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Efficacy of Continuous Real-Time Blood Glucose Monitoring During and After Prolonged High-Intensity Cycling Exercise: Spinning with a Continuous Glucose Monitoring System

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ABSTRACT

Background: Hypoglycemia is the most common and serious side effect of insulin therapy in type 1 diabetes (T1DM), frequently occurring both during and after vigorous exercise. Late-onset hypoglycemia (LOH) is of great concern, occurring 1–36 h after exercise, often going unnoticed during sleep. Repeated exposure to LOH causes autonomic glucose counterregulatory failure and sometimes coma and death. Continuous glucose monitoring systems have recently emerged as a potentially important tool in diabetes management, allowing individuals to track glucose levels continuously and learn how various behaviors influence glucose control.

Methods: In this pilot study, we determined the efficacy of using a real-time continuous glucose monitoring system (Guardian® RT, Minimed, Northridge, CA) to detect blood glucose excursions associated with exercise and LOH (i.e., blood glucose concentration <4 m*M*) after exercise in individuals with T1DM. Five subjects with T1DM were monitored before, during, and after a 60 min vigorous spin class using Guardian RT (48 h in total).

Results: Following the exercise, three of the five subjects had LOH, while the other two experienced decreases in blood glucose concentrations to 4 m*M*. The Guardian RT monitor was effective in notifying all of the subjects of such glycemic excursions over the 48 h surveillance period. A strong correlation ($r = 0.89$, $P < 0.001$) was found between conventional self-monitoring of blood glucose and Guardian RT data pairs.

Conclusion: These limited data suggest that nocturnal LOH occurs commonly following vigorous exercise and that a Guardian RT is a useful and important diagnostic tool. Further study into clinical strategies for preventing hypoglycemia associated with this common form of mixed aerobic and anaerobic exercise is urgently needed through insulin modification and carbohydrate supplementation.

INTRODUCTION

CONTINUOUS REAL-TIME (RT) glucose monitoring has recently emerged as a new tool for patients with type 1 diabetes mellitus (T1DM) to help maintain proper glucose levels. In contrast to intermittent self-monitoring of blood glucose (SMBG), RT monitoring systems [e.g., Guardian® RT by Minimed (Northridge, CA) or DexCom™ STS™ System by Dex-

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Com Inc. (San Diego, CA)] report glucose levels continuously from a small electrode inserted into interstitial fluid under the skin. A transmitter sends information wirelessly to a monitor that displays current glucose readings and stores the data for viewing and downloading to a personal computer. This new technology has facilitated management of diabetes by providing blood glucose trends and by detecting extreme fluctuations in glucose concentrations that were previously undetected with SMBG.[1] Unstable blood glucose levels that result in repeated exposure to hypo- and hyperglycemia are known to be deleterious to health in the short-term and may pose a greater risk for long-term complications from diabetes that is in addition to that predicted by mean blood glucose value (i.e., hemoglobin A1c).[2] In fact, individuals given continuous RT feedback of blood glucose levels show better overall glycemic control, with less time spent in dysglycemia.[3]

Although important for promoting fitness, health, and longevity in diabetes,[4] exercise may be the most frequent behavior that causes dysglycemia in patients with T1DM, particularly in children.[5] Indeed, hypoglycemia is the most common and deleterious side effect of intensive insulin therapy in T1DM, with exercise being the most common causal behavior.[6] Prolonged moderate-intensity exercise typically causes a pronounced decrease in blood glucose in individuals with T1DM, and hypoglycemia can occur for up to several hours after exercise, as insulin sensitivity remains enhanced.[7–9] A recent investigation in children with T1DM revealed that 75 min of discontinuous treadmill walking in the late afternoon is associated with a high frequency of hypoglycemia during nighttime sleep.[10] Frequent nocturnal blood sampling is not feasible for patients, and continuous glucose monitoring systems (CGMSs) may provide the only viable approach to accurately monitor physiological functioning during sleep caused by exercise. The alarms in RT units can be set to awaken patients of asymptomatic hypo- or hyperglycemia, providing protection for patients with T1DM since they may have impaired sympathoadrenal reactivity and a reduced awakening efficiency.[11]

The purpose of this pilot study is to illustrate glucose excursions associated with high-intensity cycling exercise, in a group of active individuals with T1DM, by using the Guardian RT monitor and to assess the usefulness of the alarm systems to alert subjects of these excursions. This study also determined the accuracy of Guardian RT sensing in the hours surrounding exercise by comparing the sensor readings with the readings from the patients' usual SMBG devices.

RESEARCH DESIGN AND METHODS

Subjects

Five individuals with T1DM (four men and one woman) and one healthy control (male) subject, all between the ages of 25 and 43 years (mean age 35.2 ± 3.0 years), participated in the study after providing informed consent. The one subject without diabetes was included to illustrate the relative stability in blood glucose levels during and after exercise, despite the large increase in glucose turnover that is associated with this type of activity. All subjects were regularly active (three to five times per week). All were asymptomatic from complications of diabetes and were in fair to good metabolic control (hemoglobin A1c 7.0 ± 0.2%). Two of the five participants with diabetes were on continuous subcutaneous insulin infusions (i.e., pump therapy), and the remaining three were receiving multiple daily injections of either NPH and a rapid-acting insulin analog ($n = 2$) or insulin glargine and a rapid-acting insulin analog ($n = 1$). The average amount of insulin taken per day was 38.8 ± 5.1 units. Three of the participants with diabetes had experience with the Guardian RT, while two were unfamiliar with the unit.

Blood glucose monitoring

Figure 1 is a timeline of the experimental protocol. Participants were fitted with Guardian RT units the day prior to exercise (day 1) and instructed to maintain their usual insulin and diet regimens. Subjects were asked to perform their usual number of finger stick samples throughout the day and to record these mea-

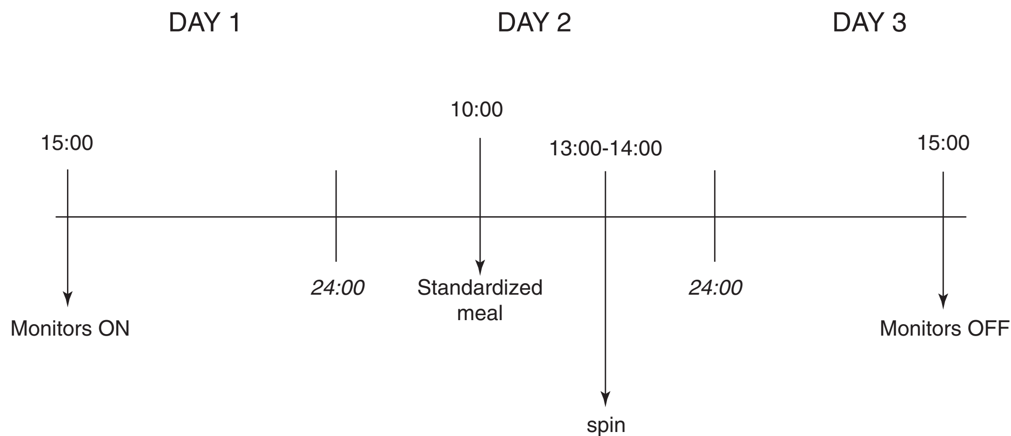

FIG. 1. The 48 h general study design: Guardian RT monitors fitted (day 1); standardized meal consumed at 10 a.m. (day 2); spin class 1–2 p.m. (day 2); Guardian RT monitors removed (day 3).

surements into their Guardian RT monitors. Participants were also advised to confirm their high (>11 m*M*) and low (<4 m*M*) glucose alarms, as identified by the Guardian RT, by performing a finger stick measurement using their own glucometer. All SMBG samples were logged into the Guardian RT monitors, and the data were downloaded onto a personalized computer to gather data pairs for SMBG and CGMS comparisons.

Exercise protocol

On the day of exercise (day 2), participants consumed a standardized meal at 10 a.m. consisting of a sandwich (~15% of daily energy requirement and consisting of 56 g of carbohydrate, 12 g of fat, and 28 g of protein; 440 total kcal) and took 50% less of their usual meal-time insulin bolus to accommodate for the forthcoming exercise.

The exercise consisted of a 60 min spin class (i.e., cycling with various degrees of resistance and cadence) intended to maintain intensity above 60% of the subjects' predetermined maximal heart rate (HR_{max}) using HR monitors (Polar, Lake Success, NY). All subjects participated in the same spin class (1 p.m.) taught by one of the investigators. Glucose concentration was monitored prior to and during exercise using both Guardian RT and finger stick monitoring taken at -60, -15, -5, 0, 30, and 60 min.

After exercise, subjects were asked to maintain their usual exercise-associated insulin and dietary regimen and to use both finger samples and the Guardian RT to monitor glycemic levels. The day following exercise (day 3, ~15:00), the monitors were removed, and the data were downloaded and analyzed. Hypoglycemia was defined as a glucose reading of <4 m*M*, as measured by the Guardian RT and confirmed with SMBG. Hyperglycemia was defined as a glucose reading of >11 m*M*, as measured by the Guardian RT and confirmed with SMBG.

Data analysis and statistics

Blood glucose and HR changes during exercise were analyzed using a repeated-measure analysis of variance and Newman-Keuls Multiple Comparison post hoc tests comparing standardized time points. For each subject, the percentage of time spent during hypoglycemia, euglycemia, and hyperglycemia was determined from both the evening prior to exercise and the evening after exercise. This comparative analysis was produced using the Guardian RT data to determine time spent (i.e., number of minutes) in euglycemia (4–11 m*M*), hypoglycemia (<4 m*M*), and hyperglycemia (>11 m*M*) for the nights before and after exercise. These times were compared between nights using nonparametric analysis (Pearson χ^2 analysis). A power calculation was performed using the preceding data using a dependent sample *t* test between two means. Glucose values obtained with the Guardian RT were compared with SMBG using Pearson product-moment correlational analysis. Significance was set at a level of $P < 0.05$.

RESULTS

HR and caloric expenditure

During the 1 h spin class, heart rate increased from 65 ± 3.5 beats per minute (bpm) at pre-exercise to 174 ± 7.0 at 30 min ($P < 0.001$) (Fig. 2). During the second half of exercise, values increased again from 144 ± 10.0 bpm at the break period (used for SMBG) to 178 ± 4.4 bpm at 60 min ($P < 0.001$). Total energy expenditure, as determined from HR, was 487.5 ± 28.1 kcal for the 60 min class.

CGMS, exercise, and hypoglycemia

Subjects' blood glucose levels were monitored for ~48 h surrounding exercise using both SMBG and Guardian RT. On average, 516 ± 20 CGMS data points were collected during the 48 h period per subject. During exercise (1–2 p.m.), the T1DM subjects had significant drops in blood glucose from 9.0 ± 2.0 m*M* at the start of exercise to 7.3 ± 1.6 m*M* at the end of exercise as measured by the Guardian RT ($P < 0.01$) (Fig. 3). SMBG over the same time course revealed a greater drop during exercise as compared with CGMS (4.1 ± 1.6 m*M* vs 1.8 ± 0.7 m*M*). The control subject without diabetes also experienced a small transient decrease in glycemia during exercise (Fig. 3). None of the subjects had hypoglycemia during the spin class.

As shown in Figure 4a, the control subject demonstrated normal glycemic levels (values between 4 and 11 m*M*) the day preceding and the day following the spin class. In contrast, continuous data from all the patients with diabetes showed frequent and large variations during the 48 h period due to several factors, including the inability of precisely matching insulin requirements with dietary intake, levels of glucose counterregulatory hormones, and physical activity. Figure 4b–d shows typical glucose excursions in three of the five subjects with diabetes. On occasion, sensors would lose communication with the Guardian monitors and report data missing (Fig. 4b).

The Guardian RT monitors detected hypoglycemia (<4 m*M*) in one subject with diabetes on the evening before exercise compared with hypoglycemia detected in three of the five subjects during the evening following exercise. In

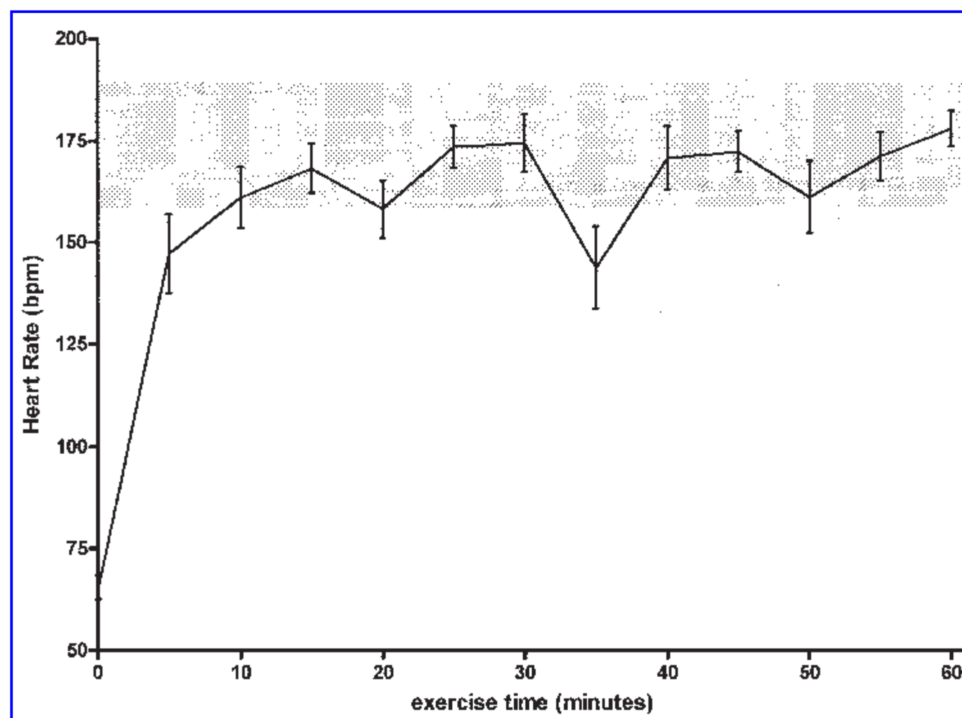

FIG. 2. HR during the 60 min spin class in five subjects with T1DM. The shaded area represents 60–80% of HR reserve. A 5 min rest period was given between 30 and 35 min for SMBG. Values represent means ± SEM.

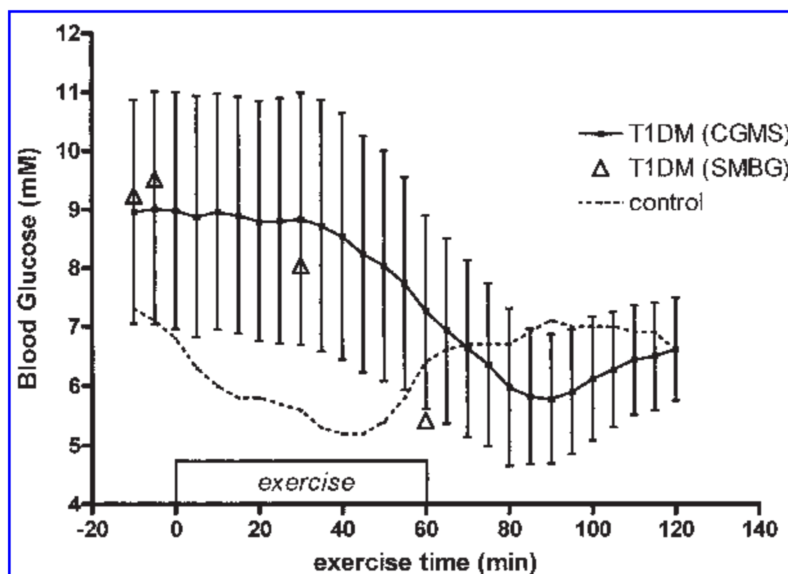

FIG. 3. Blood glucose response during the 60 min spin class in five subjects with T1DM compared with a healthy control. Values represent means ± SEM.

addition, the remaining two subjects with diabetes who did not record hypoglycemia on the evening after exercise did experience drops in blood glucose to 4 m*M* on the evening following exercise as measured with the Guardian RT, and hypoglycemia (i.e., $<$4.0 m*M*) was confirmed in these subjects' SMBG. Thus, during the 22 h period following exercise, hypoglycemia was documented in all subjects with diabetes by either SMBG or Guardian RT.

The percentage of time spent in euglycemia, hypoglycemia, and hyperglycemia in the evening prior to and following exercise was determined based on all of the data collected by the Guardian RT. For this, one subject was removed from the analysis because of too many

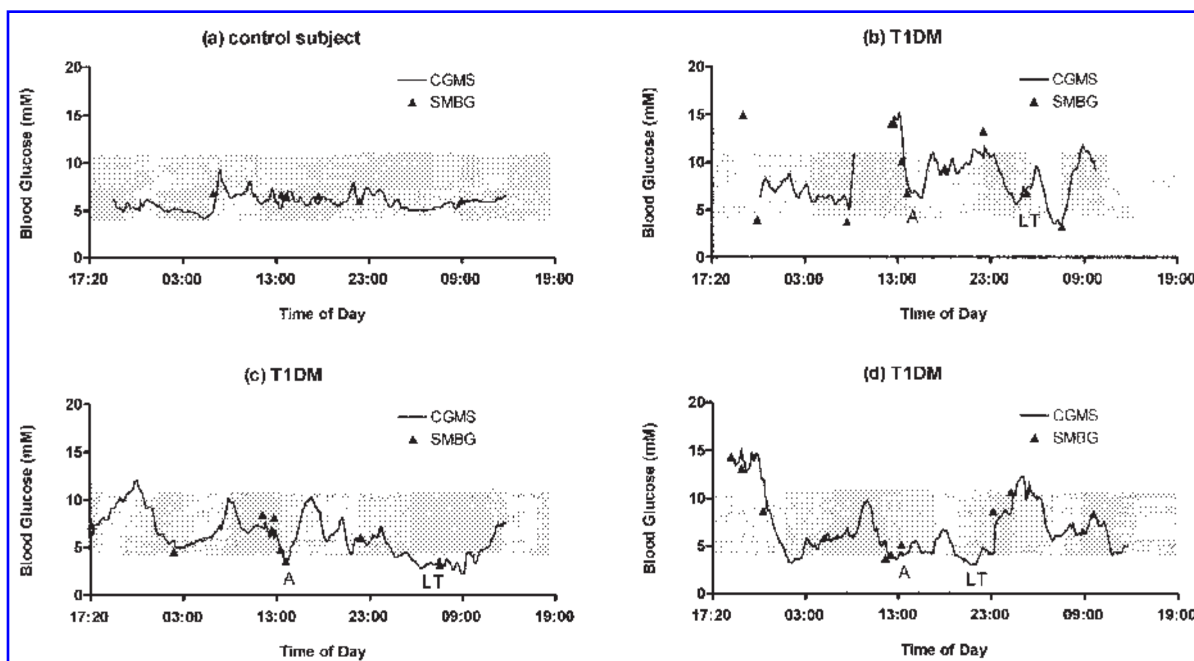

FIG. 4. Sample glycemic monitoring using CGMS (−) and SMBG (▲) over a 48 h period: (**a**) control subject and (**b–d**) three subjects with T1DM. A standardized meal was consumed at 10 a.m. A indicates acute and LT indicates long-term effects of the exercise session on blood glucose. The shaded area represents the optimal glycemic range (between 4 and 11 m*M*).

missing data points (see Fig. 4b). Time spent in hypoglycemia on the evening following exercise (133.75 ± 104.97 min; 13% of the time) was greater than on the evening prior to exercise (25 ± 28.87 min; 2% of the time), although this difference failed to reach statistical significance ($P = 0.33$).

Validity of CGMS

Using the multiple finger stick samples taken and the associated RT measurement of interstitial glucose recorded in the Guardian RT monitor (64 pairs in total), a strong correlation ($r = 0.89$, $P < 0.001$) was found between conventional SMBG and Guardian RT (Fig. 5). Too few data pairs were available to determine accuracy at low and high concentrations.

DISCUSSION

The present pilot study demonstrates the efficacy of Guardian RT monitors to map the irregular glycemic patterns associated with high-intensity exercise in the hours following exercise in a small group of active individuals with T1DM. We show that blood glucose levels drop significantly during prolonged vigorous exercise despite reductions in pre-exercise insulin delivery (Fig. 3). We also illustrate that there is a high likelihood of post-exercise late-onset hypoglycemia (LOH) in individuals with T1DM, even when blood glucose levels are provided continuously in real time to the patients. Thus, it appears that LOH is extremely common during the evening after exercise, sometimes during sleep, and the Guardian RT unit is a valuable tool in alerting individuals of this potentially deleterious side effect of exercise.

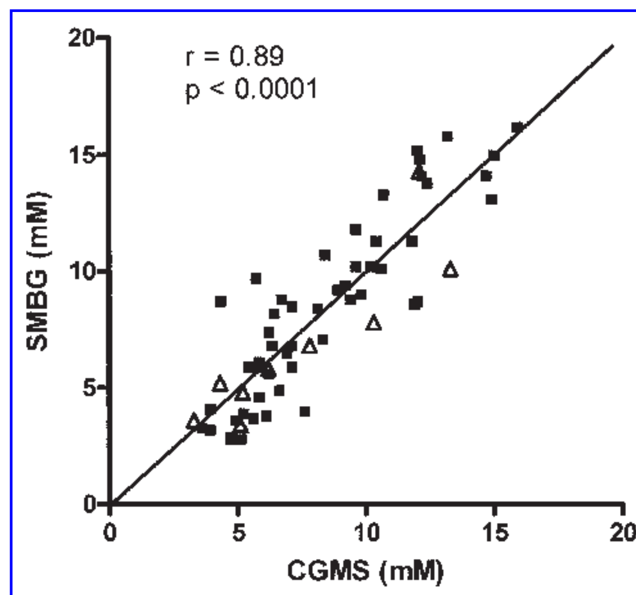

FIG. 5. Correlation using SMBG and CGMS data pairs. (△), pairs during exercise.

In healthy individuals, prolonged aerobic exercise is associated with reductions in plasma insulin levels and increases in glucose counterregulatory hormones that cause blood glucose levels to remain relatively constant both during and after exercise.[4] In patients with diabetes, insulin levels are often elevated during prolonged moderate-intensity exercise because of an inability to immediately lower circulating levels at the start of the activity.[5] Exercise also produces an increase in insulin sensitivity that persists for several hours after the activity has ended, likely to help replenish muscle and liver energy stores of carbohydrate.[5] Unfortunately, patients with T1DM who exercise repeatedly tend to have an impaired glucose counterregulatory hormone response to hypoglycemia.[12–14] As a result of these impairments, exercise-associated hypoglycemia is extremely common in active individuals with T1DM.[4] The use of Guardian RT monitors in this study illustrates the difficulty in managing glucose levels in the hours surrounding exercise, in comparison with a sedentary day, despite the fact that glucose values were available continuously to the participants (Fig. 4b–d).

We found that during a spin class session, which is a combination of aerobic and anaerobic activity, subjects with T1DM have a modest decrease in glycemia that is identifiable both with SMBG and the Guardian RT (Fig. 3). Steady-state aerobic cycling causes a similar decrease in blood glucose level in a majority of active youth with diabetes.[15] The fall in blood glucose level in this study was likely minimized because of a 50% reduction in insulin dosage at the standardized meal prior to exercise and because of the subjects' constant awareness of their glycemia during the activity. Indeed, two of the five subjects identified a decreasing trend in their glucose levels that

was attenuated by ingesting an additional 15 g of carbohydrate. Moreover, all of the subjects remarked that exercising while being able to view their blood glucose levels provided a greater level of security than they normally experience without the use of RT monitors.

The intensity of exercise in this study is typical of what active individuals with diabetes would perform on a regular basis. HRs were maintained within 60–80% of each individual's HR_{max} for the majority of the exercise session, which is typical for a recommended exercise training intensity (Fig. 2). As shown from the dramatic drop in HR at the 35 min time point, SMBG using finger stick sampling requires that the subject discontinue his or her exercise for sampling. Although such SMBG checks are beneficial to ensure proper blood glucose control during exercise, they are often challenging for individuals who are intensely training (e.g., professional athletes) or during sporting competitions when pausing the activity is impractical. A potential advantage of CGMS for those who are competitively active is the ability to acquire glucose data without interrupting their activity. These data can also be downloaded to a personal computer so that trends in glycemia caused by exercise can be learned.[16]

Although the monitor effectively tracked blood glucose in all of our subjects, independent of movement (i.e., sleep vs. activity), the monitor would occasionally lose its transmission signal, resulting in missing sample periods lasting up to 4 h (Fig. 4b). This occurrence was mostly due to one subject's inexperience with the unit as action was not taken to resynchronize the monitor with the transmitter. As a result, this subject was excluded from the data analysis comparing the non-exercise night to the night after exercise. Recently, the GlucoWatch® Biographer (Cygnus, Redwood City, CA) was shown to be ineffective in capturing data during either moderate or vigorous exercise compared with sedentary behavior.[17] Unreliable readings during exercise may be due to the rapid metabolic changes associated with aerobic activity or to some movement artifact. Readings from CGMS are also problematic because of the delayed transfer of blood glucose to interstitial fluid, where glucose levels are more rapidly depleted than those of the blood by cellular consumption.[17] Surprisingly, we show that the Guardian RT monitors captured all of the data during exercise, with no missed readings, and maintained reasonable accuracy even though blood glucose levels decreased rapidly during the spin class (Fig. 3). As shown in Figure 3, we found that there is a slight delay in Guardian RT measurements compared with SMBG, likely due to the rapid drop in blood glucose associated with exercise. For example, SMBG values taken at 30 and 60 min, respectively, appear to be more similarly matched with continuously monitored blood glucose values occurring ~20 min later (i.e., 50 and 80 min, respectively). As a result in this delay, blood glucose concentrations as measured by SMBG were lower than those measured by CGMS at the end of the 60 min spin class session. As such, individuals wearing Guardian RT monitors should be made aware that the drop in blood glucose during exercise may be underestimated compared with finger stick sampling.

During the entire 48 h of the experimental protocol, we found a strong association between CGMS and SMBG ($r = 0.89$, $P = 0.001$) (Fig. 5), results consistent with other studies comparing CGMS with either SMBG or laboratory blood samples, which ranged from $r =$ 0.82 to 0.92.[18–21] Unfortunately, because of too few data pairs, we were unable to assess the correlation at both low and high glycemic levels and future research is requires to determine if exercise influences the accuracy of RT monitoring during periods of dysglycemia.

In contrast to the consistent pattern demonstrated in the control subject (Fig. 4a), maintaining euglycemia during and after exercise was extremely difficult in the subjects with T1DM, even though they were in reasonable overall metabolic control (Fig. 4b–d). As shown, both the acute and long-term hypoglycemic effects of exercise were evident. Hypoglycemia during the evening following exercise was apparent in three of the five T1DM subjects using Guardian RT data (Fig. 4b–d). In total, the high rates of hypoglycemia following exercise (13% of time spent with glucose <4.0 m*M*) were in contrast to the night before exercise (2% of time spent with glucose <4.0 m*M*), although the small number of subjects may

have limited our ability to show a significant difference between the two nights. In fact, all five subjects with diabetes had blood glucose falls $\leq$4 m*M* requiring carbohydrate supplementation on the evening following exercise compared with only one subject $\leq$4 m*M* on the evening prior to exercise. A power calculation revealed insufficient subjects for the time spent in hypoglycemia during the sedentary and exercise nights ($n = 4$, power = 0.30). Based on the variance (an alpha value of 0.05 and a beta value of 0.80), we calculated that 10 subjects would be required to determine statistical significance. Although the drop in blood glucose during exercise was similar among the participants, LOH occurred anywhere from minutes to several hours after the end of exercise and to varying degrees. Thus, the Guardian RT was shown to be effective in alerting the subjects of ensuing hypoglycemia so that carbohydrate intake or reductions in basal insulin could be performed. The variability among the participants in the timing of LOH may have been due to the failure to standardize insulin and carbohydrate strategies or may be due to differences in the timing of heightened insulin sensitivity that occurs after exercise.

Daytime hypoglycemia may be less problematic as general awareness through symptoms and/or SMBG may provide sufficient indication for immediate correction. In contrast, nocturnal episodes are often asymptomatic and usually pass unnoticed as finger stick sampling is uncommon.[7,9,22–25] Such episodes may last for up to 4 h with deleterious effects on subsequent counterregulatory responses.[7,9] In addition to the lasting effects of exercise, T1DM patients are already susceptible to hypoglycemia because of reduced sympathoadrenal response during the night in comparison with healthy controls.[26] Therefore, our findings underscore the importance of using Guardian RT in active individuals with diabetes, as it may be the only realistic approach to investigate LOH often occurring during early morning hours (i.e., 2 a.m.–6 a.m.) when capillary sampling is not customary.

Although this pilot study demonstrates the importance of using Guardian RT in monitoring post-exercise hypoglycemia, failure to maintain careful records of insulin adjustments and carbohydrate intake makes it difficult to accurately associate exercise to episodes of LOH. Importantly, adjustments to bedtime insulin and nighttime snacks are frequently used in anticipation of nighttime hypoglycemia, but it is unclear whether these modifications are effective, as again, sampling is rarely taken during the night. These preliminary data suggest that large-scale clinical trials utilizing CGMS are needed to assist in producing effective algorithms for bedtime insulin and carbohydrate supplementation, in hopes of preventing dysglycemia during sleep.

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