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Exercise and Glycemic Control in Diabetes: Benefits, Challenges, and Adjustments to Pharmacotherapy

Eric Arthur Gulve

Exercise, along with dietary intervention, represents first-line therapy for diabetes mellitus. Aerobic exercise is recommended for its beneficial effects on glucose control as well as its abilities to retard the progression of other comorbidities common in patients with diabetes, such as cardiovascular disease. The capability of aerobic exercise to improve glycemic control in diabetes is well documented, although adherence to exercise regimens is problematic. More recently, the glucose-lowering effects of resistance training have also been documented; this form of exercise has additional benefits, such as the capability to counteract sarcopenia, which is common in older people with type 2 diabetes. Exercise in people with diabetes, however, also can present significant challenges to glycemic control. Excessive glucose lowering can occur under certain conditions, enhancing the threat of hypoglycemia; in other situations, hyperglycemia can be accentuated. An understanding of the interactions between specific antidiabetic medications and various forms and intensities of exercise is essential to optimizing glycemic control while minimizing the potential for acute derangements in plasma glucose levels. Exogenous forms of insulin and agents that stimulate insulin secretion in a glucose-independent manner (such as sulfonylureas and glinides) increase the propensity for hypoglycemia during low- to moderate-intensity aerobic exercise. In contrast, exercise protocols characterized by high intensity are more likely to result in episodes of hyperglycemia. Strategies to minimize inappropriate swings in glycemic control are reviewed.

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Exercise and diet are cornerstones of therapy in diabetes mellitus. In most patients with diabetes, the addition of pharmacologic therapy is required for the management of plasma glucose levels. In type 1 diabetes, the etiology of which involves the autoimmune destruction of insulin-producing pancreatic β -cells, exogenous insulin (ie, from a source other than the patient's own β -cells) is absolutely required. Therapy consists of the administration of various insulin preparations designed to meet basal and meal-associated insulin requirements.^{1,2} In recent years, several new insulin analogs with unique properties have been developed; these include short-acting insulin analogs that can be taken just before meals. These insulin analogs differ in their pharmacokinetic properties, such as their rate of appearance in the bloodstream and how long they remain in the plasma (Tab. 1).

Type 2 diabetes is characterized by resistance to the actions of insulin in the presence of defects in insulin secretion. Absolute insulin levels vary with the severity of the disease; early stages tend to be characterized by a compensatory hyperinsulinemic state, but progressive β -cell failure eventually occurs in most patients, leading to low absolute levels of circulating insulin. Several oral and non-insulin-based injectable therapies that act on different organ systems have been devel-

oped in an effort to modulate glucose homeostasis (Tab. 2). These therapies include agents that regulate endogenous insulin secretion (ie, drugs that stimulate the patient's own β -cells to secrete more insulin), dampen hepatic glucose production, enhance peripheral glucose metabolism, slow the gastrointestinal processing of food and ultimately the absorption of glucose, reduce secretion of the counter-regulatory hormone glucagon, or combinations of these. A review of these therapies is beyond the scope of this article, given that the primary concerns during exercise in people with diabetes are related to the use of exogenous insulin and insulin secretagogues. Many people with type 2 diabetes use insulin secretagogues, and most eventually progress to a requirement for exogenous insulin therapy.³ Detailed reviews of available antidiabetic medicines are available elsewhere.^{4,5}

To understand the challenge of blood glucose regulation in diabetes, one must consider the various organs that collaborate in the regulation of blood glucose levels in health and disease. A full review is beyond the scope of this article, but for the purposes of this review, key organ systems to consider are skeletal muscle, liver, and the endocrine pancreas.⁶ Skeletal muscle represents, quantitatively, the primary site of insulin-mediated glucose disposal. The liver is the primary organ

that both stores glucose after food ingestion and dispenses glucose to the circulation between meals in order to maintain appropriate plasma glucose levels. Fasting plasma glucose levels (ie, sampled 8 hours or more after the last meal) are ~ 80 to 100 mg/dL (~ 4.5 mM– 5.5 mM) in young adults who are healthy. Insulin is released from pancreatic β -cells in response to the ingestion of food and, in turn, stimulates glucose uptake and storage in muscle and adipose tissue while simultaneously suppressing hepatic glucose production (Fig. 1). These actions prevent large increases in plasma glucose levels after a meal in people who are healthy, because they result in the efficient processing of glucose. In contrast, diabetes mellitus is characterized by exaggerated plasma glucose levels after a meal and, as the disease progresses, by increases in plasma glucose levels in the fasting state. Diabetes mellitus is diagnosed in 1 of 3 ways⁷:

- Fasting plasma glucose level at or above 126 mg/dL (7.0 mM)
- Random plasma glucose level (irrespective of time elapsed since the last meal) at or above 200 mg/dL (11.1 mM) combined with symptoms of diabetes, such as frequent urination, excessive thirst, rapid weight loss, or any combination of these symptoms
- Plasma glucose level at or above 200 mg/dL (11.1 mM) when measured 2 hours after an oral load of 75 g of glucose

Table 1.
Pharmacokinetic Profiles of Various Insulin Preparations

Class	Insulin Type ^a	Onset	Peak	Duration
Rapidly acting analogs	Insulin aspart	5–20 min	1–3 h	3–5 h
	Insulin lispro	5–20 min	1–2 h	3–5 h
	Insulin glulisine	10–20 min	1–1.5 h	3–5 h
Short-acting human	Regular	30–60 min	2–4 h	4–8 h
Intermediate-acting human	NPH	1–3 h	4–10 h	10–18 h
Long-acting analogs	Insulin detemir	1–2 h	None (flat)	24 h
	Insulin glargine	2–4 h	None (flat)	24 h

^a NPH=isophane insulin (neutral protamine Hagedorn).

Table 2.
Classes of Non-Insulin-Based Antidiabetic Agents^a

Drug Class	Example(s)	Primary Mode of Action or Type of Drug	Advantages	Disadvantages
Biguanides	Metformin	Inhibit hepatic glucose output	Weight neutral; TG reduction; generic	GI side effects (nausea, diarrhea); lactic acidosis (rare)
Sulfonylureas	Glyburide, glipizide, glimepiride, chlorpropamide	Insulin secretagogues (stimulate insulin secretion in glucose-independent manner)	Generally well tolerated; generic	Weight gain; hypoglycemia
Glinides	Repaglinide, nateglinide	Short-acting insulin secretagogues	Generally well tolerated; less hypoglycemic risk than with sulfonylureas	TID dosing; some hypoglycemic risk; not generic
Thiazolidinediones	Pioglitazone, rosiglitazone	Reduce insulin resistance, especially in peripheral tissues	For pioglitazone: beneficial effects on lipids and positive CV outcomes demonstrated	Weight and adiposity gain; fluid retention; risk of congestive heart failure For rosiglitazone: increased risk of MI
α -Glucosidase inhibitors	Acarbose, miglitol	Inhibit intestinal carbohydrate processing	Weight neutral; slow meal-associated glucose appearance	GI side effects (flatulence, cramping, diarrhea); TID dosing; not generic
Amylin analogs	Pramlintide	Slow gastric emptying; enhance satiety	Slow meal-associated glucose appearance	GI side effects (nausea, vomiting); injected; TID dosing; efficacy lower than that of other classes
Glucagonlike peptide 1 (GLP-1) analogs	Exenatide, liraglutide	Enhance meal-associated insulin release; reduce glucagon levels; slow gastric emptying; enhance satiety	Glucose-dependent effects on insulin and glucagon (decreased hypoglycemic risk); weight loss	GI side effects (nausea, vomiting); injected
Dipeptidyl peptidase IV inhibitors	Sitagliptin, vildagliptin	Inhibit degradation of GLP-1 and GIP, raising endogenous levels of these hormones	Weight neutral; oral agents (compare with GLP-1 analogs)	Little clinical experience to date

^a TG=triglyceride, GI=gastrointestinal, TID=3 times daily, CV=cardiovascular, MI=myocardial infarction, GIP=glucose-dependent insulinotropic polypeptide.

The development of multiple therapeutic approaches to the treatment of both type 1 and type 2 diabetes has enhanced the capacity to maintain blood glucose levels closer to treatment goals. Tight control of blood glucose levels significantly reduces the incidence of diabetic complications,⁸⁻¹⁰ as reviewed elsewhere in this series. However, the availability of various therapeutic choices also imposes on the patient and health care provider the need to better understand how these therapies act in order to anticipate potential undesirable consequences of exercise sessions. Studies of tight glycemic control in sedentary people with diabetes have illustrated the

undesirable effect that occurs as plasma glucose levels are regulated closer to goal levels—that is, an increasing propensity for hypoglycemia.^{4,7} Neurons rely on glucose as their primary energy source. When plasma glucose levels fall below the lower limit of fasting values (ie, below ~70 mg/dL [~ 4 mM]), central nervous system function is impaired. Symptoms, which include irritability, confusion, dizziness, slurred speech, lethargy, and blurred vision, become progressively more severe as blood glucose levels continue to decrease. If blood glucose levels become very low, seizures and coma can occur. Other symptoms of hypoglycemia are secondary to defense systems

that attempt to counteract the decline in blood glucose through activation of the sympathetic nervous system. These symptoms include tremor, sweating, hunger, and increased heart rate.

Exercise in people with diabetes also presents challenges to glycemic control. One of the beneficial effects of exercise on glucose homeostasis is a marked stimulation of blood glucose utilization during and after exercise, as reviewed elsewhere in this series. However, the net effect of exercise on blood glucose levels in diabetes depends on several factors, such as starting levels of glycemia, type and duration of exercise, and type and

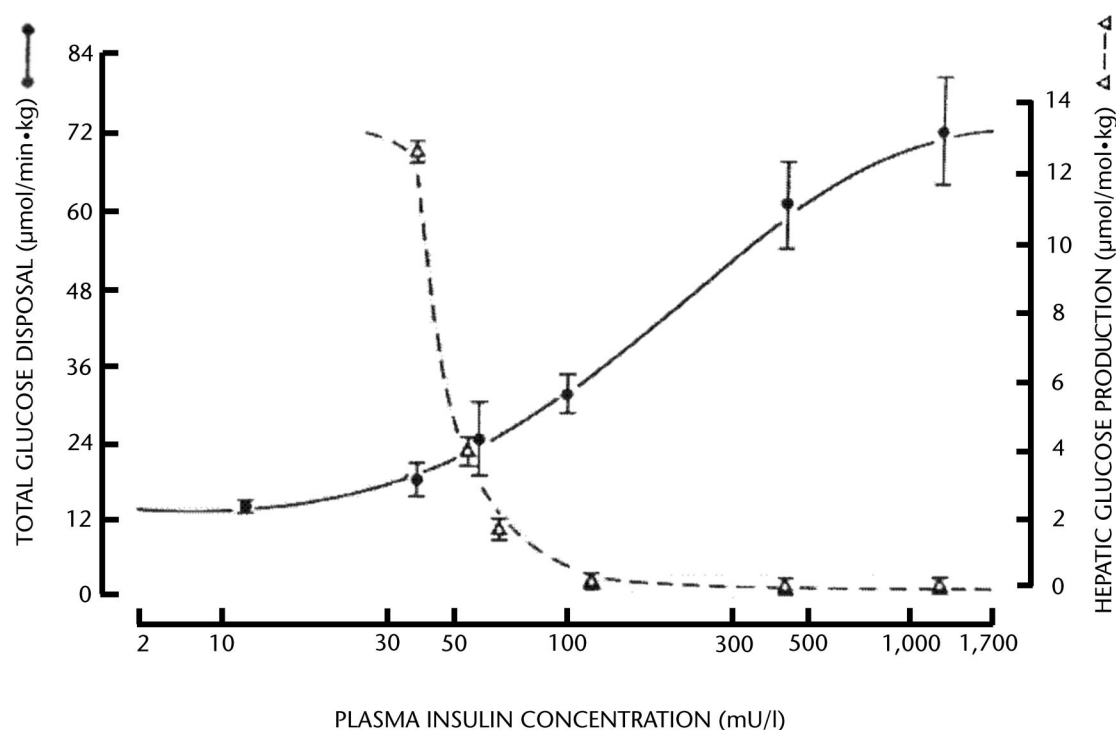


Figure 1.

Dose-response curves for insulin-mediated inhibition of hepatic glucose production and stimulation of whole-body glucose disposal in people without diabetes. Two key effects of insulin in lowering blood glucose levels are shown. Increases in insulin concentrations in the blood inhibit the release of glucose from the liver into the circulation (dashed line) and stimulate the uptake of glucose into insulin-sensitive tissues, such as skeletal muscle and adipose tissue (solid line). In concert, these actions result in reduced levels of glucose in the blood. Insulin levels are increased after a meal or after a therapeutic intervention, such as insulin injection or administration of drugs that stimulate insulin secretion from the pancreas (such as sulfonylureas). Insulin levels are presented as those in the circulatory compartment most relevant for liver or muscle: for whole-body glucose disposal, insulin concentrations in the systemic circulation are shown, whereas for hepatic glucose output, the dose-response curve is displayed relative to concentrations in the hepatic portal circulation. Reprinted with permission from Ferrannini E, DeFronzo RA. Insulin actions in vivo: glucose metabolism. In: Alberti KGMM, DeFronzo RA, Keen H, et al, eds. *International Textbook of Diabetes Mellitus*. 2nd ed. Chichester, United Kingdom: John Wiley & Sons Ltd; 1992. Copyright 2005, Wiley.

timing of antidiabetic medications. Insulin plays a critical role in regulating hepatic glucose output during many (but not all) forms of exercise and can also modulate peripheral glucose uptake during exercise and recovery. Medications that control plasma insulin levels present the greatest challenge to the management of plasma glucose levels when patients with diabetes exercise, as outlined below.

Insulin levels are altered by certain forms of exercise. In people with diabetes, a failure to adequately adjust medications or carbohydrate supplementation can result in inappropriate swings in blood glucose

levels, either too low or too high, depending on the factors involved. Acutely, the most serious danger to the health of a person with diabetes is hypoglycemia, for the reasons noted above. However, circumstances that result in inappropriate elevations in blood glucose levels (such as excessive carbohydrate supplementation or too large a reduction in insulin dosage) also have adverse implications. Knowledge of the factors that affect glucose metabolism is critical for designing strategies to minimize inappropriate swings in glycemia. Coupled with frequent self-monitoring of blood glucose levels, this knowledge can lessen the likelihood that exercise will

have deleterious effects on glycemic control.

Effects of Regular Aerobic Exercise on Glycemic Control

A full review of studies demonstrating the power of aerobic exercise in the management of diabetes is not provided here; more information can be obtained from other reviews.¹¹⁻¹³ In brief, resting skeletal muscle prefers free fatty acids as an energy source, particularly in the postabsorptive state (ie, periods between meals, after the most recent meal has been processed). Exercise induces a

shift to a mixture of free fatty acids, glycogen stores, and circulating glucose; the balance among these 3 sources varies with the duration and intensity of physical activity.^{13,14}

Circulating glucose is routed into working skeletal muscle through several complementary mechanisms.^{13,15} Contraction of skeletal muscle stimulates glucose transport and metabolism into working muscle through an insulin-independent pathway. Exercise has additional effects that enhance the ability of insulin to activate glucose transport into muscles that have exercised; this effect can persist for many hours after physical activity has ceased. The delivery of glucose to working muscle is facilitated by increased blood flow to exercising muscles. When aerobic exercise is repeated on a regular basis (ie, training), muscles recruited by the training stimulus undergo additional adaptations that involve the synthesis of key components needed for glucose uptake and metabolism (eg, the GLUT4 glucose transporter and enzymes, such as hexokinase, that control the uptake and metabolism of glucose in muscle).

These responses to exercise facilitate the clearance of glucose from the circulation and the metabolism of glucose in exercised skeletal muscle (oxidation during exercise; resynthesis of glycogen stores after exercise has been completed). In people with diabetes, plasma glucose levels decrease during and shortly after a bout of exercise. Indexes of long-term glycemic control, such as glycosylated hemoglobin (HbA1c, the level of which is elevated in diabetes), are improved (ie, lowered) when exercise is performed regularly.^{11–13}

Continuous Low- to Moderate-Intensity Exercise Glucoregulation During Exercise in People Without Diabetes

When people who do not have diabetes exercise at low to moderate

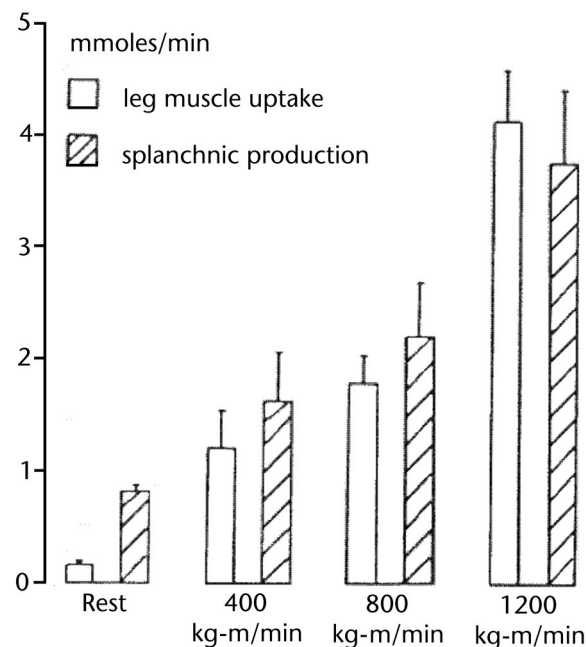


Figure 2.

During exercise at low to moderate intensity, increases in glucose production are closely matched by increases in peripheral glucose uptake. Splanchnic glucose production (representative of liver glucose output) and leg glucose uptake (representative of peripheral glucose disposal) are shown at rest and at different levels of low- to moderate-intensity exercise. With each increase in exercise workload, the rate of glucose disappearance (attributable to uptake into the working muscles) was very similar to the rate of glucose release from the liver (into the blood). As a result, blood glucose levels remained approximately constant during low- to moderate-intensity exercise. Leg glucose uptake and splanchnic glucose production are shown for people without diabetes at rest and after performing cycle ergometer exercise for 40 minutes at different workloads. Data are expressed as mean $\pm$ SE. Reprinted with permission of the American Society for Clinical Investigation from Wahren J, Felig P, Ahlborg G, et al. Glucose metabolism during leg exercise in man. *J Clin Invest.* 1971;50:2715–2725. Copyright 1971.

workloads, plasma glucose levels are maintained at or near preexercise levels.¹⁴ Euglycemia (ie, a normal glucose level) is maintained by close correlation of peripheral glucose uptake and hepatic glucose output across a range of exercise intensities up to approximately 80% of maximal oxygen uptake ($\dot{V}O_2\text{max}$). As workloads are increased over this range, muscle glucose uptake increases and the production of glucose by the liver is enhanced to a similar extent¹⁶ (Fig. 2). Moderate workloads increase glucose utilization by about 3 mg/kg of body weight per minute; if this process were not counterbalanced by an increased hepatic supply of glucose,

then overt hypoglycemia would occur within about 30 minutes¹¹ (a theoretical illustration is shown in Fig. 3). Glucose is generated by the liver through 2 processes: (1) mobilization from hepatic glycogen stores as a result of glycogenolysis (which predominates earlier during exercise) and (2) synthesis of new glucose from smaller precursor molecules through gluconeogenesis (which assumes greater importance as exercise duration increases). Hypoglycemia rarely occurs in people who do not have diabetes unless exercise is quite prolonged—that is, when liver glycogen stores become depleted and the exercise workload exceeds the ability of glu-

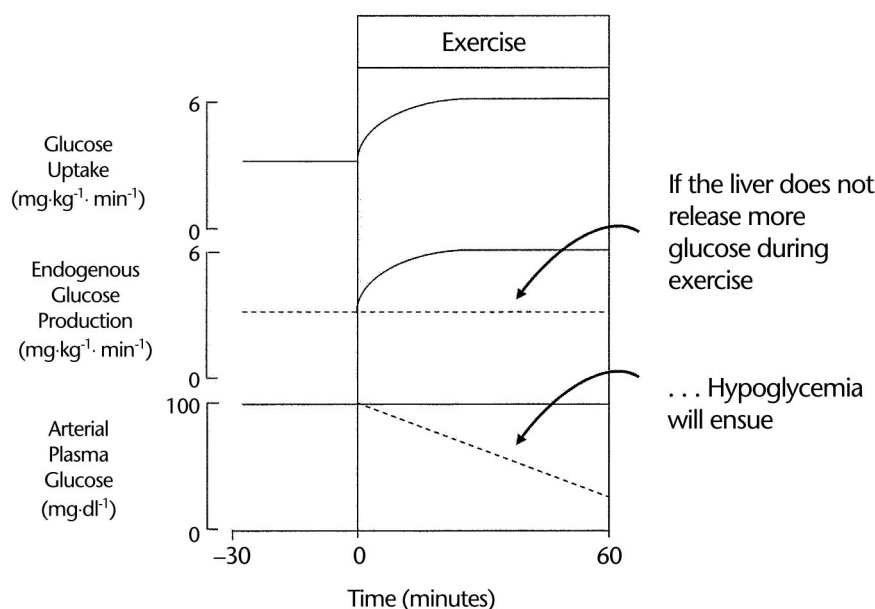


Figure 3.

Theoretical impact on plasma glucose levels of a failure to increase hepatic glucose production during exercise. Solid lines represent changes in glucose uptake and endogenous (ie, hepatic) glucose production and their impact on plasma glucose levels in people who were healthy and were performing moderate-intensity exercise. Dashed lines represent what would ensue if the liver did not increase the rate of glucose production during the exercise bout. If glucose uptake into the working muscles were not counterbalanced by a corresponding increase in liver glucose output, then blood glucose concentrations would decline from baseline levels and could reach hypoglycemic levels. Reprinted with permission of the American Diabetes Association from Sigal RJ, Kenny GP, Wasserman DH, et al. Physical activity/exercise and type 2 diabetes. *Diabetes Care*. 2004;27:2518–2539. Copyright 2004, American Diabetes Association.

coneogenesis to meet peripheral demands.

Figures 4 and 5 illustrate changes in key hormones and indexes of glucose metabolism during low- to moderate-intensity exercise (50% of $\dot{V}O_{2\max}$, performed for 40 minutes; open symbols) and during high-intensity exercise (87% of $\dot{V}O_{2\max}$, sustained for ~15 minutes; closed symbols) (the response to high-intensity exercise is discussed below). The increase in hepatic glucose output observed during low- to moderate-intensity exercise is controlled primarily by changes in insulin and glucagon secretion. This is a key point in understanding the challenges of exercise in diabetes, as discussed below. Exercise at these intensity levels results in decreased

insulin secretion (likely mediated mostly by the increase in adrenergic tone to the pancreas) and increased glucagon secretion.¹⁷ The decrease in insulin secretion is thought to be important for the activation of hepatic glycogenolysis, and the increase in glucagon secretion enhances both glycogenolysis and gluconeogenesis. In addition, exercise increases the generation and delivery to the liver of gluconeogenic precursors. The interaction between these 2 pancreatic hormones is responsible for (nearly) the entire increase in the liver glucose supply. For example, the ability of glucagon to enhance glucose output is significantly magnified when insulin levels are allowed to decline in their usual fashion during exercise, compared with experimental circum-

stances in which insulin is maintained at baseline (preexercise) levels.¹⁷

In exercise of relatively short duration, increases in arterial plasma glucagon levels are quantitatively modest. It is not the arterial concentrations of insulin and glucagon that control liver glucose output, but rather the concentrations of these pancreatic hormones in the hepatic portal vein, into which they are secreted.¹⁷ The concentrations of these 2 hormones are higher in the portal vein than in the overall systemic circulation. Animal studies (in which portal vein blood can be much more readily sampled) have revealed that alterations in the portal concentrations of these 2 hormones—in the range occurring physiologically—are the critical determinants controlling hepatic glucose supply during low- to moderate-intensity exercise.^{18,19} If the portal vein levels of insulin and glucagon are deliberately fixed at preexercise levels, then moderate-intensity exercise can lead to significant decreases in plasma glucose levels.²⁰ Mechanistically, this result derives, in large measure, from direct effects of portal vein insulin and glucagon concentrations on the liver. If the usual exercise-triggered decrease in portal vein insulin concentrations is artificially overridden and portal vein insulin concentrations are instead increased within the physiological range (Fig. 6), then the exercise-induced stimulation of liver glucose production is instead rapidly and substantially suppressed.²¹ In contrast, hyperinsulinemia in the arterial circulation without a corresponding increase in the portal vein causes only a modest and delayed reduction in hepatic glucose output (most likely the result of a secondary effect of insulin [lowering free fatty acid levels]).

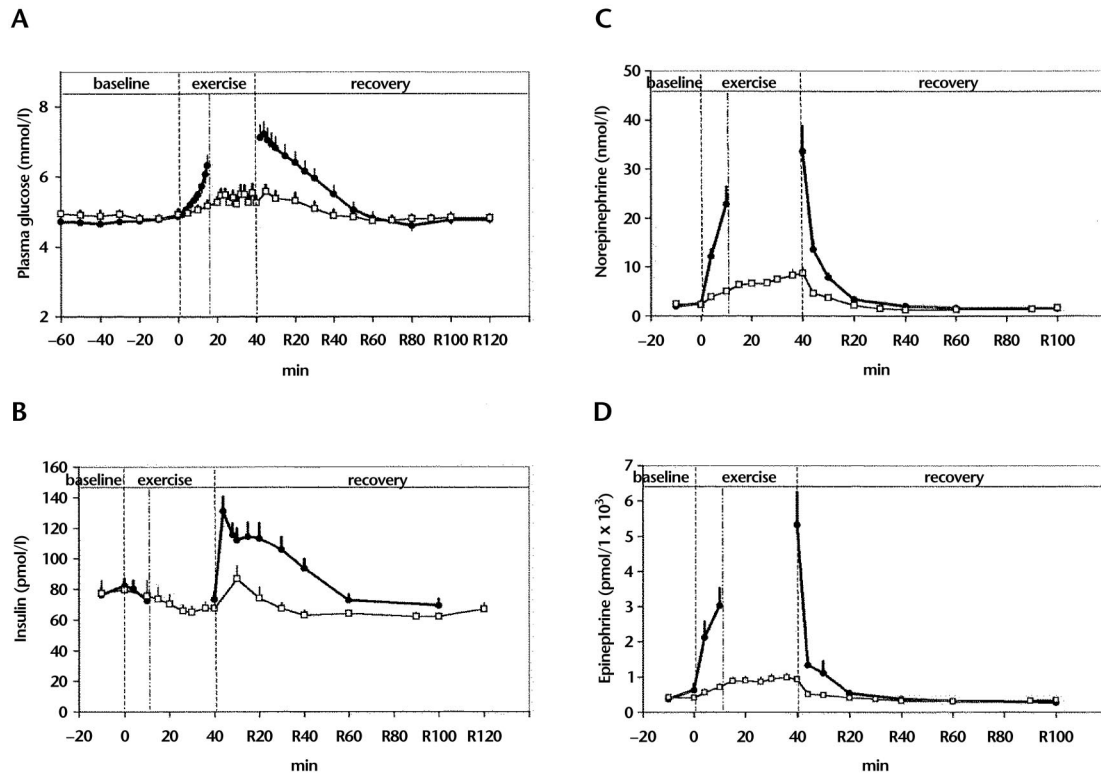


Figure 4.

Plasma glucose, insulin, and adrenergic hormone levels during and after either moderate- or high-intensity exercise in people without diabetes. Measurements were obtained in young male subjects at rest, during exercise, and for an additional 2 hours after the cessation of exercise. A rest period (baseline) was followed by exercise at the 2 durations, as shown between the vertical broken lines. Subjects exercised for 40 minutes at moderate intensity (50% of maximal oxygen uptake [$\dot{V}O_{2\max}$]) (□) or performed 15 minutes of high-intensity exercise (87% of $\dot{V}O_{2\max}$) (●) on a cycle ergometer. A break in the line representing high-intensity exercise was inserted to allow matching of the postexercise recovery (R) periods (R0–R120 minutes) for the 2 exercise protocols. Data are expressed as mean $\pm$ SE. (A) Plasma glucose. The levels changed very little with moderate-intensity exercise. In contrast, glucose levels increased sharply with high-intensity exercise, especially during the recovery period. (B) Plasma insulin. A gradual decline in levels with moderate-intensity exercise and a return to baseline levels during early recovery were observed. With high-intensity exercise, an initial downward trend was followed by a marked rise during the recovery period. (C and D) Plasma norepinephrine (C) and plasma epinephrine (D). The levels of both catecholamines increased about 3-fold during moderate-intensity exercise and to a much greater extent during high-intensity exercise, with a rapid return to baseline levels once exercise was over. The substantial increases in catecholamine levels that occurred with high-intensity exercise are believed to be critical drivers of hepatic glucose output (see the text for details). Reprinted with permission of the American Diabetes Association from Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. *Diabetes*. 2002;51(suppl 1):S271–S283. Copyright 2002, American Diabetes Association.

Effects of Low- to Moderate-Intensity Exercise on Glucoregulation in People With Diabetes

In patients who have type 2 diabetes and are taking medications that do not act by elevating (endogenous or exogenous) insulin levels, the effect of low- to moderate-intensity exercise varies with the starting levels of glycemia. During exercise, patients with slightly or moderately elevated

glucose levels generally experience a decline in plasma glucose levels that does not result in hypoglycemia.¹³ The decline in blood glucose levels under these conditions occurs because peripheral glucose uptake increases more than hepatic glucose output.²² If exercise is superimposed shortly after a meal has been ingested, then the usual meal-induced increase in glycemia is blunted.²³ For patients still possessing reasonable

pancreatic function, exercise results in a decline in blood glucose levels concomitantly with a decline in plasma insulin levels.²³

Because muscle contractile activity stimulates glucose transport activity partly through an insulin-independent mechanism,^{24–27} exercise is useful in lowering plasma glucose levels in patients lacking insulin secretory capacity, displaying insulin resistance,

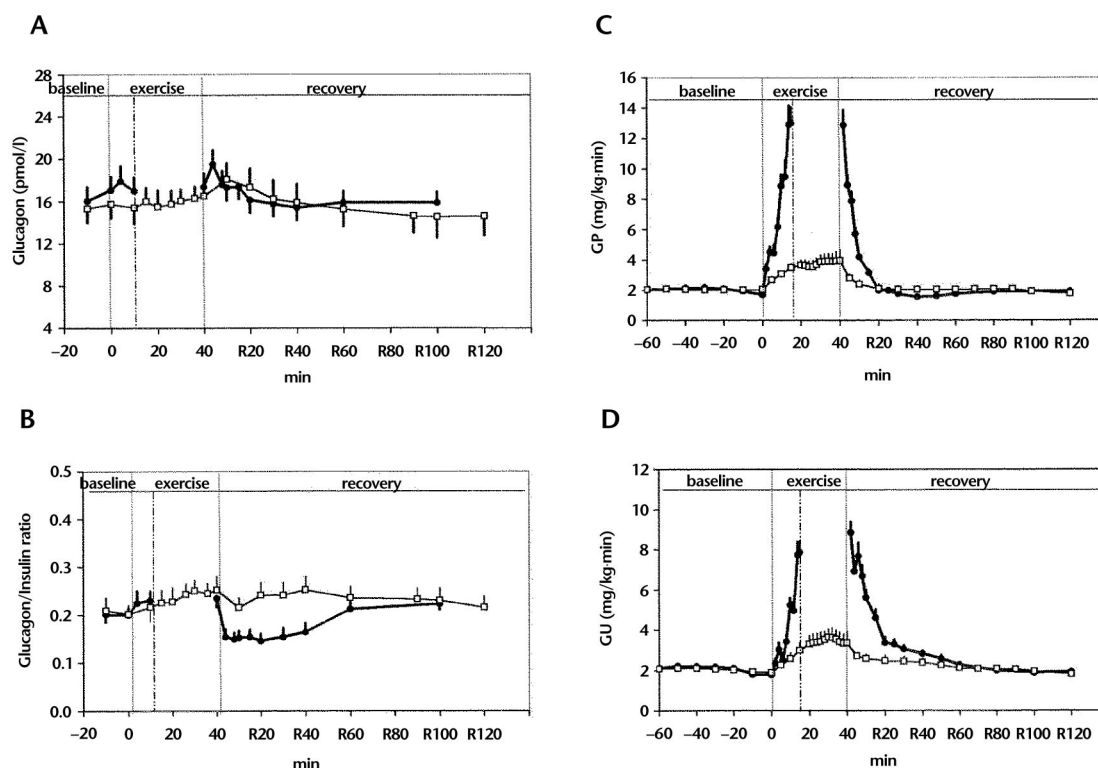


Figure 5.

Plasma glucagon levels, glucagon-to-insulin molar ratio, hepatic glucose production (GP), and peripheral glucose utilization (GU) during and after either moderate- or high-intensity exercise in people without diabetes. Measurements were obtained in young male subjects at rest, during exercise, and for an additional 2 hours after the cessation of exercise. A rest period (baseline) was followed by exercise at the 2 durations, as shown between the vertical broken lines. Subjects exercised for 40 minutes at moderate intensity (50% of maximal oxygen uptake [$\dot{V}O_{2max}$]) (□) or performed 15 minutes of high-intensity exercise (87% of $\dot{V}O_{2max}$) (●) on a cycle ergometer. As in Figure 4, a break in the line representing high-intensity exercise was inserted to permit plotting of the recovery (R) period (R0–R120 minutes) starting from the cessation of exercise. Data are expressed as mean $\pm$ SE. (A) Plasma glucagon. Changes were minimal at either exercise intensity. (B) Glucagon-to-insulin molar ratio. This ratio increased slightly during exercise (primarily because of the decrease in insulin levels [Fig. 4B]). This ratio returned to baseline during the recovery period after moderate-intensity exercise and declined markedly after high-intensity exercise. The latter finding was entirely attributable to postexercise hyperinsulinemia (Fig. 4B). (C and D) Rates of GP (C) and GU (D). GP and GU each doubled during moderate-intensity exercise. In contrast, GP increased 7-fold and GU increased 4-fold during high-intensity exercise (note the different y-axis scales); the greater magnitude of the increase in GP than of the increase in GU accounted for the hyperglycemia seen with high-intensity exercise. Reprinted with permission of the American Diabetes Association from Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. *Diabetes*. 2002;51(suppl 1):S271–S283. Copyright 2002, American Diabetes Association.

or both, if conditions are appropriately controlled. If people with diabetes are ketotic and severely hyperglycemic as a result of significant insulin underdosing, then exercise aggravates the existing hyperglycemia. In contrast, if people with either type 1¹⁴ or type 2^{28,29} diabetes are adequately treated with insulin and display mild to moderate hyperglycemia, then a session of vigorous exercise can lower blood glucose levels.

The potential beneficial effects of exercise on glucose levels are counterbalanced by potential risks to people with insulin-dependent diabetes. In the early 20th century, it was recognized that exercise performed by people with insulin-deficient diabetes under certain conditions could result in significant hypoglycemia.³⁰ Patients with type 1 and type 2 diabetes requiring exogenous insulin therapy, insulin secretagogue therapy, or both face unique challenges

during exercise. Insulin levels in these patients are derived exclusively or predominantly from their medications; as a result, they do not decrease in response to exercise. Patients whose insulin levels significantly exceed the fasting baseline level at the time of exercise tend to be overtreated with insulin relative to this physiological challenge (ie, they operate at inappropriately high points on their hepatic and muscle insulin dose-response curves). With-

out the normal exercise-induced decline in portal vein insulin levels, hepatic glucose production remains suppressed and cannot increase sufficiently to match the increase in peripheral glucose utilization. As a result, blood glucose levels decline, potentially to hypoglycemic levels. Under these conditions, hypoglycemia can develop despite adequate hepatic glycogen reservoirs. The situation can be further exacerbated if peripheral insulin levels are inappropriately elevated; higher systemic levels of insulin also stimulate greater glucose uptake into peripheral tissues, including muscle beds not activated by exercise.

The importance of prevailing insulin levels at the time of exercise in people who have diabetes and are taking insulin or insulin secretagogues is now well recognized. A few selected examples of data underlying the current understanding are discussed.

In a study of adults with diabetes, an artificial endocrine pancreas (AEP) capable of adjusting the insulin infusion in relation to blood glucose levels after a meal was used.³¹ Subjects without and subjects with diabetes were given breakfast; 45 minutes later, they performed a 45-minute session of moderate-intensity exercise. Circulating glucose and insulin levels in subjects with diabetes and using the AEP mirrored those in subjects without diabetes, increasing in response to the meal and returning to the baseline (premeal) levels during exercise. In another group of subjects, the AEP was instead programmed to deliver sufficient insulin to respond to the meal challenge but at a constant rate throughout the study; that is, the insulin levels were not allowed to decline during the exercise challenge. In the latter subjects, the exercise bout resulted in a steady decline in glucose levels to below the premeal level, such that the subjects experienced symptomatic hypoglycemia.

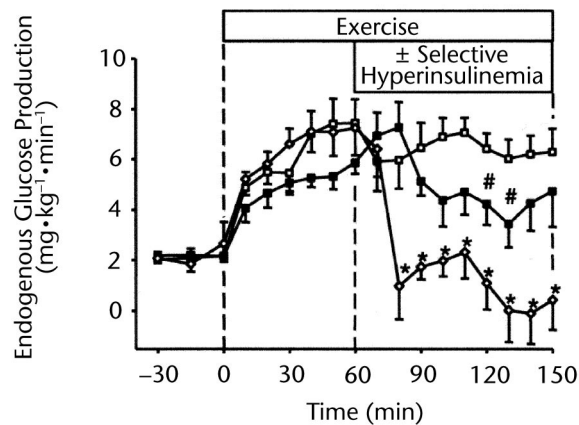


Figure 6.

Insulin excess in the hepatic portal circulation suppresses hepatic glucose production during exercise more rapidly and to a much greater extent than elevated insulin levels in the systemic circulation. Insulin levels in dogs were manipulated through pharmacological suppression of endogenous production followed by replacement in either the hepatic portal or the peripheral circulation. Dogs were studied at rest (−30 to 0 minutes) and during moderate-intensity treadmill exercise. During the rest period, insulin was replaced at “basal” levels (ie, those seen in the fasting, sedentary state). During the first 60 minutes of exercise, insulin was replaced to levels normally seen during exercise (ie, insulin levels were gradually reduced, as during moderate-intensity exercise). During the final 90 minutes of exercise, this simulation was continued (□) or increased to create mild hyperinsulinemia in the peripheral circulation alone (■) or mild hyperinsulinemia in the artery and portal vein (◇). Insulin levels higher than those normally present during exercise resulted in reduced endogenous glucose production (■ and ◇). However, the suppression of liver glucose output was greatest when insulin levels were increased in the hepatic portal circulation (◇), the blood compartment that receives insulin released from the pancreas and that, in turn, perfuses the liver. Data are expressed as mean ± SE. *Significantly different from corresponding time points in other groups ($P < .05$). #Significantly different from corresponding time points in dogs with simulated arterial and portal vein insulin replacement ($P < .05$). Reprinted with permission of Lippincott Williams & Wilkins (<http://lww.com>) from Camacho RC, Galassetti P, Davis SN, et al. Glucoregulation during and after exercise in health and insulin-dependent diabetes. *Exerc Sport Sci Rev.* 2005;33:17–23. Copyright 2005, American College of Sports Medicine.

Studies in children with type 1 diabetes confirmed the risk of exercise under conditions in which exogenous insulin levels are not adjusted. For example, in subjects treated with a subcutaneous insulin infusion designed to bring preexercise glucose levels into the normal range, a 45-minute moderate-intensity exercise session during which the insulin infusion rate was kept constant resulted in a substantial further decrease in blood glucose levels, leading to hypoglycemia, in a significant proportion of subjects.³²

In another study, the effect of moderate-intensity aerobic exercise

(treadmill walking in 15-minute segments totaling 60 minutes of activity) designed to mimic after-school activity, performed in the afternoon 4 hours after a lunch meal, was evaluated.³³ Children and adolescents treated with either an insulin pump or a combination of basal and short-acting insulin analogs were studied on both a rest day and an exercise day. Insulin regimens were deliberately kept the same on the 2 study days. On the exercise day, 83% of the subjects experienced a decline in plasma glucose levels of at least 25% from the baseline (average drop of 40% across all subjects). Hypoglycemia

was common (30% of the subjects had plasma glucose levels of <60 mg/dL or required glucose administration during or after exercise) and relatively rapid in onset (33% of episodes occurred within 30 minutes on the exercise day). The lower the baseline glucose levels were, the greater the proportion of children who experienced hypoglycemia.

In contrast to the critical role of portal vein hormones in controlling liver glucose output, it is the peripheral concentration of insulin that stimulates glucose uptake into muscle and adipose tissue after meals and into previously activated muscle fibers when insulin sensitivity has been enhanced by exercise. Thus, the type of insulin replacement and its relative effect on portal versus systemic insulin levels affect glycemic control after exercise.

Several factors can contribute to dysregulated glucose control during and for several hours after exercise in insulin-treated patients, as outlined by Camacho et al¹⁷:

- The lack of a decline in insulin secretion during exercise inappropriately accentuates the effects of insulin on the liver and peripheral tissues
- Exercise can accelerate the absorption of insulin injected at a subcutaneous site located near the muscles used during exercise
- The exercise-mediated enhancement of the action of insulin magnifies the consequences of inappropriately elevated insulin levels during exercise as well as in the postexercise period, when insulin sensitivity can remain enhanced for many hours; the net effect depends partly on the pharmacokinetics of the particular insulin preparation or insulin secretagogue used

In addition to the threat posed by excessively high insulin levels during

exercise, it is now recognized that when people experience episodes of hypoglycemia before a bout of exercise, their ability to subsequently mount counterregulatory responses to impending hypoglycemia during exercise is blunted, rendering them more susceptible to exercise-induced hypoglycemia.^{34,35} Conversely, prolonged endurance exercise sessions can impair the counterregulatory responses to subsequent hypoglycemic challenges.^{34,35} The latter phenomenon, combined with the induction by exercise of a prolonged enhancement in insulin sensitivity, may be an important contributor to the hypoglycemia seen during the evening after an afternoon exercise session in people with insulin-dependent diabetes.³⁶

Minimizing Hypoglycemic Events During Low- to Moderate-Intensity Exercise in Patients Taking Insulin

For patients who have type 1 diabetes as well as those who have type 2 diabetes and require exogenous insulin, there is no single recommendation specifying adjustments for exercise. The glycemic response to physical activity and the propensity for hypoglycemia during or after an exercise session are influenced by several factors^{37–40}:

- Type of insulin (or insulin combinations) and corresponding pharmacokinetic and pharmacodynamic properties
- Time elapsed since last insulin dose
- Form of administration (injection, inhalation, or insulin pump)
- Injection site and proximity to exercising limbs
- Type, duration, and intensity of exercise
- Amount of muscle mass involved in the activity
- Level of physical fitness
- Preexercise glucose levels
- Patency of counterregulatory responses

- With carbohydrate supplementation: type of carbohydrate (simple or complex), rate of absorption, and timing of administration

Because of the complexity of factors that can influence glucose utilization, guidelines must be relatively general in nature. Appendix 1 lists factors to consider in initiating an exercise program. Discussed below are some key points.

As a first step in the initiation of an exercise regimen or sporting activity, patients should be assessed for conditions that might contraindicate certain types of exercise or that could increase the risk of specific types of injury.^{7,13,37} These conditions include cardiovascular risk factors (because diabetes can enhance the propensity for cardiovascular disease in the presence of known risk factors), autonomic and peripheral neuropathies, and retinopathy. The presence of risk factors or diabetic complications should not preclude the use of an exercise program. When such conditions are present, exercise plans can still be prescribed but should be tailored to lessen the specific risks involved. For example, people at high risk of cardiovascular disease should be encouraged to begin with short periods of low-intensity exercise and then gradually increase the duration and intensity of their exercise sessions. Patients with autonomic neuropathy should perform only light exercise until a more thorough cardiac evaluation has been performed. For additional information on exercise in these pathologies, see the article by Cade⁴¹ in this issue. Patients with peripheral neuropathy are at higher risk of problems when performing weight-bearing activities, but non-weight-bearing activities, such as cycling, swimming, or upper-body exercise, can be prescribed.

For additional information on exercise for people with diabetes and peripheral neuropathy, see the article by LeMaster et al⁴² in this issue. Even patients with significant renal impairment requiring dialysis can be encouraged to use modalities appropriate for specific aspects of their disease.³⁷

Once an exercise program has been chosen, patients can prepare for their exercise sessions. Glucose levels should be checked shortly before patients begin exercise sessions. To minimize the risk of uncontrolled hyperglycemia, if blood glucose levels are greater than 250 mg/dL and urinary ketone body levels are moderate or high (indicating that insulin levels are very low), then the exercise session should be postponed until appropriate therapeutic measures have minimized ketone production and reduced glucose levels.^{7,39} Even if ketone levels are not high, when blood glucose levels exceed 300 mg/dL, patients should consider postponing exercise until blood sugar levels are brought under better control. Likewise, patients should not exercise when blood glucose levels are too low. Supplemental carbohydrates should be administered if pre-exercise glucose concentrations are less than 100 mg/dL.⁷

When patients are adjusting to a new exercise program, blood glucose levels should be checked shortly before, during (if practical), and immediately after the exercise session. Because exercise can result in a long-lasting enhancement of insulin action, additional checks should be made several hours after the exercise has been completed. Measurements should be repeated with each exercise session until the typical glycemic response to a given activity is understood. Even after a regular routine has been established, periodic checks should be performed because changes in factors such as diet,

medication, and body weight can influence blood glucose levels. Significant alterations to the usual exercise pattern (such as type of sport, duration, and intensity) also necessitate additional checks of the blood glucose profile.

If the exercise results in overt hypoglycemia or a tendency for hypoglycemia, then the insulin dose should be adjusted, carbohydrate supplementation should be given, or both. For exercise planned in advance, several options are available:

- The dose of insulin can be reduced beforehand
- Injections can be made distant from the exercising limbs
- Carbohydrates can be ingested before exercise, during exercise, or both

All of these strategies can be combined; it should be recognized that these strategies are dependent on each other; for example, insulin dose reductions should be smaller if undertaken concomitantly with carbohydrate supplementation. For exercise not planned in advance (which is particularly common in children), carbohydrate supplementation is the only practical option unless patients use an insulin pump; in the latter situation, the rate of insulin infusion can be decreased or the pump can be turned off entirely.⁴³

It is beyond the scope of this discussion to review all of the studies that have evaluated issues such as various exercise protocols, insulin regimens, timing of exercise onset relative to medications, and carbohydrate supplementation. A few examples are presented to help readers understand the issues.

In a common diabetes treatment regimen, a long-acting insulin is administered to meet basal insulin requirements over a prolonged time period,

accompanied by meal-associated administration of a short-acting insulin. If the patient has already administered a normal dose of a fast-acting insulin analog, then it is preferable to avoid exercise for several hours. In one study, the effects of regular insulin and the short-acting analog insulin lispro, taken at their standard premeal intervals in adults with type 1 diabetes, were compared.⁴⁴ When exercise was initiated 40 minutes after breakfast, insulin lispro lowered glucose levels 2.2-fold more than regular insulin; that is, the fast-acting analog showed more-pronounced glucose lowering at a time associated with its peak levels in plasma. In contrast, when exercise was performed 3 hours after breakfast (a time at which the levels of the analog in plasma are known to be substantially lower than peak levels), insulin lispro lowered glucose levels only half as much as regular insulin.

An alternative approach is to reduce the dose of short-acting insulin if exercise is to be performed during a time period when levels of the analog in plasma will be elevated. Rabasa-Lhoret et al⁴⁵ evaluated the effects of different reductions in insulin lispro doses and different exercise intensities in a small number of adults who had well-controlled type 1 diabetes and who began exercising 90 minutes after a breakfast meal. Because the patients already had achieved good control (mean HbA1c of 6.1%), the investigators targeted a postexercise plasma glucose level that was similar to the premeal level. Exercise intensity was varied from 25% to 75% of $\dot{V}O_{2\max}$. Even at the lowest exercise workload (25% of $\dot{V}O_{2\max}$ for 60 minutes), hypoglycemia ensued when the normal dose of lispro was not adjusted, and a 50% dose reduction provided optimal postexercise glycemia (Fig. 7). The magnitude of the dose reduction needed for optimal glucose control increased with both the intensity

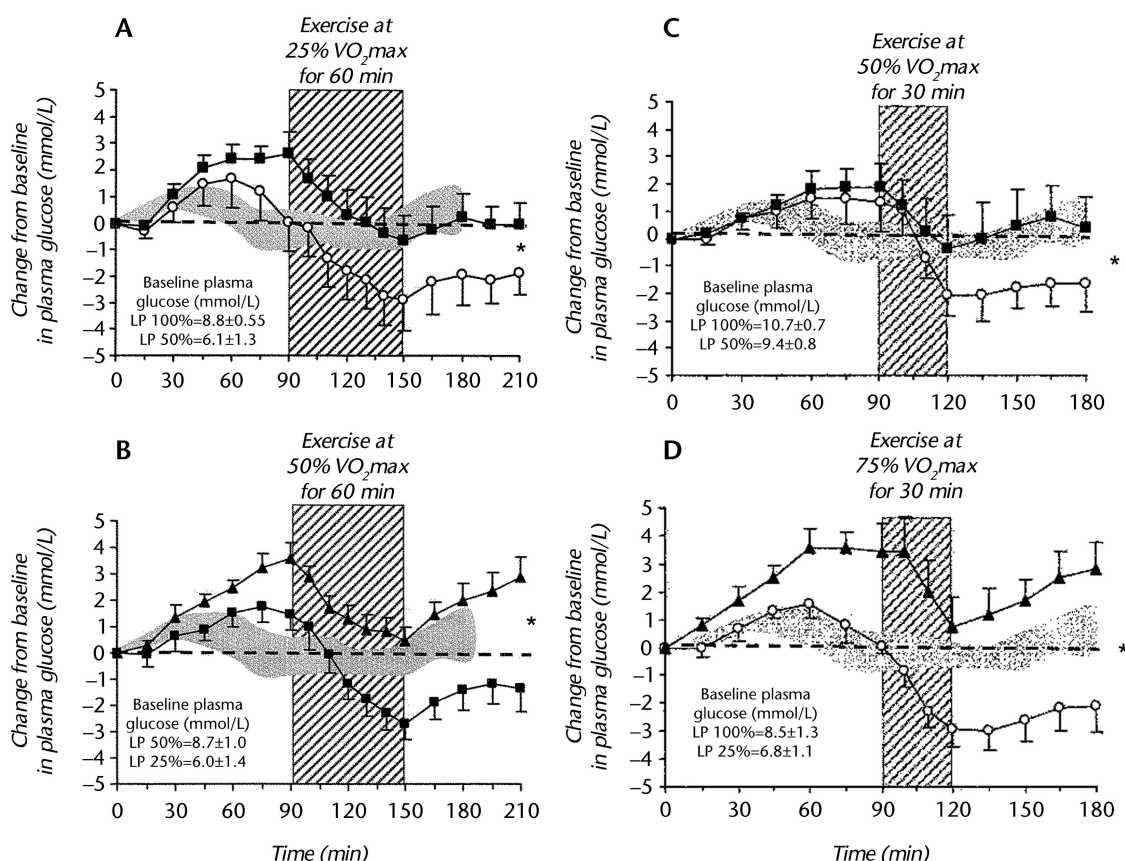


Figure 7.

Changes in plasma glucose levels in subjects with type 1 diabetes before, during, and after exercise at different intensities and durations and with various levels of reductions in the dose of insulin lispro (LP). Young males with type 1 diabetes on a basal-bolus insulin regimen were treated just before the ingestion of a standardized breakfast meal with their usual full dose of LP (LP 100%) or fixed percentages of this dose on different occasions. At 90 minutes after the meal, they performed cycle ergometer exercise (▨) for 30 or 60 minutes at different intensities. (Left) Subjects exercised at 25% (A) and at 50% (B) of maximal oxygen uptake ($\dot{V}O_{2max}$) for 60 minutes after premeal LP 100% (○), LP 50% (■) (ie, a 50% reduction in insulin dose), and LP 25% (▲) (ie, a 75% reduction in insulin dose). (Right) Subjects exercised at 50% (C) and at 75% (D) of $\dot{V}O_{2max}$ for 30 minutes after premeal LP 100% (○), LP 50% (■), and LP 25% (▲). The shaded area represents mean $\pm$ SEM postprandial plasma glucose levels at rest. Reductions in the LP dose resulted in higher meal-associated increases in plasma glucose levels (increases seen before the onset of exercise) but lessened the tendency for exercise to result in decreases in blood glucose levels to below the premeal (time 0) level. Generally speaking, the greater the increase in exercise duration, intensity, or both, the greater the exercise-induced decrease in plasma glucose levels and, therefore, the more the insulin dose should be reduced to avoid decreases in plasma glucose levels from the premeal level. Data are expressed as mean $\pm$ SEM. * $P < .05$, as determined by repeated-measures analysis of variance. Reprinted with permission of the American Diabetes Association from Rabasa-Lhoret R, Bourque J, Ducros F, et al. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects treated intensively with a basal-bolus insulin regimen (Ultralente-Lispro). *Diabetes Care*. 2001;24:625–630. Copyright 2004, American Diabetes Association.

and the duration of exercise. When exercise at an intensity of 50% of $\dot{V}O_{2max}$ was performed for 30 minutes, a 50% dose reduction was optimal; when exercise was sustained for 60 minutes, however, a 75% decrease in the dose resulted in optimal glycemia immediately after exercise. Under these conditions, the optimal dose reduction for a given

intensity or duration of exercise was associated with a 75% reduction in hypoglycemic episodes, compared with the results obtained for exercise without a change in the dose.

That study⁴⁵ also highlighted one of the challenges of insulin dose reduction strategies: The reduction in the dose needed to avoid excessive hy-

poglycemia during exercise may not be optimal once exercise is complete. Decreases in the lispro dose resulted in rebound increases in glycemia during the recovery period after exercise (Fig. 7); the greater the magnitude of the dose reduction, the greater the elevation in glucose levels during recovery. This complication is difficult to avoid in people

with insulin-dependent diabetes, who lack the normal minute-to-minute control of endogenous insulin secretion that is present in people who do not have diabetes. Modest postexercise increases in glucose levels, however, are far less dangerous than serious hypoglycemic episodes.

For patients using traditional mixtures of isophane insulin (neutral protamine Hagedorn) and regular insulin, the morning insulin dose can be reduced for planned exercise sessions. Exercise sessions in the higher range of moderate intensity require correspondingly larger dose reductions. For example, in one study, when adults with type 1 diabetes began exercising for 1 hour at 70% of $\dot{V}O_{2\max}$ 90 minutes after breakfast, 50% to 90% reductions in the morning insulin dose were needed to avoid exercise-related hypoglycemia.⁴⁶

For patients using insulin pumps, an additional option is to reduce the rate of insulin infusion during exercise. This option can be particularly helpful when basal insulin is the primary regulator of glycemia (eg, when it has been many hours since the last administration of a meal-associated insulin bolus, such as exercise in the late afternoon). In one study, the effect of variations in pump rate was examined in children performing moderate-intensity afternoon exercise for 1 hour.⁴⁷ Treadmill walking was undertaken on 2 different days to compare the effect of maintaining the basal pump rate with that of turning off the insulin pump completely. Hypoglycemia was common when the pump was used at normal rates; in contrast, exercise-related hypoglycemia was significantly reduced on days when subjects turned off the pump. In that scenario, the pump was not turned back on until 45 minutes after the cessation of exercise. On both days, glucose levels gradually rebounded after exercise was stopped, but on the day when the

pump was turned off, there was a greater propensity for glycemia to exceed the preexercise baseline. This situation is analogous to that discussed above with lispro dose reductions; however, with a pump, an insulin infusion can be resumed shortly after exercise has ended.

The use of carbohydrate supplementation to minimize the occurrence of hypoglycemia during and after exercise has been examined in several studies. As discussed for other interventions, such as alterations in insulin doses, an understanding of the conditions under which the studies were performed is needed to extrapolate findings to specific exercise bouts; these conditions can include insulin dose reductions, intensity and duration of exercise, and timing of exercise relative to the last medication. For example, in one study, subjects with type 1 diabetes were given breakfast 30 minutes after a normal morning injection of regular insulin; at time intervals ranging from 1 to 5.5 hours later, they began a 60-minute moderate-intensity (50% of $\dot{V}O_{2\max}$) exercise session.⁴⁸ The amount of carbohydrate supplementation required to prevent the development of hypoglycemia decreased as the time interval before the commencement of exercise increased; the reduction in the need for carbohydrate supplementation paralleled the gradual reduction in plasma insulin levels.

When a similar exercise protocol was initiated 3 hours after breakfast in subjects continuing their standard basal-bolus regimen (NPH and insulin lispro), it was concluded that carbohydrate supplementation of ~40 g was needed to maintain the desired glucose levels during exercise and the first hour of recovery.⁴⁹ Likewise, a study of exercise in children indicated that an older recommendation for 15 g of carbohydrate can be inadequate in preventing hypoglycemia

when the insulin dose has not been adjusted.³³

In the aforementioned studies, carbohydrate requirements in patients who ate breakfast and did not alter their usual insulin dose were examined. In contrast, if patients with type 1 diabetes exercise in the morning after skipping their normal morning insulin dose (resulting in low plasma insulin levels), moderate-intensity exercise for 45 minutes may result in only a small reduction in plasma glucose levels. Under these conditions, carbohydrate supplementation can actually result in significant *increases* in plasma glucose levels during exercise.⁵⁰ For patients who do not skip but instead reduce their insulin dose, an intermediate level of carbohydrate supplementation is appropriate. Suggestions for carbohydrate requirements and insulin dose reductions based on exercise intensity and duration have been proposed (eg, by Grimm et al⁵¹), but these should be considered merely potential starting points, to be modified on the basis of specific exercise conditions and on empirical measurements of glycemia. In addition, recommendations that minimize the practice of insulin dose reduction and rely primarily on the use of carbohydrate supplementation will lead to higher overall caloric intake; if common, this practice will negate the benefits of exercise to increase energy expenditure and stimulate weight loss.

Children can undergo large variations in physical activity levels that are sustained for many days or weeks, such as during school holiday periods. For those with insulin-dependent diabetes, sudden and sustained increases in energy expenditure can impose significant challenges to glycemic control. Strategies for optimizing glycemic control in settings such as summer diabetes camps have been examined in several studies. For example, in one

camp at which participants engaged in significant levels of physical activity, frequent episodes of hypoglycemia occurred despite significant (~30%) reductions in daily insulin doses.⁵² Repeated monitoring of blood glucose levels, increases in meal portions, and carbohydrate supplementation were all recommended.

In summary, real-world adjustments must be made on an empirical basis for each patient and pattern of physical activity. When possible, it is important to either delay exercise during anticipated times of peak insulin levels or make appropriate adjustments. Supplemental carbohydrate in a form that is rapidly absorbed should be kept on hand in the event of a hypoglycemic episode. More details,³⁷⁻³⁹ including a checklist of issues to consider,⁴⁰ are outlined elsewhere.

Minimizing Hypoglycemic Events During Low- to Moderate-Intensity Exercise in People Who Have Type 2 Diabetes and Are Taking Medications Other Than Insulin

Insulin secretagogues. Various insulin secretagogues and related preparations (eg, extended-release formulations) have been developed for use in type 2 diabetes. They differ in their pharmacokinetics and pharmacodynamics, that is, the timing of insulin appearance in and disappearance from the circulation as well as the duration of their effects. Thus, guidelines for their use with exercise cannot be generalized. Published data on the tendency of exercise to result in hypoglycemia have sometimes yielded apparently conflicting results. Critical to the interpretation of results are the specific conditions under which studies were conducted, such as the starting levels of glycemia; the duration, mode, and intensity of exercise; the pharmacokinetic and pharmacodynamic properties of the secretagogue; and the timing of exercise onset after the dose of medicine. For

example, in a study of an extended-release form of glipizide, the effects of exercise in subjects who had diabetes and exercised at a very light workload for 90 minutes were evaluated.²⁸ Under these conditions and with relatively high starting levels of glucose, this form of glipizide did not induce hypoglycemia. The glucose-lowering effect of this exercise protocol was modest, however, as shown for a control group of subjects who had diabetes but were not treated with glipizide; that is, the exercise challenge was slight, with a “buffer” of relatively high initial glucose levels.

In another study, the effects of the sulfonylurea glibenclamide were evaluated in patients exercising for 60 minutes at moderate intensity.²⁹ The same group of patients was studied after drug treatment alone, exercise alone, or a combination. The combination of glibenclamide and exercise lowered blood glucose levels more than either intervention alone. Circulating insulin levels were higher and the exercise-induced increase in hepatic glucose output was smaller with the combination protocol than with exercise alone. Preexercise glucose levels were high (~180 mg/dL); the patients did not experience hypoglycemia, but the authors appropriately noted that had exercise continued, the patients would have had a greater likelihood of reaching hypoglycemia in the combination trial.²⁹ These data are entirely consistent with the view that relative hyperinsulinemia during exercise accelerates the decrease in plasma glucose levels.

Ultimately, a critical factor for patients taking insulin secretagogues is the level of insulin in the blood at the time of exercise, just as it is in patients taking exogenous insulin. An empirical determination of the dosage adjustment for a given exercise regimen should be undertaken initially. Additional monitoring of

blood glucose levels before, during, and after exercise is recommended whenever an exercise regimen is significantly modified. Patients who are achieving tight control of blood glucose levels are, in turn, at greater hypoglycemic risk and should consider a reduction in medication dosage under conditions in which insulin levels would be relatively high during the exercise period. For unplanned exercise after medication has already been ingested, carbohydrate supplementation during exercise, after exercise, or both is recommended, particularly for patients in whom preexercise glucose levels are already relatively low (<100 mg/dL). In addition, there are less-common genetically inherited forms of diabetes in which the response to secretagogues and hence exercise can differ from that of most people with type 2 diabetes.⁵³

Other medications. For patients who have type 2 diabetes and who have achieved reasonably good glycemic control, guidelines indicate that medications other than insulin and insulin secretagogues do not require special adjustments for exercise.⁷ Drugs that act primarily by enhancing peripheral insulin action do not display a significant tendency for hypoglycemia because they do not act at steps that would interfere with the counterregulatory responses to impending hypoglycemia.⁵⁴ One exception may be for patients who receive metformin therapy and who have severe hepatic insufficiency or after excessive intake of alcohol.⁵⁴ The reason is that hepatic dysfunction under these conditions compromises the ability of the liver to generate glucose; because metformin acts primarily through the suppression of hepatic glucose production, patients in this category have a substantially reduced ability to prevent an onset of impending hypoglycemia.

Published data on the interactions of exercise and several other glucose-lowering medications are lacking, particularly for newer classes of therapy, such as glucagonlike peptide 1 analogs and dipeptidyl peptidase IV inhibitors. These agents have multiple effects (Tab. 2), but their efficacy is driven mostly by the potentiation of meal-induced insulin secretion and the suppression of glucagon release.⁵⁵ Both of these effects are glucose dependent; that is, the effects of glucagonlike peptide 1 diminish with decreasing plasma glucose levels (unlike the ability of sulfonylureas and glinides to stimulate insulin secretion). Therefore, in the sedentary state, they have been shown to reduce the propensity for hypoglycemic episodes. The current assumptions are that they also lessen the tendency for exercise-induced hypoglycemia and that adjustments for exercise are not needed.⁵⁴

Continuous High-Intensity Exercise Glucoregulation During High-Intensity Exercise in People Without Diabetes

In people who do not have diabetes, euglycemia is not maintained as exercise intensity increases. High-intensity exercise, generally defined as a workload requiring greater than 80% of $\dot{V}O_2\text{max}$, is characterized by increases in plasma glucose levels (Fig. 4, closed symbols). After the cessation of exercise, glucose levels generally continue to increase and reach a peak during the immediate postexercise period. During recovery from such strenuous exercise, the restoration of glucose to preexercise levels can take up to 1 hour.⁵⁶

High-intensity exercise increases the rates of hepatic glucose output and peripheral glucose uptake to greater extents than low-intensity exercise. Elevations in plasma glucose levels result from the fact that, unlike the situation with lighter workloads,

with high-intensity exercise the increase in hepatic glucose production exceeds that of peripheral glucose disposal.⁵⁶ Glucose production can increase by as much as 8-fold from resting rates, an increase that is as large as that seen in any physiological condition or pathological state.

The primary mechanism controlling hepatic glucose production shifts as exercise reaches more-strenuous levels (Figs. 4 and 5). Insulin secretion decreases to a lesser extent with high-intensity exercise than with moderate-intensity exercise or is maintained at basal levels. The absence of a marked reduction in insulin levels may be secondary to the prevailing hyperglycemia (a prime stimulus for insulin secretion), to a reduction in insulin degradation, or both.⁵⁶ The increase in glucagon secretion during strenuous exercise remains modest (or, more precisely, the increase in the hepatic portal glucagon-to-insulin ratio is modest) and is insufficient to account for the massive stimulation of hepatic glucose output (although it likely contributes to some hepatic production). The change in growth hormone is not essential, and the modest increase in glucocorticoid levels (a steroid whose actions are exerted only after a time lag) is inconsistent with the kinetic aspects of the response, that is, the rapidity of the increase in hepatic glucose output.

Data from several different experimental approaches have suggested that catecholamines are the primary drivers of the enhanced hepatic glucose production observed during high-intensity exercise.⁵⁶ During moderate-intensity exercise, catecholamine concentrations increase 2- to 4-fold above resting values; in contrast, circulating epinephrine and norepinephrine concentrations are elevated 10- to 20-fold during high-intensity exercise (Fig. 4). Increases in the circulating levels of both epinephrine and norepinephrine are probably required for the full stim-

ulation of glucose production. The administration of either catecholamine by itself (to levels commensurate with those seen during high-intensity exercise) stimulates hepatic glucose output partially,⁵⁷⁻⁶⁰ but only a combination of the 2 catecholamines can augment this process to levels approaching those observed with strenuous exercise.⁶¹ The role of hepatic sympathetic neural stimulation is equivocal; some authors^{59,62} have suggested that it is not essential, whereas other authors⁶¹ have suggested that the interpretation of those particular studies is complicated.

Substantial elevations in plasma catecholamine levels also may explain the observation that the hepatic production of glucose exceeds the peripheral utilization during high-intensity exercise, as others previously showed that catecholamines can partially inhibit the uptake of glucose into muscle and adipose tissue.^{57,58,63,64} In both people without and people with diabetes, a good correlation was demonstrated between circulating catecholamine levels and the net differential between hepatic glucose production and peripheral glucose uptake.⁶⁵ In a series of studies of people who were healthy, glucose uptake across the leg was evaluated in the presence or absence of added arm exercise.^{66,67} The addition of arm exercise (which increased total workload and resulted in substantial elevations in plasma catecholamine levels) reduced glucose uptake across the working leg in comparison with uptake in the absence of added arm exercise. Combined arm work and leg work increased liver glucose output more than peripheral glucose disposal and increased plasma glucose levels.

However, the importance of overall adrenergic control of hepatic function during strenuous exercise is not fully understood. The inability of an adrenergic blockade to fully block glucose production during exercise at high workloads has led some researchers to

postulate that additional control mechanisms may be important.¹⁷

Thus, high-intensity exercise presents an exception with regard to the control of hepatic glucose production, which is regulated under many circumstances primarily by insulin and the glucagon-to-insulin ratio. High-intensity exercise can stimulate sharp increases in hepatic glucose output even under circumstances normally associated with the suppression of glucose production. For example, when glucose production is attenuated at rest by interventions such as glucose infusion⁶⁸ or carbohydrate-containing meals⁶⁹ (which both result in elevations in endogenous insulin levels in people without diabetes), the subsequent imposition of high-intensity exercise still results in a substantial increase in liver glucose production (as well as the increase in circulating catecholamine levels). This hierarchy of control is important: Although most experimental investigations of glucose metabolism have been performed in the overnight fasting state, in practice people exercise much of the time in some phase of the absorptive state, that is, when endogenous glucose production is still at least partially suppressed as a result of a recent meal. A common example is the participation of children in after-school sports programs. These control mechanisms make it possible for the insulin-dependent suppression of liver glucose output to be overridden during high-intensity exercise, protecting people with diabetes from developing severe hypoglycemia.

Glucoregulation During Recovery from High-Intensity Exercise in People Without Diabetes

Plasma glucose levels peak shortly after the conclusion of a high-intensity exercise bout and then begin to return to baseline levels (Fig. 4A). Hepatic glucose output and peripheral glucose disposal decline fairly rapidly (Fig. 5). Glucose uptake initially reverses more

quickly than hepatic output, resulting in further hyperglycemia, which is gradually reversed over a 1- to 2-hour period.⁵⁶ Significant increases in insulin levels occur shortly after the cessation of high-intensity exercise (Fig. 4B), likely reflecting a response to the prevailing hyperglycemia in combination with a rapid withdrawal of α -adrenergic suppression of insulin secretion.

High-intensity exercise leads to rapid depletion of glycogen stores in contracting muscle fibers. It has been suggested that the hyperglycemic-hyperinsulinemic setting that occurs immediately after high-intensity exercise may be important in promoting rapid initial rates of glycogen replenishment in depleted fibers.⁵⁶ This feature would be particularly important in activities characterized by multiple bouts of repeated high-intensity exercise, such as soccer or ice hockey. The more persistent enhancement of insulin action induced by muscle contraction likely contributes to further refilling of glycogen stores after plasma glucose and insulin have returned to baseline levels.¹⁵

What factors govern the rate of decline in glucose production and uptake during the initial recovery period after high-intensity exercise? A study in which insulin levels were manipulated during the recovery period indicated that insulin is not the primary factor controlling the rapid reversal of hepatic glucose production.⁶⁵ More likely, the rapid shutoff of hepatic glucose output (Fig. 5C, closed symbols) is controlled by the rapid decline in circulating catecholamines, which precedes the reversal of hepatic output (possibly with an additional contribution from the shutoff of hepatic sympathetic neural stimulation). With regard to peripheral glucose metabolism, rates of glucose utilization decline when exercise ends. Although the decline in plasma glucose levels is not abso-

lutely dependent on the hyperinsulinemic environment, variations in plasma insulin levels modulate the rate of return of glucose uptake. Studies in which insulin levels were manipulated during the recovery period indicated that elevations in plasma insulin levels are associated with higher rates of decline in blood glucose levels because of a prolonged period of enhanced peripheral glucose uptake,^{65,68,69} as would be expected on the basis of knowledge of the interactions between insulin and contractile activity.

Effects of High-Intensity Exercise on Glucoregulation in People With Diabetes

Although there is an abundance of published literature describing the effects of low- to moderate-intensity exercise on glucose regulation in people with type 2 diabetes, there have been surprisingly few studies of high-intensity exercise in this population. This fact is unfortunate, given the high prevalence of type 2 diabetes. The scarcity of published studies partly reflects the demographic characteristics of the type 2 population, which make high-intensity exercise much more challenging to perform (people in this population are older, obese, more sedentary, and have low physical fitness, often coupled with contraindications such as cardiovascular risk factors). Thus, most of the data on high-intensity exercise in diabetes derives from studies of younger and more physically fit people with type 1 diabetes. It is not clear whether all of the observations derived from studies of young people with type 1 diabetes can be extrapolated to other populations of people with diabetes.

The shift in the control of glucoregulation with high-intensity exercise (compared with exercise at lower intensities) presents both comforting and complicating aspects for people with diabetes. Processes regulated

by insulin-independent mechanisms are generally preserved when people with diabetes engage in high-intensity work; these processes include normal increases in glucose production and disposal during and immediately after exercise as well as a normal rate of decline in glucose production after exercise. Because glucose production is controlled primarily by catecholamines, current data suggest that physically fit patients with insulin-dependent diabetes can exercise vigorously and engage in competitive sports requiring high-intensity workloads; they are less likely to develop hypoglycemia under these conditions than when they engage in low-intensity exercise. More data on responses to high-intensity exercise are needed for older, less-fit people with type 1 diabetes and for people with type 2 diabetes. One study of people with type 2 diabetes suggested that they develop hyperglycemia during extremely vigorous exercise.⁷⁰ In fact, they may have a propensity for more rapid and larger increases in plasma glucose levels than people without diabetes, driven by exaggerated catecholamine responses and more rapid increases in hepatic glucose production.⁷⁰ Factors controlling plasma glucose levels during high-intensity exercise are summarized in Appendix 2.

Appropriate control of glycemia during the postexercise recovery period is more challenging because of the role of insulin in modulating the postexercise decline in glucose disposal. In the recovery period after a high-intensity exercise bout, the strategies for avoiding inappropriate glucoregulation are distinctly different from those used after exercise at lower intensities. At lower intensities, a prime concern is to avoid hypoglycemia, whereas after strenuous exercise, the prevailing milieu is one of hyperglycemia. Strategies designed to mitigate the development of hypoglycemia (such as enhanced carbohy-

drate consumption or reduced insulin dose), important for low-intensity exercise, can exacerbate hyperglycemia after high-intensity exercise. Patients with insulin-dependent diabetes cannot generate hyperinsulinemia of endogenous origin, normally important for enhancing the rate of return of postexercise hyperglycemia to the baseline. Thus, low circulating levels of insulin (or carbohydrate supplementation or both) can prolong hyperglycemia during the recovery period, partially counteracting the beneficial effects of exercise on glucose control. If people find that their activity patterns lead to prolonged postexercise hyperglycemia, consideration should be given to the administration of insulin shortly after the completion of a high-intensity exercise session.⁵⁶ Appendix 3 summarizes key factors that control the recovery from hyperglycemia after the cessation of high-intensity exercise.

Given a choice, it is much more prudent to err on the side of elevated glucose levels than hypoglycemia, but optimal glycemic management over the long term in patients who have diabetes and who exercise regularly requires an appreciation of the different effects of low-intensity exercise and high-intensity exercise on glycemic control. This knowledge, in turn, leads to different strategies for appropriately managing glucose levels with exercise. As noted above, the absolute level of glycemia depends on several factors, such as pre-exercise glucose and insulin levels, type of insulin used, timing of insulin administration relative to pharmacokinetic properties, and site of insulin injection. If people perform high-intensity exercise on a regular basis, then slightly smaller increases in blood glucose⁷¹ and catecholamine^{72,73} levels will be observed (in comparisons of bouts of the same absolute workload) as a result of adaptations to training.

Intermittent High-Intensity Exercise

In most studies investigating glucoregulation during exercise in people with diabetes, exercise protocols characterized by a constant intensity level have been used.^{22,23,28,29,31,32,43–46,48–50,53} Although certain sports, such as endurance running, often involve exercise at a sustained intensity level, this is not always the case (eg, interval training workouts). Other sports, in particular, many team sports, such as soccer, football, or baseball, are characterized by intermittent levels of exertion: periods of low- to moderate-intensity exercise punctuated by brief outputs of high-intensity effort. This type of activity also is more characteristic of spontaneous play in children.

Given that continuous high-intensity exercise in people with diabetes has effects quite different from those of low-intensity activity, several recent studies have evaluated the effects of exercise protocols involving intermittent bursts of high-intensity work. In a series of studies of young adults with type 1 diabetes, Guelfi and colleagues^{74,75} used exercise protocols designed to approximate the ratio of high-intensity effort to low-intensity effort (or recovery) characteristic of many team sports. The experiments were designed to reflect conditions that would lead to large reductions in glycemia if low-intensity exercise had been performed; that is, subjects were asked to administer their usual morning dose of insulin (no adjustment for exercise), and activity was initiated during a period when plasma insulin levels were high. In control experiments, continuous exercise at 40% of peak oxygen uptake ($\dot{V}O_{2peak}$) resulted in significant decreases in plasma glucose levels (Fig. 8). The imposition of 4-second maximal sprints repeated every 2 minutes lessened the decline in plasma glucose levels and maintained glucose

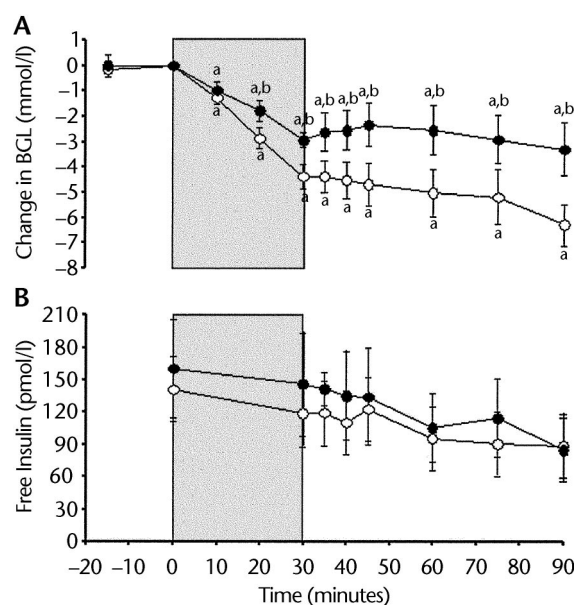


Figure 8.

Effects of intermittent high-intensity exercise (IHE) and moderate-intensity exercise (MOD) on glycemic control in subjects with type 1 diabetes. Young males and females with type 1 diabetes were treated with their usual morning dose of insulin just before the ingestion of a standardized breakfast meal. At 3.5 hours after insulin injection, subjects participated in 1 of 2 different cycle ergometer exercise protocols (shaded box). The MOD protocol (○) consisted of 30 minutes of continuous cycling at 40% of maximal oxygen uptake. The IHE protocol (●) consisted of continuous cycling interspersed every 2 minutes with 4-second maximal sprint efforts designed to simulate the activity patterns of common team sports (16 sprints in total). Plasma glucose (A) and insulin (B) levels were monitored before, during, and for 90 minutes after exercise. The substantial decrease in plasma glucose levels that occurred during continuous moderate-intensity exercise could be attenuated by interjecting occasional brief sprint bouts. Results are expressed as mean $\pm$ SE. ^aStatistically significant difference ($P < .05$) from resting value. ^bStatistically significant difference ($P < .05$) between IHE and MOD values. BGL=blood glucose level. Reprinted with permission of the American Diabetes Association from Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. *Diabetes Care*. 2005;28:1289–1294. Copyright 2005, American Diabetes Association.

at significantly higher levels during recovery (Fig. 8).⁷⁴ Similar protective effects were seen when subjects performed intermittent maximal sprints with complete rest in between.⁷⁵

Despite the fact that the intermittent protocol was characterized by a greater amount of total work and higher oxygen uptake, the periodic sprint bouts did not lead to more-pronounced hypoglycemia. The mechanism for the protective effect of the intermittent high-intensity protocol was then examined.⁷⁶ Com-

pared with the protocol involving continuous exercise at 40% of $\dot{V}O_2$ peak, the intermittent sprint protocol stimulated a more rapid increase in hepatic glucose production, which was maintained at higher levels during exercise. This was more than enough to offset a modest increase in peripheral glucose disposal. The greater stimulation of liver glucose output, in turn, was associated with higher catecholamine levels, but not with any differences in insulin or glucagon levels.^{74–76} These findings are consistent with cate-

cholamines driving the higher hepatic glucose output and perhaps limiting the increase in muscle glucose uptake, but that hypothesis has not been directly evaluated for this intermittent exercise paradigm.

These findings suggest that activities characterized by intermittent high-intensity exercise may have less of a tendency for hypoglycemia than activities characterized by only continuous low-intensity exercise. These principles could be deliberately used as a strategy to avoid hypoglycemia when people are performing continuous low- to moderate-intensity exercise, that is, with the periodic insertion of brief high-intensity efforts. In a follow-up study, the effects of a single maximal sprint performed at the end of a session of exercise at 40% of $\dot{V}O_{2\text{peak}}$ in subjects with type 1 diabetes were evaluated.⁷⁷ On one day, the subjects rested at the end of the exercise session; on that occasion, glucose levels continued to decrease during the 2-hour recovery period. On an alternative day, the subjects performed a 10-second maximal sprint at the end of the exercise session (which caused catecholamine and lactate levels to rise sharply); glucose levels quickly stabilized and were significantly higher during the recovery period than when the sprint was not performed (Fig. 9).

The deliberate use of intermittent high-intensity sprint bouts is best suited for children and relatively young adults; it would be more impractical for older, less-fit people (and more likely to be contraindicated). Nevertheless, it represents an additional strategy for mitigating the likelihood of hypoglycemia in some people. In practice, the effects of superimposing brief high-intensity efforts should be determined empirically with frequent glucose monitoring. Further experimental studies of intermittent exercise regimens are warranted.

Resistance Exercise

As noted above, aerobic exercise programs can be challenging for many people with diabetes, such as people with significant obesity, people with very low levels of aerobic fitness, or elderly patients with sarcopenia, severe arthritis, or both. For others, aerobic exercise may be contraindicated because of the presence of diabetic complications, such as cardiovascular disease or advanced peripheral neuropathy. Exercise programs based on progressive resistance training represent an alternative mode of exercise for these patients as well as a supplementary form of exercise for patients with diabetes in general.

Progressive resistance training offers multiple benefits to patients, such as increasing muscle mass and strength (force-generating capacity), increasing energy expenditure, reducing visceral adipose tissue, improving lipid profiles, increasing bone density, and counteracting the age-related tendency for sarcopenia.^{78,79} Resistance training, particularly programs that emphasize high-intensity sessions with correspondingly lower aerobic aspects, can be used for patients who have difficulty performing aerobic exercise or who have specific contraindications.⁷⁸

Few published longitudinal studies of the benefits of resistance exercise for glycemic control in diabetes had appeared a decade ago. After that time, several small studies, performed mostly with subjects who had type 2 diabetes and, in many cases, lacking randomization of subjects, had suggested that resistance training improved various indexes of glycemic control (for details, see discussions elsewhere^{13,78–80}). These studies were followed by several randomized controlled trials with subjects who had type 2 diabetes, in which resistance training programs lasting 4 to 6 months resulted in improvements in glycemic control in the

same range as that shown for aerobic exercise programs.^{81,82}

Several factors may contribute to the improvement in glycemic control seen with resistance exercise training programs: (1) increases in muscle mass, which provide a larger reservoir for glucose disposal; (2) direct effects on skeletal muscle that increase glucose transport activity; and (3) improvements secondary to a loss of adipose tissue (in particular, visceral adipose tissue, which is known to be a contributor to insulin resistance). Determining the relative

contributions of each of these factors is challenging. The direct effects of resistance exercise on muscle glucose uptake were evaluated in a study in which people who were healthy and patients with type 2 diabetes trained only one leg.⁸³ Measurements of glucose uptake and glucose transporter content in each leg demonstrated increased GLUT4 glucose transporter density per unit of muscle in the strength-trained leg. Glucose clearance in the trained leg was also increased—and to a greater extent than could be explained by the increased muscle mass of the

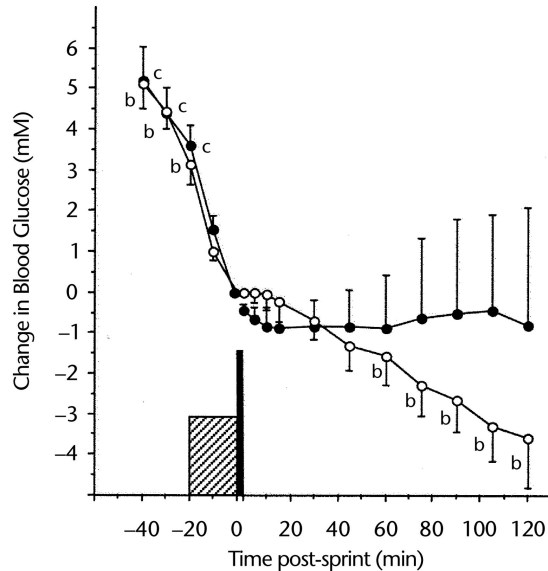


Figure 9.

Effects on glycemic control of a 10-second maximal sprint after moderate-intensity exercise in subjects with type 1 diabetes. Young male subjects with type 1 diabetes were treated with their usual morning dose of insulin just before the ingestion of a standardized breakfast meal. At 2 h after insulin injection (–20 minutes), subjects initiated 20 minutes of continuous cycle ergometer exercise at 40% of maximal oxygen uptake (▨). On one occasion (control trial), they rested at the end of the moderate-intensity exercise period (○). On the other occasion (sprint trial), they performed a 10-second all-out sprint (■) at the end of the continuous exercise period (●). Blood glucose levels were measured before, during, and for 120 minutes after completion of the exercise trials, and data are expressed relative to those obtained immediately after the moderate-intensity exercise (time 0). A single short sprint of supramaximal intensity may be sufficient to interrupt the decline in blood glucose levels that occurs with continuous moderate-intensity exercise. All data are expressed as mean ± SE. ^b $P < .05$ versus 0-minute time point (after moderate-intensity exercise) in control trial. ^c $P < .05$ versus 0-minute time point (after moderate-intensity exercise) in sprint trial. Reprinted with permission of the American Diabetes Association from Bussau VA, Ferreira LD, Jones TW, et al. The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. *Diabetes Care*. 2006;29:601–606. Copyright 2006, American Diabetes Association.

trained leg. Thus, the results of that study⁸³ demonstrated that local adaptations in skeletal muscle, similar to the well-known effects of endurance exercise protocols, is an important contributor to improvements in glucose homeostasis in people who have diabetes and undergo resistance exercise training. These effects should add to the benefits associated with increases in total muscle mass.

Other studies have demonstrated that exercise programs combining aspects of both endurance training and resistance training can lead to significant improvements in indexes of glycemic control,^{84,85} including at least one small study of adolescents with type 1 diabetes.⁸⁶ In one recently published study, the effects of aerobic training and resistance training singly and in combination were evaluated.⁸⁷ The authors reported that although each program independently lowered HbA1c levels in patients with type 2 diabetes, the combination training regimen was significantly more effective than either exercise mode alone. Interpretation of the results is complicated by the fact that the combination training regimen was characterized by a much greater total duration of exercise; thus, it cannot be deduced whether the greater benefit resulted from the increased exercise duration or the combination of the 2 different types of exercise. Nevertheless, that study⁸⁷ affirmed that these 2 types of exercise can be combined in an effort to add variety to workouts and attain benefits, such as increased muscle strength, that are complementary to those provided by aerobic exercise alone. (See the article by Marcus et al⁸⁸ in this issue for a study of combined aerobic and resistance exercise intervention in people with diabetes.)

Professional organizations, such as the American College of Sports Medicine and the American Diabetes As-

sociation, now recommend that resistance training be included in the treatment of diabetes.^{7,89} The literature on resistance exercise training, however, provides very little discussion of the frequency of hypoglycemia associated with weight training, nor are there specific recommendations regarding changes in diabetes medications.

Conclusion

Both aerobic and resistance exercise programs have the potential to improve glycemic control in diabetes. Aerobic exercise confers additional benefits to the heart and vasculature; resistance exercise counters age-related sarcopenia and provides other benefits. Aerobic exercise sessions must be carefully managed in patients with diabetes treated with exogenous insulin or insulin secretagogues because of the importance of insulin concentrations in regulating glucose metabolism during low- to moderate-intensity exercise and during recovery from exercise. An understanding of the factors that contribute to hypoglycemia or hyperglycemia is essential to the proper use of exercise programs.

Several important areas will benefit from additional research. The dearth of published data addressing potential interactions between antidiabetic medications and exercise in type 2 diabetes is surprising, given the fact that exercise and dietary modification are the first-line therapeutic interventions. More studies are needed to characterize the effects of different exercise intensities on glycemic control in type 2 diabetes (eg, exercise programs used by specific populations, such as elderly people). Data are needed to strengthen the underlying assumption that special precautions are not needed for exercise in patients who have type 2 diabetes and are taking medications other than insulin or insulin secretagogues. For type 1 diabetes, more data on the hypoglycemic and hyperglycemic poten-

tials of exercise are needed for older people, who are much less fit than the younger people who are usually the subjects of studies of type 1 diabetes. Studies of potential sex differences related to exercise in diabetes are generally lacking as well.

Additional studies of exercise protocols that more closely approximate the activity patterns of common sports are needed (eg, intermittent exertion with various intensity levels and rest periods). What combinations of intensity levels and rest intervals trigger a switch from glucose-lowering effects, with a concomitant threat of hypoglycemia, to a setting characterized by hyperglycemia? Is the propensity of high-intensity exercise to generate hyperglycemia reduced with repeated exercise sessions, given that catecholamine levels tend to be lowered by training? Is the potential for prolonged exercise to impair counterregulatory responses to a subsequent hypoglycemic challenge reduced when exercise is performed on a regular basis?

Regarding resistance training, there is a need for a more detailed evaluation of the frequency of either hypoglycemia or hyperglycemia. What are the relative benefits of various forms of resistance training (eg, powerlifting, bodybuilding, and circuit training)? What levels of training frequency and intensity are needed to derive minimal as well as maximal benefits? Of particular interest to physical therapists, who often prescribe resistance exercises for specific muscle groups, is how much muscle mass must be engaged to derive training-induced glycemic benefits or, alternatively, pose a threat of hypoglycemia? Answers to questions such as these will provide more-specific guidelines for exercise prescriptions and will enable people with diabetes to derive more of the potential glycemic benefits of exercise.

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Appendix 1.

Initiating an Exercise Program for People With Diabetes^a

Assess underlying conditions that might contraindicate specific exercise protocols

Assess severity of conditions and tailor specific exercise prescriptions that minimize specific risks

- For example, presence of cardiovascular risk factors, neuropathies, retinopathy, nephropathy, vascular disease, or ulcers in the lower extremities

Check blood glucose levels regularly

If >250 mg/dL shortly before exercise, check urinary ketones

- If ketones are moderate to high, administer insulin and postpone exercise bout until ketones return to low levels and glucose levels are <250 mg/dL
- If ketones are low but glucose is >300 mg/dL, consider treating with appropriate antidiabetic medication and postponing exercise until glucose is <250 mg/dL

If glucose is <100 mg/dL shortly before exercise, consider carbohydrate supplementation

Check glucose before, during, and after exercise as often as practical until the patient's glycemic response to a given mode of exercise is understood

- Adjust premeal insulin and carbohydrate intake as needed
- Reinitiate regular checks of blood glucose whenever significant changes are made to antidiabetic medicines or to the exercise program (such as type of exercise, intensity, duration, timing relative to meals, or medicine)

Emphasize the importance of regular exercise

Organizations such as the American Diabetes Association and the American College of Sports Medicine recommend at least 150 minutes of aerobic exercise per week, performed on at least 3 nonconsecutive days

Two additional sessions of resistance training should be encouraged

- The specific exercise programs should be tailored to adjust for risk factors

These recommendations represent long-term goals; identify exercise modalities that the patient will enjoy and gradually build toward long-term goals

- When initiating a program in patients with a history of highly sedentary behavior, divide exercise into 2 or 3 daily 10- to 15-minute sessions

^a For additional details and guidelines, see the text and references therein.

Appendix 2.

Control of Blood Glucose During High-Intensity Exercise

During high-intensity exercise in people without diabetes

Plasma glucose increases

- Peripheral glucose uptake increases in working muscles (more so than during low- to moderate-intensity exercise)
- Hepatic glucose production increases (more so than during low- to moderate-intensity exercise)
- Increase in hepatic glucose production exceeds increase in peripheral glucose uptake

Shift in control of hepatic glucose production

- Changes in insulin and glucagon are no longer dominant
- Catecholamines increase to a much greater extent than at lower intensities of exercise and act as primary regulators of liver glucose output

During high-intensity exercise in people with diabetes

Patients with type 1 diabetes and likely those with type 2 diabetes develop hyperglycemia during high-intensity exercise

- Responses are generally similar to those in people without diabetes
- Exercise-induced increases in catecholamines and hepatic glucose output are preserved

Exercise-induced hypoglycemia is not a major concern in people with insulin-dependent diabetes

- High catecholamine levels can override the effects of inappropriately high levels of insulin

Appendix 3.

Control of Blood Glucose During Recovery From High-Intensity Exercise

After high-intensity exercise in people without diabetes

Plasma glucose decreases

- Generally returns to baseline within 1–2 h
- Hepatic glucose production declines more rapidly than peripheral glucose uptake
- The decline in hepatic glucose production is driven primarily by a rapid decline in circulating catecholamines
- The decline in peripheral glucose uptake is driven primarily by factors intrinsic to the working muscles

Insulin levels rise soon after the cessation of exercise

- Insulin modulates the rate of decline in muscle glucose uptake
- Higher levels of insulin during recovery accelerate the decline in blood glucose (ie, prolong the period of enhanced glucose uptake)

After high-intensity exercise in people with diabetes

Declines in circulating catecholamines and hepatic glucose output are generally similar to those in people without diabetes

The intrinsic rate of decline in peripheral glucose uptake (ie, that driven by factors in the working muscles) is generally similar to that in people without diabetes

- The rate at which plasma glucose levels return to baseline in patients not requiring exogenous insulin or insulin secretagogues is generally similar to that in people without diabetes

Factors extrinsic to the working muscles can present challenges in patients requiring exogenous insulin or insulin secretagogues

- Lower levels of insulin during recovery (attributable to a reduction in insulin or insulin secretagogue dosing) slow the decline in glucose levels and can exacerbate postexercise hyperglycemia
- Excessive carbohydrate supplementation accentuates postexercise hyperglycemia

Physical Therapy

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Exercise and Glycemic Control in Diabetes: Benefits, Challenges, and Adjustments to Pharmacotherapy

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