

Medication and Exercise Interactions: Considering and Managing Hypoglycemia Risk

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Exercise, as part of lifestyle modification, is known to be the first line of therapy for patients with type 2 diabetes (1), and, dating back as far as 1000 AD, Greek physicians prescribed exercise as a way to improve health (2). Regular exercise provides many physiological and psychological benefits, including improvements in glycemic control (in most individuals), insulin sensitivity, blood pressure, lipid profile, muscular strength, and bone mineral density. In addition, exercise reduces total daily insulin requirements in people on insulin therapy, risk for coronary artery disease, body weight, percentage of body fat, stress, and depression and improves individuals' sense of well-being and quality of life (3–5). Given all the health benefits it provides, exercise truly can be considered “medicine.”

Despite being advised to participate in exercise as an essential part of diabetes management, only 39% of adults with diabetes are physically active (6), and many face barriers to becoming and staying physically active. Brazeau et al. (7) found four main barriers to physical activity in patients with type 1 diabetes: fear of hypoglycemia, work schedule, loss of control over diabetes, and low fitness level.

Fear of hypoglycemia is the major barrier and biggest challenge for people treated with insulin. Exercise can cause profound changes in glucose homeostasis and may lead to hypoglycemia. Some hypoglycemia

symptoms such as sweating and fatigue are similar to the physical sensations of normal exertion, which can make it difficult for patients to distinguish between the two (7).

Given that an excessive decrease in blood glucose is a primary clinical concern and barrier to being physically active for people with diabetes, it is important to consider potential interactions between antihyperglycemic medications and exercise to minimize the risk of hypoglycemia. This article provides a brief overview of medication management considerations in people with diabetes who are engaging in exercise, with a focus on antihyperglycemic medications.

Exercise and Blood Glucose

Two separate but additive pathways stimulate glucose uptake by muscles via translocation of glucose transport proteins (i.e., glucose transporter type 4 [GLUT4]). At rest, GLUT4 recruitment is insulin dependent, which aids in replenishing glycogen stores in muscles during the postprandial period. During exercise, however, blood glucose uptake into active muscles does not require insulin because GLUT4 translocation is contraction-mediated (3).

Insulin-stimulated GLUT4 translocation is generally impaired in people with type 2 diabetes, but muscle contractions during both aerobic and resistance exercise increase GLUT4 abundance and enhance muscular glucose uptake even in these individuals. Low- to moder-

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ate-intensity exercise generally leads to a reduction in blood glucose levels resulting from increased glucose uptake by active muscles. If exercise is performed after a meal, postprandial hyperglycemia is blunted in people with endogenous insulin secretion despite the usual decline in plasma insulin during exercise (8). The acute improvements in glucose tolerance and insulin sensitivity after exercise can last from 24 to 72 hours (3). In individuals with type 1 diabetes, glucose uptake by muscles increases the risk of hypoglycemia both during and immediately after exercise and frequently again 7–11 hours later as a result of increased insulin sensitivity during a prolonged period of glycogen restoration (5,9).

Medication and Exercise Interactions: Considerations for Medication Management

Several classes of diabetes medications have the potential to induce hypoglycemia during or after exercise, whereas the use of other medications carries little or no risk of hypoglycemia (Table 1). The American Diabetes Association (ADA) lists considerations for deciding among antihyperglycemic agents for the treatment of diabetes, including efficacy, body weight effects, potential side effects, costs, and hypoglycemia risk (1). Agents considered to carry high risks for hypoglycemia include sulfonylureas (insulin secretagogues) and insulin. Accordingly, a joint position statement from ADA and the American College of Sports Medicine states that medication adjustments for physical activity are generally necessary only for people using insulin or insulin secretagogues (3).

In people who have either type of diabetes and are treated with exogenous insulin, hypoglycemia risk is greater during exercise because higher peripheral levels of insulin may cause excessive blood glucose uptake. Alternately, insulin secretagogues may cause an excessive release of insulin that suppresses

Medication Class	Risk of Hypoglycemia With Exercise
Insulin	High
Sulfonylureas	High
Meglitinides	Moderate
Biguanides	Low
Dipeptidyl peptidase-4 inhibitors	Low
Glucagon-like peptide-1 analogs	Low
Alpha-glucosidase inhibitors	Low
Thiazolidinediones	Low
Sodium glucose cotransporter 2 inhibitors	Low

hepatic glucose release during exercise and results in hypoglycemia (8). The following sections briefly review medication management considerations for people using various antihyperglycemic medications and engaging in physical activity.

Insulin

Insulin use, in particular, can contribute to the development of hypoglycemia in active individuals. Exercise undertaken during the peak effect of a rapid-acting insulin dose increases the risk of severe hypoglycemia. Thus, doses administered within 1–2 hours before planned exercise likely will require reduction to prevent hypoglycemia (3). The necessary size of the reduction in prandial insulin dose varies widely among individuals (from 25 to 75%) and depends on factors such as the type of insulin being used and the type, intensity, duration, and timing of the physical activity (10).

With basal insulin, which remains active for 24 hours, hypoglycemia risks are lower during an acute exercise bout. However, an insulin such as NPH, which has a moderate duration, may cause hypoglycemia if exercise coincides with its peak effect. Although the risk of exercise-induced hypoglycemia is lower in patients who use only long-acting insulin, doses likely will need to be reduced for individuals participating in regular physical activity (3).

Overall, it is important to make adjustments in insulin doses for exercise to minimize hypoglycemia risk. These adjustments should be based on individuals' insulin regimen and unique responses to physical activity.

Insulin Secretagogues

Sulfonylureas and meglitinides stimulate insulin secretion from the pancreas and thus increase hypoglycemia risk during exercise. These medications differ from exogenous insulin in pharmacokinetics and pharmacodynamics (i.e., the timing of insulin appearance and disappearance from the circulation).

Meglitinides such as repaglinide and nateglinide are oral insulin secretagogues that are taken with meals and have a short duration of action. Thus, their potential to cause hypoglycemia is relatively low compared to longer-acting sulfonylureas. However, all insulin secretagogues can induce hypoglycemia if taken in conjunction with exercise (8,11). Although dosing adjustments are not recommended for acute exercise, these agents may require downward dose titration in response to regular exercise training if an increase in the frequency of hypoglycemia occurs (3).

Biguanides

Metformin does not cause hypoglycemia with exercise. However, in patients with severe hepatic insufficiency or after excessive alcohol intake,

hypoglycemia can occur (8). Because metformin acts primarily through suppression of hepatic glucose output and patients with hepatic dysfunction are less able to generate glucose as a counterregulatory response to hypoglycemia, such patients have a diminished ability to counteract the onset of hypoglycemia.

Incretin-Based Therapies

Dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 analogs stimulate pancreatic insulin production in a blood glucose-dependent manner and carry a lower hypoglycemia risk during exercise (8). Caution is still warranted when adding incretin-based therapies to insulin or an insulin secretagogues.

Alpha-Glucosidase Inhibitors

Acarbose and miglitol slow carbohydrate absorption and are not associated with hypoglycemia when used as monotherapy. However, their use could delay the absorption of carbohydrates taken to treat hypoglycemia related to physical activity. When used in combination with insulin or insulin secretagogues, this can result in a mismatch between peak serum glucose levels and peak prandial insulin levels, thus placing patients at increased risk for hypoglycemia (12). Patients should be counseled to carry glucose while exercising to ensure more effective treatment of hypoglycemia should it occur.

Thiazolidinediones

Rosiglitazone and pioglitazone increase insulin sensitivity but do not affect the counterregulatory response to hypoglycemia. Thus, their use is unlikely to contribute to the development of hypoglycemia during exercise (8).

Sodium Glucose Cotransporter 2 Inhibitors

One of the newest classes of diabetes antihyperglycemic agents, sodium glucose cotransporter 2 (SGLT2) inhibitors such as canagliflozin, dapagliflozin, and empagliflozin, carry a low inherent risk of hypoglycemia.

Although these agents induce glucose excretion via urine, they do so without augmenting insulin secretion or inhibiting the counterregulatory response to hypoglycemia (13). As with other classes of medications with a low intrinsic risk of hypoglycemia, caution is still warranted when SGLT2 inhibitors are used in combination with insulin or insulin secretagogues.

Other Antihyperglycemic Medications

Colesevelam and bromocriptine are less likely to cause hypoglycemia with exercise unless they are used in combination with insulin or sulfonylureas. Pramlintide use may require further reduction in short-acting insulin doses if exercise is planned after meals (8,14).

Additional Medication-Related Considerations

Glycemic responses during and after exercise and the risk of hypoglycemia are affected by many other factors such as blood glucose level before exercise, serum insulin level at the time of exercise, pharmacokinetics and pharmacodynamics of insulin and insulin secretagogues, type and duration of exercise, exercise intensity, muscle mass involved in activity, level of fitness, robustness of the counterregulatory hormone response, carbohydrate supplementation, time of carbohydrate intake, and rate of carbohydrate absorption. Each of these factors may affect blood glucose during or after exercise and thereby affect hypoglycemia risk (8).

Conclusion

Exercise provides significant benefits to people with type 1 or type 2 diabetes, but it can have variable effects on blood glucose levels, making glucose management challenging. It is important for people with diabetes to understand the mechanisms of blood glucose response to exercise and how their medications may affect their blood glucose levels when they are physically active.

The doses and timing of certain medications may require adjustment to avoid hypoglycemia during or after exercise. Caution is particularly important in those treated with insulin or insulin secretagogues, yet patients should still be counseled about appropriate recognition and treatment of hypoglycemia regardless of their medication regimen. Given the heterogeneous response to activity among individuals, frequent monitoring to assess glycemic responses to exercise is the principal method for determining appropriate adjustments for individual patients.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

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