Clinical Reviews

Acute Hypoglycaemia: Diagnostic criteria, Investigation and Management for the Emergency Physician

T Richardson & D Kerr

Abstract

Hypoglycaemia is a common condition, which may easily be missed due to the variation in clinical presentation in patients with or without diabetes. The most common cause is related to the treatment of diabetes. Non-diabetes related hypoglycaemia is rare. Nonetheless, the need for careful evaluation of the underlying cause is important as well as relieving symptoms.

The diagnosis and investigations involved in management of hypoglycaemia are discussed with a direct relevance to the acute general physician.

Keywords

Hypoglycaemia, diabetes, diagnosis, c-peptide, fasting

Introduction

Hypoglycaemia is commonly encountered in patients presenting acutely to the medical 'take'. The commonest cause is treatment with insulin or sulphonylurea for diabetes. Many other drugs have been implicated as causes of hypoglycaemia, often in frail, elderly patients with co-existing renal, cardiac or hepatic failure.[1] More rarely, low blood glucose levels can be the first presenting feature of endocrine disorders such as hypoadrenalism or hypopituitarism. Insulin-secreting tumours are very uncommon.

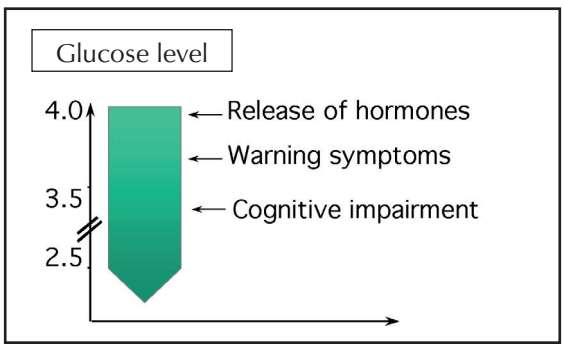


Figure 1. Perception of Hypoglycaemia

One potential difficulty relates to correct identification of hypoglycaemia as the underlying problem. In patients with diabetes, acute hypoglycaemia is very common but permanent neurological disability is rare unless other factors, such as alcohol, are involved. This is because complex physiological mechanisms have evolved in order to protect substrate delivery to the brain.[2] The brain is almost entirely dependent upon a continuous supply of glucose from the peripheral circulation for normal function. As blood glucose levels fall below 4 mmol/l, there is activation of the autonomic nervous system with release of counter-regulatory hormones (glucagon, catecholamines, cortisol and growth hormone) in an effort to raise blood glucose levels back towards normal.[3] At around 3.5 mmol/l there is the development of characteristic warning symptoms (sweating, shaking, light-headedness, hunger) alerting individuals to take appropriate action and eat rapidly absorbed carbohydrate. If glucose levels continue to fall to around 3 mmol/l, impairment of higher cerebral (cognitive) function occurs. As blood glucose levels drop further, the patient is at risk of marked neuroglycopaenia with altered consciousness, seizures or coma.[4] (Figure 1)

The classical symptoms of hypoglycaemia are sweating, shaking, light-headedness, palpitations and hunger. The nature and intensity of these can change with the passage of time e.g. in individuals with long-standing type 1 diabetes and patients with insulinomas (Table 1). Pallor is invariably present as a sign associated with a low blood glucose level. For patients with diabetes, in whom low blood glucose levels are a fact of life, the nature of the presentation can make self-reporting unreliable. In up to 25% of such patients, however, loss of warning symptoms may develop with increased duration of diabetes. Other risk factors for hypoglycaemia are shown in Table 2.

Dr Tristan Richardson
BSc, MRCP
Clinical Research Fellow
Royal Bournemouth
Hospital, Bournemouth.

Dr David Kerr
MD, FRCP
Consultant
Royal Bournemouth
Hospital, Bournemouth.

Correspondence:
Dr Tristan Richardson,
BDEC
Royal Bournemouth
Hospital
Bournemouth
BH7 7DW
UK.
Tel: 01202-704603
Fax: 01202-704759
Email:Tristan.Richardson@
rbch-tr.swest.nhs.uk

Autonomic	Neuroglycopenic
Sweating	Confusion
Palpitations	Drowsiness
Trembling	Odd behaviour
Hunger	Difficulty speaking
Tingling	Inco-ordination
Nervousness	Weakness
Pallor	
Light-headedness	

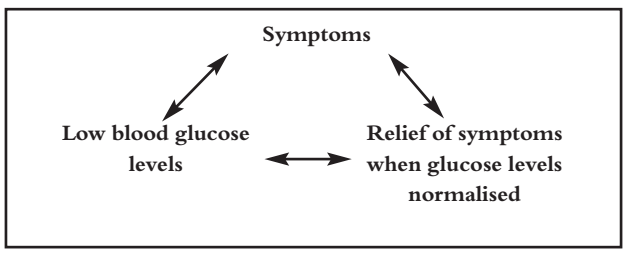
Table 1. Classical symptoms and signs associated with hypoglycaemia

Risk factors for recurrent hypoglycaemia in diabetes
• Previous hypoglycaemia
• Intensive insulin therapy
• Impaired hypoglycaemia awareness
• Long duration of diabetes
• Strict glycaemic control
• Renal Failure
• Pregnancy
• Sleep
• Alcohol
• Exercise

Table 2. Risk factors for hypoglycaemia in patients with diabetes

Diagnosis

Hypoglycaemia is common but not always easy to define. For patients with diabetes treated with insulin or sulphonylureas, a blood glucose level below 4 mmol/l is considered to represent hypoglycaemia and rapidly absorbed carbohydrate should be ingested. Metformin is antihyperglycaemic, rather than hypoglycaemic and therefore does not cause hypoglycaemia.[5]



For non-diabetic individuals, the diagnosis of hypoglycaemia should be based on 'Whipple's triad' (see above).

In otherwise healthy young adults, blood glucose levels can fall to around 2.5 mmol/l in the absence of symptoms and is therefore a normal variant. For diagnostic purposes, hypoglycaemia should be considered only after blood glucose levels have fallen to 2.5 mmol/l or less, in association with suggestive symptoms.

Treatment of Hypoglycaemia

For conscious patients, oral ingestion of rapidly absorbed carbohydrate such as dextrose tablets, lucozade or fresh fruit juice is recommended. Following this, more slowly absorbed complex carbohydrate may prevent recurrent hypoglycaemia.

In the patient with a reduced level of consciousness, intravenous glucose will rapidly elevate blood glucose levels. Although 50% glucose is commonly used (25-50ml), the viscosity makes this difficult to administer, and severe thrombophlebitis may occur if a peripheral vein is used, particularly if the cannula is not adequately flushed after use. Larger volumes (65ml) of 20% glucose or even 125ml 10% glucose may therefore be more appropriate. In patients with difficult venous access, or in the pre-hospital setting, glucagon (1mg) can be given subcutaneously or intra-muscularly. The effect is short-lived, is slower than IV glucose and it may be ineffective in patients with inadequate glycogen stores (alcoholics, liver failure, malnourished, etc).

Investigation of Non-diabetes related hypoglycaemia

Glucose

Spontaneous hypoglycaemia should be investigated in anyone who presents with symptoms of autonomic or neuroglycopenic origin (Table 1). A blood sample for glucose should be collected when the patient is symptomatic and analysed in the laboratory. Fingerstick capillary glucose levels should not be used as they lack sensitivity at low blood glucose levels.[6] Unfortunately, measurement of plasma glucose is often not feasible as spontaneous episodes occur sporadically. In such circumstances, the decision to proceed with further investigation depends on a suggestive history or, if available, a confirmed plasma glucose of <3.0mmol/l.

Whole blood glucose may be 15% lower than the corresponding plasma level, and may continue to fall at a rate of 0.5-1mmol/l per hour at room temperature due to continued cell metabolism. Any condition associated with increased number of metabolically active cells, such as polycythaemia rubra vera or the leukaemias, may accelerate glycolysis. Prompt separation of plasma or the use of oxalate and fluoride (grey) tubes is necessary to prevent glycolysis, and artificially low glucose measurements.

There may also be significant differences between arterial and venous blood glucose concentration. In the fasting state, there is little difference. However, after a meal, venous glucose concentrations may be 1-2mmol/l lower due to tissue uptake of glucose. This may also give rise to apparent hypoglycaemia.

Insulin and C-Peptide

Whenever blood is drawn in the investigation of hypoglycaemia, it is important to freeze a sample for later determination of insulin and C-peptide concentration.

C-peptide and insulin are produced as breakdown products of pro-insulin. Insulin has a short half-life due to its rapid breakdown in the liver, so that C-peptide concentrations may be several times higher than those of

insulin. This may be exaggerated in renal impairment. Since exogenous insulin does not contain pro-insulin when administered by injection, the finding of insulin levels higher than C-peptide levels suggests an exogenous source.

Hydroxybutyrate

Hydroxybutyrate is one of the keto-acids. It is produced by the liver when there is insulin deficiency, and is suppressed by insulin. Low hydroxybutyrate levels suggest increased insulin (or insulin-like growth factor - produced by some mesenchymal tumours), autoimmune hypoglycaemia and liver failure. Most other causes of hypoglycaemia are associated with at least moderate ketonaemia.

Anti-insulin antibodies

The presence of anti-insulin antibodies may suggest either prior exposure to exogenous insulin, or autoimmune insulin syndrome, which may cause reactive hypoglycaemia. The finding of anti-insulin antibodies in the normal population limits the specificity of this investigation.

Provocation Tests

Provocation of hypoglycaemia involves fasting (± exercise) in an attempt to precipitate fasting hypoglycaemia. The most widely used test is the prolonged (48 hour) fast (Table 3). Other provocation tests such as the iv tolbutamide test (no longer available in the UK), iv glucagon test and selective arterial pancreatic calcium stimulation test may have limited roles in the differentiation of the underlying cause once hypoglycaemia is established as the diagnosis.

Protocol for 48 hour fast

1. Admit to investigation unit @8am- fasting from midnight (clear fluids allowed)
2. Discontinue non-essential medications
3. Allow drinking of calorie- and caffeine-free fluids
4. Reasonable activity allowed + free access to water
5. Appropriate medical supervision to observe for symptoms of hypoglycaemia + individual visual analogue hypoglycaemia symptom questionnaire
6. Measure plasma glucose (& save serum for insulin/ C-peptide) every 6 hours until glucose < 3.0mmol/l or fast ends (48hrs)
7. If plasma glucose < 3.0mmol/l, repeat blood test battery hourly
8. If plasma glucose < 2.5mmol/l, stop fast after measuring matched C-peptide, insulin and plasma glucose
9. If after 48 hours, glucose > 2.5mmol/l, exercise patient for 10 minutes (e.g. walking up stairs), then repeat bloods
10. Feed patient after 48 hours or once test terminated (glucose < 2.5mmol/l)

Table 3. 48 hour fast protocol

1. Prolonged fast

The prolonged fast is the mainstay of investigation for fasting hypoglycaemia. The 48 hour fast has similar diagnostic sensitivity to, and is preferred over the 72 hour fast.[7] This investigation should be reserved for those in whom hypoglycaemia remains a strong possibility, despite the absence of other documented evidence of spontaneous hypoglycaemia.

The fast must be conducted under vigilant medical supervision. The patient may be ambulant and can consume non-caloric fluids (Table 3). Blood samples are analysed immediately for plasma glucose and serum is frozen and stored for later analysis as necessary. Regular testing for subtle neuroglycopenia is essential as it can be easily missed. The fast is terminated at 48 hours or when the patient has a plasma glucose of <2.5mmol/l with neuroglycopenic symptoms.

A few healthy individuals (usually young women) may have blood glucose levels in the hypoglycaemic range (~2.5mmol/l) following prolonged fasting, and may be misdiagnosed as suffering from true hypoglycaemia. However, they do not develop neuroglycopenic symptoms, underlying the importance of clinical supervision during the fast.

2. Mixed Meal Test

The mixed meal test is used to investigate post-prandial hypoglycaemia. There are various ways of applying this test, and no defined protocol has been established. However it is important to replicate the meal which gave rise to the original symptoms. Capillary blood rather than venous blood should be used (see above), with samples collected immediately before the meal and then every 30 minutes after until six hours. The association of neuroglycopenic symptoms and a plasma glucose of < 3.0mmol/l is considered as positive.

The glucose tolerance test has been abandoned as a useful test for post-prandial hypoglycaemia as it is unphysiological, with an excess of false positive results.

Special situations

Alcohol and hypoglycaemia

The acute effects of alcohol are well recognised but may mimic neuroglycopenic hypoglycaemia. This potential pitfall may be exacerbated by concurrent alcohol ingestion with associated hypoglycaemia, leading to a delay in the treatment of the low blood glucose. Alcohol and hypoglycaemia may be associated in 4 ways:

- Inhibition of hepatic gluconeogensis
- Potentiation of hypoglycaemic agents and prolonged exercise

- Causing reactive hypoglycaemia in susceptible individuals
- Recognised complication of chronic alcoholism.

More than 90% of ethanol is metabolised by the liver. Utilisation of nicotinamide adenine dinucleotide (NAD) in this process reduces the availability of NAD+ for hepatic gluconeogensis. Therefore, an acute alcohol load leads to a fall in gluconeogenesis. This becomes important only when blood glucose is being maintained by gluconeogenesis rather than glycogenolysis. This situation arises during starvation (including chronic alcoholism), liver failure, underfeeding or prolonged exercise. Alcohol is not associated with hypoglycaemia if patients are well nourished. For similar reasons, in patients with depleted liver glycogen stores, glucagon (which acts via glycogenolysis) will be ineffective in reversing hypoglycaemia.

Hypoglycaemia associated seizure

As the brain is dependent on glucose as the main substrate for normal function, neuroglycopenia can result in abnormal cognition. Continued decline in brain glucose delivery can result in increasingly profound changes in cerebral activity eventually leading to seizures. This led to the use of insulin-induced neuroglycopenic seizure as shock therapy in the treatment of schizophrenia.[8] Electroencephalographic (EEG) changes occur commonly during hypoglycaemia,[4] but fortunately seizures related to hypoglycaemia are rare.

Seizures in a patient with diabetes can pose a diagnostic challenge, as it may be difficult to measure concomitant plasma glucose. EEG changes during hypoglycaemia are non-specific and similar changes occur with several other conditions. Clinical clues as to the aetiology are important in making the correct diagnosis. Timing of fits, relationship to meals/ fasting/ exercise/ sleep as well as the type of insulin regime may be helpful indicators that the seizures may be related to hypoglycaemia.

The progression of new technology has developed novel methods of assessing hypoglycaemia. Glucose sensing is now available. It allows the identification of glycaemic excursions overnight which has been difficult until now. The use of this new technology has aided investigation of possible hypoglycaemia induced seizures by providing a continuous monitoring of interstitial glucose (which may relate to brain glucose).

Continuous Glucose Monitoring System (CGMS) (Figure 2)

The *Medtronic* Continuous Glucose Monitoring System (CGMS) is designed to continuously monitor subcutaneous glucose levels in tissue fluid. The sensor is inserted under the skin of the anterior abdominal wall and interstitial glucose levels are "sensed" every 10 seconds and

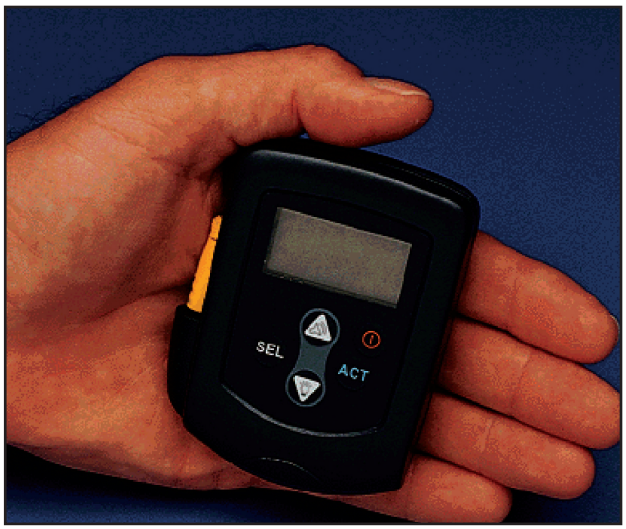


Figure 2. *Medtronic* Glucose Sensor

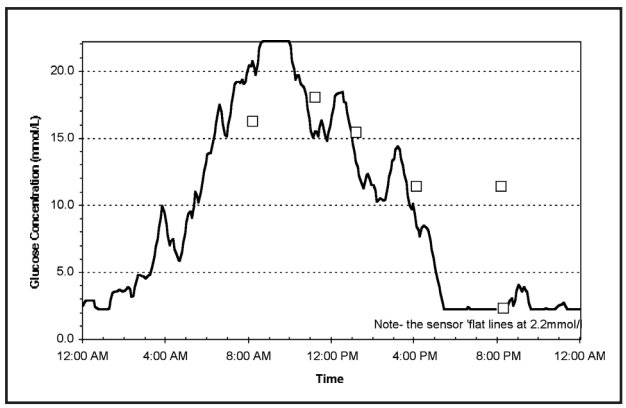


Figure 3. CGMS profile of a patient on twice-daily insulin with hypoglycaemia unawareness

averaged over 5 minutes for a total of 288 measurements each day. Individual glucose sensors are worn for a maximum of 3 days and calibrated on the basis of 4 or more capillary glucose readings each day. The system is designed to provide continuous measurements of glucose values in the range 2.2-22 mmol/l. Data are stored in the monitor together with event markers for meals, insulin injections, exercise and symptoms suggestive of hypoglycaemia. In addition, patients keep written diaries of all "events" during the sensor period. After 3 days the data are downloaded to an external computer where it can be viewed in a graphical format and as numerical data with summary statistics.

The CGMS (Figure 2,3) is a useful aid in dealing with suspected hypoglycaemia in diabetic patients. It does not have a routine role in the investigation of non-diabetic individuals suspected of suffering from hypoglycaemia.

Factitious hypoglycaemia

Factitious hypoglycaemia is characterised by the use of a hypoglycaemic agent (usually insulin or a sulphonylurea)

through surreptitious self-administration, malicious administration to others or innocent compliance to wrongly prescribed medication. Suspected factitious hypoglycaemia should be relatively easy to confirm and investigate. Factitious hypoglycaemia from insulin or sulphonylureas is usually seen in patients with diabetes, their relatives or friends or in health care professionals.[9]

Driving and hypoglycaemia[10]

Insulin-treated drivers may retain their licence (for group 1 entitlement), and are supplied with 1, 2 or 3 year licences. Patients on temporary insulin treatment, e.g. post myocardial infarction, may retain their licence but must stop driving if experiencing disabling hypoglycaemia. The DVLA must be notified if treatment with insulin continues for longer than 3 months. Patients using oral hypoglycaemic agents will be able to retain the driving licence until the age of 70 years, as long as there are no relevant other disabilities (such as diabetic eye disease) or until insulin treatment is required. Patients recently converted to insulin (after 1/4/1991) are barred from the group 2 licence (heavy goods vehicles/ public service vehicles).

Diabetic drivers must be able to recognise symptoms of hypoglycaemia. Patients with impaired awareness of hypoglycaemia (see above) must be advised to stop driving and inform the DVLA. Driving may resume if awareness symptoms return with support from the GP or consultant.

Patients with frequent hypoglycaemic episodes likely to impair driving must also cease driving until satisfactory control is re-established and supportive evidence is provided by the appropriate health care professional.

Management

The management of hypoglycaemia depends upon the correct diagnosis. Following an algorhythm (Figure 4) with a logical approach can be helpful so as not to miss certain scenarios such as sulphonylurea poisoning. Hypoglycaemia is still commonly misdiagnosed, resulting in wastage of resources and un-necessary patient anxiety. In one tertiary referral centre, 57% of patients referred for further investigation of hypoglycaemia never had a plasma glucose of less than 3mmol/l.[11]

Management of the hypoglycaemia then depends upon the nature of the underlying condition. Diabetes-related hypoglycaemia requires investigation of the risk factors, with special regard to those who are hypoglycaemia unaware. Even when hypoglycaemia has been relatively easy to investigate, early referral to the diabetes team is important because of the increased likelihood of future hypoglycaemic episodes.

Management of non-diabetic hypoglycaemia often depends on the health of the individual. In the sick, hospitalised patient where liver failure, renal failure, sepsis or an underlying tumour may be causing hypoglycaemia, further investigation is unnecessary and simply treating the hypoglycaemia is all that is required. Unfortunately, when hypoglycaemia is associated with these conditions, the mortality is high. At the extremes of age, the presence of renal impairment and polypharmacy increases the

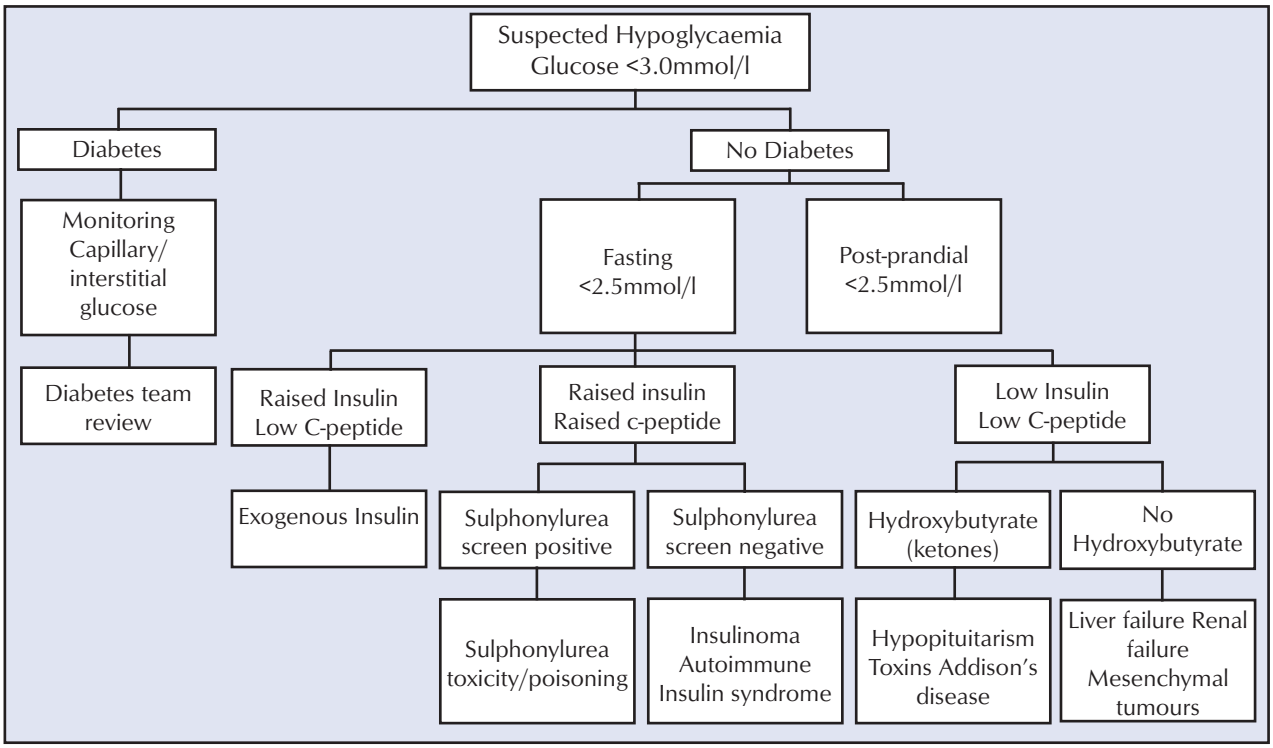


Figure 4. Algorhythm for investigation and diagnosis of acute adult hypoglycaemia

possibility of hypoglycaemia, and careful evaluation of the drug history is essential prior to embarking on extensive investigations.

In the well patient, episodes of suspected hypoglycaemia need to be related to the fasting or post-prandial state. Symptoms occurring 2-4 hours after meals are defined as post-prandial, whilst symptoms after more than 5 hours are defined as fasting. True post-prandial hypoglycaemia is rare, but frequently misdiagnosed because neuroglycopenic symptoms are not linked to a concurrently low plasma glucose.

Fasting hypoglycaemia in a healthy-looking patient is usually either factitious or caused by an insulinoma. If an insulinoma is suspected, a variety of localisation procedures are useful prior to surgery. These include ultrasound (including per-operative), CT/ MRI scanning. Specialist referral for confirmation and excision is recommended.

In patients with malignant tumours and ectopic insulin or IGF-2 secretion, the risk of hypoglycaemia can be reduced by the use of steroids. Chemotherapy (e.g. Streptozotocin) may also have a role.

Conclusions

Hypoglycaemia is common. Elucidation of the underlying cause is important with regards to the most appropriate future management. There are many potential pitfalls in making the diagnosis. These include the failure to document true biochemical hypoglycaemia (plasma glucose < 2.5mmol/l), missing subtle neuroglycopenic symptoms, mismatching of symptoms and low plasma glucose, omitting a thorough drug history and failure to measure sulphonylurea concentration.

Once hypoglycaemia has been appropriately diagnosed, investigation of the underlying cause is vital to prevent further episodes or in some instances provide a cure.

References

1. Arem R. Hypoglycaemia associated with renal failure. *Endocrinol Metab Clin North Am,* 1989. **18 (1)**: 103-21.
2. Cryer PE, Gerich JE. Glucose counter-regulation, hypoglycaemia and intensive insulin therapy in diabetes mellitus. *NEJM,* 1985. **313**: 232-41.
3. Cryer PE. Glucose counter-regulation: the physiological mechanisms that prevent or correct hypoglycaemia. *Hypoglcaemia and Diabetes. Edward Arnold (London),* 1993. **3**: 34-55.
4. Tallroth G, Lindgren M, Stenberg G., *et al*. Neurophysiological changes during insulin-induced hypoglycaemia and in the recovery period following glucose infusion in type 1 diabetes mellitus and in normal man. *Diabetologia*, 1990. **33**: 319-23.
5. Davidson MB, Peters AL. An overview of metformin in the treatment of type 2 diabetes mellitus. *Am J Med*, 1997. **102 (1)**: 99-110.
6. Burden ML, Jarvis J, Dromgoode P., *et al*. Precision of glucose meters in the hypoglycaemic and normoglycaemic range. *Practical Diabetes International,* 1998. **15**: 133-4.
7. Hirshberg B, Livi A, Bartlett D L., *et al*. Forty-eight hour fast: the diagnostic test for insulinoma. *J Clin Endocrinol Metab,* 2000. **85**: 322-6.
8. Hoagland H, Rubin MA, Cameron DE. The electroencephalogram of schizophrenics during insulin hypoglycaemia and recovery. *Am J Physiol,* 1937. **120**: 559-70.
9. Service FJ. Facticial hypoglycaemia. *The Endocrinologist,* 1992. **2**: 173-176.
10. www.dvla.gov.uk
11. Marks V, Teale JD. Investigation of hypoglycaemia. *Clin Endocrinol (Oxf),* 1996. **44**: 133-6.