Lack of hypoglycaemia awareness in diabetes

Why it matters in clinical care

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In people with diabetes and hypoglycaemia unawareness the counter-regulatory hormone response to hypoglycaemia is impaired and the early adrenergic signs of hypoglycaemia are absent. This article describes the diagnosis, causes, clinical impact and complications of hypoglycaemia unawareness and discusses management strategies.

Key points

- **In patients with diabetes and hypoglycaemia unawareness the adrenergic response to hypoglycaemia (anxiety, trembling and sweatiness) may be absent and the first symptoms may relate to neuroglycopenia (poor concentration, headache, slurred speech, emotional lability, coma and seizures).**
- **Patients with type 1 or type 2 diabetes can have hypoglycaemia unawareness and are at increased risk of severe hypoglycaemia.**
- **Hypoglycaemia unawareness is more common in people with diabetes with frequent antecedent hypoglycaemia and those with a longer duration of diabetes.**
- **Hypoglycaemia awareness can be improved by avoidance of hypoglycaemia over several weeks or months.**

ENDOCRINOLOGY TODAY 2014; 3(5): 27-30

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Most Australians with diabetes do not achieve optimal glycaemic control and fear of hypoglycaemia is a major contributing factor. The glycaemic management of diabetes requires balancing the patient's circulating insulin levels with their insulin requirements, which are impacted by their insulin sensitivity, glycaemia drug type and dosage, food intake, physical activity, stress and any intercurrent illness.

Current therapeutic tools for diabetes have limitations and do not always allow for a precise match between circulating insulin and an individual's requirements. An absolute or relative deficit in insulin will result in elevated blood glucose levels (BGLs). In people with type 1 diabetes, if this deficit in insulin is extreme, diabetic ketoacidosis may result. Conversely, an excess of insulin in patients with type 1 or type 2 diabetes can result in hypoglycaemia. Hypoglycaemia may particularly impact people with type 1 diabetes and may also be a barrier to the initiation and titration of insulin in patients with type 2 diabetes.[1] This article describes hypoglycaemia and reduced hypoglycaemia awareness (which is also sometimes referred to as hypoglycaemia unawareness), detailing its diagnosis, causes, clinical impact and complications, and discusses management strategies.

Hypoglycaemia

Hypoglycaemia is conventionally defined as a low BGL, usually below 4.0 mmol/L. Hypoglycaemia is normally associated with two broad symptom categories, as described below.

Adrenergic symptoms: These include anxiety, trembling, sweating and palpitations, and are due to catecholamine release and activation of the sympathetic nervous system. The adrenergic response usually alerts the individual to the presence of hypoglycaemia. In addition, the adrenergic hormones and associated sympathetic activation form part of the counter-regulatory response that raises circulating BGLs. The level of glucose that produces symptoms of hypoglycaemia varies from person to person and may vary for the same person under different circumstances. Adrenergic symptoms usually commence at glucose levels at the upper end of the hypoglycaemic range (4.0 to 3.6 mmol/L). In some cases, adrenergic symptoms can commence even when BGLs are above 4.0 mmol/L as the onset and intensity of adrenergic symptoms also correlate with antecedent glycaemia and the developing rate of

hypoglycaemia, being most marked when it is acute in onset in people with chronically elevated glucose levels. Conversely, the adrenergic symptoms are usually less intense if the person is asleep, has recently exercised, has had antecedent tight glycaemic control or has had a recent episode of severe hypoglycaemia.[2]

Neuroglycopenic symptoms: These manifest when the brain is deprived of glucose, and include poor concentration, impaired judgement, headache, inco-ordination, slurred speech, emotional lability, coma and seizures. Neuroglycopenic symptoms usually commence when BGLs are between 2.8 and 3.0 mmol/L, and increase in severity with progressive reductions in circulating glucose levels. Although most organs can compensate for reduced BGLs, the brain is particularly vulnerable. This is because the brain is dependent on glucose as it is unable to synthesise it and has limited glycogen stores, sufficient for only a few minutes of the brain's requirements.[2]

Adrenergic symptoms usually manifest themselves before neuroglycopenic symptoms. The early warning adrenergic symptoms provide a window of opportunity allowing the individual to eat carbohydrates and address the situation before BGLs drop below a threshold whereby neurological impairment becomes severe enough to preclude the individual from taking remedial action. With severe hypoglycaemia, there is marked impairment in conscious state or a loss of consciousness that may be associated with a seizure, a cardiac arrhythmia or death if left untreated. Severe hypoglycaemia is a medical emergency. Recovery from a severe hypoglycaemic event, by definition, requires assistance by another person, usually with administration of a glucagon injection or intravenous glucose.

Factors predisposing to hypoglycaemia

People with type 1 diabetes are at greatest risk of hypoglycaemia. This relates to an absence of endogenous insulin secretion by pancreatic islet cells, therefore mandating the use of exogenous subcutaneous insulin that bypasses physiological feedback mechanisms. Insulin secretion by the beta-cells in the pancreas also acts in a paracrine manner to enhance the glucagon secretory response to hypoglycaemia. The defect in beta-cell function therefore impacts adversely on the secretion of glucagon by islet alpha-cells in response to hypoglycaemia. Therefore people with type 1 diabetes, and also those with longstanding type 2 diabetes with minimal residual beta-cell function, are largely dependent on their sympathetic response to mount a counter-regulatory response in the face of hypoglycaemia.

Most people with type 1 diabetes experience mild hypoglycaemia events on average once a week, and a severe hypoglycaemia event on average once per year.[3] A subset of patients with type 1 diabetes is particularly prone to frequent episodes of severe hypoglycaemia.[3,4] Individuals with type 2 diabetes in general are at substantially lower risk of severe hypoglycaemia than those with type 1 diabetes. The overall rate of severe hypoglycaemia in people with type 2 diabetes managed with insulin has been estimated as 10% of that observed in people with type 1 diabetes.[3] In people managed with nonsulfonylurea-based oral therapy this rate would be expected to be significantly lower. However, people with type 2 diabetes of long duration and minimal residual islet cell function who require insulin may be at significant risk, and deaths in patients with type 2 diabetes treated with sulfonylureas following an episode of hypoglycaemia have been reported.

The major risk factor for the development of severe hypoglycaemia is a past history of severe hypoglycaemia. Other contributing factors predisposing to an increased risk of hypoglycaemia in people with diabetes include age, alcohol ingestion, chronic liver disease, delayed gastric emptying, coeliac disease, Addison's disease, thyroid disease, eating disorders, sporadic physical activity, renal impairment and coadministered medications (e.g. beta blockers; see Box 1).[5] As described below, reduced hypoglycaemia awareness also increases the risk of severe hypoglycaemia episodes.

Reduced hypoglycaemia awareness

Hypoglycaemia unawareness refers to hypoglycaemia occurring in a person with diabetes who has reduced or absent warning symptoms of hypoglycaemia. The counter-regulatory hormone response to hypoglycaemia is impaired or lost and the early adrenergic signs of hypoglycaemia are absent. The first signs of hypoglycaemia may be confusion and an altered conscious state.

Although the cause of this condition is unclear and remains the subject of ongoing research, reduced hypoglycaemia awareness is most common in people with diabetes who experience frequent hypoglycaemic events and those with a long duration of diabetes (e.g. >10 years). It may be permanent or reversible. It is estimated that one in three or four people with type 1 diabetes will experience reduced hypoglycaemia awareness at some stage of their life. The adrenergic response to hypoglycaemia is reduced during sleep. Exercise and a recent episode of severe hypoglycaemia increase the likelihood of reduced hypoglycaemia awareness. Although more common in older patients and in those with a longer diabetes duration, reduced hypoglycaemia awareness may occur at any age or diabetes duration. Reduced hypoglycaemia awareness is not restricted to patients managed with insulin but can also occur in people with type 2 diabetes who are taking oral agents that can induce hypoglycaemia, such as sulfonylureas. One survey of over 300 patients with insulin-treated diabetes indicated that 16% had only partial awareness and 7% had complete unawareness of hypoglycaemia.[6] The prevalence of hypoglycaemia unawareness may be under-reported as episodes of hypoglycaemia that are not severe enough to draw attention to the patient may have been unrecognised.

The main clinical methods to identify reduced hypoglycaemia awareness are the presence of one or more of the following, typically occurring repeatedly:

- low BGLs (e.g. below 3.5 mmol/L) with an absence of symptoms of hypoglycaemia
- symptoms of hypoglycaemia but the symptoms are neuroglycopenic symptoms without the usual early warning adrenergic symptoms
- many BGLs in the hypoglycaemic range are documented either on review of a patient's glucose meter upload or in their home blood glucose monitoring record book, without a patient historical report of hypoglycaemia.

1. Is the patient at risk of severe hypoglycaemia?

Patient with diabetes are at risk of severe hypoglycaemia if they:

- are managed with insulin or sulfonylurea
- have experienced a recent episode of severe hypoglycaemia
- have reduced hypoglycaemia awareness
- are elderly or very young
- have a significant alcohol intake
- have irregular food intake/sporadic exercise
- have coexistent medical conditions that increase the risk of hypoglycaemia (e.g. chronic renal disease, chronic liver disease, coeliac disease, thyroid disorders, Addison's disease)
- are taking medications that can influence the counter-regulatory response (e.g. beta blockers).

In practice these features are usually reliable and helpful indicators of reduced hypoglycaemia awareness.

Consequences of reduced hypoglycaemia awareness

Reduced hypoglycaemia awareness places the person at greater risk of recurrent hypoglycaemia. Reduced awareness of hypoglycaemia impairs the ability of the patient to recognise and respond to falling glucose levels and therefore it is also associated with an increased risk of severe hypoglycaemia and its sequelae. It is often also associated with increased fear of hypoglycaemia, reduced quality of life, and the patient deliberately maintaining higher than optimal BGLs, with a resulting increased risk of long-term diabetes complications.[4,7] There are also implications relating to employment and the status of the individual's driving license. If a patient who drives a motor vehicle (or undertakes other safety critical activity) has had a severe hypoglycaemic episode they should be advised not to drive (or undertake the high-risk activity) until cleared to do so by his or her endocrinologist or GP.

Management of reduced hypoglycaemia awareness

To address the problem of hypoglycaemic unawareness, input is required from a patient-centred multidisciplinary team, which usually includes an endocrinologist, diabetes educator, dietitian and (if required) a psychologist and exercise physiologist in conjunction with the patient's GP (see Box 2).

Avoidance and treatment of hypoglycaemia

Hypoglycaemia awareness can be improved by avoidance of hypoglycaemia over several weeks or months. Frequent blood glucose testing and early and appropriate interventions to prevent impending hypoglycaemia are important adjuncts in the restoration of hypoglycaemic awareness. Patients should be advised to promptly treat (with refined carbohydrate intake) all self-monitored BGLs below a certain threshold (such as <4.0 mmol/L), even in the absence of any hypoglycaemia symptoms. In people with hypoglycaemia unawareness, it should be advised that all hypoglycaemic events need to be avoided for approximately two to four weeks to improve awareness of hypoglycaemia. This may require raising the patient's target BGLs.

It is possible for people to learn to identify subtle signs that their BGL is dropping. Blood glucose awareness training is a structured approach for patients aiming to enhance the early recognition of their own hypoglycaemia symptoms.[8] All people taking insulin therapy should be advised to routinely check their glucose readings before driving a car or operating machinery where they (or others) may be at risk. Being 'above 5 to drive' reflects that BGLs should be at least above 5 mmol/L in such circumstances (the reader is referred to the 2011 NHMRC clinical care guidelines in type 1 diabetes for further details).[9]

2. Recognition and management of hypoglycaemia unawareness

Recognition

- Hypoglycaemia occurs without any adrenergic symptoms.
- First symptoms of hypoglycaemia are neuroglycopenic.
- Severe hypoglycaemia occurs with minimal warning.
- Low glucose levels, which are asymptomatic, are documented.

Management

- Input from a patient-centred multidisciplinary team.
- Minimise hypoglycaemia: frequent glucose monitoring, treat hypoglycaemia early even if few or no symptoms, review medication regimens, raise target glucose levels, regular meals, treat contributing co-existing medical conditions.
- Prompt and early treatment of all hypoglycaemia events, including education to recognise early (nonadrenergic) signs of hypoglycaemia.
- Minimise risk of injury (e.g. patient should not drive or undertake safety critical activities with a blood glucose level below 5.0 mmol/L), review work and home environment, use of a medical bracelet, ready availability of appropriate hypoglycaemia treatment food.
- Education of relevant third parties in managing severe hypoglycaemia, including use of glucagon.

However, despite strategies aimed at hypoglycaemia avoidance, hypoglycaemia may still occur. Prompt assessment and treatment of these hypoglycaemic episodes may also assist in restoring, either partially or completely, hypoglycaemia awareness. A glucagon kit should be kept at home and if appropriate at work and the expiration date checked. Family members and friends of people with type 1 or type 2 diabetes with hypoglycaemia unawareness should be educated in the administration of glucagon in the event of severe hypoglycaemia, as well as seeking emergency medical care and dialling 000. Patients with reduced hypoglycaemia awareness should be encouraged to wear a bracelet or carry ID identifying them as having diabetes and also listing the contact phone numbers for the medical team.

Real-time continuous glucose monitoring

Real time continuous glucose monitoring (RT-CGM) may increase the recognition of and reduce hypoglycaemia in people with impaired hypoglycaemia awareness. Glucose levels may be very unpredictable in these patients and strategies such as taking a glucose reading, for example, at 3.00 am would not be practical on a daily basis in the setting of significant day-to-day glycaemic variability.

RT-CGM could potentially be of assistance in the restoration of hypoglycaemic awareness. These devices are minimally invasive and measure interstitial fluid glucose levels in patients on a near-continuous basis. Glucose levels are detected by a fine flexible sensor inserted (by the patient or carer) into subcutaneous fat, usually on the abdomen or buttock. The read-out device displays the current glucose level every two to five minutes, along with the rate and direction of change in the readings as represented by trend arrows. The trend arrows are of particular use because they inform the patient of the rate of change in

the levels of glucose. This information is not available when using a conventional glucose meter using capillary blood derived from a single finger-prick reading. Auditory and/or vibratory alarms are linked to absolute glucose thresholds as well as predicted glucose levels.

RT-CGM, in conjunction with a compatible insulin pump, preferably with a low glucose (insulin delivery) suspend option, incorporated into the insulin delivery device is a potential therapy for patients with recurrent severe hypoglycaemia. This may not always prevent the occurrence of severe hypoglycaemia but can reduce the severity and duration of these events.[10-13] RT-CGM devices at present in Australia are almost solely used for the care of patients with type 1 diabetes. In spite of being cost effective for Australians with type 1 diabetes and hypoglycaemia unawareness,[13] the sensor is currently not reimbursed by either government funding or private insurance, and may impose a significant economic burden on the patient.

Other nonglucose-related hypoglycaemia detectors

Hypoglycaemia is usually associated with an initially subtle behavioural change and also with perspiration, tremor (although these can be reduced in people with reduced hypoglycaemia awareness), a small fall in body temperature, and changes in electrocardiography and electroencephalography. There are some devices that do not quantify glucose levels but which detect changes in perspiration, tremor and body temperature, which have proven useful in some patients with diabetes. There are clinical trials with these devices underway.

Islet cell transplantation

Another possible therapy for patients with type 1 diabetes and particularly debilitating recurrent severe hypoglycaemia is islet cell transplantation and ongoing immunosuppression. In Australia recurrent severe hypoglycaemia, usually in association with reduced hypoglycaemia awareness, which cannot be resolved by other means, is the usual indication for islet cell transplantation in vascular complication-free adults with type 1 diabetes.[14]

Conclusion

As Elliot Joslin said in 1928, 'The effort of diabetes care is great, but the reward is also great, for the prize is life itself'. This is particularly so for our patients with reduced hypoglycaemia awareness, who are as a consequence at high risk of severe hypoglycaemia. Today, we believe that advances in medical knowledge and therapeutic options should improve the quantity and quality of life for people with diabetes and reduced hypoglycaemia awareness who are a particularly vulnerable group. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr O'Neal has received honoraria, travel assistance and research support from Sanofi, Novo Nordisk, Roche Medtronic, Merck and Astra Zeneca. Dr Jenkins has received honoraria, domestic travel assistance and research support from Sanofi, Novo Nordisk, Eli Lilly, Roche Medtronic, Merck and AMSL.

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