Exercise Strategies for Hypoglycemia Prevention in Individuals with Type 1 Diabetes

Jane E. Yardley (PhD)[1,2] and Ronald J. Sigal (MD, MPH)[3]

[1]Department of Social Sciences, University of Alberta, Augustana Campus, Camrose, AB
[2]Manitoba Institute of Child Health, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba [3]Faculties of Medicine and Kinesiology, University of Calgary, Calgary, AB.

Address for correspondence:
Jane E Yardley (PhD)
Augustana Campus
University of Alberta
4901 – 46th avenue
Camrose, AB T4V 2R3

Email: jeyardle@ualberta.ca
Phone: +1 (780) 679-1688
Fax: +1 (780) 679-1590

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In Brief: Fear of hypoglycemia is one of the main barriers to physical activity for individuals with type 1 diabetes. Recent studies indicate that anaerobic forms of exercise (i.e. resistance exercise/weight lifting, sprints and high intensity intervals) can attenuate exercise-related declines in blood glucose both during and after exercise in young, healthy adults with type 1 diabetes. These responses might vary based on age, sex and fitness level and their general safety in usage in the prevention of hypoglycemia.

Regular physical activity is associated with a plethora of health benefits for individuals with type 1 diabetes including improved cardiovascular fitness and vascular health, decreased insulin requirements, improved body composition and better self-rated quality of life[1]. Where blood glucose control is concerned, observational studies of individuals with type 1 diabetes have associated higher physical activity levels with lower incidence[2,3], prevalence[2] and severity[3] of diabetes complications. Intervention studies, however, have generally failed to show substantial improvements in HbA_{1c} with physical activity[1,4,5]. While some of this may be due to inconsistencies in study design and exercise dosage[6], adjustments to carbohydrate intake and insulin administration surrounding the prescribed exercise sessions may also play a role.

Increasing glucose consumption and decreasing insulin dosage for exercise is often recommended for maintaining safe blood glucose in individuals with type 1 diabetes[7]. Both of these methods are known to decrease the risk of exercise-associated hypoglycemia when used correctly, and are reviewed in detail elsewhere[8-12]. Where fear of hypoglycemia is often cited as the main barrier to exercise in this population[13], there may, however, be a tendency for individuals with type 1 diabetes to overcompensate for exercise by ingesting excessive amounts of additional carbohydrate or decreasing insulin dosage to a greater degree than necessary (Figure 1)[6]. This can potentially negate some of the beneficial effects of exercise by causing weight gain and a possible worsening of blood glucose control. In fact, a recent cross-sectional study of 35 physically active individuals with type 1 diabetes found that those with higher energy expenditure resulting from moderate to intense physical activity reported a higher proportion of energy intake from carbohydrate consumption and significantly higher HbA_{1c} than individuals with lower energy expenditure[14]. In light of these findings, it would seem that alternate approaches to preventing hypoglycemia during exercise should be explored. Several recent studies on the effects of anaerobic exercise (short sprints, weight lifting) on blood glucose levels in individuals with type 1 diabetes [15-23] suggest that the inclusion of these activities during aerobic exercise sessions may be one such alternative. This article reviews exercise-related strategies that can be used to complement existing strategies (i.e. insulin dosage reduction and carbohydrate consumption) of hypoglycemia prevention during exercise, which may help in optimizing the benefits of physical activity in this population.

The Difference between Aerobic and Anaerobic Exercise

By definition, aerobic exercise (swimming, jogging, cycling, walking etc.) involves the continuous and repeated movements of large muscle groups for at least 10 minutes at a time[24]. The initial stages of this type of exercise are fueled mostly by muscle glycogen, after which glucose and non-esterified fatty acids become the main source of fuel. In individuals without diabetes, insulin release from pancreatic beta cells decreases, and glucagon secretion increases, during moderate-intensity aerobic exercise. These changes ensure that fatty acids (stored in adipocytes) and glucose (stored mainly in the liver as glycogen) are released from storage to fuel the exercising muscles. As a result, blood glucose levels can remain relatively stable during exercise for several hours without food intake.

For individuals with type 1 diabetes, the lack of beta-cell function leads to the requirement for exogenous insulin (introduced into the body by injection or infusion). Circulating levels of insulin consequently cannot be regulated endogenously, and depend on the quantity and timing of insulin taken by the individual prior to exercise. Insulin levels are often higher than they would be in the absence of diabetes, which has the result of limiting glucose production by the liver while stimulating glucose uptake by muscle, adipose, and liver cells for storage. As a result, blood glucose levels often decrease dramatically during physical activity for individuals with type 1 diabetes, unless carbohydrates are consumed before, during and after exercise.

As exercise intensity increases, the relative roles of insulin and glucagon decrease[25]. Glucose breakdown becomes rapid, and exceeds the capacity of the oxidative systems. This results in the breakdown of glucose to lactate without the use of oxygen in the muscles (anaerobic glycolysis). Circulating levels of catecholamines (epinephrine and epinephrine) increase substantially, and exert an overriding influence on glucose release by the liver[26]. This can lead to glucose production exceeding demand, resulting in an increase in blood glucose concentration[26,27]. High intensity exercise is also associated with increases in growth hormone and lactate, both of which can serve to spare circulating blood glucose. Growth hormone promotes lipolysis, potentially decreasing the body's reliance on circulating glucose and lactate is a gluconeogenic precursor which can be used by the liver to create new glucose. Intuitively, it thus makes sense that any situation increasing the circulation of these four compounds in the blood would be associated with either increases, or attenuated declines in blood glucose levels. Short bursts of high intensity exercise, in the form of short sprints, intermittent high intensity [(>85% of peak aerobic capacity (VO_{2peak})] intervals, and resistance exercise (weight lifting), have consequently become a topic of interest to those in the diabetes research community, as it has been suggested that the inclusion of these types of activity in exercise sessions involving moderate aerobic exercise, may provide a level of protection against hypoglycemia apart from that already demonstrated by increases in carbohydrate consumption and decreases in insulin dosage. Table 1 lists the main hormonal and blood glucose responses to aerobic and sprint exercise in people with and without type 1 diabetes.

Short Sprints and Intermittent High Intensity Exercise

Similar to individuals without diabetes, short sprints and intermittent high intensity exercise are associated with increases in circulating epinephrine, norepinephrine, growth hormone and lactate in individuals with type 1 diabetes when compared to aerobic exercise performed on its own[15,16,18-21,28]. A series of studies has used this knowledge to explore the possibility that including a simple all-out 10-second sprint either prior to[16] or following[15,17] a 20 to 30-minute bout of moderate aerobic exercise (cycling at 40% of VO_{2peak}) could protect against exercise-induced hypoglycemia in individuals with type 1 diabetes. Bussau et al.[16] found that performing a 10-second sprint prior to 20-minutes of moderate intensity (40% of VO_{2peak}) cycling did not protect against declines in blood glucose during exercise in seven individuals with type 1 diabetes, but did prevent further declines in blood glucose in the 45 minutes following exercise compared to an exercise session where no sprint was performed. When the 10-second sprint was performed at the completion of a similar 20-minute moderate intensity aerobic exercise session, there was no significant change in blood glucose levels for the subsequent two hours post-exercise, compared to a decline of 3.6 ± 1.2 mol/l measured after 20 minutes of exercise where a sprint was not included[15]. A follow-up study of the 10-second sprint (performed in isolation) found that the increases in blood glucose concentration arising from the sprint were due to a decrease in the rate of glucose uptake, rather than a disproportionate increase in glucose appearance[19]. The authors conclude that a likely cause of this phenomenon is a build-up of intramuscular glucose-6-phosphate (associated with the rapid glycogen breakdown that would be found during a sprint) which would result in the inhibition of the enzyme hexokinase, and subsequently a decrease in muscle glucose uptake[19].

A handful of studies over the past decade have examined the use of repeated bouts of intermittent high intensity exercise (4 to 15-second intervals at >85% VO_{2peak} performed every two to five minutes) for preventing hypoglycemia both during and after exercise in individuals with type 1 diabetes[20,21,28-31]. In attempting to mimic the demands of field sports, Guelfi et al.[20] asked seven young, healthy individuals with type 1 diabetes to perform two separate exercise sessions. One of these sessions involved moderate intensity (40% of VO_{2peak}) cycling for 30 minutes, while the second session involved an identical intensity and duration of cycling with 4-second sprints performed every two minutes throughout exercise[20]. In spite of the higher energy demands of the exercise session that included sprints, declines in blood glucose during exercise were lower when the sprints were included (-2.9 ± 0.8 mmol/L versus -4.4 ± 1.2 mmol/L; p=0.006)[20]. In addition, whereas blood glucose levels continued to decline for 60 minutes post-exercise after the moderate intensity exercise session, further declines in blood glucose did not occur after the completion of the exercise session when the intermittent sprints were included[20]. A follow-up study using the same protocol[21] further elucidated that the slower decline in blood glucose levels during the intermittent sprint session could be attributed to an increased rate of glucose appearance early in the exercise session in comparison to the moderate exercise session, while glucose disappearance in the intermittent sprint session was attenuated during and after exercise compared to the moderate-intensity session. Both studies found an increase in epinephrine and norepinephrine by the end of exercise[20,21], which may have contributed to higher rates of glucose appearance through an increase in hepatic glucose production[32], and a decrease in glucose disposal.

A similar study of intermittent high intensity activity performed by Maran et al.[28] showed a statistically nonsignificant trend towards smaller declines in blood glucose when eight participants with type 1 diabetes performed 30 minutes of moderate (40% VO_{2peak}) cycling with 5-second intervals at 85% VO_{2peak} performed every two minutes, compared to when the same participants performed continuous moderate cycling. In contrast, Dubé et al.[31] found that changes in blood glucose during exercise were similar when eleven participants with type 1 diabetes performed 60 minutes of moderate (50% VO_{2peak}) cycling and when the same participants performed 60 minutes of moderate cycling with 10-second sprints included every two minutes. It is important to note, however, that twice as many participants required glucose infusion both during (7/11 versus 4/11) and after exercise (7/11 versus 3/11) in the moderate exercise session compared to the intermittent high intensity session[31]. Similarly, when high intensity intervals (15-second maximal sprints) were spaced farther apart (5 minutes) during 45 minutes of cycling at 50% of the subjects' maximum work rate in a study by Iscoe and Riddell [29], changes in blood glucose were very similar to those found in a continuous moderate cycling session. Once again, however, more carbohydrate intake was required to prevent hypoglycemia during the moderate exercise session compared to the session where high intensity intervals were included[29].

Only one study to date has examined the effects of intermittent high intensity running on blood glucose levels in individuals with type 1 diabetes. Campbell et al.[30] argued that intermittent high intensity cycling protocols, which rely mainly on concentric muscle action, fail to adequately replicate the physiological demands of repeated changes in speed and direction involved in field and ice sports, which involve a significant amount of eccentric muscle work. Consequently, they decided to compare the effects of the Loughborough Intermittent Shuttle Test[33] performed for 45 minutes, to the effects of a 45-minute moderate to high intensity (~77% VO_{2peak}) treadmill run in nine individuals with type 1 diabetes. The shuttle test consisted of the following sequence: 3 X 20 meter shuttle walking and 1 X 20 meter sprinting with a 4-second rest between each, followed by 3 X 20 meters at a speed equivalent to 55% VO_{2peak}, and 3 X 20 meters at a speed corresponding to 95% VO_{2peak} [30]. The change in blood glucose during exercise was approximately four times greater during the continuous exercise session compared to the shuttle test. During the hour post-exercise, declines in blood glucose after the shuttle test were also significantly smaller than those found during the aerobic running session (-1.1 ± 1.4 versus -5.3 ± 0.4 mmol/L, P=0.037)[30]. The authors suggest that the 10-fold higher lactate levels measured at the end of the shuttle test likely contributed substantially to the attenuated rates of blood glucose decline during the 60 minutes post-exercise by increasing gluconeogenesis over this period.

These studies indicate that the inclusion of short sprints and intermittent high intensity exercise (lasting 5 to 15 seconds) into aerobic exercise sessions may be an effective way to counter declines in blood glucose during exercise and shortly after exercise. In addition, while antecedent hypoglycemia may increase the risk of subsequent exercise-induced hypoglycemia[34-36], there is evidence to indicate that the blood glucose raising effect of a short sprint is not impaired by prior hypoglycemia[18] and may therefore still be effective for maintaining blood glucose levels. As opposed to moderate intensity exercise after antecedent hypoglycemia where cortisol, epinephrine, and glucagon responses are blunted[34,36] thereby increasing the risk of exercise-induced hypoglycemia, one study has shown that these responses are intact when a 10-second all-out sprint is performed after a similar low blood glucose event[18]. It should be noted, however, that antecedent exercise of sufficient intensity and duration to deplete glycogen stores may decrease the amount of glucose available, and therefore diminish the protective effect of a sprint. The magnitude of this dampening is currently unknown, as there are no published studies on this topic to date.

Review of resistance exercise studies

Resistance exercise, which involves lifting weights or working against a resistive force, also results in increases in epinephrine[37,38], norepinephrine[37,38], lactate[38] and growth hormone[39] which could help in stabilizing blood glucose levels in a manner similar to other forms of anaerobic exercise [23,40]. The type of training protocol selected, which can range from performing a very low number of repetitions (3-5) with a very heavy weight and long rest periods to performing a very high number of repetitions (15-25) with a light weight and short rest periods affects the magnitude of the hormonal responses[41,42], and thus probably affects the fuel used by the body for the activity. To date, acute changes in blood glucose during resistance exercise have only been measured for resistance exercise protocols involving three sets of eight repetitions at the maximum weight that can be lifted eight times safely with good form[43] —"8 RM", or 8 Repetition Maximum)[22,23,44]. This regimen is at an intensity appropriate for "general conditioning"[43] and corresponds to a moderately high intensity.

Resistance exercise at 8 RM on its own results in modest declines in blood glucose in comparison to a similar duration of aerobic exercise in individuals with type 1 diabetes[22]. Performing resistance exercise prior to aerobic exercise has been shown to have a protective effect against hypopglycemia[23,44]. In one of our studies, when twelve participants with well-controlled type 1 diabetes who were regular exercisers performed 45 minutes of resistance exercise prior to 45 minutes of aerobic exercise, declines in blood glucose during the aerobic portion of the exercise session were attenuated (from 9.2 ± 3.4 to 5.8 ± 2.0 mmol/L, $p=0.001$ without prior resistance exercise; from 9.2 ± 4.0 to 6.9 ± 3.1 mmol/L, $p=0.04$ with prior resistance exercise) (Figure 2)[44]. Performing resistance exercise after aerobic exercise can also prevent further declines in blood glucose levels[23]. While the reasons for the protective effect of resistance exercise have still not been fully elucidated, it is likely that hormonal responses play an important role. Performing resistance exercise prior to aerobic exercise has been associated with higher growth hormone levels than when aerobic exercise is performed first[40], which may promote a greater reliance on lipolysis during the aerobic portion of the exercise session, thereby sparing blood glucose. It is also possible that resistance exercise stimulated the release of epinephrine[45], thereby allowing greater access to both muscular and hepatic glycogen as a fuel source during exercise. Finally, the lactate produced during the performance of resistance exercise may assist in stabilizing subsequent blood glucose levels via production of new glucose through the Cori cycle in the liver.

Overall, the few studies of resistance exercise performed thus far seem to indicate that this form of physical activity may produce less of a disturbance in blood glucose levels during exercise, and may attenuate declines in blood glucose when aerobic exercise is performed immediately subsequent to it. Further studies of different intensities and durations of resistance exercise, as well as different combination of aerobic and resistance exercise (e.g. circuit training) will help shed more light on the utility of resistance exercise in the prevention of exercise-related hypoglycemia in individuals with type 1 diabetes.

How responses might differ with age, sex, and fitness level

It is important to note that the majority of the studies described in the present review have performed their testing on mostly young (<30 years of age), physically active individuals. In addition, most of the participants in these studies were male. Both of these points are important: the factors (mostly hormones) that have been suggested as providing sprints, high intensity intervals and resistance exercise with their protective effect against declines in blood glucose during exercise vary with the age[46] and sex[46,47] of the participant. It is also possible that responses vary depending on the fitness level[26] of the person performing the exercise. Finally, most of the studies involved cycling exercise, which has different energy requirements, and potentially different hormonal responses, than other forms of activity such as running or swimming. Further studies varying the types of exercise performed are required, as are more studies involving females, older individuals, and participants of different fitness levels in order to determine how these variations affect the magnitude of the protective effects of anaerobic exercise against declines in blood glucose in individuals with type 1 diabetes. Until then, frequent blood glucose testing or continuous glucose monitoring should be recommended until individuals have ascertained their own responses to different exercise modalities.

Safety Concerns

a) **Frequent high intensity or long duration exercise**

Individuals who exercise regularly will eventually recognize that many factors influence their performance levels, and that responses to exercise can be extremely variable. Some of these factors can include sleep, hydration, immune system responses and prior exercise. Where blood glucose responses to high intensity exercise are concerned, prior exercise is likely to have a substantial impact. Performing a prior bout of either very intense or very protracted exercise can deplete glycogen stores in the body. As mentioned above, when access to glucose stores are limited, it is likely that the protective effects of high intensity exercise will be attenuated, as these rely to a great extent on glucose stored in the liver. We are not aware of any published studies examining the effect of glycogen depletion on blood glucose responses to sprints, resistance exercise, or high intensity intermittent exercise in individuals with type 1 diabetes.

b) Late-onset post-exercise hypoglycemia

The risk of post-exercise hypoglycemia in type 1 diabetes, particularly at night, has varied among studies. Prolonged exercise can result in depletion of glycogen stores, and repletion of these stores requires increasing glucose uptake from the blood. If insufficient carbohydrate is consumed post-exercise, the risk of late-onset post-exercise hypoglycemia may be increased. Four studies to date have used continuous glucose monitoring to examine the overnight period after aerobic exercise with a 10-second sprint or after intermittent high intensity exercise and have found mixed results[17,28-30]. One study following the participants for eight hours post-exercise did not find any effect of adding a 10-second sprint to the end of a moderate (40% VO_{2peak}) aerobic exercise session on the glucose requirements to prevent late-onset hypoglycemia (compared to aerobic exercise on its own)[17], indicating that the protective effects of sprinting may not extend far beyond the 2-hour window that has been examined to date. In another study, Maran et al.[28] found that blood glucose levels were significantly lower between midnight and 6:00 a.m. the night after an intermittent high intensity exercise session, as compared to a moderate exercise session. On the other hand, Iscoe and Riddell[29] found that interstitial glucose levels measured by CGM overnight were higher after an intermittent high intensity exercise session compared to moderate exercise alone. Campbell et al[30], meanwhile, found no difference in nocturnal interstitial glucose levels between a days when intermittent high intensity activity was performed in comparison to a day when moderate aerobic exercise was performed. Several factors could be responsible for the conflicting results of these latter three studies. The studies by Maran et al.[28] and Iscoe and Riddell[29] both involved cycling exercise, while that of Campbell et al.[30] involved running. Participants in the Maran et al.[28] study performed shorter (5 seconds compared to 15 seconds) and less intense (85% VO_{2peak} compared to >90% VO_{2peak}) intervals than those in the study by Iscoe and Riddell[29], which could have diminished the counter-regulatory responses associated with high intensity exercise. In addition, participants in the Iscoe and Riddell[29] study had higher aerobic fitness (42.4 ± 1.6 ml/kg/min) than the participants in the study by Maran et al.[28] (33.6 ± 6.1 ml/kg/min), allowing them to exercise at a higher absolute intensity.

Current studies examining the late post-exercise/nocturnal effects of intermittent high intensity exercise are not conclusive in determining whether the risk of hypoglycemia is increased or decreased by this type of activity, due to a great deal of variability in both the protocols and the measured outcomes. Once again, this underscores the need for more research that can tease apart the various factors at play, the magnitude of their influence, and how different physiological factors (age, sex, fitness level) affect them.

Conclusions

Research to date gives us reason to be optimistic that anaerobic activities such as short sprints, high intensity intervals, and resistance exercise can all be used successfully in preventing hypoglycemia during exercise and thus decreasing the reliance on excessive carbohydrate consumption during exercise to maintain blood glucose levels. It is, nonetheless, important for individuals to be able to understand and predict their own responses to these types of activities based on past experiences of trial and error. As a great number of physical, emotional and physiological factors influence blood glucose responses to exercise on any given day, it still remains important to monitor blood glucose levels before, during and after exercise in order to ensure an adequate level of safety.

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Biographical Information

While writing this manuscript, Jane E. Yardley (PhD) was a Post-Doctoral Fellow at the Manitoba Institute of Child Health at the University of Manitoba in Winnipeg Manitoba. She is now an Assistant Professor in Physical Education at the University of Alberta, Augustana Campus, in Camrose, Canada.

Ronald J. Sigal (MD, MPH, FRCPC) is Professor of Medicine, Cardiac Sciences, Kinesiology and Community Health Sciences at the University of Calgary, Calgary, Canada. He is a Royal College of Physicians and Surgeons of Canada -certified endocrinologist whose research focuses on exercise and diabetes.

Tables and Figures

Table 1. Expected hormonal and blood glucose responses to continuous moderate aerobic exercise and short supramaximal (sprint) exercise in individuals with and without type 1 diabetes

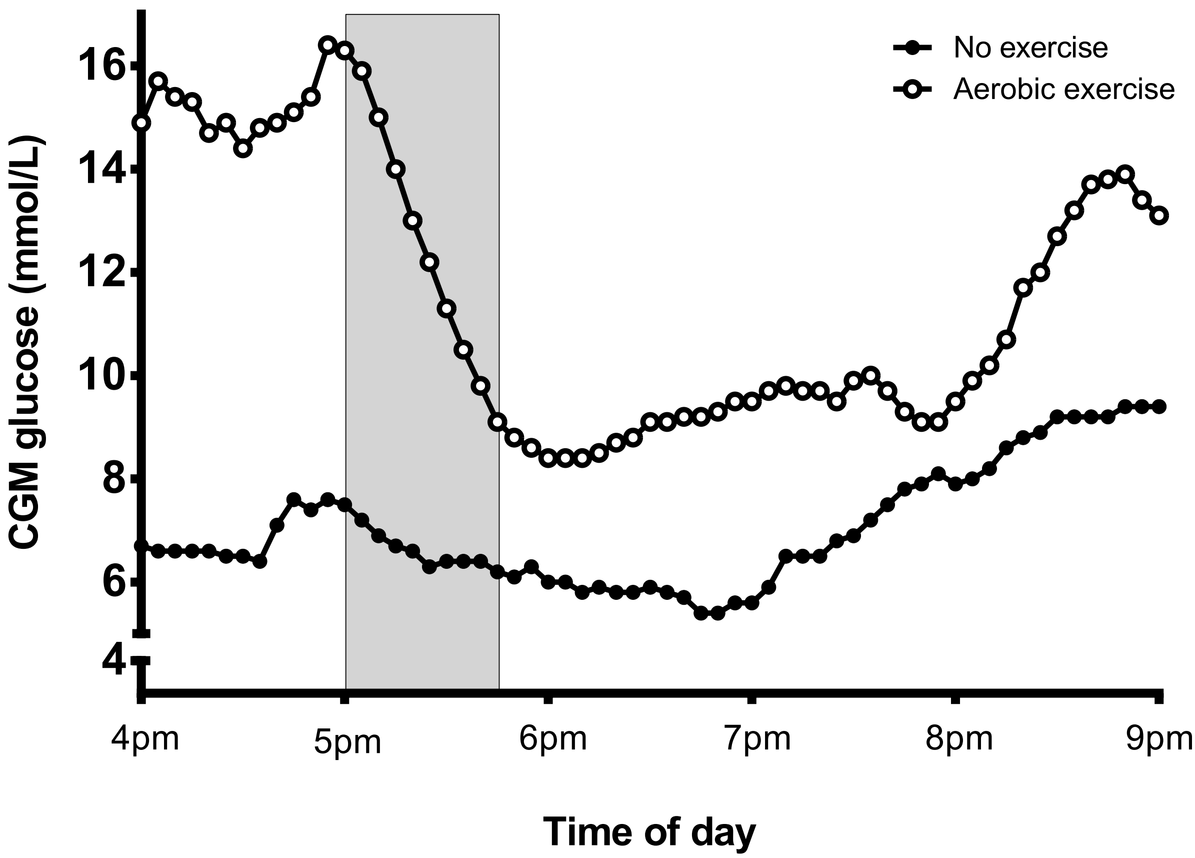
Figure 1. Continuous glucose monitoring tracings of two patients with type 1 diabetes (one patient per panel) on a day when aerobic exercise was performed (open circles) versus a day when no exercise was performed (closed circles). The gray box represents the timing of 45 minutes of treadmill running at 60% of peak fitness on the aerobic exercise day. Participant adjustments in insulin dosage before and after exercise resulted in substantially higher blood glucose levels over a 5-hour period. Reprinted from Canadian Journal of Diabetes 37, Yardley J, Mollard R, MacIntosh A. et al., Vigorous Intensity Exercise for Glycemic Control in Patients with Type 1 Diabetes, Pages 427-432, Copyright 2013, with permission from Elsevier.[6]

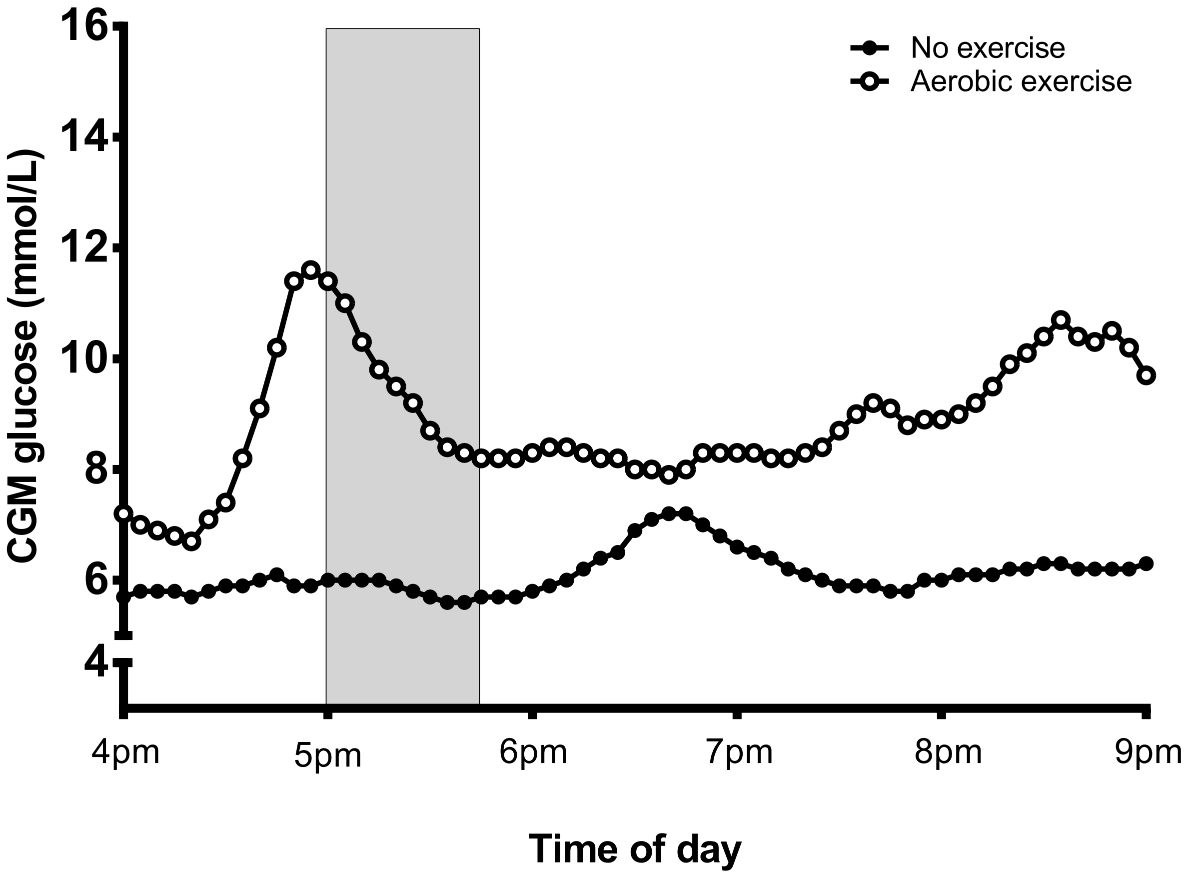
Figure 2. Plasma glucose levels during 45 minutes of aerobic exercise (AE) on its own (dashed line with open symbols ○) or after resistance exercise (RA) (solid line with closed symbols ●). Data are presented as means and error bars represent standard error (n=12 for aerobic only session and n=11 for combined resistance then aerobic session). *Statistical significance for changes from baseline (after Holm-Bonferroni adjustment). †Statistical significance for changes from the end of exercise (after Holm-Bonferroni adjustment). Reprinted from Canadian Journal of Diabetes 37, Yardley J, Sigal R, Perkins B et al., Resistance Exercise in Type 1 Diabetes, Pages 420-426, Copyright 2013, with permission from Elsevier [44]. (Original data Copyright 2012 American Diabetes Association. From Diabetes Care Vol. 36, 2013;537-542 and Vol. 35, 2012;669-675. Modified by permission of *The American Diabetes Association*).

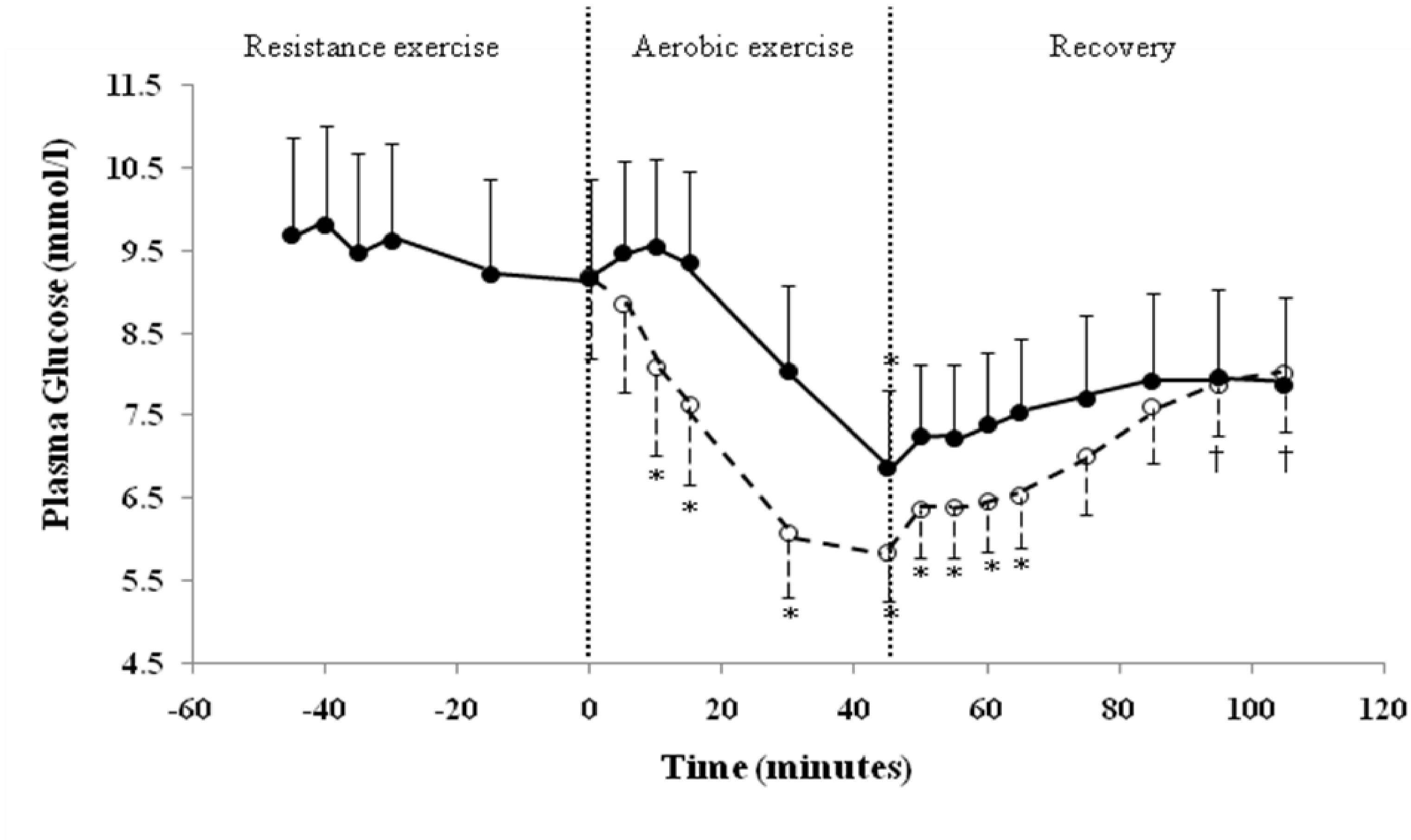
Table 1. Expected hormonal and blood glucose responses to continuous moderate aerobic exercise and short supramaximal (sprint) exercise in individuals with and without type 1 diabetes

	AEROBIC EXERCISE		**MAXIMAL SPRINT**	
	No Diabetes	**Type 1 Diabetes**	**No Diabetes**	**Type 1 Diabetes**
Initial change in glucose uptake	Increase	Increase	Decrease	Decrease
Initial blood glucose response	Slight decrease	Moderate decrease	Slight increase	Slight increase
Insulin response	Moderate decrease	No change	No change / Slight increase post-sprint	No change
Glucagon response	Moderate increase	Small increase* (may be impaired)	No change	No change
Catecholamine response	Moderate increase over time	Moderate increase* over time	Large increase	Large increase
Hepatic glucose production	Moderate increase	Small increase*	No change	No change
Resulting change in blood glucose	No change	Decrease	Increase	Increase
Overall effect	Euglycemia	Hypoglycemia	Mild hyperglycemia	Hyperglycemia

* Response may be impaired by antecedent hypoglycemia


No exercise
Aerobic exercise
CGM glucose (mmol/L)
16
14
12
10
8
6
4
4pm
5pm
6pm
7pm
8pm
9pm
Time of day


No exercise
Aerobic exercise
CGM glucose (mmol/L)
16
14
12
10
8
6
4
4pm
5pm
6pm
7pm
8pm
9pm
Time of day


Resistance exercise
Aerobic exercise
Recovery
Plasma Glucose (mmol/l)
11.5
10.5
9.5
8.5
7.5
6.5
5.5
4.5
-60
-40
-20
0
20
40
60
80
100
120
Time (minutes)