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EDITORIAL

Exercise, Hypoglycemia, and Type 1 Diabetes

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Management of patients with type 1 diabetes (T1D) during and after exercise continues to be a challenge for care providers and patients alike in terms of approach both to insulin therapy and to hypoglycemia prevention and rescue. These issues pose significant limitations from the providers' standpoint of hypoglycemia prevention and from the patients' standpoint of seeking to achieve desirable level of fitness to improve general metabolic and cardiovascular health. The purpose of this editorial therefore is (1) to summarize available knowledge of carbohydrate physiology during and after exercise in healthy and T1D individuals, (2) to elucidate possible physiological mechanisms predisposing to hypoglycemia, (3) to describe current approaches to prevent and manage exercise-induced hypoglycemia in T1D, and (4) to identify knowledge gaps in our understanding of exercise physiology in T1D that require further study.

Physical Activity, Glucose Physiology, and Hypoglycemia

Blood glucose concentration at any given time point is a reflection of the net balance between the rates of glucose appearance (R_a) into and disappearance (R_d) from the circulation. Therefore, when blood glucose concentrations are rising (immediate postprandial state), by definition, R_a (glucose appearing from the meal + rates of endogenous glucose production [EGP]) must exceed R_d (glucose uptake into tissues such as liver, muscle, and fat cells). Likewise, when blood glucose concentrations are falling, by definition, R_d (glucose uptake) must exceed R_a (either from a meal and/or EGP). It is well established that exercise increases muscle glucose uptake through insulin-dependent and insulin-independent mechanisms and that EGP must increase to meet the increased metabolic demands of the exercising muscle to prevent hypoglycemia.[1–4] These changes in glucose fluxes (Table 1) are facilitated by changes in (1) hormonal concentrations (i.e., falling insulin and rising glucagon and catecholamine levels during exercise[5]), (2) blood flow to exercising muscles,[6] and (3) adaptations to intracellular pathways that facilitate glucose uptake.[7–10]

The rise in EGP during exercise was observed to be due to increases in both gluconeogenesis and glycogenolysis in a series of elegant experiments in intact and pancreatectomized dogs.[3,11–13] We have recently demonstrated[14] that in recreationally active healthy individuals without diabetes, a 60-min bout of moderate-intensity exercise (50% of maximal oxygen uptake) 2 h after a mixed meal increased EGP eightfold, which was facilitated by a doubling of plasma glucagon concentrations. In this study, despite the fact that plasma insulin concentrations rapidly declined to fasting levels during exercise, eight of 12 subjects had biochemical but asymptomatic hypoglycemia within 15 min after starting exercise despite consuming a 600-kcal mixed meal for breakfast containing 75 g of carbohydrates, 2 h prior to the start of exercise. When these data are taken together, the falling glucose concentrations during exercise was due to the fact that the combined effect of meal glucose appearance and EGP (R_a) was unable to keep pace with exercise-induced changes in whole-body glucose uptake (R_d).

There have also been prior publications that have reported on the effect(s) of exercise of varying intensity on glucose physiology. These have included ground-breaking work by exercise physiologists using isotope dilution techniques and glucose clamps. In healthy adults, Friedlander et al.[15,16] demonstrated that R_d was directly proportional to exercise intensity and that although training did not affect the magnitude of R_d when expressed as relative exercise intensity, it did decrease R_d for a given power output, implying improved training-induced efficiency of the working muscles. Furthermore, the increased efficiency of R_d was related to up-regulation of muscle glycogen synthesis secondary to increased stimulation of glucose transport across the skeletal muscle cell membrane.[17]

Interesting gender differences in glucose kinetics and hormonal responses during exercise have also been observed,[16,18] with women shifting substrate oxidation from carbohydrates to lipids and showing lesser rises in post-exercise glucagon and epinephrine concentrations than men at submaximal workloads common to endurance levels and daily activity. Likewise, during endurance exercise and exercise training, women utilize lipids more than carbohydrates when compared at the same relative exercise intensity with equally trained men.[19,20]

In contrast, the effect size of menstrual cycle on exercise-related substrate metabolism is modest at best. In an early

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Table 1. Effects of Exercise in Healthy Individuals

	Result	*Mechanism*
During exercise		
Muscle contraction	Insulin-independent translocation of GLUT4, resulting in increased glucose uptake	• Ca^{2+}/CaMK activation • AMPK activation • PKC activation
Muscle energetic demands	Increases glucose disposal	• Increased glycolytic flux
Endogenous glucose production	Increases blood glucose availability	• Increased glucagon concentration • Increased catecholamine concentration
Muscle blood flow	Increases glucose delivery	• Elevated cardiac output • Increased capillary blood flow • Skeletal muscle vasodilation
After exercise		
Insulin sensitivity	Leftward shift of insulin response curve for 24–48 h after cessation of exercise	• Currently unknown, possibly involving phosphorylation by AMPK of TBC1D1 and AS160

Skeletal muscle glucose uptake increases dramatically in response to exercise together with a drop in plasma insulin concentrations in healthy individuals to overnight fasted levels. During exercise, the increase in glucose uptake is the result of muscle contraction that activates the Ca^{2+}/calmodulin-activated protein kinase (CaMK) family, 5'-AMP-activated protein kinase (AMPK), and atypical protein kinase C (PKC). Exercise also increases the energetic demands of skeletal muscle, resulting in increased glycolytic flux and demand for glucose as an energy substrate. Endogenous glucose production increases, making blood glucose more available as a result of elevations in circulating glucagon and catecholamine concentrations. Finally, increased skeletal muscle blood flow as a result of elevations in cardiac output and increased capillary blood flow together with local vasodilation increase glucose delivery to active tissues. After exercise, a leftward shift of the insulin dose–response curve persists for 24–48 h after the cessation of exercise through a currently unknown mechanism that increases the sensitivity of skeletal muscle to plasma insulin concentration.

GLUT4, glucose transporter type 4.

study, the effects of menstrual phases on glucose turnover during moderate- and high-intensity exercise were negligible in healthy young women.[21] It is interesting that oral contraceptive use led to reduced rates of glucose turnover during moderate-intensity exercise without altering rates of carbohydrate and lipid oxidation in healthy young women.[22] Further pioneering studies by the same investigative group demonstrated that although exercise-induced lipolysis, as measured by rate of appearance of glycerol, was not affected by menstrual cycles, use of oral contraceptives increased triglyceride mobilization via increased lipolysis during moderate-intensity exercise.[23] Confirmation that these observations on gender differences of substrate metabolism during exercise were related to estrogen came from a fascinating study in men that revealed that 8 days of estrogen supplementation resulted in reductions in glucose turnover and respiratory exchange ratio during exercise, thus implying fuel shift from carbohydrate to lipid oxidation.[24]

Exercise and "Insulin Sensitivity"

Insulin sensitivity, in the purist term, is defined as the ability of insulin to stimulate uptake of glucose by target tissues (viz., muscle, liver, adipose tissue). Hence, by definition, an increase in insulin sensitivity implies a shift of the dose–response curve of insulin to the left such that a lower concentration of insulin results in an equivalent amount of glucose uptake by the target tissue(s). Although some studies had suggested that insulin was indeed required and had a permissive effect on muscle glucose uptake during and after exercise,[25,26] others demonstrated similar findings on glucose uptake in the muscle both during and after exercise even in the absence of insulin.[27–29] Thereafter, several studies have demonstrated that muscle contractions, per se, induce muscle glucose uptake even in the absence of insulin[7,30–32] and that the effects of insulin and contractions on muscle glucose transport are additive.[7,33–35] Table 1 summarizes some of the physiological adaptations to exercise as related to carbohydrate metabolism.

Mechanical factors that modulate muscle glucose uptake include, among others, tissue permeability to glucose and changes in blood flow to exercising muscles. In an elegant and pioneering series of experiments in isolated frog muscle, Hollozsy and Narahara[27] demonstrated that both muscle contractions and insulin separately stimulated muscle glucose uptake, presumably through a common transport pathway. However, further mechanistic studies in isolated rat skeletal muscle revealed that effects of insulin and muscle contractions on glucose uptake were additive but caused glucose transporter type 4 (GLUT4) translocation via independent pathways in contracting skeletal muscle.[7–10] It is noteworthy that although insulin effects on glucose transport showed a threshold and saturable kinetics, isometric exercise increased glucose transport in a linear fashion without a threshold effect.

A single endurance exercise bout increased insulin action on skeletal muscle[36,37] predominately because of an increase in GLUT4 protein content.[38–40] Consecutive exercise sessions significantly increased muscle GLUT4 content, and the increase was proportional to the increase in insulin sensitivity of the muscle.[41] Exercise training also increased the amount of GLUT4 that translocated to the skeletal muscle surface in response to a given insulin dosage.[42] These exercise-induced adaptations result in improved skeletal muscle insulin sensitivity in previously healthy, but sedentary, humans.[43] Intracellular modulators of GLUT4 translocation in contracting human skeletal muscle include kinases (5'-AMP-activated protein kinase, Akt) and the Rab GTPase-activating proteins TBC1D1 and AS106.[44,45] These mediators are also involved in the increase in post-exercise insulin-independent changes

to glucose uptake that last for 24–48 h after an exercise bout.[46] Taken together, it appears that an increase in insulin sensitivity that occurs in a trained muscle is related to training-induced changes in GLUT4 availability to the cell surface as a result of activating intracellular signaling pathways specific to muscle contraction, which further promotes muscle glucose uptake and shifts the insulin dose–response curve to the left.

Muscle blood flow, a factor beside blood glucose concentration that determines delivery to skeletal muscle, markedly increases during exercise. During light to moderate exercise, contracting skeletal muscle blood flow increases to 6–10 L/min in healthy adults, whereas vigorous activity demands over 12 L/min.[6,47] This hemodynamic effect results in more glucose being delivered to active skeletal muscle together with a greater surface area for exchange. However, estimates are that the relative importance of blood flow alone (without skeletal muscle contraction) likely accounts for less than 30% of the increase in muscle glucose uptake during exercise.[48]

Strategies to prevent exercise-induced hypoglycemia could prolong exercise ability and delay exhaustion. In a series of experiments, various investigators[49,50] demonstrated that carbohydrate feeding and water ingestion during prolonged exercise delay fatigue and increase neuromuscular power, at least in part by preventing hypoglycemia, by avoiding muscle glycogen depletion. A similar effect of carbohydrate ingestion on cycling time trial performance was also reported.[51] Using the glucose clamp technique during intense exercise, Coyle et al.[52] further demonstrated that although hyperglycemia did not alter muscle glycogen use, it increased muscle glucose uptake and oxidation. In contrast, recently, Fahey et al.[53] demonstrated that a short sprint increased plasma glucose levels owing to a decline in R_d in both healthy and T1D individuals.

Intermittent Exercise and Glucose Physiology

In the free-living condition, humans frequently participate in sports activities (e.g., tennis, soccer, basketball, etc.) that involve intermittent, short bursts of moderate- to high-intensity exercise, interspersed with relative inactivity. Systematic assessments and comparisons of glucose turnover and insulin sensitivity during intermittent versus sustained exercise have been sparse in people with and without diabetes. Early investigations[54] did not demonstrate differences between sustained and intermittent exercise on intramuscular glycogen content and lactate accumulation, but subsequent studies by the same investigators[55] suggested lower rates of glycolysis with intermittent compared with sustained exercise in healthy adults. In an intriguing study,[56,57] fat oxidation was threefold lower and carbohydrate oxidation was 1.2-fold higher during intermittent versus sustained exercise of equivalent energy expenditures. A recent study[58] in type 2 diabetes subjects revealed improved insulin sensitivity, as measured by the homeostasis model of insulin resistance, during intermittent exercise performed with mild hypoxia. Unfortunately, this study did not compare intermittent versus sustained exercise at normoxia.

Physical Activity in T1D and Hypoglycemia

It is well known that physical activity (PA) influences glucose concentrations in patients with T1D not only during exercise but up to 15 h after exercise, leading to late evening and nocturnal hypoglycemia.[59,60] Reports have also demonstrated that different types of exercise (i.e., resistance vs. aerobic) have contrasting effects on the duration and severity of acute[61] and delayed[62] post-exercise hypoglycemia. Although it has been suggested[63] that there is sufficient evidence to recommend PA in the management of T1D, the duration, intensity, and form of exercise that should be recommended and whether such interventions would translate to better outcomes are presently unclear. A recent meta-analysis[64] suggests benefits of regular aerobic training, interspersed with brief bouts of sprinting, on glycated hemoglobin concentrations and incidence of delayed hypoglycemia in T1D. Although the American Diabetes Association does not provide specific suggestions regarding PA in T1D, it recommends that adults with diabetes perform at least 150 min/week of moderate-intensity aerobic PA and, in those with type 2 diabetes without contraindications, resistance training at least twice a week.[65] The American Diabetes Association also recommends ingestion of added carbohydrates if the pre-exercise glucose level is <100 mg/dL in insulin-treated individuals.

Systematic examinations of carbohydrate physiology and substrate metabolism during exercise are sparse in T1D. Increased risk of hypoglycemia during exercise in T1D individuals could be due to factors that either lower rates of EGP or increase rates of glucose uptake or a combination of both. Lower rates of EGP could be due to lower hepatic glycogen reserves, as has been demonstrated in the postprandial state in T1D subjects,[66] accompanying α-cell dysfunction leading to impaired glucagon secretion during exercise, decreased hepatic glucagon sensitivity, deficient catecholamine response to exercise, or a combination thereof. In contrast, in a study comparing individuals with and without T1D during moderate- and high-intensity exercise, Petersen et al.,[67] applying magnetic resonance technology, determined that compared with healthy individuals, those with T1D had higher rates of EGP that was entirely accounted for by increased rates of gluconeogenesis. However, to further complicate matters, defective activation of skeletal muscle and adipose tissue lipolysis during hypoglycemia in T1D subjects, as a result of insufficient catecholamine response,[68] could potentially further prolong the duration and severity of exercise-induced hypoglycemia in these individuals.

PA in T1D: Management Strategies

Apart from applying common-sense tactics to prevent hypoglycemia during and after exercise, there have been few reports that have systematically examined therapeutic approaches to mitigate hypoglycemia during and after PA in T1D. An observational field study[60] demonstrated the efficacy of real-time continuous glucose monitoring and carbohydrate loading in preventing post-exercise hypoglycemia in adolescents with T1D. Recently, short-term studies incorporating PA have shown improvements in glucose control in T1D patients. These studies have compared multiple daily insulin injections with open-loop continuous subcutaneous insulin infusion,[69] open-loop continuous subcutaneous insulin infusion with single-hormone (insulin) closed-loop control,[70] and open-loop continuous subcutaneous insulin infusion with single-hormone modular closed-loop control.[71]

Recent observational studies testing a dual-hormone (insulin and glucagon) closed-loop control system[72] have shown low rates of hypoglycemia with moderate exercise.

Usual Versus Guideline-Based PA and Glucose Physiology

The recommendation of daily PA by the American Diabetes Association refers to all patients with diabetes. Specific PA recommendations for T1D are not available simply because of lack of good evidence of the effect of PA on glucose control or outcomes. Although there is evidence of benefits of standardized training (50–70% of maximal oxygen uptake) for 16–20 weeks on insulin sensitivity measured by the glucose clamp or intravenous glucose tolerance test in healthy lean and overweight adults,[73] some of the beneficial effects on insulin sensitivity could have been attributed to accompanying weight loss. In an intriguing study[74] conducted in healthy sedentary men, reductions in daily step count from approximately 10,000 steps to approximately 2,000 steps led to reductions in fat free mass with lowering of insulin sensitivity measured before and after a 2-week period.

Closed-Loop Strategies for Exercise

A recent review[75] has identified exercise as a major obstacle in current closed-loop control efforts. Even if exercise is announced during closed-loop therapy, maintenance of optimal glucose control during and after exercise may be challenging despite dual-hormone systems without a flexible and learning program of concomitant carbohydrate ingestion. As elucidated above, even healthy trained and untrained individuals without diabetes need to resort to periodic carbohydrate ingestion during and after exercise to prevent exhaustion, fatigue, and symptomatic hypoglycemia and to improve performance, especially during prolonged, unusual, or intense physical activity or sports. Hence, it would be impractical and unnatural to expect to rely solely on closed-loop control (with dual-hormone insulin and glucagon) systems to prevent hypoglycemia without exogenous simple carbohydrate ingestion. Furthermore, the considerable intra- and interindividual variability of insulin sensitivity in T1D individuals, *even in the absence of exercise under carefully controlled experimental conditions*, as we have recently demonstrated,[76] is expected to be far greater *during exercise*, posing additional challenges to a generic closed-loop control algorithm.

Summary and Conclusions

Physiological effects of exercise on glucose metabolism have been extensively studied in healthy humans, over the last several decades. However, detailed and systematic investigations into exercise effects on glucose homeostasis and resultant hypoglycemia, pertaining especially to T1D, are scarce. Studies exploring the effects of exercise of varying intensities and duration on counter-regulatory hormonal responses, substrate (carbohydrate and fat predominantly) metabolism, muscle and hepatic glucose, glycogen, and lipid kinetics, lactate threshold, etc., are necessary to fashion rational therapeutic approaches to prevent hypoglycemia, delay fatigue, and improve exercise performance and thereby health and fitness of our patients with T1D. The roles of short- and long-term glycemic control, duration of diabetes, and accompanying comorbidities and complications of diabetes on exercise physiology in T1D are also unknown. Such large and critical knowledge gaps need to be filled so that patients and their physicians are better informed to provide logical, evidence-based therapeutic options so that this patient population becomes fitter through regular exercise and training while simultaneously minimizing the constant and sometimes disabling fear of hypoglycemia that prevents these individuals from leading healthier and fitter lives. Such an understanding of physiological effects of exercise could also inform next-generation closed-loop control algorithms currently being designed for the artificial endocrine pancreas to treat T1D.

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