Journal of Diabetes Research & Clinical Metabolism
ISSN 2050-0866

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Herbert Open Access Journals

Special Section | Endocrinology Mechanisms | Short report Open Access

Effect of intermittent high intensity exercise on counter-regulatory hormones in type 1 diabetes glargine/glulisine users

Marie-Christine Dubé[1,2], Carole Lavoie[3] and S. John Weisnagel[1,2*]

*Correspondence: john.weisnagel@crchul.ulaval.ca

[1]Diabetes Research Unit, Université Laval Medical Center, Québec City, QC, Canada.
[2]Molecular Endocrinology and Genomics, Université Laval Medical Center, Québec City, QC, Canada.
[3]Department of Physical Activity Sciences, Université du Québec à Trois-Rivières, QC, Canada.

Abstract

Background: Brief intense sprint intervals during moderate intensity exercise prevent hypoglycemia in type 1 diabetic participants. We tested the hypothesis that this exercise modality would increase counter-regulatory hormones and limit BG decrease in glargine/glulisine insulin analogs users.

Findings: Participants performed, in a repeated measures, random-ordered design, 60 minutes of moderate intensity exercise at 50% VO_{2peak} in the following conditions: ingestion of 0 g of glucose pre-exercise, 30 g of glucose pre-exercise, or 0 g of glucose pre-exercise, but interspersed with brief high intensity intervals every 2 minutes. Intermittent brief high intensity exercise significantly increased levels of norepinephrine at mid-exercise (from 3.2±1.0 to 7.8±3.2 nmol/l) and cortisol from mid-exercise (from 330±159 to 606±285 nmol/l) to even after exercise (692±334 nmol/l) compared to other conditions.

Conclusions: Our results suggest that an intermittent high intensity exercise raised counter-regulatory hormones which may contribute to the prevention of exercise-induced hypoglycaemia in participants with type 1 diabetes using glargine/glulisine. Such exercise regimen can be an alternative to prevent exercise-induced hypoglycemia in glargine/glulisine users as seen in other insulin combinations.

Keywords: Hypoglycemia, glulisine, glargine, counter-regulatory hormones, intermittent high intensity exercise, strategies, type 1 diabetes

Introduction

Glulisine, a rapid acting insulin analog, may be useful in the treatment of allergy to rapid acting insulin and analogs [1] and can be an alternative to other analogs. It is highly probable that its effect on blood glucose (BG) and catecholamine would be similar to other insulin combinations but it needs to be documented when combined with glargine under various exercise conditions.

It has been shown that intermittent high-intensity exercise increased catecholamine and attenuated the decline in BG levels in type 1 diabetes mellitus (T1DM) under various insulin regimen [2] and reduced the risk of exercise-induced hypoglycemiain subjects using glargine/glulisine [3]. With the growing popularity of sports with this variable intensity profile such as many recreational team sports and some interval training, this exercise modality may be an interesting strategy to endorse for reducing the risk of exercise-induced hypoglycemia. The effect of different modalities of exercise intensity (moderate *vs* high) on counter-regulatory hormones needs to be documented in order to better prevent hypoglycaemia in physically active individuals with T1DM, a problem with major clinical impact. Therefore, this study presents the effect of moderate *vs* high intermittent intensity exercise i.e., 10-seconds sprints every 2 minutes during 60-min exercise on counter-regulatory hormones in glargine/glulisine users.

Methods

Eleven moderately active participants with T1DM (five men and six women) participated in this study. They were free of diabetic complications and had no contra-indication for exercise. All participants were on the basal-bolus regimen using an insulin analogue glargine at bedtime and glulisine before every meal. This study was approved by the Ethic Committee of Centre Hospitalier Universitaire de Québec and all patients gave their informed written consent.

Participants were instructed not to engage in any preceding unusual or intense exercise on the days of exercise testing. Exercise tolerance was evaluated for each subject by using an incremental protocol of 15 $W \cdot min^{-1}$ (women) and 30 $W \cdot min^{-1}$ (men) after a warm-up period of 2 min performed on an electromagnetically braked cycle ergometer (Corival, Lode, The Netherlands) at a pedaling rate of 50 to 70 rpm. Participants

doi: 10.7243/2050-0866-3-8

were given strong verbal encouragement to exercise to the highest tolerated symptoms of fatigue or dyspnea. Exercise was terminated at this point and/or when participants were unable to maintain speed or Q40 revolutions per minute on the ergo-cycle. Expired air was continuously recorded on a breath-by-breath basis for the determination of $\dot{V}O_2$, carbondioxide production ($\dot{V}CO_2$), $\dot{V}E$, and the RER ($\dot{V}CO_2/\dot{V}O_2$) (CardiO2 CPX Ultima; Medical Graphics Co.). The HR was obtained from electrocardiographic monitoring. Blood pressure was measured every 2 min by using an automated sphygmomanometer with a headphone circuit option (Model 412; Quinton Instrument, Bothell, WA). $\dot{V}O_{2peak}$ was defined as the mean $\dot{V}O_2$ recorded in the last15 s of the incremental exercise protocol concurrent withan RER of 1.15 or greater. Each participant performed 60 min of aerobic exercise on a cycle ergometer (Organic V3; Bodyguard Fitness, QC, Canada) at 50% of their previously determined $\dot{V}O_{2peak}$ on two occasions and on one occasion with interspersed 10-ss prints at maximal effort every 2 min of the exercise period.

The exercise conditions varied as follows: participants ingested a placebo snack of 0g of carbohydrate (CHO) pre-exercise i.e., sucaryl in 10% water solution (0G+MOD), 30 g of CHO pre-exercise (30G+MOD), or 0 g of CHO pre-exercise, but performed brief high intensity intervals interspersed every 2 min (0G+MOD/INT) during the exercise trial. The CHO beverage consisted of 8 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$of dextrose in 10% water solution given 15 min before the beginning of exercise period. The exercise was scheduled 120 min after lunch and was followed by a 30 min-recovery period on site. To proceed to the experiments, no hypoglycemia was allowed 24 hours before testing. Moreover, subjects were requested to record their BG 24 hours following the exercise sessions and to report any hypoglycemia. All exercise tests were scheduled at least one week apart.

During the experimental protocols, a catheter (Cathlon Clear, Johnson & Johnson, New Brunswick, NJ) was placedin an antecubital vein for sampling and kept patent by salinedrip. Blood samples were collected from time-15 min at 5- to 30-min intervals for 2 h and then every 5 min duringand after the exercise period to measure BG concentrations by using a Freestyle glucometer (Abbott, California). Blood samples were centrifuged for plasma and stored at -20˚C for later analyses of glucose using a hexokinase method (13). Plasma catecholamines were measured by a method adapted from Raggi et al., [4]. Cortisol concentrations were measured by ECLIA (Roche Diagnostic GmbH, Mannheim, Germany). A glucose clamp procedure with a variable infusion of a 20% dextrose solution, adapted from DeFronzo et al., [5] was followed if needed, to avoid hypoglycemia. If at any time during the testing conditions glucose levels fell below 4 mmol/l, the dextrose infusion was initiated at a rate based on the drop in BG in order to maintain BG between 4 and 5 mmol/l. Intensity of exercise was estimated by the Borg scale of perceived exertion (6 to 20 scale) every 15 minutes. Area under the curve was calculated for BG≥8 mmol/l from the beginning of exercise until the end of the experiment. Values are expressed as means±SE. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences with overall $P<0.016$ considered as significant using JMP 7 (SAS Institute, Cary, NC).

Results

Participants' characteristics aredescribed in **Table 1**. They were considered as low to moderately active. At arrival, BG was similar between conditions and became higher 5 min after starting the exercise until 30 min post-exercise in the 30G+MOD condition compared to 0G+MOD and 0G+MOD/INT conditions, (all $P<0.02$), **Figure 1**. The first half of exercise induced a similar BG change between conditions of -1.7±2.0, -1.4±1.2 and -1.1±1.3 mmol/l, for the 0G+MOD, 0G+MOD/

Table 1. Characteristics of the participants.

	All (n=11)	Men (n=5)	Women (n=6)	*P* value
Variables	--	--	--	--
Age (yrs)	26.5±6.6	27.6±8.0	25.5±5.8	NS
HbA_{1c} (%)	7.3±0.4	7.2±0.3	7.4±0.5	NS
$\dot{V}O_{2peak}$ ($ml\ O_2{\cdot}kg^{-1}{\cdot}min^{-1}$)	33.4±6.5	39.0±3.0	28.7±4.4	0.002
Weight (kg)	74.1±6.7	76.4±5.1	72.3±7.7	NS
BMI (kg/m^2)	25.8±2.7	25.0±3.1	26.6±2.3	NS
Diabetes duration (yrs)	12.2±5.1	12.4±5.8	12.0±4.9	NS
Total daily dose (U)	58.7±22.7	52.6±22.0	63.8±25.3	NS

BMI: body mass index

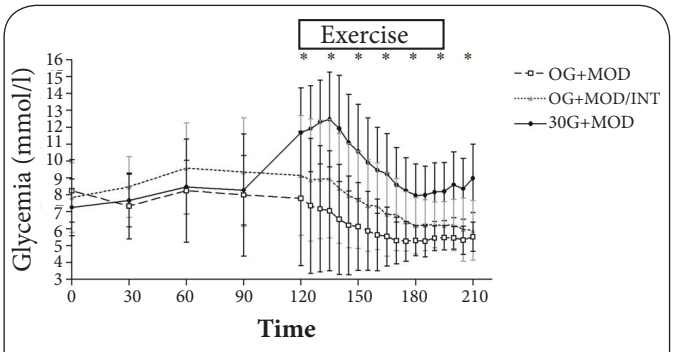

Figure 1. Glycemic excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences. Overall P values <0.016 are considered significant for time 125 to 210 minutes.

doi: 10.7243/2050-0866-3-8

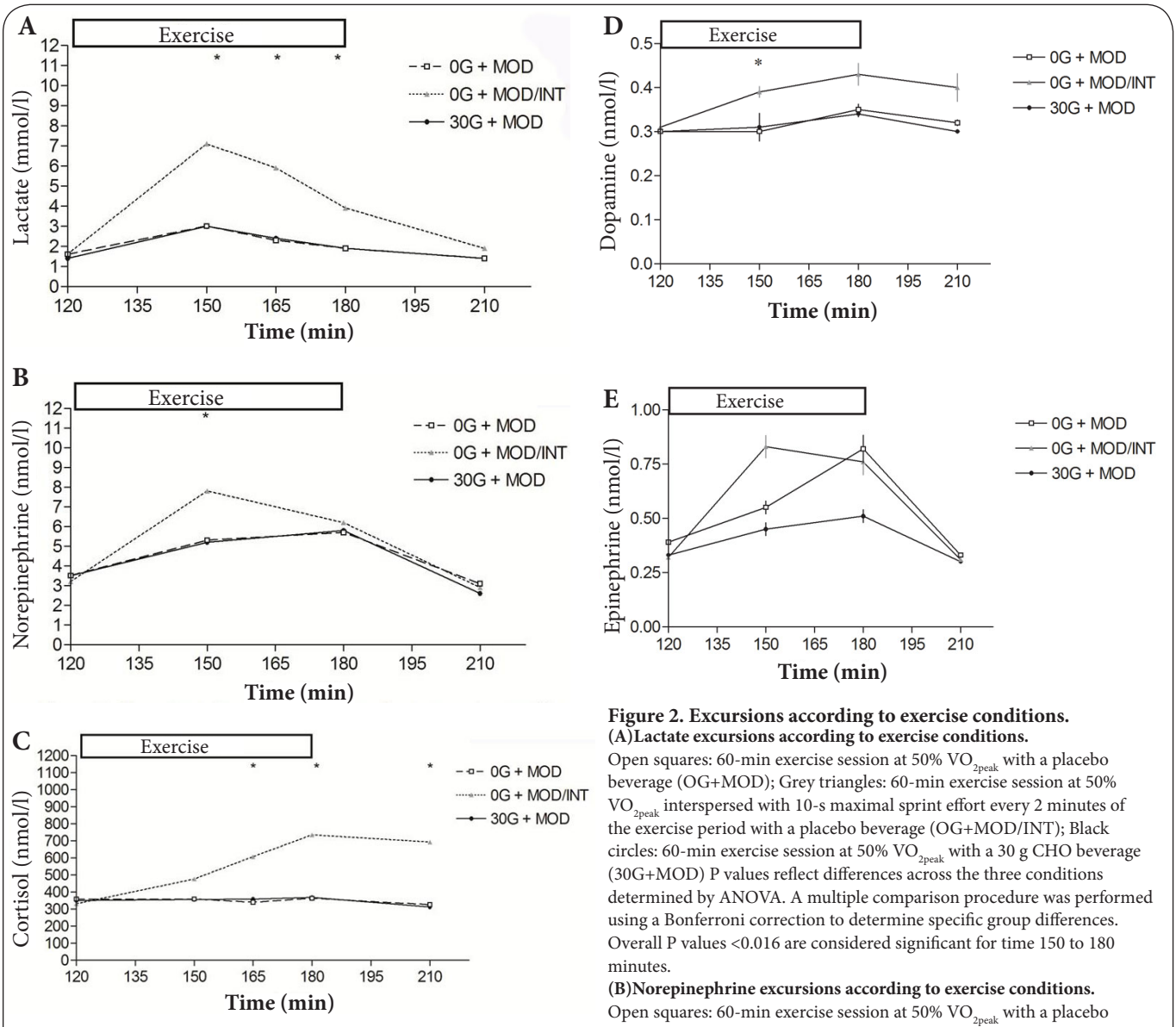

Figure 2. Excursions according to exercise conditions.
(A)Lactate excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences. Overall P values <0.016 are considered significant for time 150 to 180 minutes.

(B)Norepinephrine excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences. Overall P values <0.016 are considered significant at time 150 min.

(C)Cortisol excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences. Overall P values <0.016 are considered significant for time 165 to 210 minutes.

(D)Dopamine excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences. Overall P values <0.016 are considered significant for time 150 minutes.

(E)Epinephrine excursions according to exercise conditions.
Open squares: 60-min exercise session at 50% VO_{2peak} with a placebo beverage (OG+MOD); Grey triangles: 60-min exercise session at 50% VO_{2peak} interspersed with 10-s maximal sprint effort every 2 minutes of the exercise period with a placebo beverage (OG+MOD/INT); Black circles: 60-min exercise session at 50% VO_{2peak} with a 30 g CHO beverage (30G+MOD) P values reflect differences across the three conditions determined by ANOVA. A multiple comparison procedure was performed using a Bonferroni correction to determine specific group differences.

doi: 10.7243/2050-0866-3-8

INT and 30G+MOD, respectively, *P*=0.70. The second half of exercise induced a mean BG change of -0.8±1.8, -1.5±1.6 and -2.6±1.4 mmol/l, for 0G+MOD, 0G+MOD/INT and 30G+MOD, respectively, *P*=0.04. This is mainly due to the fact that a higher number of subjects (7 of 11) in the 0G+MOD group required dextrose infusion to prevent hypoglycemia (*P*=0.05 for group differences). Despite the infusion of dextrose in those subjects, four of them presented values slightly below 4 mmol/l, although asymptomatic. Catecholamines measurements were compared between these 4 subjects and the others and no difference was shown. The area under the curve for BG values>8 mmol/l was higher in the 30G+MOD condition compared to 0G+MOD and 0G+MOD/INT conditions, (193±35 *vs* 46±28 *vs* 102±45 mmol/l/min, *P*<0.05), respectively. The 0G+MOD/INT condition showed higher values of lactate and norepinephrine at mid-exercise compared to the other exercise conditions, *P*<0.05, **Figures 2A** and **2B**, respectively. The cortisol levels were higher in the 0G+MOD/INT condition after 45 minutes of exercise until 30 minutes post-exercise, all *P*<0.005, **Figure 2C**. The dopamine levels at mid-exercise were higher in the 0G+MOD/INT condition compared to 0G+MOD and 30G+MOD conditions, *P*<0.01, **Figure 2D**. The epinephrine levels tended to be higher in the 0G+MOD/INT condition compared to the other exercise conditions, *P*=0.07, **Figure 2E**. Mean scores of perceived exertion were similar except at 15 min before the end of exercise (10.9±2.0, 13.8±2.4 and 11.9±2.5) for the 0G+MOD, 0G+MOD/INT and 30G+MOD conditions, respectively, *P*<0.05. The rate of late-onset exercise-induced hypoglycemia was recorded and there was no difference (0.27±0.14, 0.33±0.17 and 0.20±0.13 events) for the 0G+MOD, 0G+MOD/INT and 30G+MOD conditions, respectively.

Discussion

Intermittent high intensity exercise reduced the decline in BG during exercise in participants with T1DM [2,6]. Repeated intense sprints interrupting longer periods of moderate-intensity exercise is typical of interval training which has gained in popularity for its favorable impact on cardiovascular function [7] and may simulate the type of exercise performed in many sports.

Our results show that intermittent high intensity 60 min-exercise sessions raised counter-regulatory hormones during and following exercise in glargine/glulisine T1DM users. Glulisine may be useful in the treatment of allergy to rapid acting insulin and analogs [1], and can be an alternative to other rapid-acting analogs. Therefore, in this regimen, we specifically showed that norepinephrine, dopamine and cortisol levels were significantly higher while epinephrine tended to be higher in the 0G+MOD/INT condition. Exercise-induced hypoglycemia was found in 7 subjects in the 0G+MOD condition compared to only 1 in the 0G+MOD/INT condition, requiring the start of a dextrose infusion. Despite this infusion, four subjects still presented bordeline glycemic values with BG between 3.6 and 4 mmol/l. However, catecholamine were compared between the «bordeline-hypoglycemic subjects» and the others and no differences were seen in any of the measures suggesting that higher catecholamines values in the 0G+MOD/INT condition were attributable to exercise. These increases were more pronounced around mid-exercise and after, at a period when the Borg scale was significantly elevated as well. Lactate levels were also raised, especially from mid- to end of exercise. Elevated lactate levels contribute to the stabilisation of BG by providing gluconeogenic precursors for hepatic glucose production [8], notably at the onset of recovery from moderate-intensity exercise interspersed either with several short sprints [9] or followed by a 10-s sprint [10]. Iscoe et al., [11] observed similar differences in counter-regulatory hormones between continuous moderate-intensity exercise and continuous moderate-intensity + intermittent high-intensity exercise, which was explained by a modest increase in sympathetic counter-regulatory response resulting from the performance of a heavier resistance-type exercise rather than a faster cycling cadence [12].

The reduced risk of early-onset hypoglycemia applying with a high intensity intermittent exercise was not accompanied by a higher risk of late-onset exercise-induced hypoglycemia as indicated by measured BG for 24 hours.

Although beneficial to prevent hypoglycemia, the 0G+MOD/INT condition was harder to perform compared to moderate intensity exercise conditions as reflected by the Borg scale scores. Therefore, intermittent high intensity exercise may constitute a strategic choice to prevent exercise-induced hypoglycemia but requires a certain level of fitness and tolerance to exercise exertion. However, it remains an interesting option in individuals who have not modified their pre-exercise insulin doses or prefer to avoid extra CHO. In addition, differential responses of BG levels and counter regulatory hormones to varying exercise conditions reflects the need to precisely take into account the type of exercise performed by the individual with T1DM in the management of the disease and preventive of exercise-induced hypoglycemia.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	MD	CL	SW
Research concept and design	✓	✓	✓
Collection and/or assembly of data	✓	--	--
Data analysis and interpretation	✓	--	✓
Writing the article	✓	--	--
Critical revision of the article	✓	✓	✓
Final approval of article	✓	✓	✓
Statistical analysis	✓	--	--

Acknowledgment and funding

We would like to thank all participants and the personnel of the Diabetes Research Unit of the CHUL. This study

doi: 10.7243/2050-0866-3-8

was supported by Sanofi aventis Canada inc.

Publication history
EIC: Geoffrey Burnstock, University College London, UK.
Received: 17-Apr-2014 Final Revised: 20-May-2014
Accepted: 09-Jun-2014 Published: 25-Jun-2014

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Citation:
Dubé M-C, Lavoie C and Weisnagel SJ. **Effect of intermittent high intensity exercise on counter-regulatory hormones in type 1 diabetes glargine/glulisine users**. *J Diab Res Clin Met*. 2014; **3**:8.
http://dx.doi.org/10.7243/2050-0866-3-8