Recurrent hypoglycaemia with reduced recognition

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The immediate management and investigation of an acute endocrine presentation in general practice is discussed in this section. It is inspired by, but not based on, a real patient situation.

ENDOCRINOLOGY TODAY 2017; 6(4): 36-40

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Mark is a 32-year-old builder with type 1 diabetes. He presents to you after an episode where he became confused and incoherent on the work site. A colleague, aware of his history of diabetes, assisted him in drinking some lemonade and called an ambulance. On arrival, ambulance officers recorded a blood glucose level (BGL) of 2.5 mmol/L, improving to 4.0 mmol/L after a few minutes. Mark declined being taken to hospital. Mark believes he knows how to manage his diabetes and will not let an incident like this happen again. He is keen to be given medical clearance to return to work.

What key management points will you revise with Mark?

Answer: Hypoglycaemia mortality accounts for 4 to 10% of deaths in patients with type 1 diabetes.[1] People with diabetes need to be educated about the seriousness of hypoglycaemia and its risks, including impaired performance, injury, brain damage and death. GPs can appropriately help patients to understand the signs and symptoms associated with a low BGL (Box 1) and the common precipitants of a hypoglycaemic episode (Box 2).

People with diabetes may have an altered threshold to activate a sympathetic response and experience hypoglycaemic symptoms at a higher BGL than people without diabetes if their mean glucose is high. They may also develop symptoms when their BGL falls rapidly, even at higher absolute levels of glucose.[2]

Management of hypoglycaemia starts with prevention. In people whose work requires high-level physical activity, BGLs should be monitored and in a safe range (e.g. >5 mmol/L) before starting work. BGLs should be checked every two hours and maintained above 5 mmol/L during high-risk activities such as operating machinery or driving. Access to a hypoglycaemia kit (food/drink containing fast-acting carbohydrate and a glucagon pen) is vital. Family members and work colleagues can be trained to recognise hypoglycaemia and administer glucagon. Work should be ceased immediately and BGL checked at the first suspicion of hypoglycaemia, and action should be taken to treat mild hypoglycaemia as described in Box 3.

Mark reports that he administered his usual insulin dose with his usual breakfast. The hypoglycaemic episode occurred around 11 am. He had been physically active on the work site all morning and he thinks he must have 'overdone it'. He has been well recently and had not taken any other medications. He drank a couple of beers yesterday evening.

How would you further investigate?

Answer: Further examination and investigation should include looking for lipohypertrophy at injection sites. A record of BGLs checked consistently before and two hours after meals will provide a good idea of general diabetes control, indicate if prandial insulin doses are appropriate and identify times when hypoglycaemia is most likely. Although the general glycated

1. Signs and symptoms of hypoglycaemia

- Blood glucose level less than 4.0 mmol/L with associated symptoms
- Symptoms fall into two main categories:
  - sympathetic adrenergic (tremor, palpitation, anxiety, dizziness, perspiration); typically occur first
  - neuroglycopenic (behavioural changes, inattention, confusion, focal neurological deficits [infrequently], and seizure and coma [if serum glucose concentration is critically low])

2. Common precipitants of a hypoglycaemic episode

- Reduced dietary carbohydrate intake
- Increased physical activity. Hypoglycaemia can occur during activity or may be delayed by several hours, depending on the duration and intensity of the exercise
- Inappropriate timing or dosing of glucose-lowering medication in relation to food intake. Rapid-acting insulin analogues should be administered no more than 15 minutes before a meal, at a dose appropriate for the amount of carbohydrate consumed
- Erratic absorption of insulin due to incorrect injection technique (e.g. injection into muscle or site of fat hypertrophy)
- Impaired renal elimination of insulin/other diabetes medication
- Alcohol ingestion (acutely increases insulin sensitivity[3])
- Using too high a dose of rapid-acting insulin (overcorrection) or administering correction boluses at too frequent intervals (insulin stacking) to correct for high blood glucose levels

haemoglobin (HbA_{1c}) target for patients with diabetes is below 7% or 53mmol/mol, a level well below this target (e.g. below 6% or 42mmol/mol) would increase suspicion of frequent hypoglycaemia.

Kidney and liver dysfunction, which can impair insulin excretion or the counterregulatory response to hypoglycaemia, should be excluded. Autoimmune diseases associated with type 1 diabetes (coeliac disease, Addison's disease, autoimmune thyroid disease) may also increase hypoglycaemia risk and screening should be considered. Ensure up-to-date screening for macro- and microvascular complications of diabetes, particularly retinopathy and peripheral and autonomic neuropathy, which may impact on workplace safety.

Intoxication impairs an individual's ability to recognise hypoglycaemia and respond appropriately. People with diabetes should avoid excessive alcohol consumption and consume adequate carbohydrates before drinking.

Mark was diagnosed with type 1 diabetes at 4 years of age and was managed by a regional paediatric service. At 18 years of age, he moved to the city. He has seen various GPs since, but his only contact with an adult diabetes service was through a certified diabetes educator (CDE) during a visit to the emergency department for a similar hypoglycaemic episode last year.

Mark takes rapid-acting insulin with meals and long-acting insulin at night. He does not count carbohydrate serves, dose according to carbohydrate intake or use a specific formula to calculate correction doses. Although he occasionally checks his BGL before meals, he says he can usually feel when he is high or low and will adjust the insulin dose without doing a fingerprick test. He does not keep a written record of BGLs and did not bring his glucometer to today's visit.

Mark reports a few episodes of diabetic ketoacidosis in his youth, but not in the past 10 years since becoming consistent with insulin injections. His last HbA_{1c} level was 7.1% (54.1mmol/mol). He has mild nonproliferative diabetic retinopathy and previous evidence of albuminuria, with normal estimated glomerular filtration rate.

Mark's blood pressure is 135/80mmHg, with no postural drop. His body mass index is 23kg/m^2. He has good sensation in his feet and intact pedal pulses. He has two firm lumps on either side of his umbilicus where he has been injecting insulin. Examination of other systems is unremarkable.

You advise Mark that you need more information to make a full assessment and allow him to return to work after two days, on the condition that he checks his BGL before and after every meal. You advise him not to drive or perform high-risk activities until further assessment. You refer Mark to a CDE, dietitian and endocrinologist and arrange to see him in a week's time. You advise him to avoid injecting into the lumpy areas and to rotate his injection sites widely over the abdomen. You arrange for HbA_{1c}, thyroid stimulating hormone and morning cortisol levels and coeliac serology to be tested.

3. Self-treatment of mild hypoglycaemia

- Consume 15g of fast-acting carbohydrate (e.g. six or seven jelly beans, half a glass of fruit juice, or half a can of nondiet soft drink)
- Repeat BGL in 15 minutes and if still below 4mmol/L, follow with another 15 g of carbohydrate
- If BGL >4mmol/L, eat a snack or meal consisting of longer-acting carbohydrate (e.g. a slice of bread, a glass of milk or a piece of fruit)
- Do not resume work until the hypoglycaemia is adequately treated
- Consider the cause of the hypoglycaemia, and adjust insulin dose in future as required

Abbreviation: BGL = blood glucose level.

What is lipohypertrophy and why is it important?

Answer: As insulin has anabolic properties, repeated injection into the same sites can result in thickening and hypertrophy of subcutaneous tissue (lipohypertrophy). Detection requires both visualisation and palpation of injection sites. Lipohypertrophy can cause inconsistent and unreliable absorption of insulin, either by delaying or enhancing absorption, resulting in greater BGL variability.

Lipohypertrophy can be prevented by rotating injection sites and avoiding reuse of needles. Affected areas should not be injected until it resolves, which takes months to years. If unaffected areas are used, insulin requirements may decrease by up to 50%. Frequent BGL monitoring is advised.

What are the recommendations for patients with hypoglycaemia who drive?

Answer: In Australia, people with diabetes on glucose-lowering medications are required to notify their driver licensing authority (DLA). With regard to hypoglycaemia, private vehicle drivers on insulin are eligible for a conditional license, subject to at least two-yearly review by the treating doctor if: i) there is no recent history of severe hypoglycaemia; ii) the treatment schedule minimises the risk of hypoglycaemia; iii) the person experiences early

warning symptoms of hypoglycaemia or has a documented management plan for lack of early warning symptoms; iv) there are no end-organ effects that may affect driving. If these criteria are not met, a conditional license may be granted on the advice of a diabetes specialist, with ongoing regular review. Commercial vehicle drivers on insulin may be granted a conditional license, subject to annual review, based on assessment by a diabetes specialist.

Severe hypoglycaemia is defined as a hypoglycaemic event where the person is unable to treat themselves and requires the assistance of a third party. After an episode of severe hypoglycaemia, a person should not resume driving for a minimum of six weeks and until specialist approval, based on documented BGLs.

From the healthcare provider's perspective, patients should be advised of their obligation to report changes in their fitness to drive to the DLA. A doctor may report directly to the DLA if the patient is unable to appreciate the impact of their condition and continues to drive against medical advice, possibly endangering public safety. The doctor is protected from liability, even if reporting is made without patient consent. In South Australia and the Northern Territory, reporting by the healthcare professional is mandatory if a patient is considered unfit to drive. It is the doctor's duty to notify the relevant authority. It is preferable in all instances for patient consent to be obtained, and necessary for the doctor to inform the patient of their intention to report.

Further information is available in the Austroads Assessing fitness to drive document (www.austroads.com.au/drivers-vehicles/assessing-fitness-to-drive).

Mark returns after a week. His HbA_{1c} level is 6.5% (47 mmol/mol) and other test results are unremarkable. He has checked his BGL regularly and reports no hypoglycaemic episodes. On review of his record book and glucometer, however, you note that his BGLs range between 2.8 and 14.0 mmol/L. There is no predictable pattern, with low readings occurring both pre- and postprandially. Mark expresses surprise that his BGLs were so low, but does not consider these to be 'hypos', as he did not experience any symptoms. He says that he used to experience symptoms of hypoglycaemia when his BGL was below 4.0 mmol/L.

How does reduced awareness of hypoglycaemia develop?

Answer: Under normal circumstances, sympathetic symptoms act as warning signs, allowing the person to correct hypoglycaemia before neuroglycopenic symptoms ensue. In people with a long duration of diabetes and recurrent hypoglycaemia, the adrenergic response can be blunted. Recurrent hypoglycaemia lowers the glucose threshold at which adrenergic discharge occurs.[1] A person may then have no symptoms of hypoglycaemia until their BGL is critically low, and therefore has developed reduced awareness of hypoglycaemia (or hypoglycaemia unawareness). If the first manifestation of hypoglycaemia is neuroglycopenia, serious sequelae such as accidents caused by altered mentation, seizure, permanent brain damage and death can occur.

Adequate awareness of hypoglycaemia may be restored by strict avoidance of hypoglycaemia for at least six weeks. This may necessitate resetting blood glucose targets to a higher range and tolerating a greater degree of hyperglycaemia for some weeks. Not all patients will regain full awareness.

Mark sees the CDE, who reviews his insulin injection technique. Mark is taking short-acting insulin appropriately just before eating. Although he mostly uses the abdomen, he occasionally injects into the upper arm while at work. He is using 12 mm needles. His injection technique is otherwise accurate.

How do insulin injection site and needle length influence clinical outcomes?

Answer: Intramuscular (IM) injection of insulin can result in undesirably rapid absorption, increasing the risk of hypoglycaemia. Insulin absorption is most reliable when injected subcutaneously into the abdomen or upper buttock.

Injection into the thigh and arm increases the risk of IM insulin injection because of the reduced depth of the subcutis. This risk is even higher in slim patients (up to 58% in men with a body mass index less than 25 kg/m^2).[4] Although the risk of IM insulin injection into the arm can be reduced with a lifted skin fold, it is extremely difficult to do properly by self-administration. Further, insulin may be absorbed too rapidly from these sites during exercise, as activity stimulates greater blood flow to these more vascularised areas.

Optimal needle length provides the most reliable insulin delivery into the subcutaneous space with the least discomfort. In Australia, pen and syringe needles vary from 4 mm to 12.7 mm and 8 mm to 13 mm, respectively. Needles less than 8 mm are now recommended, as shorter needles are safe and better tolerated with no compromise in glycaemic control and insulin delivery.[5] In obese patients, 4 mm needles are also as efficacious and safe. If needles of 8 mm or longer are used, injection should be performed at a 45 degree angle to reduce risk of IM insulin injection.

Mark describes inconsistent carbohydrate intake, with anywhere between 0 and 5 serves per meal, with no accompanying change in his short-acting insulin dose. He sees the dietitian for further information about carbohydrate counting and flexible insulin dosing. He has not seen a dietitian since his teenage years, when he decided that carbohydrate counting was too troublesome. Mark appreciates that flexible insulin dosing may be more suited to his lifestyle now and allow more stable BGL control.

How does flexible insulin dosing work?

Answer: Traditionally, doses of short or rapid-acting prandial insulin are fixed by the healthcare professional, requiring the person with diabetes to consume consistent amounts of carbohydrate. Many individuals find this difficult, as appetite and daily activities vary. In competent individuals, flexible insulin dosing allows insulin titration according to carbohydrate consumption. Studies indicate that flexible insulin dosing can achieve better glycaemic control and less hypoglycaemia in the right population.[6]

Flexible insulin dosing consists of two components: the insulin-to-carbohydrate (IC) ratio and the insulin sensitivity factor. The IC ratio can be expressed as the amount of carbohydrate in grams that is covered by one unit of rapid-acting insulin, or alternatively, the number of insulin units required to cover for one serve (15g) of carbohydrate. For example, a patient with an IC ratio of one unit per 15g requires three units of insulin for three slices of bread (45g). The insulin sensitivity or correction factor determines the amount of extra insulin needed to return a high BGL to normal after two to three hours. An insulin sensitivity factor of two means that one unit of insulin will lower the BGL by 2mmol/L. Both the IC ratio and insulin sensitivity factor are generally determined after assessment by an endocrinologist.

Flexible insulin dosing requires accurate carbohydrate counting skills and regular premeal BGL checking. Patients should be referred to a dietitian and demonstrate competency in carbohydrate counting before commencement. There are several smart-phone applications that can help assess the amount of carbohydrate content in different foods, and 'bolus advice meters' into which the IC ratio and insulin sensitivity factor can be programmed, allowing the glucose meter to assist with insulin dose calculation.

You explain the seriousness of the low BGLs to Mark. He is keen to better manage his diabetes. Mark switches to 6mm needles and starts injecting only into the areas of his abdomen not affected by lipohypertrophy.

He learns carbohydrate counting and sees an endocrinologist who recommends switching the dosing schedule to 2 units of rapid-acting insulin per carbohydrate serve, with a correction dose of one unit for every 2mmol/L above a target of 7mmol/L. He is advised to keep his BGL above 5 to 6mmol/L for the next six weeks until his awareness of hypoglycaemia improves. He acquires a bolus advice meter to assist with mathematical calculation.

Mark returns after two weeks. He is still having some low blood glucose readings, particularly after unplanned extra physical activity at work. He has been monitoring his BGLs regularly, but complains that he feels 'like a pincushion' with the frequency of testing and it is troublesome to clean his hands for testing on the work site.

What other options are there for people who find fingerprick testing burdensome?

Answer: Two types of systems currently provide frequently measured glucose data without the need for frequent finger pricking.

The FreeStyle Libre Flash Glucose Monitoring System (Abbott) comprises a sensor and a reader. The sensor is a small (35mm x 5mm) patch, applied on the back of the upper arm via a thin flexible sterile fibre. The sensor is designed to stay on the body for up to 14 days and is water resistant. The wearer scans the reader, of similar size to a glucometer, over the sensor, delivering the value of the interstitial glucose to the reader within a second, even through clothing. The reader displays current glucose values in real time, along with a graph of the past eight hours, and an arrow indicating if glucose is rising, falling or stable. It stores up to 90 days of downloadable glucose data.

A continuous glucose monitor (CGM) is a small wearable device which measures interstitial glucose every five minutes, notifying the wearer of current glucose level and recent glucose trend. Preset alarms are triggered when the glucose level goes beyond target range. Glucose readings are transmitted to a receiving device, such as an insulin pump or smart phone. There are several CGM systems available in Australia, including the Dexcom G5 and Medtronic Guardian Connect (which transmit data to a smart phone or other display device) and the Medtronic Minimed 640G.

These systems measure interstitial fluid glucose instead of capillary blood glucose, measured by traditional fingerprick testing. Interstitial fluid glucose lags about five to 10 minutes behind changes in BGL, but most of the time this lag is unlikely to affect day-to-day diabetes care decisions.[7] Out-of-range readings should be verified by fingerprick before taking action.

4. Practice points

- In response to hypoglycaemia, sympathetic symptoms generally occur before neuroglycopenic signs, but may be diminished in the case of reduced hypoglycaemia awareness.
- Restoring hypoglycaemia awareness requires strict avoidance of hypoglycaemia for at least 6 weeks.
- Injection technique, needle size and injection site should be reviewed in anyone with unexplained hypoglycaemia, checking particularly for lipohypertrophy or risk of intramuscular injection.
- Special consideration is required for individuals who drive or perform high risk activities.
- New technologies, including flash or continuous glucose monitoring, and insulin pump therapy can be useful in improving glycaemic control and decreasing hypoglycaemia.

Mark starts using a flash glucose monitoring system and finds it particularly useful at work. The sensor also identifies that he is having low BGLs overnight after a heavy work day or a few more drinks on a Friday night. Mark now consumes extra carbohydrates before bed if he has had a hard day. His wife likes the reassurance of being able to scan his glucose level if she is concerned while he is asleep.

How do you manage patients with recurrent severe hypoglycaemia with impaired awareness despite intensive standard management?

Answer: Insulin pumps, which are small portable electronic devices that deliver a continuous subcutaneous insulin infusion at finely titratable hourly rates via an abdominal cannula, may offer better glycaemic control with fewer hypoglycaemic episodes and reduction in glycaemic variability.[8] Studies have shown sustained reduction in the rate of severe hypoglycaemia (from 138 to 22 events per 100 patient-years) without deterioration in HbA_{1c} level in people switching from multiple daily injections to pump therapy.[9] Some CGM systems now have the ability to communicate to pumps and suspend insulin delivery at a predetermined glucose level, providing a safety mechanism, especially for people with problematic overnight hypoglycaemia and unawareness. Some pumps can also recommence insulin delivery after the interstitial fluid glucose level has returned to a predetermined safe level.

Patients with recurrent severe hypoglycaemia and documented unawareness when BGL is below 3 mmol/L, despite optimisation of insulin therapy, can be considered for islet cell transplantation. Standard medical inclusion criteria are type 1 diabetes for five years or more, age above 18 years, creatinine clearance of more than 75 mL/min/1.73m^2, serum creatinine level less than 130 mcmol/L, 24-hour urine protein estimation less than 300 mg/day, and weight ideally less than 80 kg.[10] Islet transplantation can restore hypoglycaemic awareness in most patients for two years or more after transplantation, even if insulin independence is not maintained.[11] Efficacy may wane over time and benefits must be weighed against the side effects of chronic immunosuppressive therapy.

Various pharmacotherapies such as beta-agonists, caffeine and theophylline derivatives, selective serotonin reuptake inhibitors and naloxone have been trialled with varying degrees of success in improving hypoglycaemic awareness, but further research is required before clinical implementation. Some practice points on management of patients with recurrent hypoglycaemia with reduced recognition are given in Box 4.

Outcome: Mark's diabetes control improves with regular monitoring and insulin adjustment. He is able to resume normal duties at work and you certify him fit to drive, with yearly licence review. ET

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COMPETING INTERESTS: None.