoglycaemia; endogenous hyperinsulinism; and idiopathic postprandial hypoglycaemia will usually cause hypoglycaemia without the patient appearing ill. Hypoglycaemia due to critical illnesses, hormone deficiency and nonislet cell tumours will usually cause hypoglycaemic symptoms while the patient appears ill. Drugs (including alcohol) can cause hypoglycaemia in both healthy looking and ill appearing clinical presentations.2–10

Drugs are the most common cause of hypoglycaemia,11 with insulin and sulphonylureas being the most common of these.7 Many other drugs have been reported to cause hypoglycaemia but this is usually based only on either low or very low quality evidence. Of the drugs available in Australia, only indomethacin, pentamidine and quinine have been associated with hypoglycaemia; the evidence is of moderate quality.12

Accidental hypoglycaemia occurs when there are pharmacy errors (eg. wrongly dispensing a sulphonylurea for another medication), medical treatment errors or medication errors.13 An example is the outbreak in Singapore in 2008 of severe drug induced hypoglycaemia in 150 nondiabetic patients due to four brands of sexual enhancement drugs that were contaminated with glyburide.14 Factitious hypoglycaemia due to surreptitious self administration of insulin or hypoglycaemic agent is usually manifested by erratically occurring neuroglycopenic symptoms and is observed more often in women, usually in a health related occupation.5 Malicious hypoglycaemia15–17 is due to the malicious administration of insulin or hypoglycaemic agents to others.

Insulinomas (pancreatic beta cell tumours) are rare. The estimated incidence is 1 case per 250 000 patient years.18 It is characterised by neuroglycopenia spells due to endogenous hyperinsulinaemic hypoglycaemia and occurs primarily in a fasting state, and only occasionally in a postprandial period.19 Diagnosis may require computerised tomography, ultrasonography or more sophisticated imaging and procedures in a specialist setting.9

The noninsulinoma pancreateogenous hypoglycaemia syndrome is an endogenous hyperinsulinaemia, characterised by attacks of neuroglycopenia, typically, but not invariably, after a meal.20 The pathology is diffuse pancreatic islet involvement with islet hyperplasia, sometimes with hyperplasia, with enlarged and hyperchromatic beta cell nuclei.21

Patients who have undergone Roux-en-Y gastric bypass for obesity may have endogenous hyperinsulinaemic hypoglycaemia most often due to pancreatic islet islet hyperplasia.22 This condition usually also causes postprandial spells of neuroglycopenia.

Hypoglycaemia due to anti-insulin antibody is a rare disorder occurring primarily in people of Japanese or Korean ethnicity,23 often with a history of autoimmune disease. Symptoms occur in the late postprandial period as insulin secreted in response to the meal is bound to the circulating antibody, then the insulin dissociates from the antibody in an unregulated fashion.5 Whereas most autoantibodies against the insulin receptor are antagonists and cause insulin resistance, some are agonists and cause hypoglycaemia.24

Mesenchymal tumours, hepatocellular carcinoma, adenocortical tumours, carcinoid tumours, leukaemia and lymphomas are nonislet cell tumours most commonly associated with hypoglycaemia.1 An incompletely processed insulin-like growth factor II (IGF-II) molecule, termed ‘Big IGF-II’, with decreased affinity to IGF binding proteins has been established as the cause of hypoglycaemia in some of these tumours.25

Idiopathic postprandial hypoglycaemia is a disorder in which autonomic and neuroglycopenic symptoms develop postprandially, accompanied by low plasma glucose.26 Various mechanisms have been shown to cause this disease:

- high insulin sensitivity
- an exaggerated insulin response, either related to insulin resistance or to increased glucagon-like peptide 1
- renal glycosuria, and
- defects in glucagon response.26

A small case series suggested Helicobacter pylori gastritis may contribute to the occurrence of idiopathic postprandial hypoglycaemia.27 Low carbohydrate/high protein diets, frequent feeding and avoidance of simple sugars are commonly recommended to patients diagnosed with idiopathic postprandial hypoglycaemia. The efficacy of dietary measures has not been established in controlled clinical trials.7,28

In idiopathic postprandial syndrome, autonomic symptoms (tremor, tachycardia, sweating), appear 2–5 hours after a meal, with normal plasma glucose concentration.29,30 There is enhanced catecholamine release following a meal or enhanced sensitivity to normal postprandial noradrenaline and adrenaline release. This condition is also known as pseudohypoglycaemia.30

In the beta cells of the pancreas, proinsulin is cleaved into insulin and C peptide (biochemically inert peptide fragment). Then insulin and C peptide are cosecreted from the pancreas in equimolar quantities.31 The pattern of plasma insulin, C peptide, proinsulin, sulphonylurea and anti-insulin antibody can help clinicians to differentiate various causes of hyperinsulinaemic hypoglycaemia (Table 2).1

Evidence based guidelines

The author used the advanced search function of MEDLINE with the keyword ‘hypoglycaemia’ and the article filter set for only practice guidelines; 26 items were retrieved. Article abstracts were scanned by the author: 11 were irrelevant and 14 were guidelines for diabetic patients only. Only one was a guideline on hypoglycaemia in nondiabetic adults: ‘Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline’, published in 2009 by the Endocrine Society of the United States of America.9 In the guideline there are
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Table 1. Causes of hypoglycaemia in adults

<table>
<thead>
<tr>
<th>Well appearing individual</th>
<th>Ill appearing individual</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Drugs</td>
<td>• Drugs</td>
</tr>
<tr>
<td>− insulin or insulin secretagogue</td>
<td>− insulin or insulin secretagogue</td>
</tr>
<tr>
<td>− alcohol</td>
<td>− alcohol</td>
</tr>
<tr>
<td>− other drugs</td>
<td>− other drugs</td>
</tr>
<tr>
<td>• Accidental, surreptitious, or malicious hypoglycaemia</td>
<td>• Critical illnesses</td>
</tr>
<tr>
<td>− insulinoma</td>
<td>− hepatic, renal, or cardiac failure</td>
</tr>
<tr>
<td>− functional beta cell disorders (nesidioblastosis)</td>
<td>− sepsis</td>
</tr>
<tr>
<td>− noninsulinoma pancreatic hypoglycaemia</td>
<td>− inanition</td>
</tr>
<tr>
<td>− postgastric bypass hypoglycaemia</td>
<td>• Hormone deficiency</td>
</tr>
<tr>
<td>− insulin autoimmune hypoglycaemia</td>
<td>− cortisol</td>
</tr>
<tr>
<td>− anti-insulin antibody</td>
<td>− glucagon and adrenaline (in insulin deficient diabetes mellitus)</td>
</tr>
<tr>
<td>− anti-insulin receptor antibody</td>
<td>• Nonislet cell tumour</td>
</tr>
<tr>
<td>• Idiopathic postprandial hypoglycaemia</td>
<td></td>
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</tbody>
</table>

Furthermore, when insulin secretion is increased substantially (eg. after a glucose load) the antecubital venous plasma glucose concentration can be as much as one-third lower than arterial glucose concentrations (which are relevant to maintain brain glucose metabolism). Therefore it is not possible to state a single plasma glucose concentration that unambiguously defines hypoglycaemia, hence the diagnosis of hypoglycaemia is most convincingly established when based on Whipple’s triad:

- symptoms, signs or both consistent with hypoglycaemia
- a low plasma glucose concentration, and
- resolution of those symptoms or signs after the plasma glucose concentration is raised to normal level.

A normal plasma glucose level, reliably obtained during the occurrence of spontaneous hypoglycaemic symptoms, eliminates the possibility of a hypoglycaemic disorder, and no further evaluation is required.8

To diagnose hypoglycaemic disorders accurately, hypoglycaemia should be documented by laboratory glucose measurement. Blood glucose meters are unsuitable for the diagnosis of hypoglycaemia8,8 as meters may be unreliable in the hypoglycaemic ranges;35 and may mislabel healthy individuals as having hypoglycaemia.36,37

**Recommendation 2**

Recommendation 2 is to review the history, physical findings, and all available laboratory data seeking clues to specific disorders, eg. drugs, critical illnesses, hormone deficiencies, nonislet cell tumours. Ill appearing patients presenting with hypoglycaemia are usually managed in hospital. History, physical examination and review of available laboratory data will usually provide clues to a cause of hypoglycaemia or exclude hypoglycaemia caused by medications, critical illnesses, hormone deficiencies, or a nonislet cell tumour,9 which usually require little or no investigation. Recognition of the association of disease with hypoglycaemia will be most important.8

In a seemingly healthy individual presenting with suspected hypoglycaemia, always look for evidence of hypoglycaemia induced by drugs or alcohol, even if there is no previous history of using a relevant drug (given the possibility of accidental, surreptitious, or malicious drug administration).7 Careful history taking is crucial for decision making. Among the plethora of symptoms of hypoglycaemia, neuroglycopenic symptoms will be of utmost importance. Patients with only autonomic symptoms are unlikely to have true hypoglycaemic disorder. However, even one episode of neuroglycopenia, or single severe adverse event (eg. loss of consciousness, traumatic injury) attributable to hypoglycaemia, warrants further investigation to confirm Whipple’s triad.1,8,9 Timing and duration of symptoms, aggravating and relieving factors, and exposure to any medications can greatly assist in deciding whether the patient’s history is suggestive of hypoglycaemia or not. For those without a strong history of hypoglycaemia, other differential diagnoses need to be considered.

In a seemingly well individual, the differential diagnosis narrows to drug induced hypoglycaemia; accidental, surreptitious, or malicious hypoglycaemia; endogenous hyperinsulinaemia; and idiopathic postprandial hypoglycaemia.7–10

**Recommendation 3**

The blood tests in this recommendation distinguish hypoglycaemia caused by endogenous...
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when they consult their GP after experiencing suspected hypoglycaemia. To establish that a patient has fasting hypoglycaemia, a prolonged fasting test is required.\(^\text{38}\) Similarly, a mixed meal test is required to confirm postprandial hypoglycaemia.\(^\text{38}\) Since the prolonged fasting test may require fasting for up to 72 hours, this test should be performed in hospital settings to mitigate the risks if hypoglycaemia develops.\(^\text{1}\)

The key pathophysiological feature of endogenous hyperinsulinism is that insulin secretion is inappropriately high when plasma glucose concentration is falling to hypoglycaemic levels.\(^\text{9}\) The findings of symptoms, signs, or both, with plasma concentrations of glucose less than 3.0 mmol/L, insulin of at least 3.0 mU/L (18 pmol/L), C peptide of at least 0.6 µg/L (0.2 nmol/L), and proinsulin of at least 5.0 pmol/L document endogenous hyperinsulinism.\(^\text{9}\)

In summary, when a spontaneous hypoglycaemic episode cannot be observed in a nondiabetic patient who complains of typical hypoglycaemic symptoms, they should be referred for a prolonged fasting test or mixed meal test to confirm Whipple’s triad and to confirm (or exclude) endogenous hyperinsulinism and hypoglycaemia induced by oral hypoglycaemic agents.

Table 2. Biochemical pattern in patients with various causes of hyperinsulinaemic hypoglycaemia\(^\text{7}\)

<table>
<thead>
<tr>
<th>Insulin</th>
<th>C Peptide</th>
<th>Proinsulin</th>
<th>Sulphonylurea</th>
<th>Insulin antibody</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>Exogenous insulin</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>Insulinoma</td>
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<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>+</td>
<td>–</td>
<td>Sulphonylurea</td>
</tr>
<tr>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
<td>+</td>
<td>Autoimmune anti-insulin antibody</td>
</tr>
</tbody>
</table>

Table 3. Endocrine Society clinical practice guideline 2009\(^\text{9}\) on evaluation and management of adult hypoglycaemic disorders in people without diabetes mellitus

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality of evidence(^\text{9})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Evaluate and manage hypoglycaemia only in patients in whom Whipple’s triad is documented, ie: • symptoms, signs, or both, consistent with hypoglycaemia • a low plasma glucose concentration, and • resolution of those symptoms or signs after the plasma glucose concentration is raised</td>
<td>High (\ddagger\ddagger\ddagger\ddagger)</td>
</tr>
<tr>
<td>2 Review the history, physical findings, and all available laboratory data seeking clues to specific disorders, ie: • drugs • critical illnesses • hormone deficiencies • nonislet cell tumours</td>
<td>Moderate (\ddagger\ddagger)</td>
</tr>
<tr>
<td>3 When the cause of the hypoglycaemic disorder is not evident: • measure plasma glucose, insulin, C peptide, proinsulin concentrations • screen for oral hypoglycaemic agents, during an episode of spontaneous hypoglycaemia, and • observe the plasma glucose response to IV injection of 1 mg glucagon</td>
<td>Moderate (\ddagger\ddagger)</td>
</tr>
<tr>
<td>4 When a spontaneous hypoglycaemic episode cannot be observed formally recreate the circumstances in which symptomatic hypoglycaemia is likely to occur</td>
<td>Moderate (\ddagger\ddagger)</td>
</tr>
<tr>
<td>5 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 localising an insulinoma</td>
<td>Moderate (\ddagger\ddagger)</td>
</tr>
<tr>
<td>6 Tailor treatment to the specific hypoglycaemic disorder, taking into account the burden of hypoglycaemia on patient wellbeing and patient preferences</td>
<td>Moderate (\ddagger\ddagger)</td>
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</tbody>
</table>
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Recommendation 5

This recommendation suggests conducting relevant investigations to confirm insulinoma in patients with documented fasting or postprandial endogenous hyperinsulinaemic hypoglycaemia (with negative screening for oral hypoglycaemic agents and no circulating insulin autoantibodies). This is more relevant to secondary and tertiary care settings.

Recommendation 6

Recommendation 6 is to tailor treatment to the specific hypoglycaemic disorder, taking into account the burden of hypoglycaemia on patient wellbeing and patient preferences.

Most hypoglycaemic disorders need specific specialist treatment, eg. surgical excision to cure solitary insulinomas. However, GPs can play a valuable role in managing some disorders, ie. idiopathic postprandial hypoglycaemia or postgastric bypass hypoglycaemia, where dietary advice can assist to manage daily work and activities. 7,30

A diagnostic algorithm for hypoglycaemia in nondiabetic patients in general practice can be formulated (Figure 1).

Conclusion

The diagnosis of hypoglycaemic disorders in nondiabetic patients requires a high level of suspicion, careful patient assessment and methodical evaluation on the basis of well defined diagnostic criteria and guidelines. Some patients may need referral for further investigation and management. Being familiar with the classification of hypoglycaemic disorders and the recommendations of evidence based guidelines enables GPs to carry out comprehensive initial evaluation and make appropriate and timely referrals.

In the case of Mr N, there were no neuroglycopenic symptoms and his symptoms subsided too quickly (within a few minutes) after taking a small quantity of food with low glycaemic load, to suggest a genuine hypoglycaemic disorder. Moreover, this was only the first attack of such symptoms, and the symptoms did not result in significant adverse events and did not affect his daily activities. Therefore, he does not currently warrant referral for a mixed meal test. Indeed, the clinical features were more compatible with idiopathic postprandial syndrome. A reasonable approach is to observe progress at this stage. Anxiety disorders should be considered. Should he develop neuroglycopenic symptoms or other more typical features of a hypoglycaemic disorder in future, he should then be referred for further investigation and management.

Summary of important points

- Hypoglycaemia typically presents with autonomic and neuroglycopenic symptoms.
- Evaluation and management of hypoglycaemia for nondiabetic patients should only be carried out in patients in whom Whipple’s triad is documented.
- Initial evaluation of nondiabetic patients with hypoglycaemia is to review the history, physical findings, and all available laboratory data to seek clues to specific disorders, ie. drugs, critical illnesses, hormone deficiencies and nonislet cell tumours.
- In seemingly well individuals, the differential diagnosis of hypoglycaemic disorders narrows to drug induced hypoglycaemia; accidental, surreptitious, or malicious hypoglycaemia; endogenous hyperinsulinism; and idiopathic postprandial hypoglycaemia.
- When a spontaneous hypoglycaemic episode cannot be observed, recreate the circumstances by referral to hospital for a prolonged fasting test or a mixed meal test. These tests can also confirm endogenous hyperinsulinism and hypoglycaemia induced by

Figure 1. Approach to adult nondiabetic patients with hypoglycaemia in general practice9
oral hypoglycaemic agents.

**Author**
Ching Luen Ng MBBS, FRACGP, FHKCP, FHKAM, is Associate Consultant, Department of Family Medicine, Kowloon West Cluster, Hospital Authority, Hong Kong. chingluen@yahoo.com.hk.

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**References**


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