Review

Vigorous Intensity Exercise for Glycemic Control in Patients with Type 1 Diabetes

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A B S T R A C T

Regular physical activity has substantial health benefits in persons with type 1 diabetes, including reduced risk of complications and cardiovascular mortality as well as improved self-rated quality of life. Despite these benefits, individuals with type 1 diabetes are often less active than their peers without diabetes. When factors such as time constraints, work pressure and environmental conditions are often cited as barriers to physical activity in the general population, 2 additional major factors may also explain the low rates of physical activity in young people with type 1 diabetes: (1) fear of hypoglycemia both during and after (particularly overnight) exercise and (2) a lack of empirical evidence for the efficacy of physical activity for achieving optimal glycemic control. A number of acute exercise trials recently showed that the inclusion of vigorous intensity physical activity in conventional moderate intensity (i.e. walking and light cycling) exercise sessions may overcome these barriers. No studies have tested the efficacy of high-intensity physical activity on glycemic control (A1C) or post-exercise hypoglycemia in a randomized controlled trial. This article summarizes the literature related to the role of physical activity for the management of blood glucose levels in individuals with type 1 diabetes and provides a rationale for the need of a randomized controlled trial examining the effects of vigorous-intensity physical activity on blood glucose control.

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RÉ S U M É

L’activité physique régulière a des effets positifs substantiels sur la santé des personnes ayant le diabète de type 1, y compris la réduction du risque de complications et de mortalité liée à la maladie cardiovasculaire ainsi qu’une meilleure autoévaluation de la qualité de vie. En dépit de ces effets positifs, les individus ayant le diabète de type 1 sont souvent moins actifs que leurs pairs n’ayant pas le diabète. Lorsque des facteurs tels les contraintes de temps, la charge de travail et l’environnement souvent sont cités comme des obstacles à l’activité physique dans la population générale, 2 facteurs additionnels majeurs peuvent également expliquer les faibles taux d’activité physique chez les jeunes personnes ayant le diabète de type 1 : 1) la peur de l’hypoglycémie pendant et après (particulièrement la nuit) l’exercice; 2) le manque de données empiriques sur l’efficacité de l’activité physique pour atteindre une régulation glycémique optimale. Plusieurs essais sur l’exercice intense montraient récemment que l’introduction de l’activité physique d’intensité vigoureuse à des séances traditionnelles d’exercice d’intensité modérée (c.-à-d. la marche et le vélo de faible intensité) peut surmonter ces obstacles. Aucune étude n’a testé l’efficacité de l’activité physique d’intensité élevée sur la régulation de la glycémie (HbA1c) ou sur l’hypoglycémie après exercice lors d’un essai clinique aléatoire. Cet article résume la littérature en lien avec le rôle de l’activité physique sur la prise en charge des taux de glycémie chez les individus ayant le diabète de type 1 et justifie le besoin de réaliser un essai clinique aléatoire examinant les effets de l’activité physique d’intensité vigoureuse sur la régulation de la glycémie.

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Introduction

Currently, more than 300 000 Canadians live with type 1 diabetes (1) and rates have increased globally over the past 2 decades (2). Type 1 diabetes is the most common endocrine condition in children and young adults (3). A diagnosis of type 1 diabetes increases the risk of microvascular and macrovascular complications, which can reduce life expectancy by up to 15 years (4). The increased morbidity and mortality associated with type 1 diabetes is reduced significantly with improved blood glucose (i.e. glycemic) control (5). The landmark Diabetes Control and Complications Trial and its prospective follow-up study (Epidemiology of Diabetes Interventions and Complications) clearly showed that targeting an A1C level of 7.0% reduces the risk of multiple complications, including retinopathy, neuropathy and nephropathy (6). The clinical approach to achieving this target generally relies on carefully titrated exogenous insulin and dietary control of carbohydrate intake. Increased physical activity is also often recommended for individuals with type 1 diabetes for the maintenance of overall health and the prevention of diabetes-related complications. There is strong evidence for the efficacy and optimal approaches for insulin and dietary management of A1C in individuals with type 1 diabetes (7,8). Unfortunately, the same evidence does not exist for physical activity.

Regular physical activity is associated with significant health benefits for patients with type 1 diabetes, including increased cardiorespiratory fitness, decreased insulin requirements, improved endothelial function, lower serum cholesterol, and increased vascular health along with improvements in body composition and quality of life (9). Collectively, these benefits are associated with a lower risk of complications and increased life expectancy for patients with type 1 diabetes (10). Despite these benefits, individuals with type 1 diabetes, similar to the general population in Canada, are predominantly inactive with more than 60% of adults with type 1 diabetes failing to achieve the recommended levels of physical activity for optimal health benefits (11). In addition to the commonly cited barriers to physical activity, such as lack of time, work pressure, environmental conditions and low energy, individuals with type 1 diabetes have additional challenges to contend with, such as: (1) a lack of consistent evidence for the appropriate dose (frequency, duration and intensity) of physical activity required for improving glycemic control, and (2) the fear of hypoglycemia both during exercise and subsequently overnight. Little qualitative research exploring physical activity in people with type 1 diabetes has been published. However, in the few qualitative studies that have been conducted in youth (12) and adults (13) with type 1 diabetes, fear of hypoglycemia as a prevalent barrier or “transient disruptor” (12) to participation in physical activity has been confirmed.

What is the Evidence That Physical Activity Can Reduce A1C Levels in Patients With Type 1 Diabetes?

Observational studies have shown that increased physical activity is associated with a lower A1C level among individuals with type 1 diabetes (14). In fact, cross-sectional studies identify regular time spent being physically active as one of the most important predictors of A1C level in persons with type 1 diabetes (14). Unfortunately, results from quasi-experimental and randomized controlled trials (Table 1) have yielded mixed results on the efficacy of physical activity in improving glycemic control (15–28). Some studies, particularly those of higher intensity and/or frequency of physical activity, show clinically meaningful 0.4% to 1.2% absolute reductions in A1C level in patients with type 1 diabetes whose blood glucose control at enrollment was fair to poor (A1C, 8.6%–15.1%) (15,16,19–21,23). In contrast, a significant proportion of quasi-experimental studies and some randomized controlled trials showed little effect of physical activity on A1C level (17,18,22,25–27,29). The disparity in trial results can be attributed to heterogeneity of participants at study entry (age, A1C level and duration of diabetes), heterogeneity in the intervention dose (i.e. duration, frequency and intensity of physical activity) and a lack of study power (Table 2). Also, the majority of studies were published before the introduction of the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized controlled trials and, therefore, suffer from major design flaws.

A series of descriptive and systematic reviews of physical activity for metabolic control in individuals with type 1 diabetes have been published recently (9,30,31). Reviews that included a meta-analysis of randomized controlled trials showed that the improvements in glycemic control with exercise training in individuals with type 1 diabetes are quite heterogeneous. The variability in the response to training can be explained by several factors including the age of participants at randomization, the lack of adequately powered trials, heterogeneous inclusion criteria and varying doses of physical activity delivered. For example, youth (aged <18 years) appear to achieve greater absolute reductions in A1C level (−0.37%; 95% confidence interval [CI] −0.77% to 0.02%) with physical activity than adults (0.00%; 95% CI −0.55% to 0.50%), whereas interventions lasting longer than 3 months (−0.75%; 95%

### Table 1

Summary of randomized controlled trials of aerobic exercise in individuals with type 1 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (years)</th>
<th>N (treatment/control)</th>
<th>Time (minutes)</th>
<th>Frequency (per week)</th>
<th>Intensity % HR max</th>
<th>Duration (weeks)</th>
<th>A1C Δ control (%)</th>
<th>A1C Δ treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yki-Jarvinen et al (29)</td>
<td>24–27</td>
<td>6/7</td>
<td>60</td>
<td>4</td>
<td>70%</td>
<td>6</td>
<td>0.8</td>
<td>0.3</td>
</tr>
<tr>
<td>Campagne et al (21)</td>
<td>5–11</td>
<td>10/9</td>
<td>30</td>
<td>3</td>
<td>V02 max 72%</td>
<td>12</td>
<td>−0.6</td>
<td>−1.2*</td>
</tr>
<tr>
<td>Landt et al (27)</td>
<td>14–16</td>
<td>6/9</td>
<td>45</td>
<td>3</td>
<td>HR max 80%–85%</td>
<td>12</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Wallberg-Henriksson et al (26)</td>
<td>25–45</td>
<td>7/6</td>
<td>20</td>
<td>7</td>
<td>V02 max 60%–90%</td>
<td>20</td>
<td>−0.2</td>
<td>0.1</td>
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<tr>
<td>Huttunen et al (25)</td>
<td>8–17</td>
<td>16/16</td>
<td>60</td>
<td>1</td>
<td>V02 max 68%</td>
<td>12</td>
<td>0.3</td>
<td>0.7</td>
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<tr>
<td>Laaksonen et al (24)</td>
<td>20–40</td>
<td>28/28</td>
<td>30–60</td>
<td>3–5</td>
<td>HR max 50%–60%</td>
<td>12–16</td>
<td>0.2</td>
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<td>Salem et al (20)</td>
<td>12–18</td>
<td>48/73</td>
<td>60</td>
<td>3</td>
<td>V02 max 65%–95%</td>
<td>24</td>
<td>0.6</td>
<td>−1.1*</td>
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<tr>
<td>Tunar et al (28)</td>
<td>12–17</td>
<td>14/17</td>
<td>45</td>
<td>3</td>
<td>N/A</td>
<td>12</td>
<td>−0.5</td>
<td>−0.1</td>
</tr>
<tr>
<td>Average</td>
<td>15–24</td>
<td>17/21</td>
<td>45.6</td>
<td>3.5</td>
<td>~75% HR max</td>
<td>14</td>
<td>0.08</td>
<td>−0.19</td>
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</tbody>
</table>

HR max: maximum heart rate; V02 max: maximum oxygen consumption.
* Significant change in A1C level (p<0.05).
CI – 1.03% to –0.47%), those with more than 3 sessions of exercise weekly (–0.34%; 95% CI –0.65% to –0.02%) and those in which patients display poor glycemic control at randomization (–0.25%; 95% CI –0.48 to –0.02%) achieve the greatest absolute reductions in A1C level. In general, however, the interpretation of these results is limited by several study design issues, in particular low power resulting from a limited number of underpowered trials, varying doses of physical activity (i.e. duration, intensity and frequency) and very limited trials that included exercise at intensities greater than 70% of maximal fitness. In the absence of adequately powered trials with well-defined exercise doses, the effects of physical activity on glycemic control among individuals with type 1 diabetes remain poorly understood.

The Risk of Hypoglycemia in Type 1 Diabetes

A recent survey of 100 Canadians living with type 1 diabetes identified hypoglycemia and the loss of control over diabetes as the primary barriers to being physically active (32). The same study also showed that having a greater number of perceived barriers to physical activity was correlated positively with poor blood glucose control and correlated negatively with patients’ well-being (32). Physical activity exerts a rapid increase in glucose uptake and insulin sensitivity that can persist for 48 hours. The acute glucose decreasing effect of exercise contributes to the improvements in A1C level after physical activity interventions in patients with type 2 diabetes (33). In the setting of type 1 diabetes, however, in which exogenous insulin is required to maintain glucose control, the combined effects of exercise and insulin-mediated glucose disposal increase the risk of hypoglycemia during exercise, and in the late post-exercise period.

The influence of exercise on hypoglycemia in patients with type 1 diabetes was well documented recently by The DirecNet consortium. They found that a day that included 75 minutes of moderate-intensity exercise at 55% of peak fitness (VO2peak) more than doubled (42% vs. 16%) the number of nights during which a nocturnal hypoglycemic event (blood glucose level, <3.3 mmol/L) occurred compared with a day without exercise (34). Hypoglycemia, both during and after exercise is, therefore, a major concern among individuals with type 1 diabetes. As a result, several strategies have been developed aimed at protecting patients with type 1 diabetes against exercise-induced hypoglycemia. They include decreasing or avoiding pre-exercise insulin, increasing carbohydrate intake during or after exercise and reducing basal or night time insulin. Unfortunately, the current recommendations for preventing post-exercise hypoglycemia can potentially lead to significantly increased blood glucose levels either before exercise or in the evening after an exercise session. This is illustrated in 2 separate case studies in Figure 1. The compensatory hyperglycemia that accompanies current strategies to prevent hypoglycemia (35) may explain the attenuated effect of physical activity for reducing A1C level in individuals with type 1 diabetes.

The risk of hypoglycemia is increased further in individuals who experience bouts of hypoglycemia in the days before exercise owing to a blunted counter-regulatory response to hypoglycemia (36). This hypoglycemia-associated autonomic failure attenuates the counter-regulatory response to decreasing blood glucose levels, leading to hypoglycemia unawareness and potentially a vicious cycle of worsening risk for hypoglycemia in individuals with type 1 diabetes (36). Hypoglycemia-associated autonomic failure is more prominent in male patients than in female patients and appears to be proportional to the duration and magnitude of the antecedent hypoglycemic episode (36). Prolonged exercise (>60 minutes) at low to moderate intensity (30%–60% of peak fitness) also significantly attenuates the neurohormonal response to hypoglycemia up to 24 hours after the exercise session (36). Interestingly, this blunting of the autonomic response to hypoglycemia after exercise may be attenuated when exercise is performed at intensities of more than 70% of peak fitness (37). From a clinical standpoint, kinesiologists and allied health professionals should be aware that patients may be unaware of hypoglycemia during an exercise session if they experienced hypoglycemia or performed prolonged submaximal exercise in the days before an exercise session. From a research standpoint, the role of vigorous intensity in the prevention of hypoglycemia-associated autonomic failure remains poorly understood and warrants further study.

In addition to attenuating the glucose-lowering effects of physical activity, the strategies for preventing hypoglycemia are difficult to implement in the exercise-naïve patient. The glucose-lowering effect of physical activity is not uniform but depends on the timing, duration and intensity of an exercise session and the individual patient’s response. Therefore, it is initially difficult to predict how much insulin to withhold or carbohydrates to consume to prevent hypoglycemia. Furthermore, the insulin-sensitizing

<table>
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<td>12</td>
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<tr>
<td>Average</td>
<td>8–15</td>
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<td>45</td>
<td>3</td>
<td>~80% HR max</td>
<td>18</td>
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<td>12</td>
<td>−0.5</td>
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<tr>
<td>Average</td>
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<td>43</td>
<td>4.2</td>
<td>~70% HR max</td>
<td>12.8</td>
<td>0.1</td>
<td>0.02</td>
</tr>
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HR max, maximum heart rate; VO2 max, maximum oxygen consumption.
* Significant change in A1C level (p < 0.05).
A Novel Approach to Preventing Hypoglycemic Events: The Importance of Intensity

Exercise, regardless of intensity, is associated with an array of health benefits, including improved mental health, reduced cardiometabolic risk factors, reduced incidence of several chronic diseases and reduced mortality. Prospective cohort studies have clearly shown that the benefits of exercise increase in a dose-response manner with both increased duration and intensity of exercise (40). In recent years, a series of observational and experimental studies showed that the health benefits associated with exercise are more significant after higher-intensity exercise than after moderate-intensity exercise (40,41). Specifically, individuals who either engage in regular vigorous-intensity activity or are randomized to vigorous-intensity exercise display greater improvements in serum lipoprotein levels, cardiovascular disease risk factors, cardiorespiratory fitness, endothelial function and all-cause mortality rates (41). Studies in sedentary young adults and older patients with type 2 diabetes have shown that high-intensity interval training is feasible and yields similar or greater improvements in cardiorespiratory fitness, cardiovascular function, insulin sensitivity (both muscle and hepatic) and muscle oxidative capacity compared with prolonged moderate-intensity exercise (41). Despite the growing evidence for the health-related benefits of vigorous-intensity physical activity, less evidence exists for the benefits of vigorous-intensity exercise on glycemic control in patients with type 1 diabetes.

Exercise intensity and metabolic control in patients with type 1 diabetes

Moderate-intensity physical activity (generally between 3 and 6 metabolic equivalents) corresponds roughly to a quick walk or light cycling, and is the intensity universally recommended by expert panels for overall health benefits. Physical activity performed at this intensity causes a rapid increase in glucose uptake into skeletal muscle (defined herein as “glucose disposal”). The increase in glucose disposal observed with exercise is similar and additive to that seen with insulin. Under normal circumstances, to prevent hypoglycemia, the exercise-mediated increase in glucose disposal is counteracted by a corresponding reduction in circulating insulin. This reduction in insulin occurs concurrently with an increase in glucagon, both of which prevent additional glucose disposal into skeletal muscle and simultaneously stimulate hepatic glucose output in an effort to stabilize blood glucose levels. The combination of increased hepatic glucose output and reduced circulating insulin is so effective that blood glucose levels can remain higher than 4 mmol/L for up to 2 hours during moderate-intensity activity in otherwise healthy individuals despite a profound increase in glucose disposal (42).

In individuals with type 1 diabetes, insulin is supplied exogenously and, therefore, the autoregulatory reduction in insulin at the onset of exercise is absent. The absence of an autoregulatory reduction in circulating insulin levels results in a state of excessive glucose disposal and prevents the normal increase in hepatic glucose output. The combination of insulin and exercise-mediated glucose disposal, coupled with an attenuated hepatic glucose output, creates a physiological perfect storm for hypoglycemia. Because moderate exercise is associated with health benefits and is perceived to be easy for most sedentary patients to achieve, it is the most common form of physical activity in clinical guidelines. Considering that there is an increased risk of hypoglycemia with moderate-intensity physical activity, it is not surprising that most patients living with type 1 diabetes report hypoglycemia as the primary barrier to physical activity (32).

Similar to moderate-intensity exercise, vigorous-intensity physical activity (>6 metabolic equivalents: running or cycling for fitness) significantly increases glucose disposal into skeletal muscle. In contrast to moderate-intensity physical activity, vigorous-intensity physical activity causes a rapid and sustained increase in counter-regulatory hormones (catecholamines, glucagon and cortisol) proportionate to exercise intensity, which acts to stimulate hepatic glucose output (43). The evolutionary purpose of this surge of hormones is to provide an additional source of glucose during intense exercise (fight or flight response). In type 1 diabetes, however, the increased hepatic glucose output can cause hyperglycemia if the exercise is sufficiently vigorous and sustained because levels of glucose production can exceed those of peripheral use (43) and the compensatory release of insulin to normalize blood glucose levels is absent. For the exercise-naïve individual, the paradoxic increase in blood glucose level after intense exercise may be perceived as compromising glucose management and could strengthen their concerns regarding adopting a physically active lifestyle.
A series of recent experimental trials have cleverly capitalized on the hyperglycemic response to vigorous-intensity physical activity to prevent hypoglycemia during and after exercise (44–49). For example, adding a single 10-second maximal sprint at the end of 20 minutes of low-to-moderate intensity (∼40% VO2peak) cycling essentially eliminated the decrease in blood glucose level observed after an exercise session without a sprint (44). Although the effect was slightly less pronounced, performing the 10-second maximal sprint at the beginning of an exercise session prevented the decrease in blood glucose levels during and for 2 hours after 20 minutes of moderate-intensity cycling (46). Shorter bouts of high-intensity exercise have also been used to prevent the exercise-mediated decrease in blood glucose level that normally occurs during exercise in individuals with type 1 diabetes. For example, the addition of 4-second sprints at 80% to 100% of peak fitness performed every 2 minutes throughout a low-to-moderate intensity (40% VO2peak) cycling session reduced the decrease in blood glucose during and after exercise by approximately 50% (−2.9 ± 0.8 mmol/L vs. −4.4 ± 1.2 mmol/L; p < 0.05) (47). Collectively, these acute studies suggest that incorporating bouts of higher-intensity exercise may protect against hypoglycemia during or immediately after exercise. Preventing the decrease in blood glucose concentration during exercise would reduce the need for individuals to withhold insulin or increase carbohydrate intake before exercise, reducing the glucose variability on exercise days.

The observations from these acute studies support the anti-hypoglycemic effect of vigorous intensity exercise, but they failed to extend the follow-up period into the nocturnal hours when the risk of post-exercise hypoglycemic events is still high. To the best of our knowledge, only 2 studies of the acute glucose response to exercise have extended the follow-up period into the nocturnal hours, and these studies yielded conflicting results (48,49). Specifically, the addition of 15-second bouts at 100% of peak fitness every 5 minutes during moderate-intensity cycling (50% of peak fitness) replicated studies presented earlier and completely attenuated the decrease in post-exercise nocturnal blood glucose levels for up to 12 hours after the exercise session (49) (Fig. 2). In contrast, adding 5-second bouts at 80% of peak fitness every 2 minutes during moderate-intensity cycling (40% of peak fitness) seems to have had no effect on blood glucose decreases during exercise, and potentially a negative impact on nocturnal blood glucose levels (48). The disparate findings may be related to differences in fitness levels of participants studied (33.7 ± 6.1 vs. 42.4 ± 1.6 mL kg (−1·min (−1)) or to differences in the intensity (80% vs. 100% of peak fitness) and duration (5 vs. 15 seconds) of the brief bouts of exercise (48,49). It also should be noted that sample sizes in all of these acute studies are small (n<12) and restricted to a single exercise session. Adequately powered trials with multiple exercise sessions are needed to determine if adding high-intensity exercise bouts to a moderate-intensity session is a practical approach for protecting against hypoglycemia in individuals with type 1 diabetes over the long term.

To date only 1 randomized controlled trial has examined the effects of low-volume, high-intensity training on glycemic control in individuals with type 1 diabetes. Harmer et al (19,50) examined the effects of performing repeated 30-second maximal exercise bouts on a cycle ergometer, separated by 4 minutes of rest in individuals with type 1 diabetes (n=8). Training occurred 3 times weekly over 7 weeks, with the number of bouts per session increasing from 4 in the first 6 weeks of training to 10 by the seventh week. Study participants experienced an increase in muscle oxidative enzyme activity, increased reliance on fat oxidation during submaximal exercise (50) and a decrease in A1C level (from 8.6% ± 0.8% to 8.1% ± 0.6%; p < 0.09) (19). Unfortunately, in the absence of a control group, it is unclear if the glucose-lowering effects were related to the training or the increased monitoring that accompanies interventions studies. Adequately powered randomized controlled trials with repeated sessions of vigorous physical activity and extensive monitoring of glucose both during and after exercise are needed to determine the true benefit of vigorous physical activity on post-exercise hypoglycemia to resolve this clinically relevant question.

**Knowledge Gaps**

Although the recent studies examining the acute effects of brief high-intensity exercise bouts indicate that this may be a successful approach to preventing hypoglycemia during and up to 2 hours after exercise, several significant gaps exist in our understanding of the long-term benefits of vigorous-intensity exercise for patients with type 1 diabetes. The majority of studies to date have relied on small sample sizes of patients across a broad range of ages and fitness levels, have generally tested very short maximal-intensity (i.e. sprint) intervals and have limited their observations to a short post-exercise window. Therefore, the translation of this knowledge into a clinical or practical setting is limited. Larger, well-designed, randomized controlled experimental trials are needed to determine the effect of including more vigorous-intensity exercise into regular physical activity sessions on health-related outcomes, in particular glycemic control, in patients with type 1 diabetes. It also will be necessary to undertake more studies examining larger post-exercise windows of time so that the risks of nocturnal hypoglycemia can be quantified more adequately. Finally, the effects of this type of training regimen on physical activity participation should be examined to determine if it will lead to greater participation in regular physical activity. Studies in this area will provide important information in the development of evidence-based exercise recommendations for individuals with type 1 diabetes.

**Summary, Rationale and Significance of a Randomized Controlled Trial of High-Intensity Activity for Glycemic Control in Patients With Type 1 Diabetes**

Despite the well-described health benefits of physical activity, individuals with type 1 diabetes are at particularly high risk of being physically inactive. The risk of hypoglycemia is a well-established...
and relevant barrier to becoming more physically active for persons living with type 1 diabetes. A series of recent studies examining acute exercise effects (44,46,47,49) have indicated that the addition of intermittent bouts of vigorous-intensity physical activity is an effective way to prevent hypoglycemia during exercise and have the potential to stabilize blood glucose levels on exercise days as well as the nights after exercise sessions. Although the data appear promising, the efficacy of adding intermittent bouts of vigorous exercise to standard exercise recommendations for improving glycemic control and reducing the risk of hypoglycemic events have never been tested empirically using a randomized controlled trial design. An adequately powered randomized controlled trial would provide much-needed empirical evidence for the role of vigorous-intensity physical activity for metabolic control in the setting of type 1 diabetes. This information would contribute significantly to the current physical activity guidelines for individuals living with type 1 diabetes.

References