



The Limiting Factor

The Link Between Hypoglycemia and Diabetes

By Vincent Woo, MD, FRCPC

In this article:

1. How are hypoglycemia and oral antihyperglycemic agents linked?
2. How are hypoglycemia and insulin therapy linked?
3. How is hypoglycemia treated?

Hypoglycemia is an abnormal decrease of sugar in the blood. It often prevents patients from achieving the glycaemic targets needed to impede the development or progression of chronic complications related to diabetes. This article reflects many of the recommendations listed in the Canadian Diabetes Association's (CDA) Clinical Practice Guidelines for the Prevention and Management of Hypoglycemia in Diabetes, published in 2001.¹

Recent guidelines from European health organisations and from the American Association of Endocrinologists have recommended target hemoglobin A1c (HbA1c) levels of $\leq 6.5\%$. Proposed guidelines from the CDA (to be released late 2003) will recommend targeted HbA1c levels of 7%, or even 6%, if this level can be achieved safely. These targets are meant to decrease the rates of diabetic complications, but may also increase rates of hypoglycemia.

What exactly is hypoglycemia?

The symptoms of hypoglycemia vary, but are generally divided into neurogenic (autonomic) and neuroglycopenic symptoms (Table 1). The severity of hypoglycemia is based on the clinical presentation of the hypoglycemic episode. The classifications are:

- **Mild hypoglycemia:** characterised by neurogenic symptoms; patients are able to self-treat.

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Table 1

Neurogenic and neuroglycopenic symptoms of hypoglycemia

Neurogenic symptoms

- Tremulousness
- Palpitations
- Diaphoresis
- Anxiety
- Hunger
- Nausea
- Tingling

Neuroglycopenic symptoms

- Decreased concentration
- Confusion
- Weakness
- Drowsiness
- Visual changes
- Difficulty speaking
- Headache
- Dizziness
- Tiredness

- **Moderate hypoglycemia:** neurogenic and neuroglycopenic symptoms are present; patients are able to self-treat.
- **Severe hypoglycemia:** unconsciousness may occur and plasma glucose levels are usually < 2.8 mmol/L; treatment requires assistance of another person.
- **Hypoglycemic unawareness:** occurs when an individual with diabetes does not feel or recognise the neurogenic symptoms of hypoglycemia, but presents with neuroglycopenic symptoms; the first signs of this type of hypoglycemia will often be confusion or loss of consciousness.

How are hypoglycemia and oral antihyperglycemic agents linked?

Many factors can increase the risk of hypoglycemia, including oral antihyperglycemic drugs (Table 2). In fact, hypoglycemia due to antihyperglycemics is common and estimated to occur in 5% to 20% of patients annually.² Some other drugs which may further increase or predispose individuals to hypoglycemia are listed in Table 3.

Insulin secretagogues, such as sulfonylureas, repaglinide, and nateglinide, may cause hypoglycemia on their own or when combined with other oral agents or insulin.

Long-acting sulfonylureas have been associated with prolonged and severe hypoglycemic episodes and should be avoided in patients who are at risk for hypoglycemia. However, some sulfonylureas have less of an association with hypoglycemia than others. Gliclazide and glimepiride are two sulfonylureas which have been associated with less hypoglycemia than glyburide.³ Repaglinide and nateglinide may be also associated with less hypoglycemia than glyburide if a meal is missed.⁴ The frequency of hypoglycemia

tends to decrease after a few years of treatment with sulfonylureas.

In the elderly, sulfonylureas should be used with caution because the risk of hypoglycemia increases exponentially with age. In

Dr. Woo is an assistant professor, University of Manitoba, and staff, Health Sciences Centre, Winnipeg, Manitoba.

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general, initial doses for this population should be half the usual dose; any dose increases should be done slowly. Hypoglycemia caused by sulfonylureas can be long-lasting and may require hospitalisation.

There are three oral antihyperglycemic agents which, when used alone, have not been associated with significant hypoglycemia. These agents are acarbose, thiazolidinediones, and metformin. They should be considered before insulin secretagogues in patients at a high risk for hypoglycemia. There are some cautions with these drugs. If acarbose is used in combination with insulin or an insulin secretagogue and hypoglycemia should subsequently occur, glucose or dextrose should be used, as sucrose or starch may have delayed absorption. Metformin is contraindicated in the presence of significant renal, cardiac, or hepatic insufficiency, as it may cause lactic acidosis. Thiazolidinediones are contraindicated in patients with Class 3 or 4 heart failure.

Table 2

Factors which can increase the risk of hypoglycemia

- Advanced age
- Renal or liver dysfunction
- Adrenal insufficiency
- Gastrointestinal disease
- Lack of exercise
- Missed meals
- Alcohol consumption
- Oral antihyperglycemic drugs

Table 3

Drugs which may predispose people to hypoglycemia

- High-dose salicylates
- Sulfonamide antibiotics
- Tricyclic antidepressants
- Phenylbutazone
- Warfarin
- Fibrates
- Monoamine oxidase inhibitors
- Pentamidine
- Acetaminophen
- Angiotensin-converting enzyme inhibitors
- Beta blockers



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¹COXIB is the designation conferred by the World Health Organization (WHO designations, November 1999/October 2000). At present, there are only two members of this category: celecoxib and rofecoxib.

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Hypoglycemia

How are hypoglycemia and insulin therapy linked?

All individuals with Type 1 diabetes and many individuals with Type 2 diabetes require insulin to achieve target HbA1c levels.

For individuals with Type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) demonstrated that intensive insulin therapy, using a multi-dose technique or an insulin pump, significantly decreased the rate of diabetic complications.⁵ However, the intensively treated group had a higher rate (threefold) of hypoglycemia compared to the conventional group. In general, the lower the HbA1c level, the higher the risk of hypoglycemia. Not all studies have shown such an increase in hypoglycemia and, even in the DCCT, not all participating centres had increased hypoglycemic rates.

The risk of severe hypoglycemia is lower in individuals with Type 2 diabetes compared to Type 1 diabetes. Patients with Type 1 or Type 2 diabetes using neutral protamine Hagedon (NPH) insulin or lente insulin at dinnertime, are at risk for overnight hypoglycemia, as the peak of these insulins occurs in the middle of the night. Reduction of overnight hypoglycemia in these situations may be avoided by taking NPH or lente insulin closer to bedtime.

In many studies, the rapid-acting insulin analogues—lispro insulin and insulin aspart—have been associated with less hypoglycemia compared to regular insulin.¹ Most of the reduction is linked to lower rates of overnight hypoglycemia. Overnight is the time most patients worry about, as hypoglycemic awareness may be reduced when sleeping.

The long-acting insulin analogue, insulin glargine, will soon be released in Canada, and is currently available in the U.S. Compared to NPH insulin, insulin glargine results in less overnight hypoglycemia, yet similar HbA1c levels in patients with either Type 1 or Type 2 diabetes.⁶

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How is hypoglycemia prevented and treated?

Most, if not all, patients should be performing self-blood glucose measurements. These patients should also be instructed about their medications and possible adjustments of their medications or insulin in relation to meal changes and exer-



Practice pointer

Mild to moderate hypoglycemia should be treated by the oral consumption of 15 g of carbohydrates, preferably as glucose or sucrose tablets. Severe hypoglycemia in a conscious, but confused, person should be treated by the oral consumption of 20 g of carbohydrates. Severe hypoglycemia in an unconscious person outside a medical facility should be treated, if possible, by an injection of glucagon, 1 mg, intramuscularly or subcutaneously.

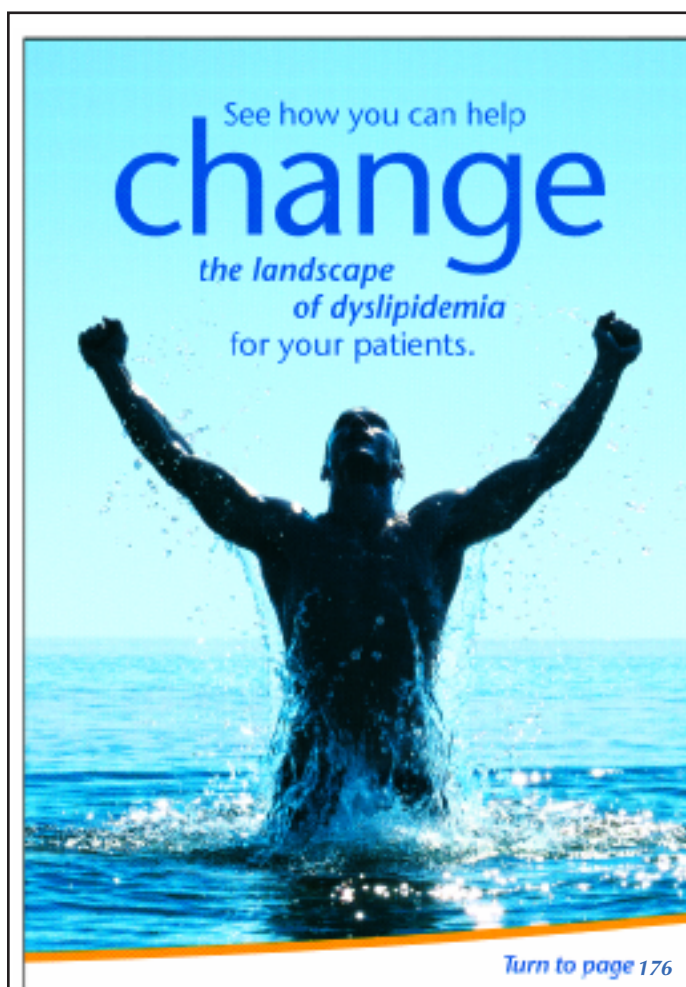
Take-home message

- Hypoglycemia often prevents people with diabetes from reaching target glycemic levels.
- Some oral antihyperglycemic agents and insulin therapies increase the risk of hypoglycemia and need to be individualised.
- All patients at risk should perform self-blood glucose measurements.
- Mild to moderate hypoglycemia should be treated by orally consuming 15 g of carbohydrates; 20 g are needed for severe hypoglycemia.

cise. Patients should understand their response to exercise and should monitor their glucose levels during exercise and for several hours thereafter. To avoid overnight hypoglycemia, patients can monitor glucose levels prior to sleeping and, if necessary, have a small snack containing 15 g of carbohydrates and protein if their glucose level falls to < 7.0 mmol/L. As well, individuals can set an alarm clock overnight to periodically check glucose levels and ensure they are not having undetected overnight hypoglycemia.

Mild to moderate hypoglycemia should be treated by the oral consumption of 15 g of carbohydrates, preferably as glucose or sucrose tablets. A glucose solution or hydrolysed polysaccharide can also work. These treatments are preferable to orange juice or milk, which are slower to raise glucose levels.⁷ After treatment, the patient should wait 15 minutes and retest if possible. If the glucose level is < 4.0 mmol/L, another 15 g of carbohydrates should be taken.

Severe hypoglycemia in a conscious, but confused, person should be treated by the oral con-



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Glucose gel is poorly absorbed from the oral mucosa and should not be given to an unconscious person.

sumption of 20 g of carbohydrates. Severe hypoglycemia in an unconscious person outside a medical facility should be treated, if possible, by an injection of glucagon, 1 mg, intramuscularly or subcutaneously. Glucose gel is poorly absorbed from the oral mucosa and should not be given to an unconscious person. To prevent hypoglycemia from reoccurring, a snack or meal of at least 15 g of carbo-

hydrates and a protein source should be taken.

Newer devices are available which may help detect hypoglycemia in high-risk individuals. Twenty-four hour continuous glucose monitoring is now available over a 72-hour period. In the U.S., a glucose watch is available which measures glucose readings every 20 minutes. Both of these devices measure interstitial glucose levels, but have to be calibrated using standard finger glucose monitoring.

Hypoglycemia is one of the major obstacles preventing individuals with diabetes from achieving their glucose targets. Educating patients about self-monitoring and medications, and providing adequate professional support, is paramount in striving to achieve targets for glycemic control and decreasing hypoglycemic rates. [Dx](#)

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