# Game changers in diabetes **Recurrent severe** hypoglycaemia

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Severe hypoglycaemia in people with type 1 diabetes is often recurrent and self-perpetuating, and the cycle needs to be broken for good glycaemic control to be achieved. Causes of hypoglycaemia and the appropriate response to episodes are discussed, illustrated by the case of a young woman who has recently had several hypoglycaemic episodes without warning and from which she needed help to recover.

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Hypoglycaemia is like a 'hard place' across from the 'rock' of hyperglycaemic-related diabetes complications and limits the capacity and will of many people with diabetes, especially those with type 1 disease, to achieve the desired levels of glycaemic control.<sup>1</sup> This article discusses what needs to be done when managing recurrent hypoglycaemia by presenting a case where hypoglycaemia threatened the wellbeing of a young woman with type 1 diabetes.

This is the sixth and final article in a series reviewing clinical situations that indicate a major change in a person's risk of diabetes-related complications and prompt the need for a major review of their diabetes management.

#### CASE SCENARIO: JODIE'S TYPE 1 DIABETES

Jodie is 17 years old and has had type 1 diabetes since the age of 5 years. She has managed her diabetes since she was 10 years old and currently follows a basal-bolus schedule using analogue insulins.

Jodie is in Year 12 and enjoys playing netball and tennis. She adjusts her shortacting insulin dose and her carbohydrate intake and monitors her blood glucose level more closely when her daily routine varies.

Her glycaemic control has been moderate – glycosylated haemoglobin  $(A_{1c})$  ranging between 7.2 and 8.1% (55 and 65 mmol/mol) over the past two years – and she has minor background diabetic retinopathy but no microalbuminuria or neuropathy. She has easily controlled the occasional symptomatic hypoglycaemic episode by eating biscuits, which she carries with her at all times. Jodie has no other medical problems and is not taking any medication. She does not smoke,



take any recreational drugs or drink alcohol (apart from a glass of sparkling wine on her 17th birthday).

Jodie's mother, Elizabeth, has brought Jodie to see you because 'we don't know what's going wrong with Jodie's diabetes'. Over the previous six months, Jodie's blood glucose control has been much less stable, with more frequent HIs and LOs on her meter. Until recently Jodie was managing her blood glucose without major problems but in the past two weeks she has had a series of hypoglycaemic episodes during which it has been difficult for her to increase her blood glucose levels. In the past few days *she has had four severe hypoglycaemic* episodes without warning and has needed help to recover. Fortunately these episodes have happened at home and Jodie's parents have been able to give her a sugar drink and revive her. Everyone is worried that Jodie will have an episode when there is no one around to help.

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#### Figure 1. The vicious cycle of hypoglycaemia. Hypoglycaemic risk depends on the balance between hypoglycaemic tendency and hypoglycaemic protection. Both sleep and exercise increase hypoglycaemic tendency and decrease hypoglycaemic protection. Insufficient carbohydrate or behaviour such as excess hypoglycaemic medication may further increase hypoglycaemic tendency. Any hypoglycaemic episode reduces hypoglycaemic protection and further increases overall hypoglycaemic risk.

#### What should be done to reduce Jodie's short-term risk of severe hypoglycaemia?

#### For Jodie

Unfortunately Jodie is in the 'vicious cycle' that occurs when one hypoglycaemic episode reduces hypoglycaemic symptoms and the physiological counter-regulatory responses.<sup>2</sup> This makes further episodes of hypoglycaemia more likely (Figure 1). This impairment of the counter-regulatory responses also occurs with the autonomic neuropathy associated with diabetic neuropathy, when the person is asleep or exercising and with certain medical conditions and medications.

To break the cycle Jodie should reduce her insulin dose and let her blood glucose level increase for some time to allow her physiology to re-set the threshold for hypoglycaemic symptoms and the counterregulatory responses. These normally start at blood glucose levels of around 3 to 4 mmol/L rather than at a lower level where someone like Jodie is not able to respond. Jodie should reduce both her basal and bolus insulin doses by about 20% to make sure her blood glucose level increases and she does not have further episodes of hypoglycaemia. Reducing insulin doses by 10% may not increase blood glucose level enough.

Jodie is dependent on her blood glucose measurements to monitor her blood glucose levels. It is important to check that the results she is getting accurately reflect her blood glucose levels. She can do this by measuring her fasting blood glucose level immediately before and after a blood sample is taken for laboratory glucose analysis. This will allow her to compare the accuracy of the average of her two measurements compared with the laboratory value, and the variability between her two measurements. The fasting blood glucose level is taken because it is likely to be on the low side and at a level where accuracy is most important.

If Jodie has a driving licence, she should be counselled not to drive. She should also not put herself in a position where she could hurt herself or others if she became confused or unconscious. Ideally she would at all times be in the company of someone who could recognise and respond appropriately if she became hypoglycaemic. She should maintain these precautions until she has been free of hypoglycaemic episodes for at least a week.

#### For Jodie's parents

Jodie's parents should have available a dose of parenteral glucagon and know how to administer it so that they can still help Jodie if she is unable to swallow.

Although sugar (sucrose)-containing foods and drinks usually increase blood glucose levels, glucose-containing foods (powder, gel or tablets) and drinks are more effective and work more quickly. Drinks are preferable and Jodie's parents may like to keep several bottles of glucose-containing soft drink (e.g. Lucozade) in the house so it is immediately available should Jodie need it.

They should also understand that the full response to severe hypoglycaemia includes the following:<sup>3</sup>

- acute resuscitation (with quick-acting carbohydrate, preferably glucose or intramuscular glucagon)
- ensuring that the blood glucose level increases (e.g. to above 6 mmol/L)
- provision of long-acting carbohydrate (e.g. biscuits, sandwiches) to maintain higher blood glucose levels
- ongoing blood glucose monitoring at least hourly over the next six hours
- reducing insulin doses for about two weeks (as discussed above)
- identifying the cause or causes of the episode of severe hypoglycaemia and finding ways to avoid them and subsequent hypoglycaemia.

#### What common causes of severe hypoglycaemia should be sought?

The usual causes of severe hypoglycaemia are related to day-to-day diabetes management – the balance between insulin and exercise versus food and physiological stress:

• mistakes with insulin doses (e.g. giving the basal dose of the bolus insulin if

both are clear solutions – as are Jodie's analogue insulins – and/or they are both in the same type of pen injector)

- skipping meals or having meals containing insufficient carbohydrate (e.g. the classic Aussie barbeque of steak and salad)
- not adjusting insulin doses and/or carbohydrate intake when exercising (particularly prolonged exercise for more than 40 minutes).

As noted, the temporary hypoglycaemic unawareness following hypoglycaemia makes further hypoglycaemic episodes more likely, particularly during the night or with exercise when symptom recognition and physiological counter-regulation are already impaired.

In Jodie's case, this recent bout of severe hypoglycaemia may have been started by glycaemic changes associated with her menstrual cycle, with her blood glucose level increasing with and after the ovulatory oestrogen surge and decreasing abruptly with the fall of oestrogen during and after the period. This is a special problem if cycles are irregular and the woman does not have any premenstrual symptoms to warn her that she needs to take action to prevent her blood glucose level falling. Sometimes the oral contraceptive pill is used to regulate the cycles and to allow prediction of the time the period occurs.

## What are the 'red flags' for high hypoglycaemic risk?

Jodie has two of the five 'red flags' warning of high hypoglycaemic risk in type 1 diabetes: a history of recent hypoglycaemia and hypoglycaemic unawareness (see the box on this page).<sup>2</sup>

Her lifestyle is fairly predictable and she knows how to adjust her carbohydrate intake and insulin doses when exercising or if the timing or type of meal is different from usual. Her glycaemic targets have not been particularly tight: her  $A_{lc}$  has ranged between 7.2 and 8.1% (55 and 65 mmol/mol), 'tight' being below 7% (53 mmol/mol) or, according to some authorities, below 6.5% (48 mmol/mol).<sup>4</sup> She sleeps alone but lives

#### TYPE 1 DIABETES: RED FLAGS FOR HYPOGLYCAEMIA\*

- Past history of hypoglycaemic episode
- Hypoglycaemic unawareness
- Erratic lifestyle
- Tight glycaemic targets
- Sleeping alone

\* In order of importance.

with her parents, who would become aware that something was wrong if she acted irrationally, became unconscious or did not wake up as usual one morning.

Fortunately, Jodie's two 'red flags' can be addressed by titrating her insulin doses so that her blood glucose level increases and she breaks the vicious cycle of hypoglycaemia causing hypoglycaemic unawareness that in turn causes further hypoglycaemia.

#### CASE CONTINUED: CONTROLLED GLYCAEMIA

Jodie and her mother have come to see you a week later. Jodie has not had another severe hypoglycaemic episode and only one minor episode when she 'felt a bit shaky and hungry'. At the time, she noted her blood glucose level was 3.5 mmol/L. The family is very pleased that the vicious cycle has been broken but worried that it might start again.

## What action would be taken if frequent episodes of severe hypoglycaemia continued?

Apart from accelerating the investigation into potential underlying causes for hypoglycaemia and ensuring Jodie's safety, the options in a general practice environment are limited regarding what to do if Jodie continued to have frequent episodes of severe hypoglycaemia without warning despite everyone's best efforts.

Referral to a specialist diabetes centre would ensure a thorough and rapid investigation and access to more complex interventions. These could include continuous glucose monitoring, insulin pump therapy and even consideration of pancreatic islet transplantation.

#### CASE CONTINUED: AUTOIMMUNE CONTRIBUTORS TO HYPOGLYCAEMIA

Jodie's mother, Elizabeth, has asked if Jodie's thyroid may have been partly responsible for the hypoglycaemic episodes 'because thyroid problems run in my family'. Elizabeth and her mother take thyroxine supplements and one of Jodie's maternal aunts was treated with radioactive iodine for an overactive thyroid.

#### What thyroid problem can be associated with hypoglycaemia and is Jodie likely to have it?

Overt or subclinical hypothyroidism (i.e. free thyroxine [T4] and free triiodothyronine [T3] levels in the normal range but a high thyroid stimulating hormone [TSH] level) can cause more frequent and/or more severe hypoglycaemia.

Jodie has one autoimmune problem (type 1 diabetes) and is likely to have others, particularly autoimmune thyroid disease.<sup>5</sup> Thyroid autoantibodies occur in up to 20% of people with type 1 diabetes, with a higher prevalence in females, with increasing age and in those with a diabetes-specific autoantibody (the pancreatic autoantibody anti-glutamic acid decarboxylase). Most of these patients with type 1 diabetes and thyroid autoantibodies remain euthyroid but 2 to 5% develop hypothyroidism and 1 to 2% have hyperthyroidism.

# What other autoimmune conditions associated with type 1 diabetes contribute to hypoglycaemia?

Coeliac disease, hypoadrenalism and hypopituitarism due to hypophysitis are other autoimmune conditions associated with type 1 diabetes that might have contributed to Jodie's hypoglycaemia. Coeliac disease is common, but hypoadrenalism and hypopituitarism due to hypophysitis are uncommon, with the latter extremely uncommon.

#### Coeliac disease

In Australia, about 5% of children and adolescents with type 1 diabetes have coeliac

disease, and its incidence is one per 100 person-years. Coeliac disease is more common in those diagnosed with type 1 diabetes at a young age and in those with autoimmune thyroid disease. The condition is often asymptomatic, but like subclinical hypothyroidism can be associated with an increased risk of hypoglycaemia.

#### Hypoadrenalism

Two polyglandular autoimmune syndromes are associated with type 1 diabetes: type 1 and type 2. Type 1 polyglandular autoimmune syndrome is associated with hypoadrenalism and hypopituitarism. It is extremely rare and will not be discussed further.

Type 2 polyglandular autoimmune syndrome is characterised by hypoadrenalism and is associated with autoimmune thyroid disease, type 1 diabetes, primary hypogonadism and, less commonly, other autoimmune conditions.<sup>5</sup> Both hypoadrenalism and hypopituitarism can cause more frequent and more severe hypoglycaemia, and one of the diagnostic features of primary autoimmune hypoadrenalism (Addison's disease) is hypoglycaemia itself.

### What tests should be arranged for Jodie?

Jodie should be tested for the common autoimmune problems that may be asymptomatic and yet cause hypoglycaemia, as discussed below.<sup>4-6</sup>

#### Autoimmune thyroid disease

Testing for autoimmune thyroid disease would include thyroid function tests, particularly the TSH value (which becomes abnormal first in hypothyroidism). Thyroid autoantibodies, such as thyroid peroxidase (TPO), should also be tested as their presence identifies the risk of future hypothyroidism (a condition for which such patients should be monitored).

#### Coeliac disease

Serological tests for coeliac disease include IgA or IgG endomysial antibody (EMA) and tissue transglutaminase (TTG) antibodies. If IgA tests have negative results, total IgA should be measured because IgA deficiency occurs in about one in 500 people and may give a false negative result.

#### Hypoadrenalism

Hypoadrenalism is less likely in Jodie than coeliac or thyroid disease but should be tested for if there is clinical suspicion (e.g. abnormal pigmentation, hyponatraemia and/or hyperkalaemia). A normal morning cortisol or short Synacthen test suggests normal adrenal function. If in doubt, an endocrinologist may be able to advise.

#### **CASE CONTINUED: TEST RESULTS**

Jodie's test results were:

- free T4, 10 pmol/L (normal range, 10 to 25 pmol/L)
- free T3, 0.7 pmol/L (normal range, 0.5 to 50 pmol/L)
- TSH, 26 mIU/L (normal range, 0.5 to 4.0 mIU/L)
- thyroid antibodies, 300 IU/L (normal range, below 50 IU/L)
- coeliac antibodies, IgG-EMA-negative and anti-TTG-negative.

## How do you interpret Jodie's test results?

Jodie has subclinical hypothyroidism but coeliac disease is very unlikely. The hypothyroidism may well have contributed to her hypoglycaemic vicious cycle. She should start thyroid replacement, and her thyroid function tests should be rechecked some six weeks later to make sure the TSH is not too high or too low (indicating that too little/much T4 is being taken).

Some practitioners would start with the lowest effective thyroxine dose (e.g. 50 µg per day) and increase it if the TSH remains high or increases later. Others would start with the expected full thyroxine dose (1.7  $\mu$ g/kg per day), which reduces the frequency of thyroid function testing and thyroxine dosage adjustment. Dose adjustment to achieve appropriate levels should be made based on the results of thyroid function tests after about five to six weeks to allow steady-state values to be reached. Thyroid function should then be checked at least yearly in case some other medical condition or medication reduces free T4 levels.

#### **CASE CONTINUED: PREGNANY PLANNING**

Eight years later, Jodie (now aged 25 years) and her partner are seeing you because they are planning to have a child.

## What schedule of thyroid function testing should you arrange preconception?

It would be important to check Jodie's thyroid function before conception because subclinical hypothyroidism could reduce her fertility and increase the risk of miscarriage. Thyroid function should also be checked during the pregnancy as thyroxine requirements increase. Untreated hypothyroidism during pregnancy, subclinical or clinical, increases the risk of anaemia, pre-eclamptic toxaemia and placental abruption and, for Jodie, the risk of hypoglycaemia as well.

Thyroid function should also be checked postpartum if the dose of thyroxine was increased during the pregnancy, to ensure that the thyroxine dosage used before pregnancy is still adequate. Although it is unlikely that other autoimmune endocrine disease (especially hypoadrenalism) will occur postpartum because the immunomodulatory effects of pregnancy cease, it is worth remembering the possibility exists. Jodie's baby should also be checked for thyroid disease and a schedule should be established to re-check thyroid function in the future.

#### CONCLUSION

Hypoglycaemia can trigger a 'vicious cycle' where one episode reduces both hypoglycaemic symptoms and counterregulatory responses and makes future episodes likely. To break this cycle, insulin doses should be reduced to allow blood glucose levels to increase and the normal threshold for hypoglycaemic responses to be re-set.

People who have severe hypoglycaemia should understand that the appropriate response includes more than just acute resuscitation. Blood glucose levels should be monitored closely for several hours, insulin doses should be reduced for two weeks or so and the underlying cause of the episode should be identified and avoided in future.

Symptomatic or subclinical autoimmune diseases associated with type 1 diabetes can

be associated with hypoglycaemia and should be tested for (autoimmune thyroid disease, coeliac disease) or considered (hypoadrenalism). Thyroxine replacement in hypothyroidism should be monitored regularly and a testing schedule be established for women planning pregnancy (testing before conception and during and after the pregnancy). The child should also be tested when born and regularly thereafter. MI

#### REFERENCES

1. Phillips P. Hypoglycaemia. Australian Diabetes Educator 2010; 13.

 Phillips P. Hypoglycaemia: a major barrier to glycaemic control. Med Today 2011; 12(8): 55-60.
Australian Diabetes Educators Association (ADEA). Guidelines for sick day management for people with diabetes. Canberra: ADEA; 2009.
Available online at: www.adea.com.au/asset/view\_ document/979316048 (accessed July 2013).

4. Craig ME, Twigg SM, Donoghue KC, et al; for the Australian Type 1 Diabetes Guidelines Expert Advisory Group. National evidence-based clinical care guidelines for type 1 diabetes in children, adolescents and adults. Canberra: Commonwealth of Australia (Australian Government Department of Health and Ageing); 2011.

 Phillips P, Phillips J. Autoimmune conditions associated with type 1 diabetes. Med Today 2012; 13(9): 38-44.

 Karavanaki K, Kakleas K, Paschali E, et al.
Screening for associated autoimmunity in children and adolescents with type 1 diabetes mellitus (T1DM). Horm Res 2009; 71: 201-206.

#### FURTHER READING

Seaquist ER, Anderson J, Childs B, et al. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013; 36: 1384-1395.

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