Published in final edited form as:

Expert Rev Endocrinol Metab. 2011 January 1; 6(1): 93–108. doi:10.1586/eeem.10.78.

Exercise-related hypoglycemia in diabetes mellitus

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Abstract

Current recommendations are that people with Type 1 and Type 2 diabetes mellitus exercise regularly. However, in cases in which insulin or insulin secretagogues are used to manage diabetes, patients have an increased risk of developing hypoglycemia, which is amplified during and after exercise. Repeated episodes of hypoglycemia blunt autonomic nervous system, neuroendocrine and metabolic defenses (counter-regulatory responses) against subsequent episodes of falling blood glucose levels during exercise. Likewise, antecedent exercise blunts counter-regulatory responses to subsequent hypoglycemia. This can lead to a vicious cycle, by which each episode of either exercise or hypoglycemia further blunts counter-regulatory responses. Although contemporary insulin therapies cannot fully mimic physiologic changes in insulin secretion, people with diabetes have several management options to avoid hypoglycemia during and after exercise, including regularly monitoring blood glucose, reducing basal and/or bolus insulin, and consuming supplemental carbohydrates.

Keywords

exercise; hypoglycemia; hypoglycemia-associated autonomic failure; insulin; insulin secretagogues; physical activity; Type 1 diabetes mellitus; Type 2 diabetes mellitus

Diabetes is a chronic disease state characterized by absolute or relative insulin deficiency and is a leading cause of death and disability in the USA. In 2008, the CDC reported that approximately 23.6 million people in the USA have diabetes and, of that population, 5.7 million cases are undiagnosed [1].

Approximately 5–10% of individuals with diabetes have Type 1 diabetes mellitus (T1DM), an autoimmune disorder involving pancreatic β -cell destruction and consequent abolition of insulin secretion. Comprising the bulk (90–95%) of diabetes cases [1], Type 2 diabetes mellitus (T2DM) results from a combination of environmental and genetic factors, which lead to insufficient insulin secretion and insulin resistance.

Diabetes can lead to an array of microvascular and macrovascular complications. It is the main cause of kidney failure, limb amputation and new-onset blindness in American adults

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Financial & competing interests disclosure

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

[1]. Rates of both cardiovascular disease mortality and stroke are up to fourfold higher among people with diabetes versus those without.

Positively, several historic studies conducted over the past 20 years have established that aggressive blood glucose control can prevent and slow the progression of diabetic complications, including retinopathy, microalbuminuria and neuropathy [2–5]. These findings have informed and redirected patient care strategies with the American Diabetes Association (ADA) setting general target glycosylated hemoglobin (HbA1c) values at less than 7% in 1995 [6].

Unfortunately, at this point in time, the primary negative consequence of intensified glycemic control in T1DM or T2DM is an increased frequency of hypoglycemic episodes [2–5,7,8]. These events chiefly occur in individuals treated with insulin secretagogues (sulfonylureas and meglitinides) and/or insulin [9,10]. In this context, hypoglycemia often occurs when insulin levels in excess of metabolic requirements are compounded by blunted neuroendocrine, autonomic nervous system (ANS) and metabolic counter-regulatory responses and associated symptoms. This phenomenon of blunted physiologic responses is referred to as hypoglycemia-associated autonomic failure (HAAF) and can occur in T1DM [11] and in insulin- and secretagogue-dependent T2DM populations [9,12–16]. When blood glucose goes unchecked and blunted symptoms go unnoticed (hypoglycemia unawareness) severe hypoglycemia ensues.

It has been long understood that severe hypoglycemia can result in seizure, coma and/or fatality. Newer evidence suggests that acute mild hypoglycemia (45–52 mg/dl; 2.5–2.9 mmol/l) may adversely affect cardiovascular parameters, including inflammatory markers and endothelial function [17–19]. Fear of hypoglycemia is prevalent among individuals with diabetes reliant upon exogenous insulin and/or insulin secretagogues. This fear poses a major barrier to achieving beneficial glycemic targets [20].

Physical activity (exercise) is a cornerstone for effective diabetes prevention and management. Exercise promotes weight loss and maintenance, hepatic and peripheral insulin sensitivity, glucose uptake and utilization, and cardiovascular health. In people with prediabetes, risk of developing diabetes can be decreased by 58% with combined diet, exercise and behavior modification [21]. Recent data from the 4-year Action for Health in Diabetes (Look AHEAD) trial showed that intensive lifestyle interventions (including exercise) lead to sustained improvements in bodyweight, aerobic fitness, glycemic control, blood pressure and lipid profile in people with T2DM who are overweight or obese [22]. Although less evidence specific to T1DM exists, an elegant meta-analysis found that use of multiple interventions to increase physical activity improves glycemic control in this group [23]. Importantly, it has also been demonstrated that physical activity improves measures of quality of life in chronically ill patients, including those with diabetes [24].

However, just as with intensified glucose control, exercise can increase the risk of hypoglycemia in individuals with diabetes. Without sufficient insulin reduction and/or carbohydrate supplementation, exercise-related hypoglycemia can occur in T1DM during [25–28], immediately after and several hours after [26–29] a single bout of exercise. Recent studies have implicated HAAF as a contributing cause in this increased risk of hypoglycemia after exercise [30–35].

Fear of hypoglycemia has also been identified as the greatest barrier to exercise in people with T1DM [36], and it is likely that the same holds true for insulin- and secretagogue-dependent individuals with T2DM. In light of the potential benefits of exercise it is crucial that researchers, medical care providers, diabetes educators and patients fully understand

hypoglycemia risk factors and develop effective strategies to avoid detrimental decreases in blood glucose without sacrificing glycemic control.

In the following sections, we discuss exercise physiology during moderate aerobic exercise in T1DM and T2DM. The associated risk of hypoglycemia under these conditions will be explored, highlighting the importance of the role HAAF plays in elevating this risk. We conclude with an overview of basic exercise recommendations for individuals with diabetes, and literature-supported management strategies and techniques for preventing hypoglycemic episodes during exercise. Although integral to a balanced exercise program, strength training, stretching and sport-specific activities are beyond the scope of this review (for additional reading please refer to [37,38]).

Fuel metabolism during moderate-intensity exercise

At rest, in a fasted state, the nondiabetic body relies primarily on nonesterified fatty acids (NEFAs) for energy requirements (FIGURE 1). Initiating exercise increases energy utilization and decreases energy storage through neuroendocrine changes, muscular contraction and blood flow redistribution (FIGURE 2). At the onset of exercise, muscle glycogen provides an immediate fuel for the working muscle. As exercise continues and muscle glycogen decreases, fuel preference shifts to NEFA and increasingly circulating glucose [39,40].

Endogenous insulin secretion falls during exercise under normal physiologic conditions. In diabetes the primary dysfunction is an absolute or relative loss of insulin secretory capacity. However, specific glucose-lowering treatments for diabetes can cause a relative hyperinsulinemic state, providing an excess of insulin for metabolic needs. Thus, a physiologically appropriate insulin level at rest may become unsafe under exercise conditions if the level is sufficient to prevent the requisite shift from energy storage to energy release and utilization.

All forms of exogenously administered insulin, when used in the treatment of either T1DM and T2DM, can increase the risk of iatrogenic hypoglycemia [9]. Insulin secretagogues prescribed for T2DM with residual β -cell function can have the same result [10]. Sulfonylureas (chlorpropamide, tolbutamide, glimepiride, gliclazide, glipizide and glyburide) and meglitinides (repaglinide and nateglinide) comprise the insulin secretagogues currently available. Both classes of drugs stimulate endogenous insulin secretion by inducing the closure of ATP-sensitive potassium channels on the β -cell membrane, which causes cellular depolarization and subsequent insulin release [41]. Nateglinide appears to exert its insulin exocytotic effects through a second, direct mechanism as well [42]. Other drug classes used for treatment of T2DM do not generally cause hypoglycemia under resting or exercise conditions [43].

Glucagon, an energy-releasing hormone secreted from pancreatic α -cells, stimulates hepatic glycogenolysis and gluconeogenesis. The glucagon response to hypoglycemia no longer occurs within the first few years of onset of T1DM [44,45] and becomes progressively diminished in patients with T2DM [16,46]. Fortunately, this deficit does not extend to exercise conditions. Normal glucagon responses during exercise have been documented in people with T1DM [47] and T2DM [48].

Epinephrine, secreted from the adrenal medulla, also enhances energy availability during moderate exercise via stimulation of lipolysis [49]. This energy hormone becomes increasingly important and is secreted in greater quantities with both increasing duration and intensity of exercise [50], and stimulates muscle glycogenolysis and inhibits glucose uptake during vigorous exercise [51]. As discussed later, the epinephrine response to hypoglycemia

and exercise can become blunted in diabetes [15,30–32,34,35,52–57], further contributing to altered metabolism.

Even in the presence of intact glucagon and epinephrine responses, elevated insulin levels can inhibit exercise-induced metabolic responses directly and indirectly by opposing the effects of these hormones.

Endogenous glucose production

Without an increase in endogenous glucose production (EGP; primarily from the liver) to meet the increased metabolic demands during exercise, blood glucose levels would fall precipitously. An increase in glucagon coupled with a decrement in insulin to decrease the insulin-to-glucagon ratio within the portal vein is the major stimulus for increased EGP during low- to moderate-intensity exercise (FIGURE 2) [58–60]. In nondiabetic individuals, glucagon induces a significant increase in both glycogenolysis and gluconeogenesis during exercise to meet the metabolic demands of working muscles [61]. Net hepatic glycogenolysis is the major contributor to increased EGP at exercise levels up to 70% of maximum aerobic capacity ($\text{VO}_2 \text{ max}$) [62,63]. The decrease in insulin may be required for a full glycogenolytic response, as elevated levels of this hormone suppress glycogenolysis [64]. Gluconeogenesis is crucial to the preservation of hepatic glycogen stores, and becomes increasingly important with intense or prolonged exercise.

While it has been generally established that changes in glucagon and insulin levels function as primary regulators of hepatic glucose production during moderate exercise, the mechanisms by which insulin is suppressed and glucagon is elevated are less well understood. Proposed mediators of these changes include hepatic and hypothalamic glucoreceptors [65], and carotid bodies or nearby sensors which may detect subtle changes in blood glucose levels or a closely associated signal [66].

Despite the preserved exercise-induced glucagon response, relative hyperinsulinemia can blunt the EGP response to exercise in people with well- and poorly controlled T1DM [67] by directly suppressing glycogenolysis and gluconeogenesis [64] and by attenuating the change in insulin-to-glucagon ratio to blunt glucagon effects [61]. Similarly, in people with T2DM, increases in hepatic glucose production occurred during exercise under fasting conditions when the insulin-to-glucagon ratio decreased [48,68] but were inhibited when the hormone ratio did not change [69]. In one study, sulfonylureas and insulin were shown to have an additive inhibitory effect on hepatic glucose production during fasting exercise [70]. Consequentially, blood glucose decreased by a greater degree under the combined stimuli than under either condition alone.

Fatty acids

Although a greater proportion of energy is derived from carbohydrate during exercise as compared with at rest, lipid oxidation increases at the working muscle during low- to moderate-intensity exercise (FIGURE 2), contributing up to 40% of total energy expenditure in healthy individuals [71]. Increased lipolysis and delivery of triacylglycerols from white adipose tissue and hydrolysis of plasma very low density lipoprotein (VLDL)-triacylglycerols and intramuscular triacylglycerols within skeletal muscle may all contribute to greater fatty acid availability. Plasma-derived fatty acids account for approximately 55–65% of total lipid utilization during exercise [72].

Studies indicate that hormone-sensitive lipase activation is primarily responsible for upregulation of NEFA mobilization from white adipose tissue during moderately intense aerobic exercise [73,74]. Enhanced phosphorylation of this enzyme occurs with exercise-

induced increases in circulating natriuretic peptides (released from the heart during exercise) [75] and catecholamine-stimulated β -adrenergic receptor signaling [49,76]. Lipolysis is additionally activated by decreasing levels of insulin, a strong antilipolytic, pro-lipogenic hormone. The fraction of NEFA re-esterified by the liver is also reduced compared with resting conditions, thereby aiding in the increased circulation of the energy substrate [77].

Under fasting, mildly hyperglycemic conditions, Chokkalingam *et al.* infused low and high doses of insulin into exercising subjects with T1DM to simulate pre- and postprandial therapeutic insulin concentrations, respectively [78]. High-dose insulin infusion reduced the contribution of fat oxidation to overall energy expenditure during exercise compared with the low dose (15 vs 23%, respectively). Notably, both interventions involved insulin levels that were significantly greater than generally found in nondiabetic adults [78]. Consequently, even in the lower dose insulin group, percentage energy expenditure from fat was decreased compared with healthy individuals [71]. A limitation of the study may have been the mild hyperglycemic level of the subjects. Hyperglycemia has been shown to independently inhibit lipid oxidation during exercise [79]. Thus, when subjects with T1DM exercised under euglycemic conditions (~ 97 mg/dl; 5.4 mmol/l) with insulin levels of approximately 122 pmol/l, lipid oxidation was normalized. Reduced lipid utilization in T1DM during exercise is concerning, as it induces a greater reliance on carbohydrate sources and this could ultimately lead to decreases in blood glucose levels [78].

More research is needed to understand lipid metabolism in tightly controlled and/or excessively hyperinsulinemic T2DM during exercise. The general unselected population of individuals with T2DM is plagued by metabolic inflexibility, with elevated levels of lipolysis, circulating NEFA and lipid oxidation during postprandial periods due to adipose tissue and hepatic insulin resistance, and altered fuel selection at the skeletal muscle [80]. One study did show that rates of lipid oxidation were normal compared with controls during exercise (50 vs 70% VO_2 max) when subjects with T2DM withheld their sulfonylurea medications at least 1 week prior [48].

Glucose uptake

Skeletal muscle provides a major sink for glucose disposal and is therefore pivotally involved in maintaining blood glucose homeostasis (FIGURES 1 & 2). Increased blood flow to working muscle enhances the delivery of glucose to myocytes. Glucose is transported from blood into myocytes predominantly by the glucose transporter isoform GLUT4, which translocates to both the cell membrane and the t-tubules under insulin- and contraction-/exercise-stimulated conditions [81]. Longstanding *in vitro* evidence exists regarding an additive or partially additive effect of insulin and contraction on both glucose transport [82] and GLUT4 translocation [83]. *In vivo*, glucose uptake under combined exercise and hyperinsulinemic conditions is actually greater than the sum of glucose uptake measurements when each stimulant is applied independently [84,85].

Supporting these observations, another study found that increased insulin levels exaggerated the rise in carbohydrate oxidation during mildly hyperglycemic exercise, resulting in greater reliance on exogenous glucose infusion [78]. Under euglycemic conditions (or when carbohydrate ingestion is inadequate), this phenomenon could be dangerous. Jenni *et al.* demonstrated that substrate utilization in men with well-controlled T1DM in a euglycemic state (insulin level ~ 122 pmol/l) is quite similar to people without diabetes [79]. If these individuals were exposed to the hyperinsulinemic levels of the former study [78], a much greater rate of exogenous glucose would be required to prevent hypoglycemia.

Despite insulin resistance and reduced insulin-stimulated glucose uptake [80], GLUT4 translocation [86] and glucose uptake [87] are preserved in T2DM during exercise. In fact, a

decrease in blood glucose is often observed in this population during fasting and postprandial exercise [88]. Although this suggests that hypoglycemia could occur, Gaudet-Savard *et al.* found that decreases in glycemia during exercise were correlated with pre-exercise blood glucose levels [89]. Therefore, blood glucose fell less when levels were lower before starting exercise. This could confer some protective benefit for people with T2DM, but importantly, the individuals studied had only been diagnosed for a relatively short duration (5.3 ± 5.7 years) and their diabetes was being controlled by diet, glyburide, metformin, or a combination of glyburide and metformin, and not insulin. Whether or not the findings could be extrapolated to more advanced stages (i.e., insulin-treated T2DM) is unknown.

Post-exercise metabolism

In healthy adults, upon cessation of exercise, lipid and glucose oxidation decrease to near-basal levels and, appropriately, lipolysis and glucose production decrease as well [85]. Hepatic insulin sensitivity is improved, as shown by studies in dogs in which net hepatic glucose uptake was enhanced during hyperinsulinemic/hyperglycemic conditions following a bout of exercise [90,91]. Exercise *per se* can increase skeletal muscle glucose uptake for up to a few hours after an exercise session, while skeletal muscle insulin sensitivity is enhanced up to 48 h following exercise [92,93].

The aforementioned physiological alterations that take place following exercise may provide both short- and long-term benefits in both health and in diabetes. However, increased insulin sensitivity may alter insulin and/or insulin secretagogue requirements post-exercise for those with diabetes. Several studies in T1DM have demonstrated a need to reduce insulin doses following a bout of exercise in order to avoid hypoglycemia [28,94,95]. Praet *et al.* have also found that hyperglycemia is reduced for 24 h following a bout of exercise in people with insulin-treated T2DM, indicating enhanced insulin sensitivity [96]. Studies specifically investigating the risk of hypoglycemia following exercise in people with advanced T2DM are lacking. However, if the evidence just discussed can be extrapolated to this population, the risk of hypoglycemia following exercise is likely to be elevated.

Hypoglycemia-associated autonomic failure

Counter-regulatory responses to hypoglycemia

In healthy individuals, as blood glucose decreases below normal fasting levels (~ 90 mg/dl; ~ 5 mmol/l), counter-regulatory responses are initiated in a hierarchical fashion to combat further decrements in glycemia [97]. Insulin levels respond first, decreasing at blood glucose levels approximately 81 mg/dl (~ 4.5 mmol/l). At blood glucose concentrations of approximately 65–70 mg/dl (~ 3.6 – 3.9 mmol/l), glucagon and epinephrine levels increase. Autonomic and neuroglycopenic symptoms then become apparent at blood glucose levels of approximately 60 mg/dl and approximately 50 mg/dl (~ 3.3 and ~ 2.8 mmol/l, respectively), stimulating a behavioral response of carbohydrate ingestion [97].

As discussed previously, individuals with diabetes treated with insulin and/or insulin secretagogues have a partial or complete inability to reduce circulating insulin levels. In addition, the glucagon response to hypoglycemia is abolished in T1DM [44,45] and becomes increasingly diminished in T2DM [16,46]. Hence, the first two major lines of defense against hypoglycemia are non-functioning in T1DM and advanced T2DM. In the presence of these impairments, epinephrine becomes the primary line of defense in the counter-regulatory response to hypoglycemia. Unfortunately, the epinephrine response can progressively become less robust and occur at lower blood glucose concentrations in patients with either T1DM [32,34,35,52–57,98,99] or T2DM [15,16]. In addition, autonomic

symptoms associated with hypoglycemia (e.g., sweating, tremors and palpitations, and feeling hot, thirsty and agitated), are also reduced, resulting in decreased hypoglycemia awareness [15,16,54,57,100].

It has been postulated that blunted epinephrine and symptom responses are a part of a larger phenomenon known as HAAF [54]. In HAAF, an antecedent hypoglycemic episode blunts counter-regulatory responses (neuroendocrine, ANS and metabolic) to subsequent hypoglycemia. In addition, the glycemic levels at which the hierarchy of responses are initiated are lowered [16,56], further increasing the risk of hypoglycemia.

The theory of HAAF provides a physiologic explanation for why people with insulin- and/or insulin secretagogue-treated T1DM and T2DM – and in particular those with tighter glycemic control – experience higher rates of hypoglycemia [101]. While excess levels of circulating insulin must be present to precipitate a hypoglycemic episode, it is the blunting of counter-regulatory responses that leads to the vicious cycle of recurring hypoglycemia [54]. Importantly, stringently avoiding hypoglycemia for a period of only a few weeks can improve the epinephrine response, the glycemic threshold for counterregulation and hypoglycemia awareness [57,100].

Individuals with T1DM are at risk for hypoglycemia and development of HAAF from disease onset [102]. Determining hypoglycemic risk in T2DM is more complicated because it is a heterogeneous disease that progresses over time [88]. Physiologically however, advancing T2DM begins to mirror T1DM, with diminishing insulin secretion that eventually leads to complete reliance on exogenous insulin and increased rates of hypoglycemia [13,14,103,104]. As such, research has found independent associations between increased hypoglycemic risk and disease duration, duration of insulin therapy and previous hypoglycemia [13,14,104].

Individuals with diabetes that are older may be particularly prone to hypoglycemia and HAAF because age can independently confound hypoglycemia awareness [46]. Matyka *et al.* showed that in nondiabetic men aged 60–70 years compared with nondiabetic men aged 22–26 years, hypoglycemic symptoms began at lower blood glucose values (54 vs 65 mg/dl; 3.0 vs 3.6 mmol/l) and were less robust [105]. Also, performance on the four-choice reaction time test, used in the assessment of cognitive function, declined at higher blood glucose levels in the older group (54 vs 47 mg/dl; 3.0 vs 2.6 mmol/l). Therefore, hypoglycemia awareness and cognitive function were both impaired in older individuals. This could negatively impact a person's ability to follow normal self-care steps upon recognition of hypoglycemia [55].

Counter-regulatory responses to exercise

Exercise substantially increases energy utilization and the body must be precisely tuned to react to large, abrupt changes in metabolic demand. In healthy individuals a drop in blood glucose of only 8 mg/dl (4 mmol/l) is sufficient to induce a counter-regulatory response [66]. Qualitatively, neuroendocrine and ANS counter-regulatory responses to hypoglycemia and exercise are very similar. The major difference is that during exercise norepinephrine responses are much larger and epinephrine together with glucagon values are significantly reduced as compared with hypoglycemia. However, recent studies have determined that antecedent hypoglycemia also has deleterious effects on the body's ability to combat subsequent nonhypoglycemic stressors. These stressors include certain cardiovascular challenges [106], hypotension (in rats [107]) and euglycemic exercise [30,31,33]. Unfortunately, exercise can also increase rates of hypoglycemia in diabetes [25–29], and work has demonstrated that HAAF is implicated in this exercise-associated hypoglycemia [30–35].

In a 2-day study, hypoglycemia on day 1 blunted a wide array of counter-regulatory responses in healthy individuals during 90 min of next-day, moderate (50% VO_2 max) euglycemic exercise [30]. Epinephrine, norepinephrine, glucagon, growth hormone, pancreatic polypeptide and cortisol responses were all significantly blunted, indicating deficits in pituitary, neuroendocrine and ANS responses. Associated metabolic responses were also blunted, as evidenced by reduced EGP, lipolysis and ketogenesis. The rate of exogenous glucose infusion required to maintain euglycemia was nearly 15-fold higher in subjects exposed to antecedent hypoglycemia versus controls.

Similar blunting effects were observed in subjects with T1DM [31]. In this study, the glucagon response was completely abolished after day 1 hypoglycemia, while epinephrine, norepinephrine and cortisol responses were significantly blunted. The critical metabolic mechanisms of EGP and lipolysis were also significantly reduced, resulting in greater reliance on exogenous glucose infusion.

Of cause for concern, counter-regulatory responses to prolonged exercise can be blunted by even mild levels (70 mg/dl; 3.9 mmol/l) of antecedent hypoglycemia in individuals with T1DM [33]. Glucagon, epinephrine, norepinephrine, cortisol, EGP and lipolytic responses become progressively blunted with increasing severity of prior hypoglycemia (70, 60 and 50 mg/dl; 3.9, 3.3 and 2.8 mmol/l, respectively). Importantly, the deficits become more pronounced with exercise duration exceeding 30 min.

Antecedent exercise affects counter-regulatory responses to subsequent hypoglycemia in a manner qualitatively and quantitatively similar to antecedent hypoglycemia [32,98]. Galassetti *et al.* found that nondiabetic subjects exposed to two 90-min periods of cycle exercise (50% VO_2 max) on day 1 experienced significant reductions (~30–90%) in several neuroendocrine and metabolic counter-regulatory responses during hypoglycemia (50 mg/dl; 2.8 mmol/l) on day 2 [32].

Both low- and moderate-intensity exercise (30 and 50% VO_2 max, respectively) can induce blunting of next-day counter-regulatory responses to hypoglycemia (50 mg/dl; 2.8 mmol/l) in people with T1DM [34]. Two bouts of cycle exercise at either intensity on day 1 blunted epinephrine, pancreatic polypeptide, EGP and symptom responses to day 2 hypoglycemia compared with nonexercised controls.

Sandoval *et al.* investigated whether or not altered counter-regulatory responses also play a role in more immediate post-exercise hypoglycemia [35]. The group measured the effects of morning exercise (90 min at 50% VO_2 max) or hypoglycemia (2 h at 50 mg/dl; 2.8 mmol/l) on afternoon hypoglycemia in subjects with T1DM. While both morning interventions blunted epinephrine and muscle sympathetic nerve activity (MSNA) responses to subsequent afternoon hypoglycemia (occurring ~2.5 h after the initial stress), morning exercise further reduced EGP and prevented the reduction of glucose disposal that occurred in the morning hypoglycemia group.

The latter observations suggest that antecedent hypoglycemia confers some protection against (although does not prevent) the glucose-lowering effects of subsequent hyperinsulinemia and exercise by inducing transient relative insulin resistance [35,99]. Conversely, increases in hepatic and peripheral insulin sensitivity following exercise may indicate an even greater risk for subsequent hypoglycemia following stress [34,35].

Mechanisms of hypoglycemia-associated autonomic failure

The mechanisms by which hypoglycemia and exercise blunt counter-regulatory responses have been the subject of intense work that has recently focused on multiple neural and

hormonal factors. Bao *et al.* recently demonstrated a supporting role for increases in cortisol in the development of exercise-induced HAAF [108]. In this study of subjects with T1DM, a physiologic (low) or pharmacologic (high) dose of cortisol was infused on day 1 so that cortisol levels equaled or surpassed, respectively, concentrations observed during hypoglycemia. Both doses blunted counter-regulatory responses (i.e., glucagon, growth hormone, epinephrine, norepinephrine and pancreatic polypeptide) to subsequent day 2 exercise. Metabolic defenses during exercise were also lower following cortisol such that glucose infusion rates significantly increased during the last 30 min of exercise. While this was the first study to examine the relationship between antecedent elevations in cortisol and counter-regulatory responses during exercise, controversy exists in the literature regarding whether or not cortisol mediates the blunting of counter-regulatory responses to hypoglycemia [109–113]. Pharmacologic levels of cortisol were found to attenuate counter-regulatory responses to subsequent hypoglycemia [109–110], but physiologic levels of cortisol (similar to levels that occur during hypoglycemia) were not found to have the same effect [112,113]. These findings do not, however, preclude the possibility that cortisol is a factor in blunted counter-regulatory responses to exercise following a hypoglycemic episode.

Sexual dimorphism in counter-regulatory responses to exercise

Gender has been demonstrated to significantly influence counter-regulatory responses to falling glucose levels. In subjects with T1DM who cycled for 90 min without antecedent glucoregulatory stress, glucagon, cortisol, pancreatic polypeptide and EGP responses were similar between sexes [114]. However, females showed significantly lower epinephrine, norepinephrine and growth hormone responses compared with males. Despite a lower catecholamine response, lipolytic rates were actually greater in the women than in the men, suggesting greater β -adrenergic sensitivity in the adipose tissue of females.

Changes in counter-regulatory responses during exercise following prior hypoglycemia also exhibit sexual dimorphism in T1DM [115]. Male subjects experienced greater blunting of glucagon, catecholamines, growth hormone, fat oxidation and EGP relative to female subjects. In fact, the glucagon response to exercise in the male subjects was completely abolished, while a residual, albeit blunted, glucagon response was still apparent in the female subjects. This difference was likely responsible for the sexual dimorphism in EGP responses, as men had a decreased glucagon to insulin ratio compared with women. As a result of greater blunting of fat oxidation and EGP, male subjects required greater amounts of exogenous glucose than female subjects. The preservation of the fat oxidation response following hypoglycemia may confer some gluco-protective benefit to females.

Very similar results occurred when counter-regulatory responses to hypoglycemia were studied following day 1 exercise [116]. Again, males experienced greater blunting of glucagon and catecholamine responses during hypoglycemia. In addition, MSNA, cardiovascular responses, lipolysis, adrenocorticotrophic hormone (ACTH) and lactate were blunted to a greater extent in males.

Other studies have demonstrated that in both healthy and T1DM individuals, males show a more robust sympathetic nervous system response than females during a single bout of exercise. This sexual dimorphism also occurs similarly during hypoglycemia [117]. Intriguingly, as both antecedent hypoglycemia and exercise cause greater blunting of multiple counter-regulatory factors to subsequent stressors in males compared with females, it may be that women are less susceptible to HAAF caused by hypoglycemia or exercise.

Managing diabetes mellitus in the context of exercise

Regular exercise confers many health benefits, including reduced risk of cardiovascular disease, weight management, reduced blood pressure, improved glycemia, and an enhanced sense of wellbeing. Thus, in the absence of contraindications (see the following sections), individuals with T1DM and T2DM should be encouraged to participate in a regular exercise program. Individuals with diabetes taking insulin or insulin secretagogues may need to tailor their normal treatment regimens, including reducing preprandial and basal insulin doses and consuming supplemental carbohydrates to prevent episodes of hypoglycemia. Appropriate adjustments require consideration of type, intensity and duration of exercise, prandial state, and the time of day.

Exercise screening

The American College of Sports Medicine considers people with diabetes to be at high risk for cardiovascular disease and recommends that this population should undergo a thorough health examination and graded exercise test prior to beginning an exercise program that includes moderate to vigorously intense exercise [118]. The ADA has published more refined guidelines to help determine whether or not a person with diabetes requires an exercise stress test [119]. The ADA recommends a graded exercise test for individuals with diabetes aged over 35 years or those with T2DM for over 10 years, T1DM for over 15 years, additional cardiovascular risk factors, microvascular disease, peripheral vascular disease and/or autonomic neuropathy. Routinely screening for coronary artery disease in low-risk patients with diabetes who are asymptomatic, however, is not recommended at this time [120].

Individuals with diabetes should be evaluated for diabetic complications that may contraindicate certain types or intensities of exercise [121]. For instance, high-intensity aerobic exercise may be contraindicated for patients with proliferative retinopathy, severe nonproliferative retinopathy, or uncontrolled hypertension. Those diagnosed with peripheral neuropathy should be considered on a case-by-case basis, and weight-bearing or non-weight-bearing activities should be prescribed depending on the individual's susceptibility to foot ulcers. Severity and effects of autonomic neuropathy should be assessed to identify safe modes and intensities of exercise [121].

General exercise recommendations

An individualized exercise regimen should be developed with respect to results from the health screening and evaluation, and the individual's age, physical activity level [121], and exercise goals and objectives. In general, however, a recent position statement from the ADA concluded that exercise guidelines developed for nonspecific populations can also be applied to individuals with T1DM or T2DM. Therefore, those who are able should participate in moderate-intensity exercise (50–70% VO_2 max) a minimum of 150 min per week [121]. Individuals should strive to maintain a regular exercise schedule, avoiding aerobic exercise for no more than two consecutive days [122]. Eriksen *et al.* found that people with T2DM may benefit from multiple shorter duration bouts of exercise performed daily [123]. The authors studied the glucose homeostatic effects of moderate-intensity exercise (60% VO_2 max) completed as either three 10-min bouts per day or one continuous 30 min session. The experimental period continued for 5 weeks, with subjects participating in three home-based cycle exercise sessions per week. While both groups gained improved aerobic fitness, fasting glucose concentrations and glucose tolerance improved only in the group that participated in the shorter bouts of exercise.

In the absence of contraindications (proliferative diabetic retinopathy, severe nonproliferative retinopathy or uncontrolled hypertension), the ADA also recommends that T2DM patients should engage in a resistance training program three times per week [121]. Both resistance training and aerobic exercise provide similar beneficial insulin-sensitizing effects [124] and equally improve glycemia in T2DM patients. Changes in HbA1c over a 22-week exercise training intervention [125] were -0.51% for aerobic training and -0.38% for resistance training. However, combining the two forms of exercise afforded even greater improvements in HbA1c (-0.46 and -0.59% , combined exercise vs aerobic and resistance training, respectively). Moreover, participants with lower baseline HbA1c ($<7.5\%$) were only able to achieve improvements in glycemia through combined aerobic and resistance exercise training [125].

Older patients with T2DM can benefit from regular strength training, as this form of exercise attenuates the declines in muscle mass, functional capacity and resting metabolic rate, and the increases in insulin resistance and adiposity that occur naturally with age [126]. However, the health status of these individuals should be considered prior to implementing this type of physical activity [121].

Glucose monitoring

Measurement of blood glucose levels before and during exercise as well as immediately and several hours after is necessary in patients treated with insulin or insulin secretagogues in order to avoid extreme excursions in blood glucose levels. After typical glycemic responses to a given activity are determined, it is important to continue monitoring blood glucose especially if changing diet, bodyweight, and/or exercise duration and intensity.

In people with well-controlled diabetes treated with insulin or insulin secretagogues, moderately intense exercise can induce hypoglycemia, and the ADA advises that supplemental carbohydrate should be consumed if blood glucose levels are less than 100 mg/dl (5.6 mmol/l) prior to the start of exercise [121]. Patients should not exercise during periods of hypoglycemia. In addition, exercise should be avoided for 24 h after an episode of hypoglycemia because, as discussed above, antecedent hypoglycemia severely blunts counter-regulatory responses to exercise, thereby increasing the risk of recurrent hypoglycemia [31].

Previous ADA guidelines urged caution during exercise if blood glucose levels exceeded 300 mg/dl (16.7 mmol/l) without concomitant ketosis [119]. The newest recommendations do not restrict exercise in the presence of any level of hyperglycemia. If ketosis is detected however, exercise should be postponed, irrespective of glycemic level [121].

Continuous glucose monitoring (CGM) systems have been introduced as a tool to enhance glycemic control and prevent extreme glucose excursions [127]. A recent study explored the effects of CGM over a 12-month period in adults with intensively-treated T1DM [128]. Comparing the first and second half of the study period, severe hypoglycemic episodes (requiring assistance) dropped from 21.8 to 7.1 events per 100 person-years. Similarly, reduced rates of severe hypoglycemia were associated with initiation of CGM in a retrospective study of over 100 people with T1DM and T2DM [129].

Taken from these findings, such systems may assist patients in identifying and reversing trends in falling blood glucose levels during and after exercise. However, several barriers to widespread CGM still exist [127]. Frequent calibration requirements and low sensor lifespans can make CGM systems time consuming and cumbersome. Access to this technology is costly as well, with many insurance companies refusing to reimburse CGM equipment. Because most current CGM systems sample interstitial fluid instead of blood,

there is speculation that rapid fluctuations in glucose level could cause a lag time during which interstitial fluid glucose levels do not accurately reflect circulating blood glucose levels. Finally, decreased accuracy at hypoglycemic levels is cause for concern. Nonetheless, much work is currently underway to make CGM a reality for more people with diabetes [127].

Insulin dose adjustment

Two forms of intensive insulin therapy, multiple daily injections (MDI) and continuous subcutaneous insulin infusion (CSII), attempt to closely mimic physiologic insulin fluctuations and have evolved to afford patients greater flexibility in adjusting insulin doses to accommodate blood glucose level, caloric intake, meal composition and anticipated activity levels. MDI currently combines administration of a long-acting insulin analog (i.e., glargine or detemir) or an intermediate-acting insulin (neutral protamine hagedorn [NPH]) with mealtime boluses of a rapid-acting insulin analog (i.e., lispro, aspart or glulisine) or a short-acting insulin (regular). CSII involves continuous subcutaneous delivery of rapid-acting or short-acting insulins and premeal bolus doses given via an insulin pump [130]. CSII allows individuals to immediately adjust the exogenous insulin infusion rate, which is especially useful for unplanned exercise.

People using MDI can reduce basal insulin before and/or after exercise to help prevent hypoglycemia. It may be important to consider the pharmacokinetics and pharmacodynamics of different intermediate- or long-acting insulins in the context of exercise to determine if and how much basal insulin should be reduced. For example, in nondiabetic subjects that exercised 3 h after injection of NPH insulin, insulin concentrations rose significantly during 60 min of treadmill exercise compared with a separate resting protocol [131]. Consequently, the exercising subjects required significantly more exogenous glucose during the exercise period to maintain euglycemia. On the other hand, subcutaneous insulin glargine absorption did not increase during 30 min of continuous exercise (65% VO_2 max) compared with resting conditions [132]. The authors of this study concluded that insulin glargine can be administered without a dose change in individuals planning to be physically active. In another study however, exercising 5 h after the previous meal and insulin injection led to significantly higher rates of hypoglycemia when glargine was used as the basal insulin compared with detemir and NPH [133].

With CSII therapy, basal insulin can be turned off before, during and/or after exercise. The basal insulin rate may need to be reduced at least 30 min prior to the start of exercise to allow time for receptor-bound insulin to become inactivated [130]. Admon *et al.* demonstrated that in children and adolescents with T1DM, the risk of acute hypoglycemia was similar in subjects exercising (40–45 min) with basal insulin reduced by 50% and those exercising with their pump turned off [134]. However, there was a trend toward increased late-onset hypoglycemia in subjects exercising with their pumps turned on, supporting the authors' suggestion that patients stop basal insulin infusion during exercise. A separate study in children and adolescents found that discontinuing basal insulin during and for 45 min following post-absorptive afternoon exercise significantly reduced the frequency of hypoglycemic episodes [94]. Importantly, there was a trend for hyperglycemia in the group that suspended basal insulin, suggesting that only reducing basal insulin during exercise or restarting suspended insulin sooner after exercise may be appropriate.

Basal insulin may need to be reduced for several hours after exercise. Sonnenberg *et al.* demonstrated that a 25% reduction in basal insulin infusion rate for 5.5 h following a 60-min exercise session reduced episodes of hypoglycemia without causing unwanted increases in blood glucose levels [28]. Separately, in youths who exercised in the late afternoon with

their pumps turned off, a 20% reduction in basal insulin for 6 h overnight decreased the frequency of blood glucose readings to less than 70 mg/dl and less than 80 mg/dl (<3.9 and <4.4 mmol/l), compared with the control group in which basal insulin was not reduced [95]. The mean overnight glucose nadir for the experimental and control groups was 172 and 127 mg/dl (9.5 and 7.0 mmol/l, respectively), raising concerns over unnecessarily elevated glucose levels.

In either MDI or CSII, bolus insulin can also be reduced before and/or after exercise to reduce the risk of hypoglycemia. Exercise should be avoided or postponed for several hours if a full dose of fast-acting insulin has already been administered. When patients with T1DM exercised 40 min after a breakfast meal [135], a premeal bolus of insulin lispro led to significantly greater reductions in blood glucose compared with regular soluble human insulin. Exercising 180 min after the meal, however, caused blood glucose to fall only half as much in the lispro group compared with the regular insulin group. In people with well-controlled T1DM, appropriate reduction (50–75%, based on exercise intensity and duration) of the premeal lispro injection was shown to significantly decrease the risk of hypoglycemia during postprandial exercise [26]. From the data, the researchers proposed reductions in premeal bolus insulin lispro of 25, 50 and 75% for 30 min of exercise at 25, 50 and 75% VO_2 max, respectively. For 60 min of exercise, reductions of 50 and 75% for 25 and 50% VO_2 max, respectively, were proposed. The primary negative consequence of such reductions was associated mild increases in postprandial and post-exercise glycemia.

Importantly, the researchers pointed out that the suggested reductions were designed as a safe starting point for people with diabetes who wish to exercise during postprandial conditions [26]. However, monitoring blood glucose levels and making further adjustments to insulin doses is crucial to an individualized exercise prescription. This process will involve some trial and error, but will ultimately help to prevent unwanted effects of both hypo- and hyperglycemia.

Injection site

It is generally recommended that individuals who inject insulin do so in a region that will not be involved in exercise. Furthermore, insulin should be injected consistently into the same general area prior to exercise to achieve smaller variations in insulin action. During leg exercise, absorption of rapid-acting insulin injected into the leg is increased compared with insulin injected into the arm or the abdomen, resulting in greater decreases in blood glucose [136]. Therefore, injections administered distal to the exercising limbs at sites not involved in physical activity should be encouraged to prevent increased insulin absorption and consequent hypoglycemia. Patients may have more flexibility in choosing an injection site for long-acting insulins. When glargine was injected into the thigh at night and cycle exercise was performed the next morning, absorption rate was comparable to resting conditions [132].

Supplemental carbohydrate

Carbohydrate replacement during and after exercise may help prevent hypoglycemia. Unlike insulin adjustments, supplemental carbohydrate can offer individuals the freedom to engage in unplanned activities [137]. Studies have demonstrated that adequate replacement of carbohydrate during physical exercise prevented almost all hypoglycemic episodes without insulin dosage adjustments [138,139]. In fact, the quantity of replaced carbohydrate was negatively correlated with the frequency of hypoglycemia, while reductions in insulin dose showed no correlation [139].

Longstanding guidelines recommend consuming 10–15 g of carbohydrate to prevent exercise-induced hypoglycemia [140]. However, research by Dubé *et al.* suggests that 40 g of a liquid glucose supplement may be necessary to prevent hypoglycemia during and after 1 h of late postprandial exercise in people using insulin lispro in basal-bolus therapy [137]. In addition, another laboratory found that carbohydrate requirements progressively decreased when 1 h of exercise was performed 1, 2.5, 4 and 5.5 h after a meal preceded by an injection of a standard dose (1 U/kg) of regular insulin [138]. These findings illustrate the fact that carbohydrate supplementations must be individualized to type of insulin and absorptive state. Those involved with patient care and education should help patients understand how different therapies affect timing of peak insulin levels and duration of insulin action [37]. Learning to identify trends in blood glucose shortly before exercise may also be useful in determining carbohydrate requirements [37].

A few studies of individuals with T1DM have analyzed the effects of various types of carbohydrate-replacement drinks on the prevention of hypoglycemia during and shortly after exercise [141] and overnight [27]. In one study, 13 g of carbohydrate from orange juice, skimmed milk or whole milk attenuated decreases in glucose levels during 45 min of moderately intense exercise performed on the morning following an overnight fast and over a 90-min period following exercise [141]. The area under the curve for blood glucose was less with whole milk than the other two drinks during exercise and similar among the three beverages during the post-exercise period. The study authors concluded that whole milk may be the drink of choice, as it did not cause excess increases in exercise glucose levels and prevented a fall in glucose following exercise. Hernandez *et al.* found that without altering the regular insulin regimen, consuming whole milk, a sports drink with carbohydrate and electrolytes, or a sports drink with carbohydrate, fat and protein, but not skimmed milk, before, during and after 60 min of exercise was helpful in preventing late-onset hypoglycemia [27].

As with insulin dose reduction, using supplemental carbohydrate to avoid hypoglycemia will require experimentation with different types and quantities of food or beverages, and timing of intake to find what works best for a particular individual. Again, diligent trial and error will lead to a plan that prevents the dangerous effects of hypoglycemia and the weight gain that can result from regularly consuming excess carbohydrate for exercise needs.

Time of day

When exercise is performed it will affect the need to adjust insulin and/or consume carbohydrate. Prebreakfast exercise [142] significantly increased plasma glucose, but afternoon exercise did not. An earlier study however showed that CSII users may need to decrease basal infusion rates to prevent decreases in blood glucose during fasting morning exercise [143].

For those who exercise in the afternoon, it is also important to recognize that glucose requirements post-exercise are increased in a biphasic manner, occurring immediately and 7–11 h after a bout of exercise [144,145]. This means that extra carbohydrate may be needed during sleeping hours to prevent hypoglycemia.

Intermittent high-intensity exercise

Moderate-intensity exercise combined with intermittent high-intensity exercise (IHE) may provide an intriguing strategy for prevention of exercise-associated hypoglycemia. While insulin and glucagon primarily control glucose production at lower intensities (as described in the previous sections), these two hormones do not appear to mediate the dramatic increases in blood glucose observed during intense exercise [146]. Rather, evidence suggests

that catecholamines drive a 'feedforward' glucoregulatory mechanism that causes a seven- to eightfold increase in glucose production and a three- to fourfold increase in glucose uptake [147,148]. While glucose uptake does increase, β -adrenergic stimulation is associated with increased muscle glycogenolysis, which ensures maintenance of blood glucose concentration to protect the brain [51]. The result is a disproportionate rise in glucose production compared with glucose uptake and successive hyperglycemic conditions not seen at moderate exercise levels.

Theoretically, if high-intensity exercise can raise blood glucose levels, a short bout might be able to counter the glucose-lowering effects of lower-intensity exercise. As such, a few studies have investigated the implementation of IHE before, during and after moderate-intensity exercise to attenuate detrimental decreases in blood glucose. Guelfi *et al.* showed that when people with T1DM performed 4-s maximal sprints every 2 min during 30 min of exercise (40% VO_2 max), blood glucose fell significantly less than when the sprints were not included in the session [148]. During the first 60 min of the recovery period, blood glucose levels in the nonsprint group continued to decrease, while the glucose levels in the intervention group stabilized.

The same group demonstrated that a 10-s maximal sprint effort performed immediately before 20 min of exercise (40% VO_2 max) inhibited the fall in blood glucose during early recovery [149]. The sprint, however, did not attenuate decreases in blood glucose during exercise or during late recovery. Alternatively, when a 10-s sprint was instead performed immediately following the exercise session [150], decrements in blood glucose levels were prevented during the entire duration of a 2-h recovery period.

In these three studies, the exercise period was brief. Subjects exercised in a post-absorptive state, with pre-exercise blood glucose levels of approximately 198 mg/dl (~11 mmol/l) and hyperglycemia persisted during and after exercise [148–150]. Additional research is required to establish whether or not similar results can be achieved during different prandial phases, under euglycemic conditions, and during exercise of higher-intensity and/or longer duration. Future studies should also investigate the potential role of IHE in the prevention of late-onset exercise-associated hypoglycemia. Importantly, the evidence presented cannot be extrapolated to T2DM at risk for hypoglycemia. This group is generally older and comorbidities are common [88], making strenuous exercise potentially unsafe. Furthermore, physiologic responses to high-intensity exercise in people with T2DM are not fully understood and may not mirror observations reported for T1DM [151].

At this time, IHE cannot be recommended for all individuals with T1DM. Consideration of a patient's overall health and ability to perform such intense exercise is necessary before implementing such an exercise plan. It should be noted that intermittent intense exercise is very different from prolonged intense exercise, as the latter can substantially increase blood glucose levels both during and up to 60 min following exercise [151]. While this hyperglycemic state is quickly corrected in healthy individuals via increased insulin secretion during recovery, it poses a challenge to those with diabetes who must mimic the normal physiological insulin response with exogenous insulin dosing to avoid prolonged episodes of hyperglycemia [151]. As further information regarding intermittent intense exercise becomes available, it will be interesting to observe whether or not this strategy can indeed be used by some to decrease the risk of hypoglycemia.

Implications for Type 2 diabetes mellitus

Although it is understood that intensive glycemic control increases the risk of hypoglycemia in T2DM [5,7,8], very little research exists specifically regarding the prevention of exercise-induced hypoglycemia in this population. We could find only one study on this topic. Herz

et al. investigated the effects of a mixture of 25% (short-acting) lispro and 75% (intermediate-acting) neutral protamine lispro versus human insulin 30/70 on postprandial plasma glucose before, during and after exercise [152]. In the lispro intervention, plasma glucose was lower 2 h after a meal and fell to a lesser extent during and after exercise compared with the insulin 30/70 group. The authors concluded that the lispro mixture may be useful in reducing the risk of exercise-induced hypoglycemia. Beyond this study, patients and healthcare professionals are left to results from T1DM studies and trial and error to develop self-care plans for exercise in insulin and/or insulin secretagogue-treated T2DM. More research is very much needed.

As noted previously, hypoglycemia is rare in individuals with diabetes who are not treated with insulin or insulin secretagogues [43]. Usually these individuals do not need any adjustments in treatment medications for exercise [121].

Expert commentary

Intensive insulin therapy, while providing a means of improving glycemia and reducing the occurrence of microvascular complications, is associated with increased episodes of hypoglycemia. Hypoglycemia-associated autonomic failure appears to be an important mechanism responsible for this occurrence. Stringent avoidance of hypoglycemia can improve the threshold and the magnitude of counter-regulatory responses. Moreover, MDI and CSII offer flexibility in insulin dosing not previously available and, with practice, should provide better individualization of insulin therapy before, during and after exercise to help prevent exercise-induced hypoglycemia.

Five-year view

Current insulin therapies, including intensive interventions, still do not successfully mimic physiologic fluctuations in endogenous insulin secretion. The optimization of MDI and CSII with combinations of newer insulins that have improved pharmacokinetic and pharmacodynamic profiles is a subject of intense investigation. Studies of MDI or CSII in T2DM during exercise are lacking, and this subject requires greater attention as insulin is now being prescribed for more and more people with T2DM. Newer technologies, such as CGM and hypoglycemia avoidance, will hopefully provide improved means of glycemic control during and after exercise.

Acknowledgments

This work was supported by the following NIH grants: R01-DK-069803 and P01-HL-056693.

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Figure 1. Glucose metabolism at rest in nondiabetic individuals

This diagram depicts the interplay between insulin secretion and substrate metabolism under resting conditions. Under post-prandial conditions, insulin levels are elevated, inhibiting endogenous glucose production and NEFA release from adipose tissue. NEFA oxidation decreases and insulin-stimulated muscle glucose uptake increases, providing a major sink for disposal of excess blood glucose. Under post-absorptive conditions, insulin levels decrease, allowing endogenous glucose production to increase to maintain an adequate supply of glucose to the brain. NEFA release from adipose tissue is increased and becomes the primary energy substrate for skeletal muscle metabolism. Gray arrows show hormone signaling pathways, and black arrows show substrate production and uptake. NEFA: Nonesterified fatty acid.

Figure 2. Glucose metabolism during exercise in nondiabetic individuals

This diagram depicts the interplay between metabolic hormone (i.e., insulin, glucagon, epinephrine, norepinephrine) release and substrate metabolism under exercise conditions, during which energy needs drastically increase. Insulin secretion is suppressed and glucagon secretion is increased, which stimulates an increase in endogenous glucose production sufficient to maintain euglycemia. Release of NEFA from adipose tissue is increased, although the contribution of NEFA to skeletal muscle metabolism becomes proportionally smaller. Although insulin levels decrease, muscle glucose uptake increases substantially in response to contraction. High intensity exercise stimulates large increases in epinephrine, which in turn stimulates additional increases in hepatic glucose production and skeletal muscle glycogenolysis to ensure maintenance of euglycemia. Gray dotted lines show nervous system signaling pathways; gray arrows show hormone signaling pathways; and black arrows show substrate production and uptake.

NEFA: Nonesterified fatty acid.