Ching Luen Ng

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, ie. 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

Hypoglycaemia is a medical emergency. It signals an inability of the central nervous system to meet its energy needs. Untreated, hypoglycaemia can result in permanent neurologic damage and death.[1] Hypoglycaemia is a common complication of drug treatment for diabetes mellitus. Reported severe hypoglycaemia ranged from 62–320 episodes per 100 patient years in patients with type 1 diabetes mellitus,[2,3] and 3–73 episodes per 100 patient years in patients with type 2.[4,5] However, hypoglycaemia is an uncommon condition in nondiabetic patients and a diagnostic challenge for general practitioners.

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?'

Clinical presentation

Symptoms of hypoglycaemia can be divided into two categories:

- neurogenic (autonomic), and
- neuroglycopenic symptoms.[6]

Autonomic symptoms result from sympatho-adrenal discharge triggered by hypoglycaemia. They include palpitations, tremor, anxiety, sweating, hunger and paraesthesias.[6] Neuroglycopenic symptoms are caused by compromised central nervous system function due to brain glucose deprivation. They include weakness, fatigue, confusion, unusual or bizarre behaviour, seizures, focal neurologic deficit, and coma.[1,7] There are no genuine hypoglycaemic disorders characterised solely by autonomic symptoms.[8] Although some patients with true hypoglycaemic disorder may experience only autonomic symptoms initially, eventually episodes of neuroglycopenia will also occur in subsequent attacks.[8]

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).[7]

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 characteristics[7–10] (*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.[7–10]

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.[8] Malicious hypoglycaemia[15–17] 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 pancreatogenous 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 nesidioblastosis (islet hypertrophy, 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 nesidioblastosis.[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.[9] Whereas most autoantibodies against the insulin receptor are antagonists and cause insulin resistance, some are agonists and cause hypoglycaemia.[24]

Mesenchymal tumours, hepatocellular carcinoma, adrenocortical 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*).[7]

Evidence based guidelines

The author used the advanced search function of MEDLINE with the keyword 'hypoglycemia' 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

Table 1. Causes of hypoglycaemia in adults[9,10]

Well appearing individual	Ill appearing individual
• Drugs – insulin or insulin secretagogue – alcohol – other drugs • Accidental, surreptitious, or malicious hypoglycaemia • Endogenous hyperinsulinism – insulinoma – functional beta cell disorders (nesidioblastosis) – noninsulinoma pancreatogenous hypoglycaemia – postgastric bypass hypoglycaemia – insulin autoimmune hypoglycaemia – anti-insulin antibody – anti-insulin receptor antibody • Idiopathic postprandial hypoglycaemia	• Drugs – insulin or insulin secretagogue – alcohol – other drugs • Critical illnesses – hepatic, renal, or cardiac failure – sepsis – inanition • Hormone deficiency – cortisol – glucagon and adrenaline (in insulin deficient diabetes mellitus) • Nonislet cell tumour

six recommendations relevant to hypoglycaemic disorders in nondiabetic adult patients based on either high or moderate quality evidence (*Table 3*). Seven relevant original articles listed in the references of this guideline were also reviewed looking for further evidence.

Application of evidence based guidelines in general practice

In the Endocrine Society clinical practice guideline 2009, recommendations 1, 2, 4 and 6 can be applied to guide GPs to formulate diagnostic and management plans for hypoglycaemic disorders in nondiabetic adults.[9]

Recommendation 1

This recommendation discusses evaluating and managing hypoglycaemia only in patients in whom Whipple's triad[7] is documented.

Hypoglycaemia manifestations are nonspecific, vary among different people, and can change from time to time in the same person.[7] Although symptoms of hypoglycaemia typically develop at mean plasma glucose concentration of approximately 3.0 mmol/L in healthy individuals, the glycaemic thresholds for response to hypoglycaemia shift to lower plasma glucose concentrations in patients with recurrent hypoglycaemia.[32,33] 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).[34]

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 hypoglycaemia[8,9] 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 hyperinsulinism; and idiopathic postprandial hypoglycaemia.[7–10]

Recommendation 3

The blood tests in this recommendation distinguish hypoglycaemia caused by endogenous

(or exogenous) insulin from that caused by other mechanisms. However, often patients are already asymptomatic when they attend the clinic, so this is more applicable to emergency department settings.

Recommendation 4

When a spontaneous hypoglycaemic episode cannot be observed, the recommendation is to formally recreate the circumstances in which symptomatic hypoglycaemia is likely to occur, ie. during a fast of up to 72 hours or after a mixed meal.

Often patients are already asymptomatic when they consult their GP after experiencing suspected hypoglycaemia. To establish that a patient has fasting hypoglycaemia, a prolonged fasting test is required.[38] Similarly, a mixed meal test is required to confirm postprandial hypoglycaemia.[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.[1]

The key pathophysiological feature of endogenous hyperinsulinism is that insulin secretion is inappropriately high when plasma glucose concentration is falling to hypoglycaemic levels.[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.[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 Whipples' 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[7]

Insulin	C Peptide	Proinsulin	Sulphonylurea	Insulin antibody	Diagnosis
↑	↓	↓	–	–	Exogenous insulin
↑	↑	↑	–	–	Insulinoma
↑	↑	↑	+	–	Sulphonylurea
↑	↑	↑	–	+	Autoimmune anti-insulin antibody

Table 3. Endocrine Society clinical practice guideline 2009[9] on evaluation and management of adult hypoglycaemic disorders in people without diabetes mellitus

	Recommendation	Quality of evidence[9]
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	High ⌖⌖⌖⌖
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	Moderate ⌖⌖⌖
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	Moderate ⌖⌖⌖
4	When a spontaneous hypoglycaemic episode cannot be observed formally recreate the circumstances in which symptomatic hypoglycaemia is likely to occur	Moderate ⌖⌖⌖
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	Moderate ⌖⌖⌖
6	Tailor treatment to the specific hypoglycaemic disorder, taking into account the burden of hypoglycaemia on patient wellbeing and patient preferences	Moderate ⌖⌖⌖

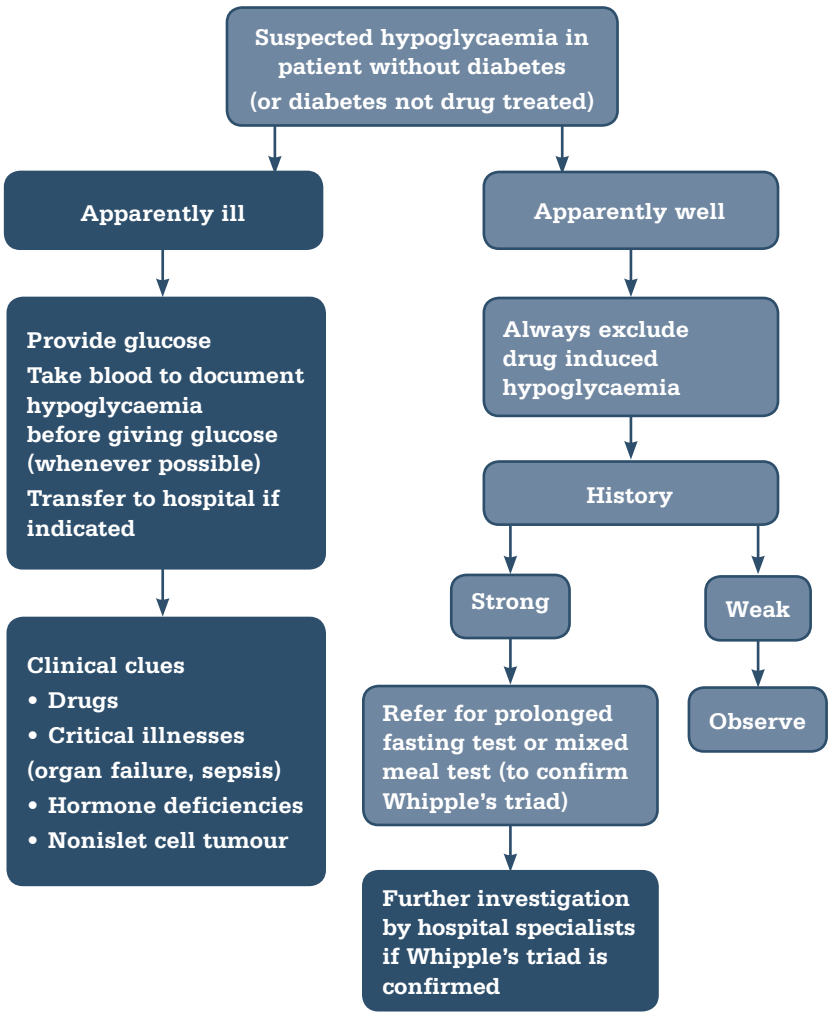

Figure 1. Approach to adult nondiabetic patients with hypoglycaemia in general practice[9]

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 adult 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

oral hypoglycaemic agents.

Author

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

Conflict of interest: none declared.

References

1. Guettier J-M, Gorden P. Hypoglycemia. Endocrinol Metab Clin N Am 2006;35:753–66.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin–dependent diabetes mellitus. N Engl J Med 1993;329:977–86.
3. United Kingdom Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–7.
4. Abraira C, Colwell JA, Nuttall FQ, et al. Veterans Affairs Cooperative Study on glycemic control and complications in type II diabetes (VA CSDM). Results of the feasibility trial. Veterans Affairs Cooperative Study in type II diabetes. Diabetes Care 1995;18:1113–23.
5. MacLeod KM, Hepburn DA, Frier BM. Frequency and morbidity of severe hypoglycaemia in insulin-treated diabetic patients. Diabet Med 1993;10:238–45.
6. Towler DA, Havlin CE, Craft S, et al. Mechanisms of awareness of hypoglycemia: perception of neurogenic (predominately cholinergic) rather than neuroglycopenic symptoms. Diabetes 1993;42:1791–8.
7. Cryer PE. Glucose Homeostasis and hypoglycemia. In: Kronenberg H, Melmed S, Polonsky K, et al, editors. Williams textbook of endocrinology. 11th edn. Philadelphia: Saunders Elsevier, 2008;1503–33.
8. Service FJ. Hypoglycemic disorders. N Engl J Med 1995;332:1144–52.
9. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2009;94:709–28.
10. Service FJ. Classification of hypoglycemic disorders. Endocrinol Metab Clin North Am 1999;28:501–17.
11. Malouf R, Brust JCM. Hypoglycemia: causes, neurological manifestations, and outcome. Ann Neurol 1985;17:421–30.
12. Murad MH, Coto-Yglesias F, Wang AT, et al. Drug-induced hypoglycemia: a systematic review. J Clin Endocrinol Metab 2009;94:741–5.
13. Bates DW. Unexpected hypoglycemia in a critically ill patient. Ann Intern Med 2002;137:110–6.
14. Kao SL, Chan CL, Lim CC, et al. An unusual outbreak of hypoglycemia. N Engl J Med 2009;360:734–6.
15. Marks V, Teale JD. Hypoglycemia: factitious and felonious. Endocrinol Metab Clin North Am 1999;28:579–601.
16. Giurgea I, Ulinski T, Touati G, et al. Factitious hyperinsulinism leading to pancreatectomy: severe forms of Munchausen syndrome by proxy. Pediatrics 2005;161:e145–8.
17. Manning PJ, Espiner EA, Yoon K, et al. An unusual cause of hyperinsulinaemic hypoglycaemia syndrome. Diabet Med 2003;20:772–6.
18. Service FJ, McMahon MM, O'Brien PC, et al. Functioning insulinoma: incidence, recurrence, and long-term surivival of patients. Mayo Clin Proc 1991;66:711–9.
19. Kar P, Price P, Sawers S, et al. Insulinomas may present with normoglycemia after prolonged fasting but glucose-stimulated hypoglycemia. J Clin Endocrinol Metab 2006;91:4733–6.
20. Won JG, Tseng HS, Yang AH, et al. Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome. Clin Endocrinol (Oxf) 2006;65:566–78.
21. Anlauf M, Wieben D, Perren A, et al. Persistent hyperinsulinemic hypoglycemia in 15 adults with diffuse nesidioblastosis: diagnostic criteria, incidence, and characterization of beta-cell changes. Am J Surg Pathol 2005;29:524–33.
22. Goldfine AB, Mun E, Patti ME. Hyperinsulinemic hypoglycemia following gastric bypass surgery for obesity. Curr Opin Endocrinol Diabetes 2006;13:419–24.
23. Hirata Y, Ishizu H, Ouchi N, et al. Insulin autoimmunity in a case with spontaneous hypoglycemia. J Japan Diab Soc 1970;13:312–20.
24. Arioglu E, Andewelt A, Diabo C, et al. Clinical course of the syndrome of autoantibodies to the insulin receptor (type B insulin resistance). Medicine (Baltimore) 2002;81:87–100.
25. Ishida S, Noda M, Kuzuya N, et al. Big insulin-like growth factor II-producing hepatocellular carcinoma associated with hypoglycemia. Intern Med 1995;34:1201–6.
26. Brun JF, Fedou C, Mercier J. Postprandial reactive hypoglycemia. Diabetes Metab 2000;26:337–51.
27. Açbay Ö, Çelik AF, Kadioglu P, et al. Helicobacter pylori-induced gastritis may contribute to occurrence of postprandial symptomatic hypoglycemia. Dig Dis Sci 1999;44:1837–42.
28. Franz MJ. Medical nutrition therapy for diabetes mellitus and hypoglycemia of nondiabetic origin. In: Mahan LK, Escott-Stump S, editors. Krause's food and nutrition therapy. 12th edn. St Louis: Saunders Elsevier 2008;764–809.
29. Charles MA, Hofeldt F, Shackelford A, et al. Comparison of oral glucose tolerance tests and mixed meals in patients with apparent idiopathic postabsorptive hypoglycemia. Diabetes 1981;30:465–70.
30. Foster DW, Rubenstein AH. Hypoglycemia. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, editors. Harrison's principles of internal medicine. 14th edn. New York: McGraw-Hill, 1998;2081–7.
31. Gale EAM, Anderson JV. Diabetes mellitus and other disorders of metabolism. In: Kumar P, Clark M, editors. Clinical medicine. 6th edn. Edinburgh: Saunders Elsevier, 2005;1101–52.
32. Cryer P. The prevention and correction of hypoglycemia. In: Jefferson L, Cherrington A, Goodman H, editors. Handbook of physiology; the endocrine pancreas and regulation of metabolism. New York: Oxford University Press, 2001;1057–92.
33. Boyle PJ, Schwartz NS, Shah SD, et al. Plasma glucose concentrations at the onset of hypoglycemic symptoms in patients with poorly controlled diabetes and in nondiabetics. N Engl J Med 1988;318:1487–92.
34. Jackson RA, Peters N, Advani U, et al. Forearm glucose uptake during the oral glucose tolerance test in normal subjects. Diabetes 1973;22:442–58.
35. American Diabetes Association. Consensus statement on self-monitoring of blood glucose. Diabetes Care 1987;10:95–9.
36. Gama R, Anderson NR, Marks V. 'Glucose meter hypoglycaemia', often a non-disease. Ann Clin Biochem 2000;37:731–2.
37. Burden ML, Jarvis J, Dromgoole P, et al. Precision of glucose meters in the hypoglycaemic range and normoglycaemic range. Practical Diabetes International 1998;15:133–4.
38. Service FJ. Diagnostic approach to adults with hypoglycaemic disorders. Endocrinol Metab Clin North Am 1999;28:519–32.