Treatment of Mild Hypoglycemia

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“Let food be thy medicine and medicine be thy food.”

—Hippocrates

It has been well established by studies such as the landmark Diabetes Control and Complications Trial (DCCT) that metabolic control delays the development and progression of microvascular complications in adults with type 1 diabetes. Unfortunately, improvement in metabolic control is associated with an increased incidence of treatment-induced hypoglycemia. This is a common side effect of insulin, as well as the insulin secretagogues frequently used in the treatment of type 2 diabetes.

As insulin secretion diminishes in type 2 diabetes, hypoglycemia becomes more frequent and limiting. Five years after initiation of insulin therapy, the rate of severe hypoglycemia is reported to be as high as 35–70 episodes per 100 patient-years, higher than that in type 1 diabetes. Abnormal glucose counterregulation (and hypoglycemia unawareness) progresses based on the progression of insulin deficiency. Thus, because type 2 diabetes is more prevalent than type 1 diabetes, most episodes of hypoglycemia occur in people with type 2 diabetes.

In both type 1 and type 2 diabetes, counterregulatory responses to hypoglycemia steadily decline with frequent and repetitive episodes. This can become a vicious circle; a hypoglycemia episode impairs defenses against a subsequent episode, and thus hypoglycemia can result in recurrent hypoglycemia. Hypoglycemia causes increased morbidity in most people with type 1 diabetes and in many with a long duration of type 2 diabetes and is sometimes fatal.

There is growing evidence that older adults with known cardiovascular disease (CVD) and very young children who cannot independently recognize low glucose levels may be particularly vulnerable to adverse events associated with hypoglycemia. Findings such as these led a workgroup from the American Diabetes Association (ADA) and The Endocrine Society (TES) to publish a joint scientific statement in 2013 on hypoglycemia and diabetes. The report provides guidance about how to incorporate this new information into clinical practice. It also confirms the importance of assessing the risk of hypoglycemia and providing hypoglycemia education at every medical appointment for individuals treated with insulin secretagogues or insulin (Table 1).

Hypoglycemia often can be attributed to a mismatch between available glucose and circulating insulin levels caused by missed meals or snacks, unexpected physical activity, excess insulin administration, or alcohol consumption. When hypoglycemia occurs, symptoms may or may not be present and are typically unique to the individual. Those at risk of hypoglycemia need education about symptoms and how they may vary from one individual to another depending on factors such as diabetes duration and age.

Unfortunately, many individuals who are at risk for this acute diabetes complication do not now know how to prevent or treat it effectively. For mild hypoglycemia, people with...
diabetes usually are instructed to self-treat with food or drink containing carbohydrate. But what types of food or drink should health care professionals recommend—chocolate candy bars, cheese and crackers, fruit juice, or glucose tablets? This article reviews research about intervention strategies to treat mild hypoglycemia and addresses some common misconceptions. Treatment of severe hypoglycemia, which requires assistance from another person or a glucagon injection, will not be discussed.

**Treating Mild Hypoglycemia With Food or Drink: What Is the Evidence?**

Historically, it has been reported that mild hypoglycemia episodes can be effectively treated by ingestion of oral glucose or carbohydrate-containing foods such as juice, regular soda pop, candy, or a meal. Over the years, several studies have attempted to determine how much and what type of carbohydrate can effectively treat mild hypoglycemia. Brodows et al. reported in 1984 that the glycemic response is better correlated to the amount of glucose consumed rather than to the specific...
carbohydrate content of the feeding. They advised treatment with a 20-g dose of glucose (0.3 g/kg of body weight in children). In 1993, among intensively treated patients in the DCCT, Delahanty and Halford observed a 0.5% difference in A1C levels resulting from treatment of mild hypoglycemia. Participants in the intensive intervention group who admitted to continuing to eat until they felt better had higher A1Cs than those who said they “never” overate to treat hypoglycemia.

In 1993, Wiethop and Cryer investigated a model of insulin-induced hypoglycemia in subjects with type 1 diabetes. They found that 10 g of oral glucose raised plasma glucose levels from 60 to only 97 mg/dl over 30 minutes; the levels started to decrease after 60 minutes and reached placebo levels in 2 hours. Twenty grams of glucose raised plasma glucose levels from 58 to 122 mg/dl over 45 minutes, with a greater response at 15 minutes; again, the levels started to decrease after 60 minutes and approached placebo levels in 2 hours. In the same study, glucagon increased glucose levels to 212 mg/dl in ~ 60 minutes with a return to pretreatment levels at ~ 3–4 hours. The researchers noted that the glycemic response to oral glucose is transient, typically less than 2 hours. In the case of persistent or recurrent hypoglycemia, they concluded, although oral glucose is effective, it is a temporary measure, and subsequent ingestion of a more substantial snack or meal may be required. This early research by Weithop and Cryer, as well as early observations in the DCCT, may well have been the source for the “rule of 15,” a popular treatment strategy for mild hypoglycemia that recommends treating blood glucose that is < 70 mg/dl by eating or drinking 15 g of carbohydrate and repeating this treatment if symptoms persist after 15 minutes.

More recently, Husband et al. conducted a randomized, crossover-control trial in 33 youths with type 1 diabetes to compare the effectiveness of glucose, sucrose, or fructose (in the form of Becton Dickenson glucose tablets, Skittles candies, or Fruit to Go fruit snacks) on blood glucose levels 15 minutes after treatment. They found the treatment effectiveness of fructose to be significantly lower than that of sucrose. This finding reinforces earlier conclusions by Crapo et al. who studied the euglycemic state in subjects with normal glucose control, impaired glucose control, or diabetes. These researchers documented a decreased glycemic response after consumption of fructose compared to other forms of carbohydrate. It also should be noted that the fructose (Fruit to Go snacks) used in the study by Husband et al. contained soluble fiber, which can increase the viscosity of the intestinal contents and delay the action of enzymes on the carbohydrate source, possibly diminishing the glucose response. Nonetheless, sucrose or glucose in the form of tablets, liquid, or gel may be the preferred treatment over fruit snacks or fruit juice, although cost, availability, and convenience should be considered.

Do protein and fat play a role in hypoglycemia treatment?
For individuals with type 2 diabetes, protein does not appear to have a significant effect on blood glucose. However, protein does appear to increase the insulin response in people with type 2 diabetes. There is no clear consensus regarding the effect of protein on blood glucose levels in type 1 diabetes. Therefore, protein ingestion is not recommended for the treatment or prevention of hypoglycemia.

No published studies have evaluated the potential role of fat in hypoglycemia treatment.

Do bedtime snacks prevent nocturnal hypoglycemia?
The DCCT revealed that iatrogenic hypoglycemia often occurred at night, specifically during sleep, in people with type 1 diabetes. Although not as commonly prescribed as they once were, insulin regimens that have a peaked action profile (e.g., those involving intermediate-acting NPH insulin administered in the evening) can lead to an increased need for glucose around mid-sleep (i.e., after ∼ 4 hours of sleep), putting individuals at risk for nocturnal hypoglycemia in the early-morning hours. However, the availability of newer insulin preparations such as rapid- and long-acting insulin analogs, which have more physiological kinetic profiles, has led clinicians to question whether bedtime snacks are still necessary to prevent nocturnal hypoglycemia.

Before the introduction of rapid- and long-acting insulin analogs, several research trials attempted to identify an appropriate bedtime snack that would provide a nocturnal glucose supply to balance insulin action and reduce the risk of hypoglycemia. Previous research conducted in people with glycogen storage disease had shown that raw cornstarch reduced nocturnal hypoglycemia by serving as a glucose reservoir in the intestinal tract, where it is digested slowly over a period of 6 to 8 hours. Using this hypothesis, Kaufman et al. conducted two small studies investigating the addition of 5 g of uncooked cornstarch to a bedtime snack as a strategy to prevent nocturnal hypoglycemia in children with diabetes. Such a snack was shown to diminish the frequency of nocturnal hypoglycemia compared to a conventional snack. Another small study conducted by Axelson et al. found that ingestion of uncooked cornstarch at bedtime led to a lower (52 ± 0.9 vs. 94 ± 11 mg/dl, P = 0.01) and delayed (4.3 ± 0.6 vs. 2.0 ± 0.0 hours, P < 0.01) blood glucose peak compared to a conventional snack in subjects with type 2 diabetes. In subjects with type 1 diabetes, the same researchers found that 4 weeks of a bedtime supplement of uncooked cornstarch led to a 70% reduction in the frequency of self-reported hypoglycemia (P < 0.05) 3 hours after ingestion of the supplement.

More recent studies using newer insulin preparations have not supported these earlier findings. In adults with type 1 diabetes, Kalergis et al. found that a bedtime snack was necessary to prevent hypoglycemia if the bedtime blood glucose level was < 180 mg/dl. Another study conducted by Raju et al. demonstrated that typical bedtime snacks...
increase plasma glucose only during the first half of the night. Based on these conflicting results, bedtime snacks should be determined on an individualized basis after evaluating the patient’s glycemic response to the medication plan.

Role of Technology in Hypoglycemia Treatment
For many years, the use of a blood glucose meter to confirm and treat hypoglycemia has been a standard of practice. Real-time continuous glucose monitoring (CGM) has now provided people with diabetes with another useful tool. Personal CGM devices may be able to help individuals with hypoglycemia unawareness proactively avoid severe hypoglycemia. People who use CGM devices can set alarms to sound when their glucose falls below a predetermined level, which may help them identify impending or unrecognized hypoglycemia. CGM devices also provide information not just on current glucose level, but also on the trend and rate of change in glucose levels (i.e., whether the glucose level is rising or falling and how quickly). The U.S. Food and Drug Administration recently approved an insulin pump with integrated CGM that offers an overnight basal-suspend feature. By programming the device to suspend basal insulin if blood glucose falls below a predetermined level, users of this device will have another strategy for preventing nocturnal hypoglycemia.

Best practices for treating hypoglycemia based on CGM-identified glucose results or trends (e.g., with more or less carbohydrate-containing foods or beverages than traditionally recommended) have not yet been established. Future research may include studies to determine how to more accurately titrate an individualized treatment response using varying amounts of carbohydrate based on glucose trends and active insulin.

Summary: Education and Treatment Strategies
All individuals receiving treatment with insulin secretagogues or insulin should be routinely counseled about the risk factors and recognition of hypoglycemia, especially those with history of recurrent hypoglycemia or impaired hypoglycemia awareness.11,12 Other high-risk groups include older adults with known CVD or other comorbidities, and very young patients with diabetes. A basic understanding of how these medications can cause hypoglycemia is important and can help people with diabetes learn to adjust their food intake or medication doses to match, for example, changes in their physical activity level, delayed or skipped meals, or consumption of alcohol.

Providing education about how to treat mild hypoglycemia also includes assessing individuals’ ability to recognize carbohydrate-containing foods and to understand how these foods affect their blood glucose. (Table 2 provides a list of carbohydrate sources.)

Based on the 2013 ADA/TES joint scientific statement,11,12 patients should, as a starting point, carry carbohydrate-containing foods or glucose tablets and know the following procedure for treating hypoglycemia when it is detected through self-monitoring of blood glucose (SMBG):

• Take 15 g of glucose.
• Wait 15 minutes.
• Re-measure blood glucose.
• Repeat this treatment if hypoglycemia persists.

The use of SMBG and now personal CGM will allow people with diabetes to individualize the amount of carbohydrates they need to consume for hypoglycemia treatment based on variables such as body size, age, active insulin remaining from their last dose, and the rate at which their glucose level is falling. The ADA/TES statement included an Internet link to a free one-page patient education handout, which can be accessed at http://clinical.diabetesjournals.org/content/30/1/38 and used for nonprofit educational purposes free of charge.

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<th>Table 2. Carbohydrate Sources for the Treatment of Mild Hypoglycemia</th>
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<td><strong>Food</strong></td>
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| Glucose tablets  
(1 tablet = about 5 g of carbohydrate; check the label) | 4 tablets | 16 | 60 |
| Sugar  
(1 teaspoon = 4 g of carbohydrate) | 4 tsp | 12 | 40 |
| Fruit juice  
(1/2 cup = 15 g of carbohydrate) | 1/2 cup | 15 | 60 |
| Regular soda pop (not diet)  
(1 oz = 3 g of carbohydrate) | 1/2 can (6 oz) | 18 | 70 |
| Milk (nonfat or 1% milk fat) | 1 cup | 12 | 90–105 |
| Lifesavers candies (1 piece = 2.5 g of carbohydrate) | 6 pieces | 15 | 60 |
| SweeTarts candies  
(1 piece = 1.7 g of carbohydrate) | 8 pieces | 14 | 60 |
| Skittles candies  
(1 piece = 0.9 g of carbohydrate) | 15 pieces | 15 | 60 |
| Raisins  
(1 tablespoon = 7.5 g of carbohydrate) | 2 Tbsp | 15 | 60 |
| Fruit Roll-Ups snacks  
(1 packet = ~ 15 g of carbohydrate) | 1 packet | 12–15 | 50–75 |
References


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Note of disclosure: Ms. Evert serves on the certified diabetes educator advisory board for Medtronic Diabetes, which manufactures insulin pumps and CGM devices.