COMMENTARY

Is Mini-Dose Glucagon the Answer to Preventing Exercise-Related Dysglycemia?

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Hypoglycemia is a potentially fatal complication of insulin therapy. In normal physiology, glucagon acts as a counterregulatory hormone to raise circulating glucose, defending against hypoglycemia. This defense is lost early in type 1 diabetes (1,2). The absence of normal counterregulation in patients with type 1 diabetes, combined with the slow offset of subcutaneous insulin therapy, results in a significant risk of hypoglycemia in this population. Mild hypoglycemia can be treated with the ingestion of simple carbohydrates, but frequent treatments may lead to unwanted weight gain. Frequent hypoglycemic episodes also put a patient at risk for hypoglycemia unawareness, which significantly increases a person's risk of severe hypoglycemia (3).

For decades, the use of glucagon has been largely limited to a rescue treatment for severe hypoglycemia. The available rescue kits require the user to reconstitute glucagon from a lyophilized powder. After reconstitution into an aqueous solution, native glucagon quickly forms fibrils and degrades (4). For this reason, rescue glucagon kits are currently designed to be used immediately after reconstitution and then discarded.

To address this issue, multiple companies have developed stable forms of glucagon. These companies include Xeris Pharmaceuticals (G-Pen), Zealand Pharma (dasiglucagon), and Adocia (BioChaperone glucagon) (5). The development of these stable forms of glucagon has opened up the possibility of uses beyond rescue, including mini-dose glucagon (6–8) and automated glucagon delivery (9). The concept of mini-dose glucagon was first published in detail by Haymond and Schreiner (8). In their 2001 article, they described their experience with treating children with impending or mild hypoglycemia with so-called mini-doses of glucagon. These doses were much below that of a typical rescue dose and were based on age, up to a maximum dose of 150 μg. In an article in this issue of *Diabetes Care*, Rickels et al. (10) extend the use of mini-dose glucagon to prevent exercise-related hypoglycemia. The authors demonstrated that 150 μg of stable glucagon delivered via the G-Pen Mini eliminated hypoglycemia during the exercise period. Glucose tablets (40 g) similarly prevented hypoglycemia but resulted in significant hyperglycemia in one-third of participants. The authors did not test 20 g of glucose, so it is unknown if this amount of carbohydrate would have avoided both hypoglycemia and hyperglycemia. The use of a 50% basal insulin reduction starting 5 min prior to exercise resulted in hypoglycemia in one-third of participants. Interestingly, the 50% basal reduction performed almost as poorly as no intervention during the exercise and early recovery periods (hypoglycemia in 5 vs. 6 subjects), and the insulin levels were unchanged compared with the other arms despite the basal reduction. This highlights the need to make basal insulin adjustments 60–90 min prior to exercise (11), which is a burden to patients and not commonly done. Furthermore, a more aggressive basal reduction may be required to prevent hypoglycemia but may lead to hyperglycemia.

The study by Rickels et al. was performed under tightly controlled conditions. Participants were required to be on insulin pump therapy, to be fasting, to start exercise with a glucose level of 100–140 mg/dL, and to perform 45 min of moderate exercise in the morning. Outside of the research setting, a fixed dose of 150 μg of glucagon is not likely to be as successful at avoiding exercise-related dysglycemia. The glucagon dose needed in any particular situation will likely be impacted by multiple factors including the patient's weight, starting glucose, timing of the last meal, and insulin on board (12). Different types of exercise also clearly have different impacts on glucose, as do the intensity and duration of exercise (13). Given these considerations, glucagon dosing outside of research should be individualized to minimize the risk of exercise-related dysglycemia. Notably, glucagon did not impact the rate of

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hypoglycemia in the late recovery period. Prevention of these late-onset hypoglycemic events requires either ingestion of carbohydrates or insulin adjustments.

Mini-dose glucagon was clearly a success in this study, both preventing hypoglycemia and minimizing the risk of hyperglycemia during the exercise period. Nausea was uncommon but did occur in two participants after eating. Another potential barrier to adoption of mini-dose glucagon is cost and the question of insurance coverage. One can clearly make a case that mini-dose glucagon could reduce the risk of unwanted weight gain that could otherwise occur with frequent rescue carbohydrate treatments. The use of mini-dose glucagon to avoid hypoglycemia may also reduce the risk of hypoglycemia unawareness that may occur with repeated episodes of hypoglycemia. Longer-term studies are needed to address these issues and also to evaluate the efficacy and safety of long-term glucagon therapy in the outpatient setting.

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