Case Study: Exercise-Related Hypoglycemia in Type 2 Diabetes Treated With Oral Glucose-Lowering Medications

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Presentation

D.L. is a 58-year-old African-American man and business executive who was diagnosed with type 2 diabetes at the age of 52 years. In addition to diabetes, he has a history of hypertension and coronary artery disease (CAD). The diagnosis of CAD was made in late 2005, after D.L. experienced an episode of chest pressure and shortness of breath while at work.

He consulted his primary care physician, who referred him for a cardiovascular evaluation to assess probable myocardial ischemia. The evaluation included a graded exercise test with thallium nuclear imaging, which revealed ischemic changes with exercise and reduced exercise tolerance. Coronary arteriography showed occlusion of the left anterior descending branch of the coronary artery (LAD), and angioplasty of the LAD with stent placement was performed. D.L. was referred to cardiac rehabilitation for an exercise and lifestyle change program.

D.L. had completed 2 months of supervised exercise when he returned to his primary care physician after experiencing hypoglycemia both during and after exercise. Before this time, progression of his physical activity program had been excellent. He was exercising three mornings per week from 7:30 to 8:30 A.M. in the rehabilitation program and was walking 30–45 minutes on weekend days. Hypoglycemia was now a safety concern for both D.L. and the cardiac rehabilitation staff and was a barrier to further progression of his exercise program.

On examination, D.L.'s height was 6 feet, 2 inches, and his weight was 215 lb (BMI 27.6 kg/m^2). He had lost 15 lb in 2.5 months by consistently exercising and following a reduced-fat, calorie-controlled meal plan. His medications included glyburide, 7.5 mg with breakfast and 5 mg with dinner, plus metformin, 1,000 mg twice daily with breakfast and dinner. He was taking enalapril, 10 mg twice daily, and aspirin, 325 mg daily. His blood pressure was 118/76 mmHg and had been well controlled when measured pre- and post-exercise.

D.L.'s blood glucose record revealed that, in the past 2 weeks, four values were < 70 mg/dl, indicating hypoglycemia, and three additional values were below his target range of 80–140 mg/dl but not low enough to indicate hypoglycemia. Two episodes of hypoglycemia occurred during and two occurred ≥ 1 hour after exercise. His blood glucose meter showed a 14-day glucose average of 118 mg/dl.

Because continued weight loss was a goal, D.L. and his physician considered the additional food and calories that he was consuming to treat hypoglycemia. D.L. initially treated hypoglycemia by drinking 6 oz of orange juice. However, each episode occurred at least 2 hours before his next planned meal. Therefore, he followed this treatment with an additional carbohydrate-containing snack. D.L.'s physician estimated that D.L. was consuming a minimum of 200 unplanned calories with each episode of hypoglycemia.

Based on these findings, the physician modified D.L.'s medication plan by discontinuing glyburide and initiating glimepiride (a sulfonylurea associated with lower risk of hypoglycemia[1]), 4 mg each morning. D.L. was to continue his metformin dosage at 1,000 mg twice daily. He was also advised to monitor his blood glucose before, during, and after each exercise session in addition to continuing routine monitoring and to call the office in 1 week with his blood glucose readings.

One week later, D.L. reported that he was feeling better overall when exercising and was again making progress in cardiac rehabilitation. His blood glucose values were within his target range during and after exercise with the exception of three values that were between 70 and 80 mg/dl. D.L.'s physician advised him to reduce his glimepiride dose to 3 mg each morning, to continue monitoring frequently with exercise, and to again follow up by phone in 1 week. At this time, D.L. reported that all blood glucose values during and after exercise were within his target range.

Questions

1. What metabolic adaptations to exercise contribute to improved glycemic control and reduced cardiovascular risk factors in type 2 diabetes?
2. How do these adaptations contribute to the development of hypoglycemia in individuals treated with sulfonylureas?
3. When a pattern of exercise-related hypoglycemia is apparent, why is adjustment of medications a primary option to consider?

Commentary

Multiple metabolic adaptations to exercise contribute to improved glyce-

mic control and reduced cardiovascular risk factors in type 2 diabetes. These include improved muscle and liver insulin sensitivity, reduced basal and glucose-stimulated circulating insulin levels, improved muscle glucose uptake and utilization, reduced hepatic glucose production, and enhanced capacity of muscle to extract and oxidize nonesterified fatty acids.[2,3]

In type 2 diabetes, blood glucose lowering from exercise is the result of the cumulative effects of the most recent exercise sessions. Insulin sensitivity is enhanced for 24–72 hours after a single session of exercise, and glucose tolerance is improved for up to 72 hours.[2,4] As a result, individuals who exercise consistently may experience significant reductions in blood glucose levels, especially if they make considerable gains in physical fitness and significantly increase their energy expenditure through physical activity.

Though improvements in insulin sensitivity and glucose tolerance are metabolically beneficial in type 2 diabetes, individuals treated with insulin or insulin secretagogues can experience exercise-related hypoglycemia. For those on sulfonylureas, this results from the inability of the pancreas to reduce medication-stimulated insulin secretion. This causes suppression of liver glucose output despite an increase in muscle glucose uptake and utilization during and after exercise.[5] Thus, an elevated circulating insulin level relative to physiological need leads to a mismatch between muscle glucose uptake and liver glucose output and an excessive reduction in blood glucose with exercise.

Prevention of exercise-related hypoglycemia is of primary importance, especially for individuals with CAD. Hypoglycemia has been linked to development of cardiac ischemia and major vascular events, including myocardial infarction, acute heart failure, ventricular arrhythmia, and stroke.[1,6] For individuals with type 2 diabetes who establish a consistent, long-term exercise routine and who are on sulfonylurea therapy, a change in medication, a dosage reduction, or an increase in intake of carbohydrate at times of exercise may be necessary to prevent hypoglycemia.[5]

Adjustment of medication dosage or type is a primary option to consider. A reduction in dosage of secretagogues can lower the circulating insulin level and correct a pattern of exercise-related hypoglycemia that occurs if medication dosage is not adjusted as an individual becomes more "metabolically fit" and insulin sensitive. Some sulfonylureas are associated with greater potential to contribute to hypoglycemia than others. Caution with secretagogues with high affinity for the β-cell and long duration of action is warranted.[1] In certain cases, changing medication to one that has a lower association with hypoglycemia can be effective.

Although consumption of additional carbohydrate before, during, or after exercise can prevent hypoglycemia, this strategy should be used conservatively, especially if weight loss or prevention of weight gain is a goal. Intake of unnecessary extra calories should be cautioned against. The energy deficit and metabolic improvements that result from exercise can easily be countered if additional energy intake is excessive. If medication dosages are correctly adjusted for physical activity, intake of extra carbohydrate at times of exercise becomes less necessary.

Clinical Pearls

- Metabolic adaptations to exercise lead to many health benefits for individuals with type 2 diabetes, including improved glycemic control, reduced cardiovascular risk factors, and greater success with weight maintenance. However, these same adaptations can contribute to development of hypoglycemia if medications and/or carbohydrate intake are not modified.
- Adjustment of medications is of primary importance if a pattern of exercise-related hypoglycemia becomes apparent.
- Consumption of additional carbohydrate may be necessary when an activity is unplanned, unusually intense, or of long duration but should be used conservatively in other situations.

REFERENCES

[1]Zammitt NN, Frier BM: Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. *Diabetes Care* 28:2948–2961, 2005

[2]Sigal R, Kenny GP, Wasserman DH, Castaneda-Sceppa C: Physical activity/exercise and type 2 diabetes. *Diabetes Care* 27:2518–2539, 2004

[3]Wasserman DH, Davis SN, Zinman B: Fuel metabolism during exercise in health and diabetes. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, Va., American Diabetes Association, 2001, p. 63–99

[4]Marrero D: Initiation and maintenance of exercise in patients with diabetes. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, Va., American Diabetes Association, 2001, p. 289–309

[5]Berger M: Adjustment of insulin and oral agent therapy. In *Handbook of Exercise in Diabetes*. Ruderman N, Devlin JT, Kriska A, Eds. Alexandria, Va., American Diabetes Association, 2001, p. 365–376

[6]Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V: Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. *Diabetes Care* 26:1485–1489, 2003

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