Trends of glucose, lactate and ketones during anaerobic and aerobic exercise in subjects with type 1 diabetes : the ACTION-1 study

Trends of glucose, lactate and ketones during anaerobic and aerobic exercise in subjects with type 1 diabetes: The ACTION-1 Study

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Abstract

Background: Exercise is part of type 1 diabetes (T1D) management due to its cardiovascular and metabolic benefits. However, despite using continuous glucose monitoring, many patients are reluctant to exercise because of fear for hypoglycaemia.

Aims: We assessed trends in glucose, lactate and ketones during anaerobic and aerobic exercise in people with T1D and compared incremental area under the curve (AUC) between both exercises.

Methods: Twenty-one men with T1D (median [IQR]: age 29 years [28-38], BMI 24.4 kg/m^2 [22.3-24.9], HbA1c 7.2% [6.7-7.8]), completed a cardiopulmonary exercise test (CPET) and a 60-minute aerobic exercise (AEX) at 60% VO_2peak on an ergometer bicycle within a 6-week period. Subjects consumed a standardised breakfast (6 kcal/kg, 20.2g CHO/100ml) before exercise without pre-meal insulin and basal insulin for pump users.

Results: During CPET, glucose levels increased, peaking at 331mg/dL [257-392] 1-3h after exercise and reaching a nadir 6h after exercise at 176mg/dL [118-217]. Lactate levels peaked at 6.0mmol/L [5.0-6.6] (max 13.5mmol/L). During AEX, glucose levels also increased, peaking at 305mg/dL [245-336] 80 min after exercise and reaching a nadir 6h after exercise at 211mg/dL [116-222]. Lactate levels rose quickly to a median of 4.3mmol/L [2.7-6.7] after 10 min. Ketone levels were low during both tests (median ≤0.2mmol/L). Lactate, but not glucose or ketone AUC, was significantly higher in CPET compared to AEX (p=0.04).

Conclusions:

Omitting pre-meal insulin and also basal insulin in pump users, did prevent hypoglycaemia but induced hyperglycaemia due to a too high carbohydrate ingestion. No ketosis was recorded during or after the exercises.

Abbreviations: AEX, Aerobic Exercise Test; AUC, Area Under the Curve; CPET, (symptom limited maximal) CardioPulmonary Exercise Test; CSII, Continuous Subcutaneous Insulin Infusion; HbA1c, Haemoglobin A1c; HIE, High Intensity Exercise; IPAQ-SF, International Physical Activity Questionnaire Short Form; IQR, InterQuartile Range; LT, Lactate Threshold; MIE, Moderate Intensity Exercise; MDI, Multiple Daily Injections; PA, physical activity; RE, Resistance Exercise; RPE, rate of perceived exertion; (RT-)CGM, (Real-Time) Continuous Glucose Monitoring; T1D, Type 1 Diabetes Mellitus; TAR, Time Above Range; TBR, Time Below Range; TIR, Time In Range; UZA, University Hospital of Antwerp.

Introduction

Type 1 diabetes (T1D) is characterized by a complete lack of insulin production. In addition to exogenous insulin administration and intensive glucose monitoring, regular exercise represents one of the cornerstones in the management of T1D. Regular physical activity improves insulin sensitivity with improved glucose uptake, controls body weight and lipid profiles, boosts self-confidence, improves the psychological status, protects against cardiovascular disease and can increase muscle mass (1). However, exercise induces rapidly changing glucose levels due to the high demands of glucose from the contracting muscles (2) and changes in counterregulatory hormone secretion (3). Thus, practical issues should be considered by the individual before commencing exercising: adjustment of dose and timing of insulin, type and quantity of carbohydrate ingestion before, during and after exercise and trying to prevent hypoglycaemic or hyperglycaemic events during or after exercise (1). Therefore, implementing an exercise training program into the treatment plan of an individual with T1D is not easy. Consequently, a lot of people with T1D are reluctant to perform prolonged physical activity, mainly because they fear the risk of hypoglycaemia (4, 5). Although the use of continuous glucose monitoring (CGM) enables to alert people for impending hypoglycaemia, correct interpretation and management of glucose trends during and after exercise are difficult (6).

The glycaemic response to exercise depends on several factors such as the type, intensity, duration and frequency of physical activity, initial glucose concentration, nutrition, level of physical fitness, as well as circulating levels of insulin and counterregulatory hormones. The timing of exercise (time of day) and exercise sequence (e.g. high intensity interval sprint training before prolonged aerobic exercise to try to avoid hypoglycaemia after exercise) also influence the glycaemic response (3). Continuous aerobic exercise of moderate intensity has been associated with a decline in blood glucose because of the inability of circulating insulin levels to be lowered fast enough (7) and a greater glucose disposal in combination with less

glucose appearance (8-10). Prolonged exercise can even blunt counterregulatory hormone secretion and therefore increase the risk of hypoglycaemia (11). This has also been associated with mechanisms such as an increase in insulin sensitivity and a contraction-mediated activation of glucose utilization in skeletal muscle (12). Conversely, anaerobic exercise or intermittent high-intensity exercise (HIE) may result in an increase in counterregulatory hormones (13-19). Furthermore, HIE is associated with raised lactate concentrations by increasing reliance on muscle phosphagens and glycogen (20) and by promoting gluconeogenesis, leading to a diminished decline in glycaemia (21). These findings indicate high flexibility of exercise-related fuel metabolism in T1D and point towards a potentially beneficial role of HIE in these individuals (22). Although glucose metabolism during exercise in this population has been studied in detail, the changes in other important biomarkers such as lactate and ketones involved in the regulation of glucose during exercise still needs further elucidation. Data concerning ketone levels during exercise in adults with T1D are sparse, but they seem to decrease with exercise according to some studies (10, 19). When starting physical activity (PA), many persons with T1D experience hypoglycaemia. In order to avoid hypoglycaemia, they adopt a trial-and-error approach and omit their bolus insulin before exercising as described in the study of Vartak et al. (23). Furthermore, ketone esters are becoming more popular as alternative source of fuel during exercise (24) which makes it interesting to monitor the effects on glycaemia.

In this pilot study, the ACTION-1 (cArdiopulmonary exerCise Test assessing multiple bIOmarkers iN type 1 diabetes), we aimed to document simultaneous values and trends of different biomarkers (glucose, lactate and beta-hydroxybutyrate) before, during and after morning aerobic (AEX) and symptom limited maximal exercise (CPET) (cycling). We hypothesised that glucose would increase more during a maximal exercise than an aerobic exercise test, and that an aerobic exercise would be more likely to provoke hypoglycaemic events. We also speculated that an increase in glucose levels would be preceded by a rise in

lactate levels. Next, we aimed to actively monitor the ketone levels as one could expect ketones to increase due to the lack of pre-meal insulin while they also could be absent due to the increased insulin sensitivity induced by exercising. We aimed to evaluate if the exercise tests with a high carbohydrate intake without an insulin bolus and without basal insulin for pump users were safe under the current settings in T1D.

Research Design and Methods

Study Design:

In this prospective, observational multicentre pilot study, 21 adult men with well controlled T1D were included. A symptom limited cardiopulmonary exercise test (CPET) was first performed to determine the VO_2peak. Next, a 60-minute aerobic exercise test (AEX) was performed at 60% of the VO_2peak. The exercise tests were conducted between May 2019 and February 2020 in three centres in three countries: Belgium (Antwerp), France (Montpellier) and Italy (Rome), in accordance with the Declaration of Helsinki and principles of Good Clinical Practice. The study was approved by the ethics committees (EC) in all 3 centres, with the Antwerp University Hospital (UZA) acting as central EC [EC number 1849572]. A written informed consent was obtained from each participant prior to conducting any protocol.

Aims and outcomes:

The aim of this study was the simultaneous monitoring of glucose, lactate and ketones during a 60 min exercise, which is longer than most of the current literature, with insulin omission. A longer exercise duration might better reflect a real-world situation for a patient with type 1 diabetes when performing prolonged exercise while preventing hypoglycaemia. The primary endpoint was to compare the evolution of glucose, lactate and ketone levels during and after exercise. The area under the curve (AUC) for 450 min post-exercise commencement was

calculated using trapezoidal rule for glucose, lactate and ketones. The secondary endpoint was time spent in different glucose ranges during the CGM data collection: time in range (TIR) 70–180 mg/dL (3.9–10 mmol/L) (%); TIR 70–140 mg/dL (3.9–7.8 mmol/L) (%); time below range (TBR) <70 mg/dL (<3.9 mmol/L) (%); TBR <54 mg/dL (<3.0 mmol/L) (%); time above range (TAR) >180 mg/dL (>10 mmol/L) (%) and TAR >250 mg/dL (>13.9 mmol/L) (%).

Inclusion and exclusion criteria

Participants were included according to the following selection criteria: male adults (18-40 years old), diagnosed with T1D for at least one year before the trial, C-peptide level <0.2 nmol/l, on intensified insulin therapy (multiple daily insulin injections (MDI)) or insulin pump therapy (continuous subcutaneous insulin injections (CSII)), using a CGM Dexcom G5 or G6 or willing to wear such a CGM for the duration of the study starting from at least 48 hours prior to the exercise test, HbA1c between 6-8% (42-64 mmol/mol), a body mass index (BMI) between 20-25 kg/m^2 and no change in their self-reported physical activity in the 2 months prior to and during the exercise tests. Each study participant fulfilled the IPAQ Short Form (IPAQ-SF) which asks about physical activity during the last 7 days and was used to categorize weekly physical activity level (high-moderate-low) (25).

The following exclusion criteria were applied: having an acute illness (e.g. viral or bacterial infection) or condition that interferes with glucose metabolism, musculoskeletal disorders which can affect cycling capacity or having a cardiorespiratory disease or ECG abnormality which are a contraindication for vigorous physical activity, having a metabolic disorder other than T1D or current use of agents known to significantly interfere with glucose metabolism (such as systemic corticosteroids), presence of comorbidities such as heart failure, liver failure, kidney failure (defined as eGFR <45ml/min), or not being able to understand or willing to sign the informed consent form.

Protocol

Two exercise tests were performed on an ergometer bike: a symptom-limited maximal exercise test (CPET) and a 60-minute continuous aerobic workout at 60% of the VO_2peak (AEX) within a 6-week period. Exercise tests were performed in the morning after a standardised breakfast without an insulin bolus and a pump stop for the insulin pump users.

Glucose levels were monitored using a Dexcom G5 or G6 continuous glucose monitoring device. Since CGM sensors differ in accuracy, we opted to use only Dexcom sensors (26). CGM data were collected continuously from 8 hours before till 24 hours after the start of the exercise tests. Neither exercise nor meals with a high glycaemic index were allowed the day prior to the exercise tests. The target glucose level in the morning before starting the exercise tests was between 100-150 mg/dl (5.6-8.3 mmol/l) in line with the consensus statement for exercise in T1D (18). Patients who suffered a hypoglycaemic event (<70 mg/dl) 12h prior to the exercise test had to be rescheduled. A standardized breakfast was given of 1g of carbohydrates per kilogram bodyweight (Ensure Abbott®, 6 kcal/kg, 20.2g CHO/100ml) without administering an insulin bolus before the start of the exercise test in order to assess the evolution of ketones and to avoid hypoglycaemia. For the participants with CSII therapy, the insulin pump was stopped right before and during the exercise.

Blood sampling was done before the exercise, every 3 minutes during CPET (according to the steps with increasing workload) and every 5 minutes during AEX, every 15 minutes during the first hour of recovery and every 20 minutes during the rest of the 6-hour follow-up. Blood samples were taken via an IV catheter in the antecubital vein and stored in a tube with sodium fluoride 1 ml and lithium heparin 1 ml for analysis of glucose and lactate measurements through YSI (YSI Life Sciences, Yellow Springs, OH) (27). Strips were used during the testing to monitor glucose, lactate and ketones (beta hydroxybutyrate) (GlucoMen, Menarini Diagnostics® and Lactate Scout+, EKF Diagnostics® respectively).

ECG leads and breathing masks were placed for continuous monitoring of cardiac activity and for the recording and analysis of VO_2peak. Heart rate monitoring during both exercise tests was performed in Antwerp.

CPET: symptom-limited cardiopulmonary exercise test

A cardiopulmonary exercise test (CPET) was performed using a Cortex Metalyzer 3b gas-analysis system (Cortex Biophysik Metalyzer, Germany) and a 12-channel wireless ECG unit (custo cardio 100 BT, custo med, Germany). Participants were given a brief highlight of the CPET procedure. The test commenced by a 5-minute warm up at 50 Watt, followed by start of the exercise at 80 Watt and increment of workload by 40 Watt every 3 minutes. Cycling was maintained at 65 rpm and was continued until self-reported exhaustion. The exercise test was ended with a 5-minute recovery at 50 Watt. Blood samples were therefore taken every 3 minutes according to the incremental step procedure to get a steady state of lactate levels before increasing the workload. A 10-point rating of perceived exertion (RPE, Borg scale) was used at the end of each incremental phase (28). Participants were closely followed on site for 6 hours after cycling. Only light activities of daily living such as sitting and reading were allowed during follow-up. Meals or strenuous activities were prohibited during this period.

AEX: 60-minute aerobic exercise test at 60% VO_2peak

The second exercise test was performed within a period of 6 weeks (mean time frame 3.4 ±1.4) after the first exercise test. The interval between the 2 protocols was kept as short as possible but due to practical issues (getting a day off at work for the participant, availability of the research lab and personnel) a window of max 6 weeks was allowed. Participants performed a cycling test at 65 rpm for 1 hour at a constant heart rate of 60% of the heart rate at VO_2peak, which was calculated from the CPET on day 1.

Data collection:

Pre-defined clinical and demographic data were collected during the first visit through patient history from their medical records and anamnesis of the patients. Presence of nephropathy was scored positive in case of 24h urinary albumin excretion >20 µg/min or eGFR <60 ml/min/1.73m2 or creatinine level >1.5 mg/dl. Presence of retinopathy was scored positive if fundoscopy showed preproliferative (microaneurysms, intraretinal microvascular abnormalities, exudates, venous beading) or proliferative retinopathy. Peripheral neuropathy was scored positive if monofilament tests were abnormal or abnormal nerve conduction velocities were documented by electromyography of the lower limbs. Hypoglycaemia unawareness was defined as only having hypoglycaemic symptoms at a glycaemia level of <54 mg/dl (<3.0 mmol/L) or having no symptoms at all (as reported by the patient). RT-CGM data were collected using the Clarity software for Dexcom RT-CGM. Laboratory data were collected from venous blood serum samples through YSI analysis and fingerstick.

Statistical Analyses:

Statistical analyses were performed using JMP Pro 15.2 software. Descriptive statistics were used to analyse population characteristics. Distributions of continuous data were tested for normality with the Kolmogorov-Smirnov test. Data were expressed as mean and standard deviation for normally distributed data and as median and interquartile range (IQR, expressed as 25^{th}-75^{th} percentile) for skewed data. The two exercise tests were compared using the Wilcoxon signed rank test on the incremental area under the curve (AUC) for glucose, lactate and ketones. The 32-hour CGM data was also compared between exercise tests using Wilcoxon signed rank test. Incremental AUC for 450 min post-exercise commencement was calculated using trapezoidal rule. Graphs were made using GraphPad Prism software.

Results:

Demographics

Twenty-one men with T1D participated in the two exercise trials. They had a median age of 29 years [27.5-37.5], a diabetes duration of 18 years [10.5-27.0], and a BMI of 24.4 kg/m^2 [22.3-24.9]. Participants showed an acceptable to rather good metabolic control as reflected by an HbA1c of 7.2% [6.7-7.8] (55 [50-62] mmol/mol) and a time in range of 64.5% [49.0-70.8]. Eight persons were using multiple daily injections (MDI) and thirteen continuous subcutaneous insulin infusion (CSII). Most people had a moderate to high physical activity level (see Table 1).

CPET

The Score on the Borg Scale (SBS) indicated maximal exertion for all participants at the end of the symptom limited maximal exercise test (Supplemental Figure 1). This point of maximal exertion was reached at 17.3 minutes [16.3-20.0] with a maximal load of 240 Watt [200-280]. In the eight Antwerp patients, the VO_2peak was measured and reached 42.5 ml/kg/min [36.5-56.3] during CPET with a median 60% VO_2peak at 25.5 ml/kg/min [21.9-33.8] and a maximum heart rate of 188 bpm [186-196].

The median glucose level (for all subjects) immediately prior to exercise was 163 mg/dL [110-196] (9.1 mmol/L [6.1-10.9]). Glucose levels increased after the standardised breakfast without insulin bolus during the CPET trial and reached a maximum at 20 minutes of cycling of 216 mg/dL [173-223] (12.0 mmol/L [9.6-12.4]). The highest glucose values (340 mg/dL [253-376]; 18.9 mmol/L [14.1-20.9]) were observed at 80 minutes after exercise. Glucose levels started to decrease from 180 minutes onwards after the CPET with the lowest value of 176 mg/dL [118-217] (9.8 mmol/L [6.6-12.1]) being reached at the end of the follow-up at 360 minutes after exercise (Figure 1).

Before the start of the CPET trial, lactate levels were 0.9 mmol/L [0.9-1.1]. The lactate threshold (LT), an indication of a level of exercise that cannot be sustained (lactate begins to accumulate in the blood at a faster rate than it can be removed), was reached after approximately 11 minutes (median lactate of 2.2 mmol/L [1.4-3.3]). The maximum lactate level was 13.5 mmol/L at the end of the exercise test. Lactate levels dropped quickly to <3 mmol within one hour after exercise and it took another hour to return to baseline levels (Figure 2).

Ketone levels were absent in most participants before the CPET with a median value of 0 mmol/L [0-0.2]. During exercise, there were no large changes in ketone levels and all participants remained below 0.7 mmol/L. Nine participants (43%) did not develop ketones at all. After exercise, ketone levels remained <0.6 mmol/L with only two patients having a higher ketone level once of 1.4 and 1.5 mmol/L (Figure 3).

AEX

The AEX protocol lasted for 60 minutes at a constant heart rate that corresponded to a 60% VO_2peak with a median score on the Borg Scale of 6 [5-7] out of 10 at the end of the exercise (Supplemental Figure 1). The maximum heart rate of the eight Antwerp patients was 161 bpm [149-165].

Glucose levels (for all subjects) before the AEX trial were at a median value of 155 mg/dL [124-185] (8.6 mmol/L [6.9-10.3]). They reached maximal values at 60 minutes (193 mg/dL [139-237]; 10.7 mmol/L [7.7-13.2]) during the AEX. Glucose levels further increased after exercise to reach a maximum of 305 mg/dL [245-336] (16.9 mmol/L [13.6-18.7]) after 80 minutes. Thereafter glucose levels decreased with a median glycaemia of 211 mg/dL [116-222] (11.7 mmol/L [6.4-12.3]) 360 minutes after exercise (Figure 1).

Lactate levels during AEX rose quickly to 4.3 mmol/L [2.7-6.7] after 10 minutes with 17 participants rather performing a mixed aerobic anaerobic test instead of a fully aerobic exercise

with lactate levels ≥3.8 mmol/L. During the last 20 minutes of the exercise, lactate levels decreased to 2.0 mmol/L [1.4-4.7] with a further decline back to baseline levels 120 minutes onwards after exercise (Figure 2).

Ketones were absent (<0.5 mmol/L) during the AEX trial. After exercise, ketone levels were absent (<0.5 mmol/L) in 16 participants, were between 0.5-1.0 mmol/L in 4 people, and 1 person developed a ketone level of 2.2 mmol/L 300 min after exercise at a glycaemia of 304 mg/dL (Figure 3).

Comparisons between CPET and AEX

Incremental AUC values for the biomarkers are shown in Supplemental Table 1. The AUC for the glucose values was not significantly different between CPET and AEX (p=0.07), nor for the ketone values (p=0.4). Lactate AUC values were significantly higher in the maximal exercise test (CPET) compared to the aerobic exercise (p=0.04). The maximum heart rate in the eight Antwerp patients was higher during CPET (188 bpm [186-196]) when compared to AEX (161 bpm [149-165]) (p<0.001).

The 32-hour CGM data are shown in Supplemental Table 2 and Figure 4. There were no significant differences in time spent in different glucose ranges nor in mean glucose values. TIR 70–180 mg/dL (3.9–10 mmol/L) was 53.2 [41.7-63.1] during the day of CPET and 58.0 [43.4-69.3] during the day of AEX (p=0.5). There were almost no hypoglycaemic events with TBR <70 mg/dL (<3.9 mmol/L) being 2.6 [0.6-11.6] during the day of the CPET and 2.8 [0-6.4] during the day of AEX (p=0.9), median TBR <54 mg/dL (<3.0 mmol/L) (%) was zero.

Discussion:

Researchers have been studying the causes for glucose fluctuations during exercise in T1D, along with ways to prevent them and to optimize the benefits from exercise. Many studies have shown contrasting effects of aerobic and anaerobic exercise types on glycaemia (8-10, 13-19, 29).

A better prediction of the glucose levels during exercise is important for the patient to obtain and maintain euglycaemia and optimise performance. Besides, continuous monitoring of lactate levels may provide additional information. Measuring ketones during exercise could be helpful as well because exercise could increase the risk of ketosis in hyperglycaemic conditions.

The delicate balance of glucose homeostasis is significantly affected by exercise in individuals with T1D. In this study in which subjects consumed a standardised Ensure® breakfast before exercise without the administration of an insulin bolus and with the cessation of basal insulin in pump users, we observed an increment of plasma glucose during symptom-limited CPET both during exercise and the recovery period. These findings confirm results from previous studies reporting either a higher plasma glucose level, a lower incidence of hypoglycaemia or a lower need of exogenous glucose demand during high intensity exercise or the combination of high and moderate intensity exercise (12-14, 16, 17, 19). The significant increase of plasma glucose during CPET can be explained by an increased production of counterregulatory hormones; mainly growth hormone and catecholamines (12-14, 16, 19) resulting in an increased hepatic glucose production and inhibition of insulin-mediated glucose uptake by peripheral tissue (30). Increased levels of cortisol can result in the acute inhibition of glucose utilization in skeletal muscles resulting in hyperglycaemia (31).

In our AEX test, a remarkable increase in glucose levels was noted, particularly during the recovery period until 80 minutes after exercise with a subsequent decline of glucose levels but still above the baseline glycaemia. This could partly be due to the amount of carbohydrates

which were consumed before the exercise to mimic a normal breakfast but without administering a bolus of insulin. This may have provided excessive amounts of glucose, enough to diminish the physiologic effect of aerobic exercise. Furthermore, the duration of our AEX was limited to 1 hour which might not be long enough to deplete the glycogen storage in the liver. The study of Riddell et al. labelled an exercise as prolonged when the duration was longer than 3 hours (32).

A significantly higher production of lactate during CPET can contribute to the concomitant hyperglycaemia. Lactate can act as a possible alternative substrate for glucose (13) and provides gluconeogenic precursors for hepatic glucose production (33). Furthermore, a higher level of lactate might acutely inhibit the action of insulin on peripheral glucose uptake, an effect similar to that of the counterregulatory hormones (34). The Lactate Threshold (LT), which is approximately 2 mmol/L is the point where lactate begins to accumulate in the blood at a faster rate than it can be removed, providing an indication that this level of exercise cannot be sustained. Studies have suggested that LT is the most reliable predictor of endurance performance, so knowing the LT can help optimising training efforts (35). Therefore, it could be valuable to measure lactate in an attempt to continuously remain below the lactate threshold. In the CPET of our study, glucose levels increased following an increase in lactate levels after 11 minutes. Glucose levels stabilised when the lactate levels decreased again to baseline levels. A similar effect was seen in the AEX in the 17 participants with early elevated lactate levels of >2.0 mmol/L (even ≥3.8 mmol/L). There were four participants with lactate values below 2.0 mmol/L with three of them having higher glucose levels directly after the AEX, an observation that is not expected after an aerobic exercise. However, a bolus of insulin was not administered nor was basal insulin used in pump users, which might explain this finding of higher glucose levels.

No changes were observed in ketone levels during exercise and recovery in both CPET and AEX, suggesting that there is no difference in ketone production between both types of exercise. CPET and AEX could both be executed safely without risk of ketosis even in the absence of a prandial bolus of insulin. During a prolonged moderate intensity aerobic training (40-60% of VO_2peak), hypoglycaemia is expected to occur within 45-60 minutes because of depletion of hepatic glycogen stores and insufficient counterregulatory hormone secretion to enhance gluconeogenesis and glycogenolysis (32). This is exacerbated in people with T1D because they are, in contrast to healthy individuals, not able to lower plasma insulin levels after bolus insulin administration, with an inherent risk of ensuing hypoglycaemia. However, omitting insulin administration in people with T1D may lead to the liberation of free fatty acids by adipose tissue which are used as a substrate for ketogenesis (36). The resulting ketone bodies replace glucose as a primary fuel for peripheral tissue such as the brain, heart and skeletal muscles in this state. A contracting muscle has an increased capacity of extracting ketones from the blood to use it as a substrate for fuel. In one study in patients with type 1 diabetes, a moderate intensity continuous aerobic training resulted in a slight decrease in ketones during exercise and a significant increase from baseline during recovery (10). We could not confirm this finding.

Data on ketone levels during exercise are scarce. Paldus et al. compared the effects of high intensity exercise (HIE), moderate intensity exercise (MIE), and resistance exercise (RE) in 30 people with T1D and also found no differences in glucose and ketone levels between exercise tests. Their exercise duration was 40 minutes, which was shorter than our AEX. Participants used a hybrid closed loop system (Medtronic MiniMed 670G) with a temporary target of 150 mg/dL (instead of the target of 120 mg/dL) set 2 h prior to and during exercise and 15 g carbohydrates if pre-exercise glucose was <126 mg/dL to prevent hypoglycaemia. They did not

find any difference in TIR between the exercise tests while a greater increase in lactate and heart rate was seen during HIE compared to MIE and RE, which is similar to our results (37).
In a small study (n=8), Vartak et al. compared a reduced insulin bolus of 50% with no insulin bolus after 1g of carbohydrates per kilogram bodyweight before a 45-min treadmill walk and a 6-min walk test with the monitoring of glucose, lactate and ketones. The participants spent more time in hyperglycaemia when they did not administer an insulin bolus. With a 50% bolus reduction, they spent more time in normoglycaemia and mild hypoglycaemia (23).

Bracken et al. examined the effects of reductions to pre-exercise insulin bolus on changes in ketones, glucose and lactate to prolonged running in individuals with type 1 diabetes. With a 45 minutes run, their protocol was shorter than our AEX. Ketogenesis following running was not influenced by reductions in pre-exercise insulin bolus. This exercise strategy aids preservation of blood glucose but poses no greater risk to exercise-induced ketone body formation (38).
Jayawardene et al. compared closed-loop glucose control for 12 people with type 1 diabetes undertaking high-intensity interval exercise (HIIE) versus MIE. Glucose, lactate and ketones were assessed. Both exercise stages included a 45-min stationary bicycle exercise protocol. Their most important finding was that ketones increased more with HIE than MIE postexercise. They stress the need for ketone monitoring post exercise while using closed-loop pumps (39).
Ketone esters are being used as super fuel in athletes. Ketone supplementation has been proposed as an alternative (or complementary) strategy that might also boost endurance sports performance, yet through different metabolic pathways. Poffe et al. studied the effect of exogenous ketosis by the ingestion of ketone esters (in non-diabetic subjects) during prolonged exercise in acute hypoxia. Ketone esters slightly elevated the degree of blood and muscle oxygenation during prolonged exercise in moderate hypoxia without impacting exercise

performance. They suggest that the monitoring of exogenously administered ketones might be interesting to improve muscular and cerebral oxygenation status, and exercise tolerance in extreme hypoxia (24). However, as discussed by Valenzuela et al, evidence to date does not support a benefit of acute ketone supplementation on sports performance, cognition, or muscle recovery [although further research with long-duration exercise (i.e., >60 min) is needed], and the evidence for chronic supplementation is sparse. In addition, acute intake of ketone supplements might be associated with gastrointestinal symptoms, and further research is warranted on the long-term safety of repeated use of ketone supplements (40). Alternatively, in people with T1D who abstain from insulin injection before exercise because of they fear the risk of hypoglycaemia during exercise, or who are confronted with catheter occlusion of their CSII while exercising, or those using SGLT2-inhibitors, measuring ketones could be seen as a safety issue, as also suggested by Lee et al (41). Guidelines also instruct not to start exercise when ketone levels are high (18), but further insights on ketones during exercise are yet to be established. In future protocols to further explore the role of ketones and lactate, adjustments to the protocol will be tested: lower intensity (e.g. 40% VO_2peak), prolonged duration (e.g. 90 minutes), breakfast with lower carbohydrate intake with insulin administration. This is necessary to make a clear conclusion about the usefulness of these biomarkers and the effects of moderate intensity aerobic training on glycaemia.

This pilot study has some limitations as it was not a randomized controlled trial, studied a limited group of male subjects with T1D and used a pre-exercise breakfast without an insulin bolus, allowing only to provide a hint of the evolution of the three investigated biomarkers during aerobic and anaerobic exercise. No women were included in this study to rule out the effect of menstrual cycle (42-44).

This study is the first to give an impression about ketone levels during and after exercise under a high carbohydrate intake and a relative lack of insulin. Ketone levels were not very high under

these circumstances, probably because of the sustained insulin action of still circulating insulin, due to exercise.

Conclusions:

Physical activity after consuming a carbohydrate-rich breakfast and with the omission of insulin, during a stepped maximal exercise test and a 1-hour continuous aerobic workout on an ergometer bicycle resulted in an increase of glucose and lactate both during exercise and recovery periods in people with T1D. Ketones did not show any change during both tests, neither during exercise nor during recovery. Lactate, but not glucose or ketone AUC, was significantly higher in CPET compared to AEX.

Omitting pre-meal insulin and also basal insulin in pump users, did prevent hypoglycaemia but induced hyperglycaemia due to a too high carbohydrate ingestion.

Reducing fear of hypoglycaemia while exercising could result in more people with T1D being physically active. Continuous multibiomarker monitoring of glucose, lactate and ketones may help to offer more individualised treatments, certainly in conditions where there is a large interindividual variability in these parameters.

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Duality of interest:

F.D.R., K.J.L. have has nothing to disclose. C.D.B. reports consulting fees and honoraria for speaking for Abbott, AstraZeneca, Boehringer-Ingelheim, A. Menarini Diagnostics, Eli Lilly, Indigo Diabetes n.v., Medtronic, Novo Nordisk, and Roche. E.R. serves on the advisory board for Abbott, Air Liquide SI, Dexcom Inc, Insulet, Sanofi, Roche, Novo Nordisk, and Eli-Lilly, and received research support from Dexcom Inc and Tandem. Funding did not have an influence on data collection, statistical analyses and interpretation of data.

Author Contributions: F.D.R. collected and analysed the data, performed statistical analyses, discussed, and wrote the manuscript, and made figures and tables.

R.B., D.V., E.R., P.P. and S.P. performed the exercise tests and/or collected the data.

C.D.B., E.R. and P.P. included the patients.

C.D.B., D.V., E.R., P.P., and D.D. designed the study, analysed and discussed the data and wrote the manuscript. K.J.L., B.D.W. and C.D.B. edited the final manuscript after data analysis.

C.D.B and F.D.R. are the guarantors of this work and, as such had full access to all the data in the study and take responsibility for the integrity of the data and accuracy of the data analysis.

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Table 1: Baseline Characteristics of Patients in the ACTION-1 Study

General characteristics	
Men (n)	21
Age (years)	29.0 [27.5-37.5]
Height (cm)	177.0 [171.0-183.5]
Body mass (kg)	75.0 [69.5-77.9]
BMI (kg/m²)	24.4 [22.3-24.9]
Waist circumference (cm)	83.1 [76.3-93.0]
Activity level (IPAQ)	
High	8 (38)
Intermediate	11 (52)
Low	2 (10)
Diabetes-related characteristics	
Insulin therapy	
MDI	8 (38)
CSII	13 (62)
Tandem T slim (without closed loop)	1
Medtronic 670G	2
Medtronic 640G	3
Omnipod	6
Ypsopump	1
Diabetes duration (years)	18.0 [10.5-27.0]
HbA1c (max. 3 months before the study)	
(%)	7.2 [6.7-7.8]
Mmol/mol	55 [50-62]

Continuous Glucose Monitoring (CGM)	
Mean glucose value (mg/dL)	151.5 [139.5-160.0]
Estimated HbA1c (30 days) (%)	6.9 [6.5-7.3]
TIR 70-180 mg/dL (3.9–10 mmol/L) (%)	64.5 [49.0-70.8]
TBR <70 mg/dL (<3.9 mmol/L) (%)	6.5 [5.0-11.5]
TAR >180 mg/dL (>10 mmol/L) (%)	28.5 [24.3-34.5]
Chronic complications	
Microalbuminuria (yes)	2 (10)
Polyneuropathy (yes)	0 (0)
Impaired hypoglycaemia awareness (yes)	2 (10)
Retinopathy (yes)	4 (19)

Results are presented as n (% of patients) or median [IQR].

Figures

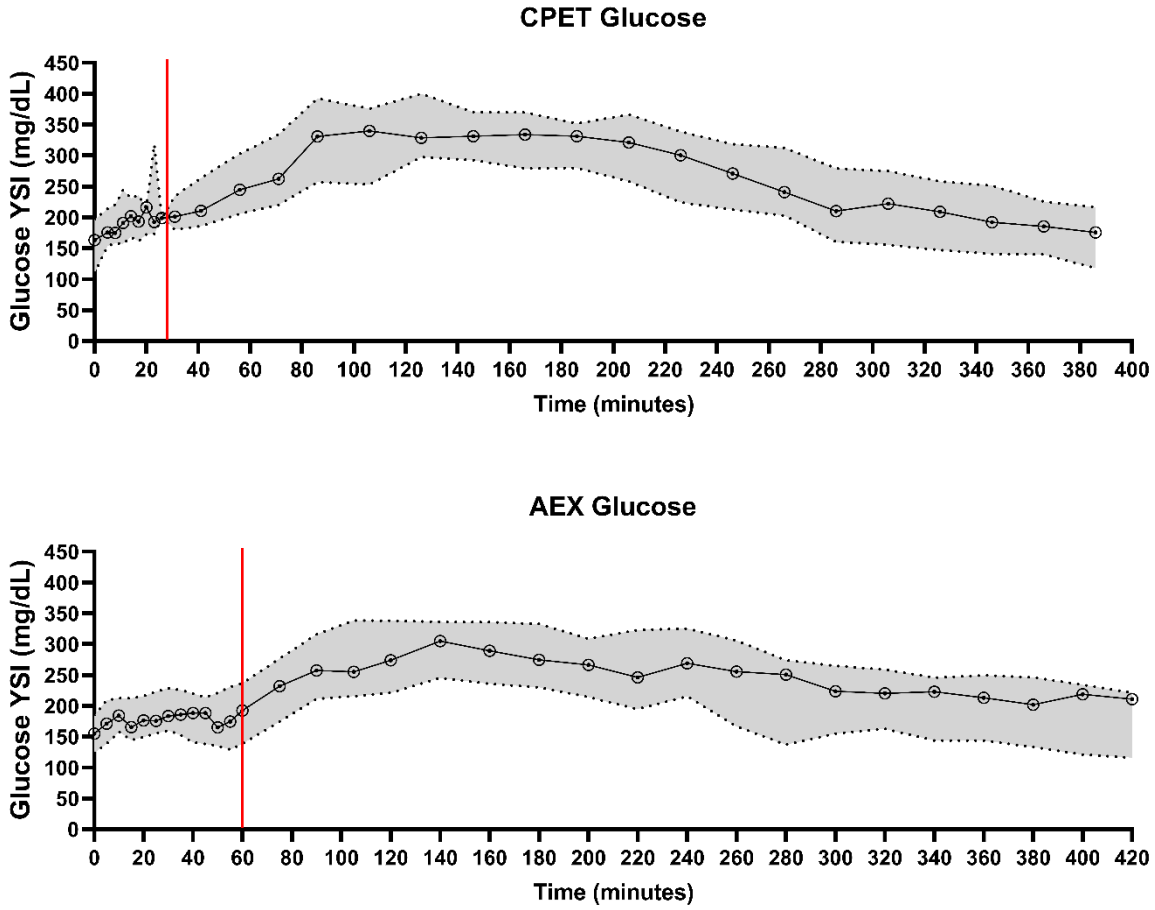


Figure 1: Evolution of glucose in mg/dL measured in the blood with YSI (median [IQR]) during and after exercise. CPET: symptom limited maximal exercise test (upper panel). AEX: 60-minute aerobic exercise test at 60% VO2peak. The red vertical line indicates the end of the exercise (lower panel).

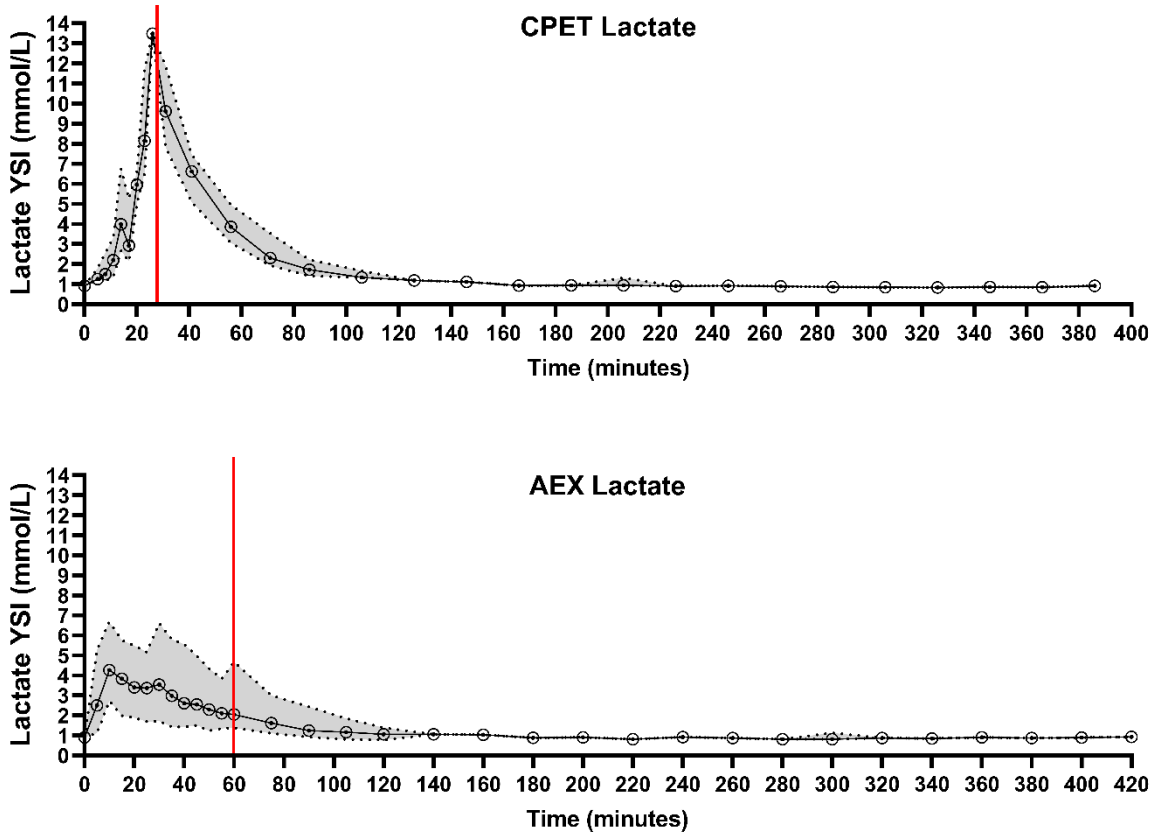


Figure 2: Evolution of lactate in mmol/L measured in the blood with YSI (median [IQR]) during and after exercise. CPET: symptom limited maximal exercise test (upper panel). AEX: 60-minute aerobic exercise test at 60% VO2peak. The red vertical line indicates the end of the exercise (lower panel).

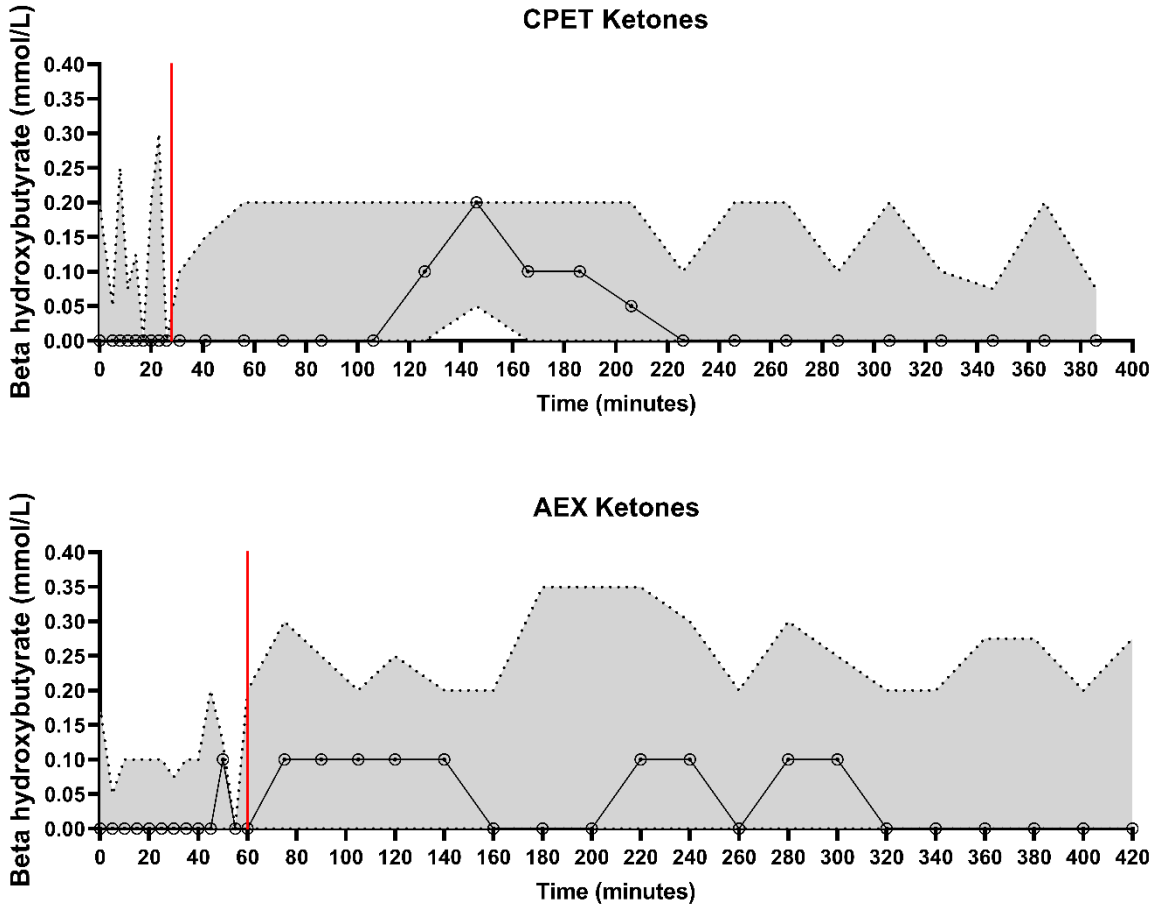


Figure 3: Evolution of ketones measured by beta-hydroxybutyrate sticks in mmol/L (median [IQR]) during and after exercise. CPET: symptom limited maximal exercise test (upper panel). AEX: 60-minute aerobic exercise test at 60% VO2peak. The red vertical line indicates the end of the exercise (lower panel).

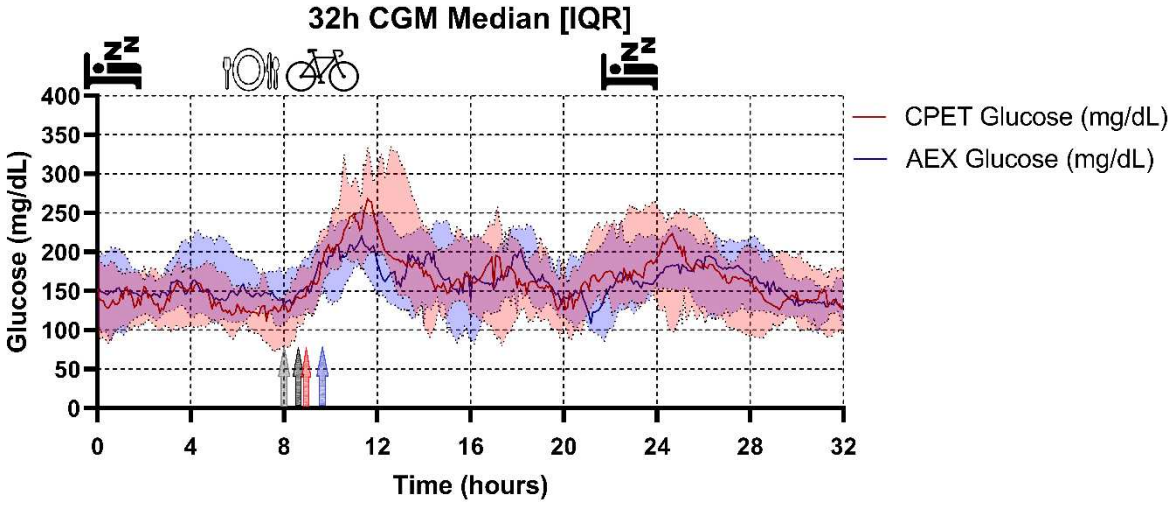
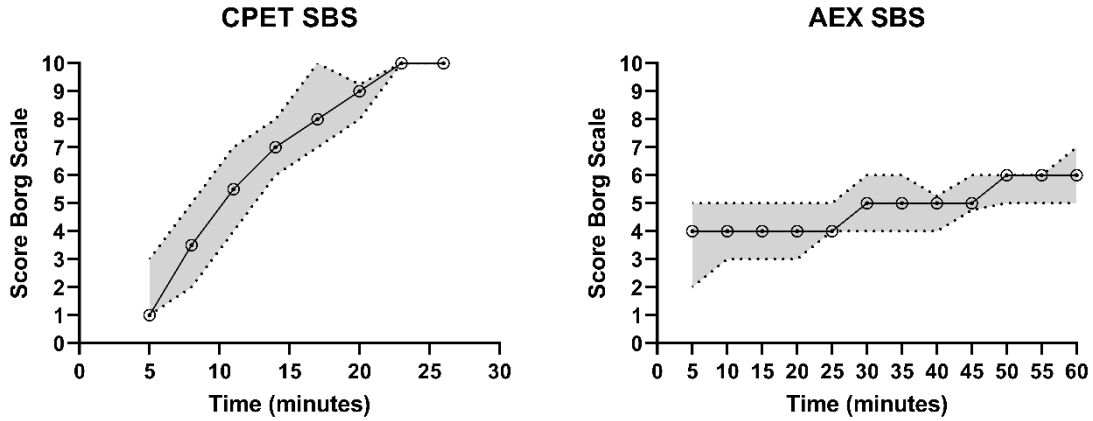


Figure 4: Continuous Glucose Monitoring profiles expressed as median [IQR] for CPET (red line) and AEX (blue line) for 32 hours of which are 23-24 hours following exercise commencement. The bed indicates sleep, the plate indicates breakfast (first arrow, light grey) and the bike indicates the exercise test (start of exercise indicated by the second arrow, dark grey). The third arrow (red) indicates the end of CPET. The fourth arrow (blue) indicates the end of AEX.

Supplementals



Supplemental Figure 1: Grade of exhaustion measured by the Score Borg Scale (median [IQR]) during exercise. CPET: symptom limited maximal exercise test (left panel). AEX: 60-minute aerobic exercise test at 60% VO2peak (right panel).

Supplemental Table 1: Changes in glucose, lactate and ketones, as incremental area under the curve during exercise and 6 hours follow-up

	CPET	**AEX**	**P-value**
Glucose AUC	43328 [36289-65763]	36646 [24492]	0.07
Lactate AUC	363 [330-471]	238 [145-519]	0.04
Beta hydroxybutyrate AUC	26 [14-55]	36 [16-72]	0.4

Results are presented as median [IQR].

Supplemental Table 2: 32h CGM outcomes (00:00 the day of the exercise test–08:00 the day after exercise) as time spent in different glucose ranges

	CPET	**AEX**	**P-value**
TIR 70–180 mg/dL (3.9–10 mmol/L) (%)	53.2 [41.7-63.1]	58.0 [43.4-69.3]	0.5
TIR 70–140 mg/dL (3.9–7.8 mmol/L) (%)	30.6 [21.5-44.1]	31.5 [23.7-40.7]	1.0
TBR <70 mg/dL (<3.9 mmol/L) (%)	2.6 [0.6-11.6]	2.8 [0-6.4]	0.9
TBR <54 mg/dL (<3.0 mmol/L) (%)	0 [0-0.8]	0.3 [0-1.4]	0.7
TAR >180 mg/dL (>10 mmol/L) (%)	44.0 [20.1-56.7]	41.5 [22.3-55.5]	0.7
TAR >250 mg/dL (>13.9 mmol/L) (%)	10.4 [5.7-21.3]	8.8 [3.2-18.4]	0.3
Mean glucose (mg/dL)	175 [141-191]	173 [147-185]	0.8

Results are presented as median [IQR].