High Rates of Nocturnal Hypoglycemia in a Unique Sports Camp for Athletes with Type 1 Diabetes: Lessons Learned from Continuous Glucose Monitoring Systems

Katherine E. Iscoe[1] MSc, Matthew Corcoran[2] MD, Michael C. Riddell[1] PhD

[1]School of Kinesiology and Health Science, York University, Toronto, Ontario, Canada
[2]Diabetes Training Camp, Orland Park, Illinois, United States

ABSTRACT

BACKGROUND

Glycemic instability related to exercise in people with type 1 diabetes mellitus is most often studied using short-term laboratory investigation. However, such acute laboratory sessions do not provide an "everyday" depiction of the frequency of blood glucose excursions during training. Continuous glucose monitoring systems (CGMS) provide a unique method of observing both the immediate and long-term effects of exercise on glycemic control in this active population. The purpose of this observational study was to quantify episodes of both hypo- and hyperglycemia during a 5-day training camp for athletes with type 1 diabetes.

METHODS

Twelve subjects from the Diabetes Training Camp were randomly selected and fitted with CGMS and were instructed to maintain their usual insulin and blood capillary sampling regimens for exercise. A support team consisting of an endocrinologist, exercise physiologists, physician assistants, professional athletes and coaches, dietitians and sport psychologists were continuously involved in the athletes' care and training throughout the camp.

RESULTS

All 12 subjects had at least 1 hypoglycemic event during the ~60 hours of data collection. Seventy-five episodes

Address for correspondence:
Michael C. Riddell
School of Kinesiology and Health Science
York University
4700 Keele Street
Toronto, Ontario
Canada M3J 1P3
Telephone: (416) 736-2100, ext. 40493
Fax: (416) 736-5774
E-mail: mriddell@yorku.ca

RÉSUMÉ

GÉNÉRALITÉS

L'instabilité glycémique liée à l'exercice chez les personnes atteintes de diabète de type 1 fait la plupart du temps l'objet d'essais de laboratoire à court terme. Toutefois, les résultats de tels essais ne reflètent pas la fréquence réelle des oscillations glycémiques pendant l'entraînement. Les systèmes de surveillance de la glycémie en continu (SSGC) sont un moyen unique de déterminer les effets immédiats et à long terme de l'exercice sur le contrôle de la glycémie dans une population active. L'objet de l'étude par observation était de déterminer le nombre d'épisodes d'hypo- et d'hyperglycémie au cours d'une période d'entraînement de cinq jours pour des athlètes atteints de diabète de type 1.

MÉTHODES

Douze sujets du camp d'entraînement pour diabétiques ont été choisis au hasard pour porter un SSGC. On leur a demandé de continuer à prendre les mêmes doses d'insuline et de mesurer leur glycémie capillaire comme lorsqu'ils font de l'exercice. On a formé une équipe comprenant un endocrinologue, des physiologistes de l'exercice, des auxiliaires médicaux, des athlètes et des entraîneurs professionnels, des diététistes et des psychologues du sport pour voir aux soins et à l'entraînement des athlètes pendant la période de cinq jours.

RÉSULTATS

Les 12 sujets ont présenté au moins un épisode d'hypoglycémie au cours des quelque 60 heures de collecte des données. Au total, 75 épisodes d'hypoglycémie (glucose interstitiel < 4 mmol/L) ont été notés, soit 45 (60 %) la nuit et 30 le jour. Les glycémies minimales selon le SSGC (6,0 ± 2,4 mmol/L) sont survenues à 3 h 45 et étaient légèrement liées à la glycémie au coucher (r^2 = 0,44, p < 0,01, n = 36 paires de données). Le moment de la glycémie minimale pendant le sommeil a été le même à deux reprises.

of hypoglycemia (interstitial glucose <4 mmol/L) were detected in total; 45 of these episodes (60%) occurred at night during sleep, with the remainder occurring during waking hours. CGMS nighttime glucose nadirs (6.0±2.4 mmol/L) occurred at 3:45 AM and were modestly related to pre-bedtime blood glucose levels (r^2=0.44, p<0.01, n=36 data pairs). The timing of the glucose nadir during sleep was reproducible on 2 separate camp days.

CONCLUSION

This field study illustrates that hypoglycemia is extremely common in regularly active individuals with type 1 diabetes, despite regular glucose testing, continuous carbohydrate availability and on-location support. Nocturnal hypoglycemia was particularly prevalent, regardless of the level of bedtime glycemia, with the lowest nighttime values typically occurring around 3:45 AM when subjects were asleep. We conclude that active persons with type 1 diabetes are highly susceptible to hypoglycemia, especially during sleeping hours. As such, CGMS may be the only practical method of detecting both asymptomatic and nocturnal episodes of hypoglycemia. These results also suggest that athletes may benefit from reductions in insulin or a slow-release carbohydrate bedtime snack during training.

KEYWORDS

Continuous glucose monitoring, endurance exercise, hypoglycemia, sports training

CONCLUSION

Cette étude sur le terrain montre que l'hypoglycémie est extrêmement courante chez les personnes atteintes de diabète de type 1 qui font régulièrement de l'exercice, même si la glycémie est mesurée souvent, si le sujet consomme régulièrement des glucides et s'il a de l'appui sur place. Quelle que soit la glycémie au coucher, l'hypoglycémie nocturne a été particulièrement fréquente et la glycémie était au minimum habituellement vers 3 h 45, pendant que les sujets dormaient. Nous concluons que les personnes actives atteintes de diabète de type 1 sont très exposées à l'hypoglycémie, surtout pendant le sommeil. Un SSGC pourrait donc être la seule méthode pratique pour déceler les épisodes d'hypoglycémie tant asymptomatiques que nocturnes. Ces résultats semblent aussi indiquer qu'il pourrait être bon pour les athlètes de réduire leur dose d'insuline ou de consommer des glucides complexes au coucher pendant l'entraînement.

MOTS CLÉS

exercice d'endurance, hypoglycémie, entraînement sportif, surveillance de la glycémie en continu

INTRODUCTION

Regular aerobic exercise is clearly an optimal method of increasing mental and physical health, preventing chronic disease and prolonging independent living. For many individuals with type 1 diabetes mellitus, these benefits often outweigh the potential drawbacks, which include exercise-related hypo- or hyperglycemia (1). In fact, many individuals with diabetes have become professional athletes despite their physiological inability to maintain stable glucose levels. While prolonged moderate-intensity aerobic exercise often causes hypoglycemia in individuals with type 1 diabetes (i.e. a blood glucose <4.0 mmol/L) (2,3), higher anaerobic bursts may in fact cause hyperglycemia, both during and after the activity has ended (4,5). As well, because insulin sensitivity remains enhanced for hours after the end of exercise (6,7) and because glucose counter-regulatory response is impaired both following exercise (8,9) and during sleep (10-14), active individuals with type 1 diabetes may be at high risk of late-onset or nocturnal hypoglycemia (15,16). It is surprising, therefore, that very few studies have investigated the effects of high-volume exercise on the frequency of hypoglycemia in athletes with type 1 diabetes. In fact, the majority of studies investigating exercise-related glycemic control in type 1 diabetes are conducted during a short-term laboratory session, with little follow-up in recovery, and are often conducted in persons not accustomed to frequent and/or intensive exercise.

We have recently shown that continuous glucose monitoring systems (CGMS) are effective in identifying glycemic excursions associated with exercise in a small cohort of active individuals with type 1 diabetes (16). CGMS allow for field assessment of blood glucose levels with minimal disturbance to the individual's normal routine. More importantly, CGMS can be used to detect episodes of asymptomatic hypoglycemia or nocturnal hypoglycemia. Using this technology in a group of regularly active athletes with type 1 diabetes attending a specialty sports camp, we determined: 1) the average level of glycemic control over a ~60 hour period, 2) the incidence of hypoglycemia during training and 3) if there was an association between pre-bedtime glucose levels and nocturnal glucose nadirs.

MATERIALS AND METHODS

Camp description

The annual 5-day Diabetes Training Camp is a sport, fitness and diabetes management camp targeted at active individuals with diabetes. It offers swimming, cycling and running training, in addition to general fitness classes and personal coaching for all levels of sports participation (www.diabetes trainingcamp.com). It also provides educational sessions to teach effective insulin and dietary strategies for optimal glycemic control, both during and after exercise.

The camp included 25 international participants with uncomplicated type 1 diabetes (15 males/10 females) and ranging in age (35.4 ± 12.3 years, mean ± SEM). Diabetes duration ranged widely (1 to 41 years; 13.4 ± 2.6 years). All participants were achieving fair to average metabolic control (glycated hemoglobin [A1C] 7.3 ± 0.3%), were accustomed to regular exercise, and regardless of diabetes duration had good knowledge of carbohydrate and insulin management strategies for exercise. A majority of the participants (80%) were already involved in competitive sports/athletic participation (i.e. cycling, marathons, triathlons and other sport competition), while the remaining individuals were recreationally active.

Each day provided a choice of activities, including road cycling, track and country trail running, swim sessions and studio fitness classes. The duration and intensity of these sessions varied widely, as some provided technical training while others targeted endurance. For example, "skill" sessions may have included repetitive drills interspersed with periods of rest or recovery, while "endurance" sessions may have included constant cycling, running or swimming for periods lasting from 30 minutes up to 2 hours. It is important to note that a support team (i.e. coaches, a physician, physician assistants, exercise physiologists) was continuously available onsite during these exercise sessions. The camp also provided daily educational lectures on blood glucose management and strategies to limit exercise-related glucose excursions by an endocrinologist, exercise physiologists and physician's assistants. Professional athletes and coaches, dietitians and sports psychologists were also on staff to provide individual counselling.

Meals were provided at conventional times (i.e. breakfast 7:00 to 9:00 AM, lunch 1:00 to 2:00 PM, dinner 6:00 to 7:00 PM) and were high in carbohydrates (~55 to 60% of energy from carbohydrate, with the remaining split between protein and fat). Snacks (e.g. sports bars, crackers), beverages (e.g. water, juice, sports drinks) and glucose tablets were continuously available to camp participants. All campers were provided with a large supply of blood glucose test strips, which promoted regular testing (minimum of 7 per day). The cost of glucose testing is often a limiting factor preventing essential testing during activity.

As each camper could choose from a variety of concurrent exercise sessions, it is difficult to summarize or provide an average level of physical activity for participants. However, a typical day may be exemplified as follows: breakfast (~25% total energy intake), educational session (9:00 to 10:00 AM), 10 km trail run with snack/rest break (11:00 AM to 12:30 PM), lunch (~30% total energy intake), educational session (2:00 to 3:00 PM), swimming drills (3:30 to 5:00 PM) and free time and dinner (~35% total energy intake). For most participants, the volume of exercise was more than customary. However, because the training was predominantly moderate (or combination low/high) in intensity, the physical challenge was similar to that of typical training at home. No participant was physically exhausted or overexerted at any point during the 5-day camp period.

Subjects

Twelve of the 25 camp participants (6 males/6 females) aged 21 to 59 (38.4 ± 3.5 years) were randomly selected to participate in CGMS evaluation and gave written informed consent. All were in good physical health and fitness (VO_2 max=44.7 ± 4.4 $mL \cdot kg^{-1} \cdot min^{-1}$; % body fat=20.2 ± 3.5%; weight=72.9 ± 2.6 kg; body mass index [BMI]=24.6 ± 0.9 kg/m^2; A1C=7.3 ± 0.3%) and were free from diabetes-related complications. Participants were fitted with CGMS (9 with CGMS Gold; 3 with Guardian REAL-Time; both by Minimed, Medtronic, Northridge, CA) and instructed to maintain their usual insulin, diet and capillary sampling regimens for exercise. This may have included modifications such as a ~25% increase in calories or a ~25 to 50% reduction in bolus insulin (or a combination of both). Nine of the 12 participants were on continuous subcutaneous insulin infusions (i.e. pump therapy), while the others were on multiple daily injection insulin therapy. The average total amount of insulin taken per day was 34.0 ± 3.0 IU, comprised of a mix of rapid-acting and long-acting insulin analogues. Subjects were encouraged to perform capillary blood glucose monitoring regularly using a provided blood glucose meter (UltraSmart 2, LifeScan, Milpitas, CA). They were also encouraged to take additional measurements surrounding exercise and throughout the day, such as to confirm low (<4 mmol/L) and high (>11 mmol/L) blood glucose measurements as identified by the CGMS (Guardian REAL-Time only). Four equally spaced samples were logged into the monitors for calibration. CGMS data were uploaded using the appropriate software and coded using numbers rather than names.

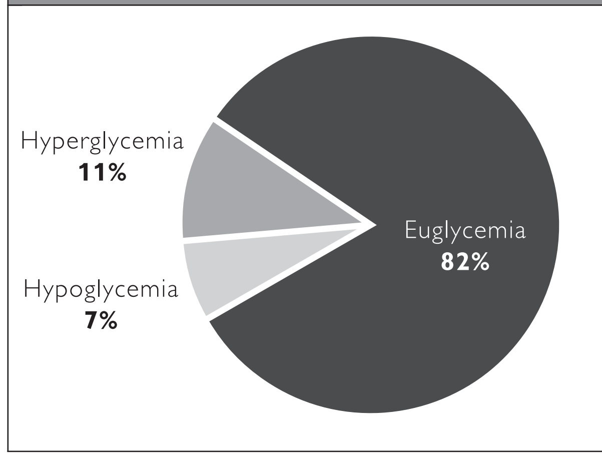
Data analysis and statistics

Results are reported as mean ± SEM unless otherwise noted. An episode of hypoglycemia was defined as a CGMS glucose reading of <4 mmol/L for ≥5 minutes. Hyperglycemia is defined as a CGMS reading >11 mmol/L for ≥5 minutes. These broad ranges were chosen due to the increased difficulty of maintaining stable glycemia during exercise. Overnight measurements were defined as those taken between 10:00 PM and 10:00 AM. Correlation of pre-bedtime blood glucose (i.e. the value at 10:00 PM) and nighttime nadir (the lowest value between 10:00 PM and 10:00 AM) was determined using Pearson product-moment correlational analysis. Episodes of daytime vs. nighttime hypoglycemia were compared using a paired Student t-test and Fisher's exact analysis. Significance was set at a level of $p<0.05$.

RESULTS

On average, each subject's interstitial glucose levels were monitored for 61.4 ± 5.3 hours using the CGMS, with 694 of the 737 potential readings successfully recorded (94% success rate). During the ~60 hours of recording, the subjects spent an average of 82% of their time within an acceptable target glycemic range (4 to 11 mmol/L), while the remaining time was split between hypoglycemia (<4 mmol/L) and hyperglycemia (>11 mmol/L) (7 vs. 11% of the time, respectively; Figure 1). Although each subject spent a variable amount of time within these "zones," all subjects experienced at least 1 episode of mild to moderate biochemical hypoglycemia (i.e. interstitial glucose <4.0 mmol/L but >2.2 mmol/L, not requiring assistance), with a total of 75 episodes of hypoglycemia detected overall. Of these episodes, 60% occurred during the night. The average number of hypoglycemic episodes per subject occurring over the ~60 hour collection period was higher during the night than during the day (4 ± 1 vs. 3 ± 1; $p<0.05$). CGMS data were pooled between subjects across all days and plotted on a 24-hour time scale to determine time-related trends (Figure 2). Using this plot, the nighttime glucose nadir was found to be at 3:45 AM. As a group, the average time of nadir was reproducible across the 2 collection days but varied considerably among participants (ranging from 10:00 PM to 10:00 AM). The nighttime glucose nadir was modestly related to the pre-bedtime glucose level ($r^2=0.44$, $p<0.01$, n=36 data pairs). A pre-bedtime glucose level of <6.2 mmol/L was associated with nocturnal hypoglycemia 71% of the time ($r^2=0.37$, $p<0.01$, n=21), while a pre-bedtime glucose level >6.2 mmol/L was not ($r^2=0.04$, $p=0.46$, n=15). A Fisher's exact test revealed no difference between the probability of hypoglycemia and pre-bedtime glucose levels both below and above 6.2 mmol/L ($p=0.18$; Figure 3).

Figure 1. Time spent in hypoglycemia, euglycemia or hyperglycemia during the study

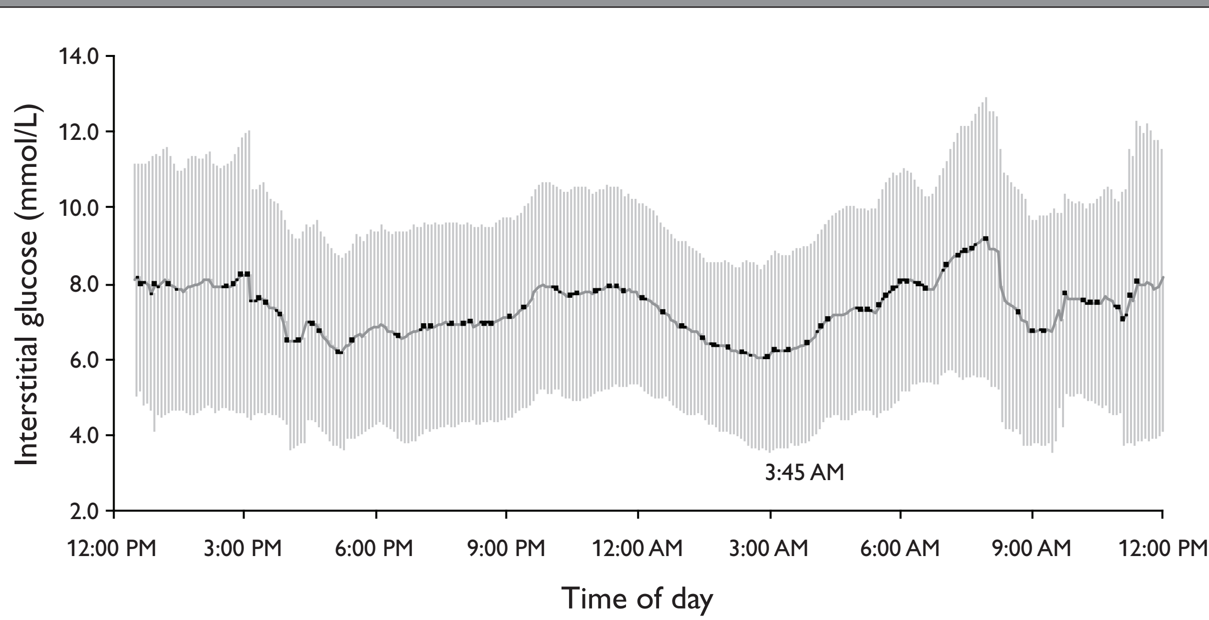


Percentage of time spent in hypoglycemia (<4.0 mmol/L), euglycemia (4.0 to 11.0 mmol/L) or hyperglycemia (>11.0 mmol/L) during approximately 60 hours of recording using CGMS data (N=12)

DISCUSSION

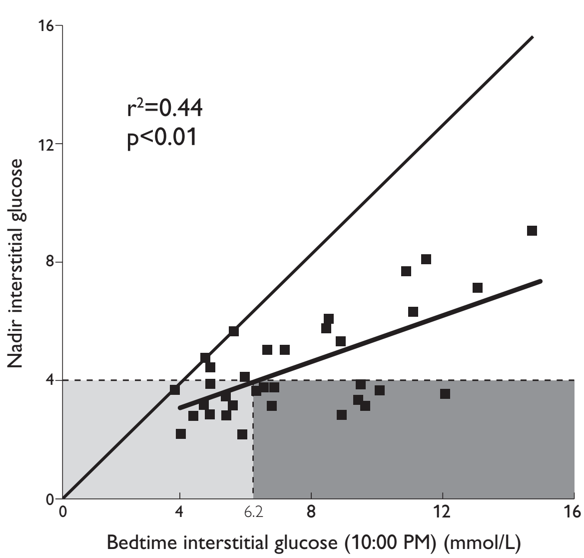
Although the acute glycemic effects of laboratory controlled aerobic exercise in type 1 diabetes is well established (17-21), little is known about the effect of sports participation on blood glucose control in the athlete's natural setting. Furthermore, as aerobic exercise is known to increase insulin sensitivity for hours following exercise and may cause

Figure 2. CGMS interstitial glucose data pooled across all recorded days



Nighttime nadir (6.0 ± 0.4 mmol/L) occurred at 3:45 AM; n=17–36 per data point. Bars represent SD

Figure 3. Correlation of pre-bedtime interstitial glucose (10:00 PM) with nighttime nadir (10:00 PM to 10:00 AM) using CGMS values



The light shaded area represents a pre-bedtime glucose <6.2 mmol/L, which resulted in a 71% rate of nocturnal hypoglycemia; the dark shaded area represents a pre-bedtime glucose >6.2 mmol/L, which resulted in a 45% rate of nocturnal hypoglycemia.

impaired glucose counterregulation, many exercise-related episodes of hypoglycemia occur long after the participant has finished his or her training (6,7). Post-exercise late-onset hypoglycemia has typically been quantified using simple questionnaires that reveal a relatively low incidence of hypoglycemia associated with sport (22). These subjective reports likely underestimate the rate of hypoglycemia, as patients may not be aware of or even exhibit the classic symptoms of hypoglycemia. This may be particularly problematic during intense exercise, as the release of catecholamines (i.e. epinephrine) may mask symptoms of low blood glucose (1). Furthermore, counterregulation, even in individuals without diabetes, has been shown to be impaired during sleep (12,14,23,24).

The present study, like a few others (16,25-28), reveals a high incidence of hypoglycemia in athletes with type 1 diabetes undergoing intensive sport coaching and diabetes education. As hypoglycemia is a common side effect of exercise, we hypothesized that these athletes may be hypervigilant to this consequence and automatically take preventative actions. Although subjects were consistently attentive to their blood glucose levels (i.e. using frequent capillary samples) and had continuous support on hand at the camp, we recorded episodes of hypoglycemia in all subjects over the span of a few days. In fact, even despite this intensive management and the diabetes-related provisions by the camp, the athletes still spent almost a fifth of their time in either hypoglycemia or hyperglycemia (Figure 1). Furthermore, 1 of the camp subjects experienced 24 sporadic episodes of hypoglycemia lasting a total of 16.5 hours during approximately 70 hours of collection time (i.e. approximately 25% of the time), despite having the Guardian REAL-Time monitor, which provided alarms for hypoglycemia.

Recently, we (16) and others (7,15) have found that the hypoglycemic response to exercise may be delayed and often occurs during early morning hours when patients are asleep. This is partly supported by our data here, which shows that hypoglycemia occurs more frequently during the nighttime hours compared to the daytime hours while the athletes are in training. This is surprising, as muscle glycogen replenishment is thought to peak approximately 60 to 120 minutes after the end of exercise, at least in athletes without diabetes (1). Ertl and Davis (29) report that a vicious cycle exists between the glucose counterregulatory responses caused by exercise and hypoglycemia that predisposes the patient to subsequent counterregulatory failure to either stressor. In support of this observation of the delayed effects of exercise in diabetes, McMahon et al recently found that the glucose infusion rate to maintain euglycemia increases approximately 140% above baseline between midnight and 4:00 AM in previously active adolescents with type 1 diabetes (30), exactly the period of the nocturnal nadir in our study (i.e. 3:45 AM, Figure 2). This timing is also similar to that reported by Matyka et al (also 3:45 AM) in 16 sedentary children with type 1 diabetes (11,31), and Radan et al, who reported 70% of the total observed hypoglycemic episodes occurred between 2:00 and 4:00 AM (32). In addition, studies published by DirecNet also reveal a high incidence of nocturnal hypoglycemia in children after just 60 minutes of intermittent treadmill exercise (33). Taken together, it appears that some physiological factor(s) predispose active persons with type 1 diabetes to hypoglycemia, especially during sleep. These may include the effects of high-volume vigorous exercise on insulin sensitivity (6,7), counterregulatory failure (29), blunted sympathetic activity that occurs during sleep (10,12-14,24) or inadequate glycogen restoration post-exercise.

Many patients with type 1 diabetes believe that they are at low risk of developing nocturnal hypoglycemia following a bout of exercise if their bedtime blood glucose is elevated. However, unlike a recent study in which a blood glucose of ≥7.2 mmol/L was protective of nocturnal hypoglycemia in sedentary individuals (15), we documented 10 cases of nocturnal hypoglycemia when bedtime glucose levels were >7.0 mmol/L (i.e. an incidence rate of approximately 50%). We also found that even subjects as high as 12 mmol/L at bedtime were still susceptible to nocturnal hypoglycemia (Figure 3). In contrast, Lerman et al found that a low bedtime blood glucose concentration predicted nighttime hypoglycemia (also occurring between 2:00 and 3:00 AM) in sedentary persons, and that bedtime hyperglycemia was protective against nocturnal hypoglycemia (34). Regardless of pre-bedtime glucose, previously active patients should be particularly aware that hypoglycemia is likely to occur between 2:00 and 4:00 AM on the evening following high-volume or vigorous exercise, regardless of what time the activity occurs. As such, we propose that a considerable reduction in bedtime basal insulin delivery and/or a bedtime snack is warranted to limit exercise-associated nocturnal hypoglycemia.

Limitations

This annual diabetes sports camp provided an appropriate environment to survey the rudimentary effects of exercise in a natural setting. However, this observational study clearly has significant limitations. For example, many variables that are known to influence glucose stability were not controlled or documented (i.e. relative exercise intensity, sleeping patterns, standardized meals, motivation to exercise). Moreover, reductions in insulin and/or increases in caloric intake to help prevent exercise-associated hypoglycemia were not standardized. We do recognize that these variables, among others, may be accountable for the high inter-subject glycemic variability that was observed (Figure 2). Also, the 2 kinds of monitors used may confound findings: 3 subjects were provided with "real-time" glucose values that sounded alarms at both low and high glucose readings, while 9 were blinded to the data and therefore relied solely on their glucometer measures. Surprisingly, those who used the "real-time" monitors experienced on average 11 hypoglycemic episodes, compared to 5 episodes in those who did not have the benefit of the hypoglycemic alarms.

Although useful, CGMS are known to have some limitations in their accuracy of estimating blood glucose concentrations, particularly during times of rapidly changing glucose levels (35). In addition, CGMS may overestimate hypoglycemia. In one study using technology similar to that used here, among all hypoglycemic episodes (<3.9 mmol/L), only 54.5% fell in Clark A zone (36). As pointed out by the Food and Drug Administration (37), these devices do not provide exact data on blood glucose levels but may be used to detect changes in glycemia. This limitation is in part because CGMS provide a signal that is proportional in intensity to the variations in glucose concentration in the interstitial fluid of the subcutaneous tissue and not directly within the plasma (38). CGMS have also been shown be less accurate in lean individuals (36,39-41). In spite of these and other limitations, however, CGMS provide valuable information. First, as mentioned above, CGMS show directional changes in glycemia. Second, CGMS permits the detection of asymptomatic hypoglycemic episodes during the night, even in subjects with normal awareness of such episodes (35). Our previous data suggests that CGMS are reasonably accurate during exercise regardless of glycemic range, although they do demonstrate a 10- to 20-minute delay (16). Finally, CGMS are showing great potential in the development of "closed-loop" or feedback systems, which use information from the CGMS sensor to change the rate of insulin infusion via the pump (40,42).

Unfortunately, because of the nature of the camp, we did not have a sedentary day or a group of persons with diabetes who were unaccustomed to exercise. As such, it is unclear if the high rate of hypoglycemia observed in these participants was specifically caused by the exercise per se or if there is simply a high incidence of nocturnal hypoglycemia in insulin-treated active subjects with type 1 diabetes, regardless of the activities performed during the day. In fact, even non-athletes appear to have a high risk of nocturnal hypoglycemia as measured by CGMS. For example, in normally active children studied over 3 days, nocturnal hypoglycemic episodes (≤2.2 mmol/L) were evident in 30% of children and in ~70% of children if the threshold for hypoglycemia was set at 3.3 mmol/L (43). Similarly, an analysis of recordings made during 167 nights in 47 children noted the occurrence of hypoglycemic episodes (≤2.2 mmol/L) in 27% of the children, and in 35% if hypoglycemia was defined as blood glucose levels ≤2.8 mmol/L (44). Thus, more research is needed to determine if athletes with diabetes are more (or less) at risk of nocturnal hypoglycemia on evenings following activity compared with sedentary nights and also compared to non-athletes.

In summary, this field study illustrates that hypoglycemia is extremely common during high-volume training in regularly active individuals with type 1 diabetes, often occurring during sleep regardless of pre-bedtime values, and that CGMS may be an effective, if not the sole available, tool for monitoring glycemia during these times. Larger-scale field studies using CGMS are desperately needed to assist in producing effective algorithms for bedtime insulin and carbohydrate supplementation, in hopes of preventing exercise-induced dysglycemia during both sports training and sleep.

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AUTHOR DISCLOSURES

No dualities of interest declared.

AUTHOR CONTRIBUTIONS

All three authors (KEI, MC and MCR) contributed substantially to conception and design, acquisition of data, and analysis and interpretation of data; drafted the article and approved the final version to be published.

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