Paradoxical Rise in Hypoglycemia Symptoms With Development of Hyperglycemia During High-Intensity Interval Training in Type 1 Diabetes

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OBJECTIVE

To assess the reliability of self-perception of glycemia during high-intensity interval training (HIIT) in subjects with type 1 diabetes (T1D).

RESEARCH DESIGN AND METHODS

This randomized crossover study included subjects who completed four fasted HIIT sessions. Subjects answered the Edinburgh Hypoglycemia Scale, estimated their blood glucose (BG), and had plasma glucose (PG) collected throughout exercise and recovery.

RESULTS

As PG increased throughout exercise, hypoglycemia scores increased across each category: autonomic (3.1–4.4, $P < 0.05$), neuroglycopenic (1.5–2.4, $P < 0.05$), and nonspecific (1.3–1.9, $P < 0.05$). Subjects' estimated BG showed a negative bias that widened as exercise progressed and peaked at -1.6 ± 3.3 mmol/L ($P < 0.001$) postinsulin correction.

CONCLUSIONS

During HIIT, despite progressing hyperglycemia, subjects experience increased hypoglycemia symptoms and tend to underestimate their BG level.

Many individuals with type 1 diabetes (T1D) feel hesitant engaging in physical activity due to fear of hypoglycemia (1). High-intensity interval training (HIIT) can maintain hypoglycemia or promote hyperglycemia (2), an effect closely associated with catecholamine release (3).

Awareness of blood glucose (BG) during exercise is challenging since self-monitored BG typically requires an unwanted activity pause and continuous glucose monitoring devices have shown increased lag time during exercise and early recovery (4). Active exercisers with T1D may be predominantly relying on their own perceptions of their glycemia, an ability that has not been widely studied. In athletes with T1D, estimated BG was correlated (R^2 = 0.69) with self-monitored BG during moderate-intensity exercise, but not during circuit-based exercise (R^2 = 0.11) (5), suggesting that different forms of exercise might alter the perception of glycemia. This study evaluated the reliability of the self-perception of hypoglycemia among people with T1D participating in HIIT.

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RESEARCH DESIGN AND METHODS

This study was part of a larger clinical trial evaluating optimal insulin correction for hyperglycemia after HIIT (6). Seventeen fit adults with T1D completed four identical, supervised weekly fasted HIIT sessions comprising three 5-min bouts. The first and last bouts included 30-s intervals of cycling progressing to 130% of peak aerobic power. The middle bout included a series of marching with dumbbells, jumping jacks, burpees, push-ups, forearm plank, and medicine ball sweeps.

During the exercise, at 5, 15, and 25 min, subjects were asked to estimate their BG level, the Edinburgh Hypoglycemia Scale (7) was verbally administered, and plasma glucose (PG) was collected (YSI 2300 STAT Plus; YSI, Yellow Springs, OH). At 15 min post-HIIT, if PG was >8.0 mmol/L, an insulin dose was administered based on the patient's own sensitivity factor, using a standard target of 6.0 mmol/L and applying a multiplier of 0%, 50%, 100%, or 150%. The Edinburgh Hypoglycemia Scale and PG collection continued every 30–180 min postinsulin correction. The protocol was approved by an independent ethics committee, and all participants provided written informed consent.

Data Analysis

Symptom scores, and estimated and measured BG, were analyzed with repeated measures mixed models. Subject BG estimation accuracy was assessed by comparing mean absolute relative difference, bias, and the %15/15 to measured YSI PG (8). Clinically relevant accuracy was determined using the Surveillance Error Grid (SEG, www.diabetestechnology.org/seg). Analyses were conducted with SAS 9.4 (SAS, Cary, NC).

RESULTS

The baseline characteristics of the 17 subjects have been previously described (6). On average, subjects were (mean ± SD) 34.9 ± 10.1 years of age, had a diabetes duration of 17.0 ± 11.0 years, and were generally well controlled (A1C 7.2 ± 0.9%). Across all HIIT sessions, PG increased from 8.8 ± 1.0 to 12.0 ± 2.3 mmol/L after the 25-min HIIT session (Fig. 1), peaking at 12.7 ± 2.4 mmol/L after the 15-min session. Insulin was then administered depending on treatment assignment, and 180 min later, PG increased further in the 0% arm and decreased in the 50%, 100%, and 150% intervention arms.

Despite the rise in PG during exercise, the Edinburgh Hypoglycemia Scale symptom scores increased, rather than decreased (Fig. 1*A*). Each score peaked at the end of exercise (total symptoms 3.0 ± 0.2, autonomic 4.4 ± 0.3, neuroglycopenic 2.4 ± 0.2, and nonspecific 1.9 ± 0.1), and each was significantly higher than the 5- and 15-min scores.

During exercise, subjects consistently underestimated their BG level, with a negative bias of −0.9 ± 3.2 mmol/L (P = 0.02) by end of exercise and by −1.6 ± 3.3 mmol/L ($P < 0.001$) after insulin correction. The 0% correction arm, which achieved the highest peak BG, showed the greatest negative bias (−2.9 ± 0.5 mmol/L vs. −1.9 ± 0.5 mmol/L in the 50% arm, P = 0.02; −1.1 ± 0.5 mmol/L in the 100% arm, $P < 0.001$; and −0.6 ± 0.4 mmol/L in the 150% arm, $P < 0.001$).

The mean absolute relative difference of estimated BG increased during exercise and recovery and peaked after insulin correction (27.3% vs. 19.9% at end of exercise, P = 0.01; and 16.0% in early exercise, $P < 0.001$). The %15/15 measure was similarly lowest postinsulin correction (33.8%) compared with end of exercise (50.0%) and early exercise (56.3%) ($P < 0.01$).

The SEG analysis showed that "no-risk" accuracy deteriorated throughout recovery, such that after insulin correction, only 52.6% of paired values were in the no-risk zone compared with 65.6% at the end of exercise and 71.9% during early exercise ($P < 0.001$) (Fig. 1*B* and *C*).

CONCLUSIONS

During and after hyperglycemia-inducing HIIT sessions, we observed a marked rise in glycemia and a paradoxical increase in false hypoglycemia symptoms with impaired self-perception of glycemia. This effect intensified throughout exercise, with each category of symptom scores (autonomic, neuroglycopenic, nonspecific, and total) exhibiting highest values at the end of exercise.

This unique divergence in PG and hypoglycemia symptom scores during HIIT may directly relate to a key physiologic response to hypoglycemia, adrenergic activation, and resulting autonomic symptoms. HIIT activity is known to produce exaggerated responses in plasma catecholamines, adrenaline, and noradrenaline (2), and the subsequent adrenergic response may produce symptoms that mimic hypoglycemia. The similarity in the symptoms may be altering the exercisers' judgement, incorrectly identifying themselves as experiencing hypoglycemia. The association is further seen in the finding that hypoglycemia symptom scores return to normal after exercise, when the adrenergic drive is halted. Exercisers with T1D may also be somewhat primed to believe they are developing hypoglycemia, given the strong association between exercise and the fear of hypoglycemia (1).

In addition to the false perception of hypoglycemia during exercise, subjects similarly believed that their BG was significantly lower than their measured PG. This negative bias widened as exercise continued and then widened further postinsulin correction. The tendency to underestimate BG during physical activity (i.e., cycling) was first implied in adolescents in 2002 (9) and recently suggested to be more prominent in circuit-based exercise as compared with continuous treadmill walking/running among fit adults (5). Our findings now quantify the negative bias, suggest a continuing duration beyond exercise itself, and finally define an increased risk of dosing error based on the SEG findings of fewer paired values in the no-risk zone (Fig. 1*B* and *C*). Other potential mechanisms include the rise in lactate during HIIT, but hyperlactatemia normally impairs perception of hypoglycemia (10), whereas we identified increased symptom perception. HIIT generally increases prefrontal cortex oxygenation and improves cognitive performance and is therefore an unlikely contributor itself (11). However, cortical glucose uptake is known to be reduced with intensive exercise (12), suggesting that depletion of brain glycogen levels may be a possible alternative explanation (13).

A study strength is that data were collected as a predefined secondary end point from a controlled trial, using a crossover design to limit variability with participants blinded to their actual PG.

Limitations include the fact that hypoglycemia symptom scores were not collected pre-exercise so calculation of

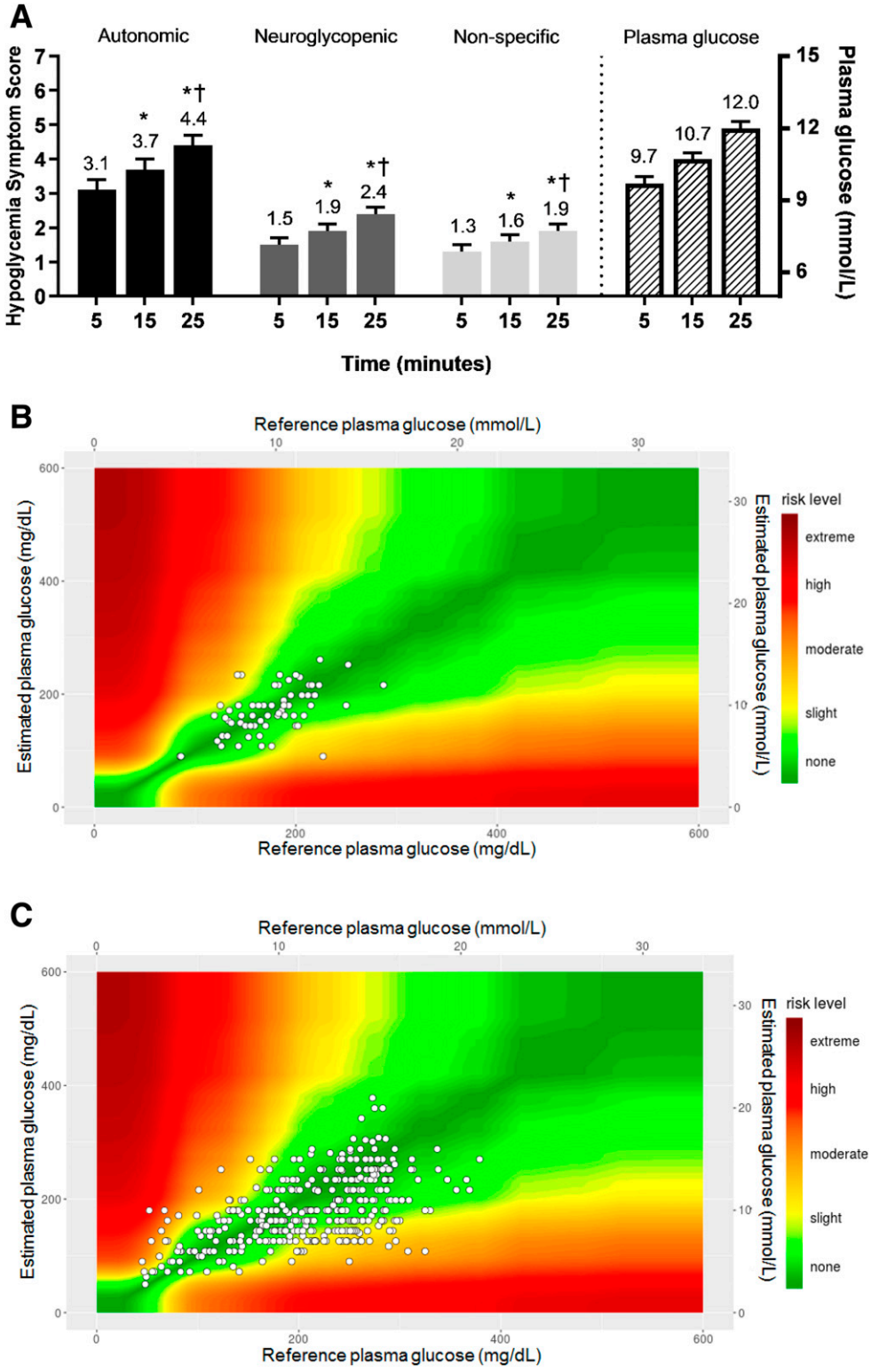

Figure 1—*A*: The hypoglycemia symptom scores during exercise and the simultaneous rise in PG. *B*: The SEG analysis for the early exercise period (5 min). *C*: The SEG analysis for the postinsulin correction period. *$P < 0.05$, significantly different compared with 5 min. †$P < 0.05$, significantly different compared with 15 min.

absolute change was not possible. These findings may be limited to HIIT training and may not generalize to other forms of exercise. BG accuracy is reported using statistical tools that are more commonly used to assess the accuracy of glucose measuring devices.

During HIIT exercise of intensity sufficient to produce hyperglycemia, subjects with T1D experience increases in symptoms of hypoglycemia and a parallel tendency to underestimate their BG, which endures postexercise. The heightened adrenergic drive of a HIIT session presents the most likely explanation, but further mechanistic

research is needed. BG awareness training might be similarly explored in future studies (14). Although HIIT is often endorsed as a safer option for patients with T1D because of reduced hypoglycemia risk (2), the paradoxical increased perception of hypoglycemia may not allay the fear of hypoglycemia and may even lead to overtreatment with carbohydrate, which may further deteriorate glucose levels.

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References

1. Brazeau A-S, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108–2109

2. Peake JM, Tan SJ, Markworth JF, Broadbent JA, Skinner TL, Cameron-Smith D. Metabolic and hormonal responses to isoenergetic high-intensity interval exercise and continuous moderate-intensity exercise [published correction appears in Am J Physiol Endocrinol Metab 2014;307:E954]. Am J Physiol Endocrinol Metab 2014;307:E539–E552

3. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. Diabetes 2002;51(Suppl. 1):S271–S283

4. Li A, Riddell MC, Potashner D, Brown RE, Aronson R. Time lag and accuracy of continuous glucose monitoring during high intensity interval training in adults with type 1 diabetes. Diabetes Technol Ther 2019;21:286–294

5. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC. The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Technol Ther 2017;19:370–378

6. Aronson R, Brown RE, Li A, Riddell MC. Optimal insulin correction factor in post-high-intensity exercise hyperglycemia in adults with type 1 diabetes: the FIT study. Diabetes Care 2019;42:10–16

7. Deary IJ, Hepburn DA, MacLeod KM, Frier BM. Partitioning the symptoms of hypoglycaemia using multi-sample confirmatory factor analysis. Diabetologia 1993;36:771–777

8. International Organization for Standardization. ISO 15197:2013: In vitro diagnostic test systems—requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus. Geneva, Switzerland, International Organization for Standardization, 2013

9. Riddell M, Bar-Or O. Children and adolescents. In *Handbook of Exercise and Diabetes*. Ruderman N, Devlin J, Schneider S, Eds. Alexandia, VA, American Diabetes Association, 2002, p. 547–566

10. Rooijackers HM, Wiegers EC, van der Graaf M, et al. A single bout of high-intensity interval training reduces awareness of subsequent hypoglycemia in patients with type 1 diabetes. Diabetes 2017;66:1990–1998

11. Bediz CS, Oniz A, Guducu C, et al. Acute supramaximal exercise increases the brain oxygenation in relation to cognitive workload. Front Hum Neurosci 2016;10:174

12. Kemppainen J, Aalto S, Fujimoto T, et al. High intensity exercise decreases global brain glucose uptake in humans. J Physiol 2005;568:323–332

13. Matsui T, Soya S, Okamoto M, Ichitani Y, Kawanaka K, Soya H. Brain glycogen decreases during prolonged exercise. J Physiol 2011;589:3383–3393

14. Cox D, Gonder-Frederick L, Polonsky W, Schlundt D, Julian D, Clarke W. A multicenter evaluation of blood glucose awareness training-II. Diabetes Care 1995;18:523–528