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ORIGINAL ARTICLE

Minimal effect of walking before dinner on glycemic responses in type 2 diabetes: outcomes from the multi-site E-PAraDiGM study

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Abstract

Aim To examine the effect of walking before dinner on 24-h glycemic control in individuals with type 2 diabetes using the standardized multi-site Exercise-Physical Activity and Diabetes Glucose Monitoring (E-PAraDiGM) Protocol.

Methods Eighty participants were studied under two conditions (exercise vs. non-exercise control) separated by 72 h in a randomized crossover design. Each condition lasted 2 days during which standardized meals were provided. Exercise consisted of 50 min of treadmill walking at 5.0 km/h before the evening meal, while control involved 50 min of sitting. The primary outcome measure was mean glucose during the 24-h period following exercise (or sitting) measured by continuous glucose monitoring.

Results Of the 80 participants who were initially randomized, 73 completed both exercise and control. Sixty-three participants [29 males, 34 females; age = 64 ± 8 years, body mass index = 30.5 ± 6.5 kg/m^2 and HbA1c = 51 ± 8 mmol/mol (6.8 ± 0.7%), mean ± SD] complied with the standardized diets and had complete continuous glucose monitoring data. Exercise did not affect mean 24-h glucose compared to control (0.03 mmol/L; 95% CI − 0.17, 0.22, $P = 0.778$) but individual differences between conditions ranged from − 2.8 to + 1.8 mmol/L. Exercise did not affect fasting glucose, postprandial glucose or glucose variability. Glucose concentrations measured by continuous glucose monitoring were reduced during the 50 min of walking in exercise compared to sitting in control (− 1.56 mmol/L; 95% CI − 2.18, − 0.95, $p < 0.001$).

Conclusion Contrary to previous acute exercise studies, 50 min of walking before dinner in the E-PAraDiGM protocol did not affect 24-h glucose profiles. However, highly heterogeneous responses to exercise were observed.

Trial registration: NCT02834689.

Keywords Continuous glucose monitoring · Glycemic control · Type 2 diabetes · Physical activity · Walking

Introduction

Many of the glucose-lowering and insulin-sensitizing benefits of chronic exercise training are attributed to the acute effects of each individual bout of exercise performed throughout the training [1, 2]. Accordingly, the Canadian physical activity guidelines [3] and the position statement of the American Diabetes Association promote daily exercise with no more than 2 days off in between sessions [4]. Continuous glucose monitoring (CGM) enables researchers to examine the effect of acute exercise sessions on many aspects of glucose control including postprandial glucose, fasting glucose and glycemic variability. These outcomes

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may help to optimize the acute glucose-lowering effects of exercise.

A meta-analysis [5] examining exercise and glycemic outcomes assessed by CGM found significant but heterogeneous reductions in mean 24-h glucose and time spent with glucose > 10 mmol/L [5]. The exercise protocols examined were highly variable with relatively small sample sizes ranging from 6 to 30 participants [5]. Exercise sessions were completed in the morning, with no studies examining the effect of exercise completed in the afternoon [5]. Interestingly, a more recent study suggested afternoon exercise to be more effective in reducing 24-h blood glucose than morning exercise in people with type 2 diabetes [6]. This study utilized high-intensity interval training and acknowledged that due to diverse hormonal responses and fuel utilization, less intense forms of exercise may have different effects. Therefore, the impact of an acute bout of afternoon walking on CGM outcomes in individuals with type 2 diabetes (T2D) remains unclear.

The Exercise-Physical Activity and Diabetes Glucose Monitoring (E-PAraDiGM) protocol was developed to be feasibly implemented across many sites to facilitate exercise and CGM data collection on a large number of participants under standardized conditions (ClinicalTrials.gov identifier: NCT02834689).

The primary objective of the present study was to examine the effect of a standardized bout of walking before dinner on mean 24-h glucose concentrations, assessed using CGM, in individuals with T2D across multiple sites. Secondary outcomes included glycemic variability, postprandial glucose and time spent with glucose > 10 mmol/L.

Methods

Participants

Participants were recruited across eight sites in Canada (see Supplemental Material). Recruitment strategies varied across sites and included newspaper or radio advertisements, posters in gyms, information sessions and recruitment through existing databases of past research participants. Ethical approval was obtained by individual research ethics boards at each site in both English and French.

A baseline visit was included to determine participant eligibility. Participants with physician-diagnosed T2D aged 30–90 years with a glycated hemoglobin (HbA1c) < 75 mmol/mol (< 9.0%) were eligible. Those who had changes in diabetes medication or body mass (i.e. > 2.27 kg) within the last 3 months were excluded until stability was achieved. Exclusion criteria included: exogenous insulin; previous myocardial infarction, stroke or coronary artery disease; unable to walk; resting blood pressure > 159/99 mmHg; or resting HR > 99 bpm. Participants completed questionnaires regarding medical history, sleep behavior (Pittsburgh Sleep Quality Index) and physical activity (PA) (Godin Leisure-Time Exercise Questionnaire). Anthropometric measurements were obtained, and a 15-min treadmill session at 5.0 km/h (0.5% grade) was included for familiarization. Participants who could not walk for the 15 min during the baseline visit were deemed ineligible.

E-PAraDiGM protocol

Eligible participants were asked to complete the 6-day E-PAraDiGM protocol (Supplemental Table S1) during which they wore a CGM and completed exercise (EX) and seated control (CON) conditions in random order. Randomization was stratified by sex and completed in blocks of 4, 6 or 8 participants using an online generator [7]. The randomization was uploaded within Research Electronic Data Capture (REDCap) software and accessed by the study coordinators at each site. Allocation was concealed until after the baseline visit.

Participants reported to the laboratory on day 1 for CGM sensor insertion in the abdominal area (iPro™ 2 professional CGM, Medtronic, Northridge, CA, USA, and Enlite™ sensor). Participants were then given standardized breakfast, lunch and snacks for the following day, and were instructed on how to fill log books (i.e., record timing and quantity of each meal and snack). They were also reminded to take and log four daily capillary glucose (ONETOUCH® Ultra2 [8], Johnson & Johnson, Burnaby, Canada), and to continue using medications as prescribed. Capillary samples were obtained before each meal and before bedtime to assess meal timing in free-living conditions and to calibrate the CGM. Participants wore a pedometer (Yamax DigiWalker 200, Yamax Corporation, Tokyo, Japan) throughout the protocol. On days 2 and 5, participants arrived at the laboratory 3–5 h after consuming their standardized lunch for their randomized conditions (i.e., walking or seated control). While the exact time of day varied slightly from one participant to another, the time was standardized within participants. 20 min after the completion of each condition, participants consumed their standardized dinner in the laboratory and were given meals for the following day. Day 4 (i.e., washout) was included to allow for 72 h between the beginning of the EX and CON conditions to minimize potential carryover effect of the bout of exercise if completed first. Participants were instructed to continue normal activity patterns and did not consume standardized meals on day 4, but wore the pedometer to assess activity levels.

The laboratory conditions included 50 min of treadmill walking (5.0 km/hour and 0.5% incline), or 50 min of sitting. A 5-min warm up and cooldown at a pace of 3.5 km/hour and 0.0% grade were included within the 50 min of

walking. This protocol was chosen as walking is an accessible, preferred and tolerable form of physical activity for many individuals with T2D [9] and since 150 min of moderate intensity physical activity, a week is recommended by many guidelines [3, 4] (e.g., 3 × 50 min bouts). Heart rate (HR) (Polar HR monitors, Polar Electro, Kempele, Finland) and ratings of perceived exertion (RPE) using a 0–10 point scale were monitored during exercise and recorded every 5 min. Intensity was estimated as a percent of maximal HR where maximal HR was estimated as 208 − 0.7 × age [10].

Blood pressure and capillary glucose were assessed before and after each session. Indirect calorimetry was used at three of the eight sites from minutes 5 to 10 and 40 to 45 during the EX and CON conditions to measure oxygen consumption for energy expenditure estimation (expressed as metabolic equivalents; METS) and respiratory exchange ratio (RER) for substrate oxidation. Camrose and Edmonton sites used the Parvo Medics TrueOne® 2400 Metabolic Measurement System (Sandy, Utah, USA), whereas the Sherbrooke site used the CCM Express system (Medgraphics Cardiorespiratory Diagnostic, St Paul, MN) during CON and a breath-by-breath system (Ergocard, MedISoft, Sorinnes, Belgium) during EX.

Standardized meals

Participants were provided with all food (breakfast, lunch, dinner and snacks) for days 2, 3, 5 and 6 of the protocol, and medications were unchanged. The Harris–Benedict equation was used to estimate participant resting metabolic rate (RMR), and was multiplied by 1.4 to estimate total daily energy expenditure of a sedentary day [11]. The same energy intake was provided on the EX and CON days. The macronutrient targets were based on Diabetes Canada recommendations (45–60% carbohydrate, 20–35% fat and 15–20% protein) [12]. Meals and snacks for each participant were the same on the EX and CON days (i.e., day 2 matched day 5) and the days following the testing days (i.e., day 3 matched day 6). Within these guidelines, each site had the flexibility to adapt foods according to participant preferences and regional availability. Most used grocery store items included fruits, vegetables, yoghurt, bread, nuts and frozen meals, as well as gift cards to sandwich restaurants with instructions to replicate between conditions.

Outcome measures

The primary outcome was mean 24-h glucose assessed by CGM. Secondary outcomes included mean 2-h postprandial glucose, fasting glucose, glycemic variability as measured by mean amplitude of glycemic excursions [MAGE] [13], time spent > 10 mmol/L, time spent < 4 mmol/L, time in range (4–10 mmol/L) and changes in glucose during the 50-min EX and CON. Data from the CGM were downloaded to Excel files using Medtronic CareLink™ software and compared between the 24-h periods, which started immediately prior to the 50 min of exercise or seated control. The specific timing of the overnight fasting period, beginning of meals and conditions was identified by the capillary glucose sample and the time indicated in participant log books. EasyGV© software (www.easygv.co.uk) was used to calculate MAGE.

Prior to the EX and CON conditions, fasting glucose and 2-h postprandial glucose concentrations for the standardized breakfast and lunch were compared between conditions to examine reliability since this time period had not been influenced by the experimental conditions. Additionally, 24-h glucose was assessed on day 4 (washout) to compare glucose outcomes from a period where standardized meals were not provided.

Statistical analysis

The primary analyses were limited to participants who had complete 24-h glucose profiles (i.e., no missing CGM data) and completed the interventions without known major issues that would affect glucose (e.g., protocol deviations, acute illness). T tests were performed to compare baseline characteristics of participants who met the criteria for primary analyses to those who did not. Linear mixed effect models were used to examine the treatment effect. The analysis was adjusted for time period effects. As separate analyses, we also assessed the carryover effect and the difference between CON and the 24-h washout using a mixed effects model. Given that carryover effect was not expected and we did not have any evidence of such effect from our analysis, carryover effect was not included in the main analysis. For the analysis of time > 10 mmol/L and time in range, linear mixed effect model was not appropriate as the data were heavily skewed. Thus, we converted the data into proportion of time > 10 mmol/L and proportion of time in range, and applied mixed effects beta model. For time < 4 mmol/L, given that few participants experienced < 4 mmol/L, mixed effect binomial regression was used to examine the likelihood of having any glucose < 4 mmol/L. For these analyses, treatment and time period effects were expressed as odds ratios.

In order to test for potential differences in treatment effect between subgroups (male vs. female; BMI < 24.9, 25.0–25.9, > 30 kg/m^2; Age < 60, 60–69, > 70 y; HbA1c quartiles < 6.2, 6.3–6.8, 6.9-7.3, > 7.3; treadmill speed as prescribed vs. lowered treadmill speed), an interaction term between treatment and the subgroup variable was included in the mixed effect model to facilitate the estimation and comparison of treatment effect by subgroup. T tests were used for simple pairwise comparisons (e.g., steps per day on the EX vs. CON day). The alpha level was set at 0.05, and

all results are presented as mean values ± standard deviation (SD) or mean differences with 95% confidence intervals (CI). Analyses were conducted using SAS 9.4 (SAS Institute, Cary NC).

Results

Between May 2016 and September 2017, 142 individuals were screened for inclusion (see Fig. 1). Eighty participants were randomized and 73 participants completed the EX and CON conditions. Overall, participants were diagnosed with T2D for 9.5 ± 6.0 years and included 33 males and 40 females. Female participants who were menstruating ($n = 2$) completed the protocol during the follicular phase. Of the 73 who completed the within-laboratory component of the EX and CON conditions, 63 participants were included in the primary analyses of CGM outcomes (see Fig. 1 for reasons for exclusion). Seventeen participants required small reductions in walking speed (walking speed at completions ranging from 3.0 to 4.8 km/h). Baseline characteristics of the 73 participants who completed both experimental conditions, and of the subsets with and without CGM data, are presented in Table 1.

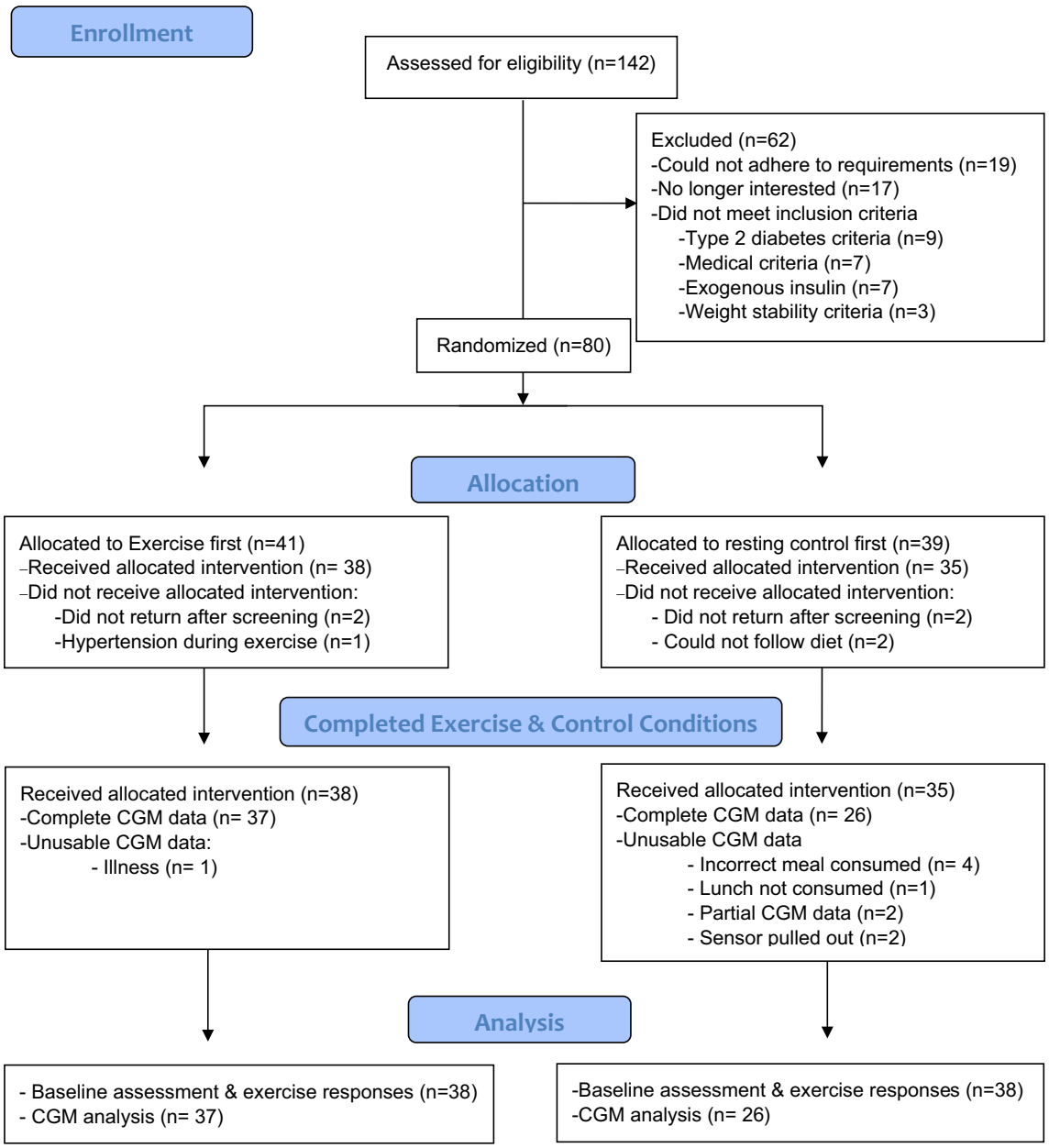

Fig. 1 CONSORT flow diagram

Table 1 Baseline characteristics

	All ($n=73$)	Per protocol + CGM data ($n=63$)	Missing data ($n=10$)	(P value per protocol vs. missing)
Sex (M/W), (*n*)	33/40	29/34	4/6	0.72
Age (years)	63.5 ± 9.1	64.4 ± 8.0	58.3 ± 13.3	*0.049
Duration of Diabetes (yrs)	9.5 ± 6.0	9.7 ± 6.1	8.6 ± 5.9	0.59
HbA1c (mmol/mol)	51 ± 0.9	51 ± 8	55 ± 11	0.20
HbA1c (%)	6.9 ± 0.8	6.8 ± 0.7	7.2 ± 0.9	0.20
HDL	1.37 ± 0.49	1.38 ± 0.51	1.33 ± 0.30	0.81
LDL	2.34 ± 0.82	2.37 ± 0.83	2.08 ± 0.80	0.38
TC	4.32 ± 0.98	4.33 ± 1.00	4.23 ± 0.80	0.80
TG	1.63 ± 0.84	1.63 ± 0.87	1.63 ± 0.61	0.99
Serum creatinine	80.12 ± 17.83	81.32 ± 17.87	71.57 ± 16.20	0.18
Resting SBP (mmHg)	127 ± 13	128 ± 13	121 ± 7	0.16
Resting DBP (mmHg)	75 ± 8	75 ± 9	75 ± 6	0.95
RHR (bpm)	71 ± 11	71 ± 10	77 ± 11 (9)	0.07
Height (cm)	166.7 ± 10.7	166.5 ± 10.2	167.7 ± 14.2	0.76
Weight (kg)	86.2 ± 20.0	84.9 ± 18.1	94.4 ± 28.9	0.16
BMI (kg/m^2)	30.9 ± 6.9	30.5 ± 6.5	33.3 ± 8.9	0.23
WC (cm)	106.2 ± 14.9	105.3 ± 14.4	111.3 ± 17.4	0.24
HC (cm)	110.0 ± 13.0	109.1 ± 12.0	116.0 ± 18.2	0.14
WC:HC	0.96 ± 0.07	0.96 ± 0.07	0.97 ± 0.05	0.71
Sleep (PSQI)	5 ± 3	5 ± 3	6 ± 5	0.19
Depression (PHQ-8)	3 ± 3	3 ± 3	3 ± 4	0.57
PA (GLTEQ)	36 ± 21	35 ± 20	45 ± 29	0.18
Glucose medications (%)				
Metformin	81	84	60	0.07
Sulfonylurea	21	19	30	0.43
DPP-4 inhibitor	25	25	20	0.71
SGLT2 inhibitor	18	16	30	0.28
TZD	1	2	0	0.69
GLP-1 agonist	3	2	10	0.13
BP medications (%)				
Calcium channel blocker	22	24	10	0.33
Beta blocker	11	13	0	0.23
ARB	22	24	10	0.33
ACE inhibitor	27	30	10	0.18
Diuretic	14	14	10	0.71
Lipid medications (%)				
Statin	53	54	50	0.82
Fibrate	3	3	0	0.57

n sample size, *M* men, *W* women, *years* years, *HbA1c* glycated hemoglobin, % percent, *mmol/L* millimole per liter, *HDL* high-density lipoprotein cholesterol, *LDL* low-density lipoprotein cholesterol, *TC* total cholesterol, *TG* triglycerides, *µmol/L* micromole per liter, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *mmHg* millimeters of mercury, *RHR* resting heart rate, *bpm* beats per minute, *cm* centimeters, *kg* kilograms, *BMI* body mass index, *WC* waist circumference, *HC* hip circumference, *PSQI* Pittsburgh Sleep Quality Index, *PHQ-8* Patient Health Questionnaire, *PA* physical activity, *GLTEQ* Godin Leisure-Time and Exercise Questionnaire (physical activity). Sample size was $n=30$ for body fat and ranged from $n=55$ to 61 for lipids and creatinine

The same meals were provided on days 2 and 5, which corresponded to 2157 ± 358 kcal. The same meals were provided on days 3 and 6, which corresponded to 2162 ± 359 kcal. The overall macronutrient distribution was 53% carbohydrate, 31% fat and 17% protein. The macronutrient breakdown (% energy) by meal ranged from 48 to

58% CHO, 25–34% fat and 16–18% protein, where breakfast and lunch had higher proportions of carbohydrate but lower proportions of fat compared to dinner (all, $P < 0.01$).

Exercise responses

Table 2 describes responses to exercise. Mean heart rate during exercise corresponded to 65 ± 9% of estimated maximal heart rate. Those who required a small reduction in walking speed exercised at a greater percent of maximal heart rate (69 ± 7 vs 64 ± 0%, $P = 0.03$). Overall, the mean RPE was 3 ± 1, which corresponded to "easy." In the subsample of 21 participants for whom metabolic cart data were available, the mean MET value was 3.9 ± 0.4 with an RER of 0.85 ± 0.05.

Total steps during the treadmill walking were available in 41 participants and corresponded to 4447 ± 1346 steps. The total number of steps on the EX condition day was greater than the CON condition day by 3175 ± 3887 steps ($P < 0.001$). However, when comparing the second day of the EX and CON conditions (i.e., days 3 or 6, after the laboratory visits), there were 1139 ± 3899 fewer steps in the EX condition compared to CON, although this difference did not reach statistical significance ($P = 0.059$).

CGM outcomes with exercise vs. control

Figure 2A shows the mean 24-h glucose profiles from the EX and CON conditions. Figure 2B shows the individual participant change in mean 24-h glucose between conditions. Table 3 describes the results relating to the CGM outcomes of interest. In initial analyses, there was an effect of time period, whereby the crossover condition that occurred second had slightly higher glucose concentrations (0.22 mmol/L; 95% CI 0.02, 0.41, $P = 0.028$) and therefore, all subsequent analyses were adjusted for time period and presented accordingly. There was no difference in mean 24-h glucose between the EX and CON conditions (0.03 mmol/L; 95% CI − 0.17, 0.22, $P = 0.778$). Results were similar when time period effect was not included in the model. On the other hand, the mean 24-h glucose was higher on the washout day when no standardized meals were provided, compared to CON (0.61 mmol/l; 95% CI 0.33, 0.89, $P < 0.001$), but there was no order effect as the mean glucose concentrations on the washout day were unaffected whether they were preceded by EX or CON (preceded by EX = 8.0 ± 1.7, preceded by CON = 8.0 ± 2.3 mmol/L, $P = 0.98$). There were no significant interaction effects detected in subgroup analyses for sex, BMI, age, baseline HbA1c or treadmill speed.

There were no differences between EX and CON conditions for MAGE, fasting glucose, postprandial glucose or proportion of time spent > 10 mmol/L. Time < 4 mmol/L was infrequent in most participants; 5 (8%) and 15 (24%) participants experienced some time spent < 4 mmol/L in the EX and CON conditions, respectively (Odds ratio = 0.20; 95% CI [0.07, 0.56], $P = 0.003$). There were no consistent interaction effects detected in subgroup analyses for sex, BMI, age, baseline HbA1c or treadmill speed.

Glucose was reduced during the 50 min of EX compared to CON (−1.56 mmol/L; 95% CI: −2.18, −0.95, $P < 0.001$) with glucose being reduced from 7.9 ± 2.1 to 6.1 ± 1.6 mmol/L after exercise ($P < 0.0001$).

Table 2 Response to 50 min of walking (or rest)

Variable	EX	CON	*P* value (EX vs CON)
HR, bpm	106 ± 14	NA	NA
HR, % max	65 ± 9	NA	NA
RPE, 0–10 scale	3 ± 1	NA	NA
METs ($n = 21$)	3.9 ± 0.4	1.0 ± 0.4	< 0.001
VO_2, L/min ($n = 21$)	1.07 ± 0.26	0.27 ± 0.14	< 0.001
RER ($n = 21$)	0.85 ± 0.05	0.85 ± 0.08	0.836
Steps			
Pre-50 min of exercise	4435 ± 3330	NA	NA
Post-50 min of exercise	8881 ± 4129	NA	NA
Total steps, first day (i.e. day 2 or 5)	10766 ± 4504	7591 ± 4215	< 0.001
Total steps, second day (i.e. day 3 or 6)	6420 ± 4079	7560 ± 3884	0.059
Total steps, washout	6783 ± 4165		

n sample size, *NA* not applicable, *SD* standard deviation, *HR* heart rate, *bpm* beats per minute, *RPE* rate of perceived exertion, *EX* exercise condition, *CON* seated control condition, *METs* metabolic equivalents, *VO_2* volume of oxygen consumed, *L/min* liters per minute, *RER* respiratory exchange ratio. Metabolic data on $n = 23$. Pedometer data on $n = 41$ during exercise, $n = 54$ during days

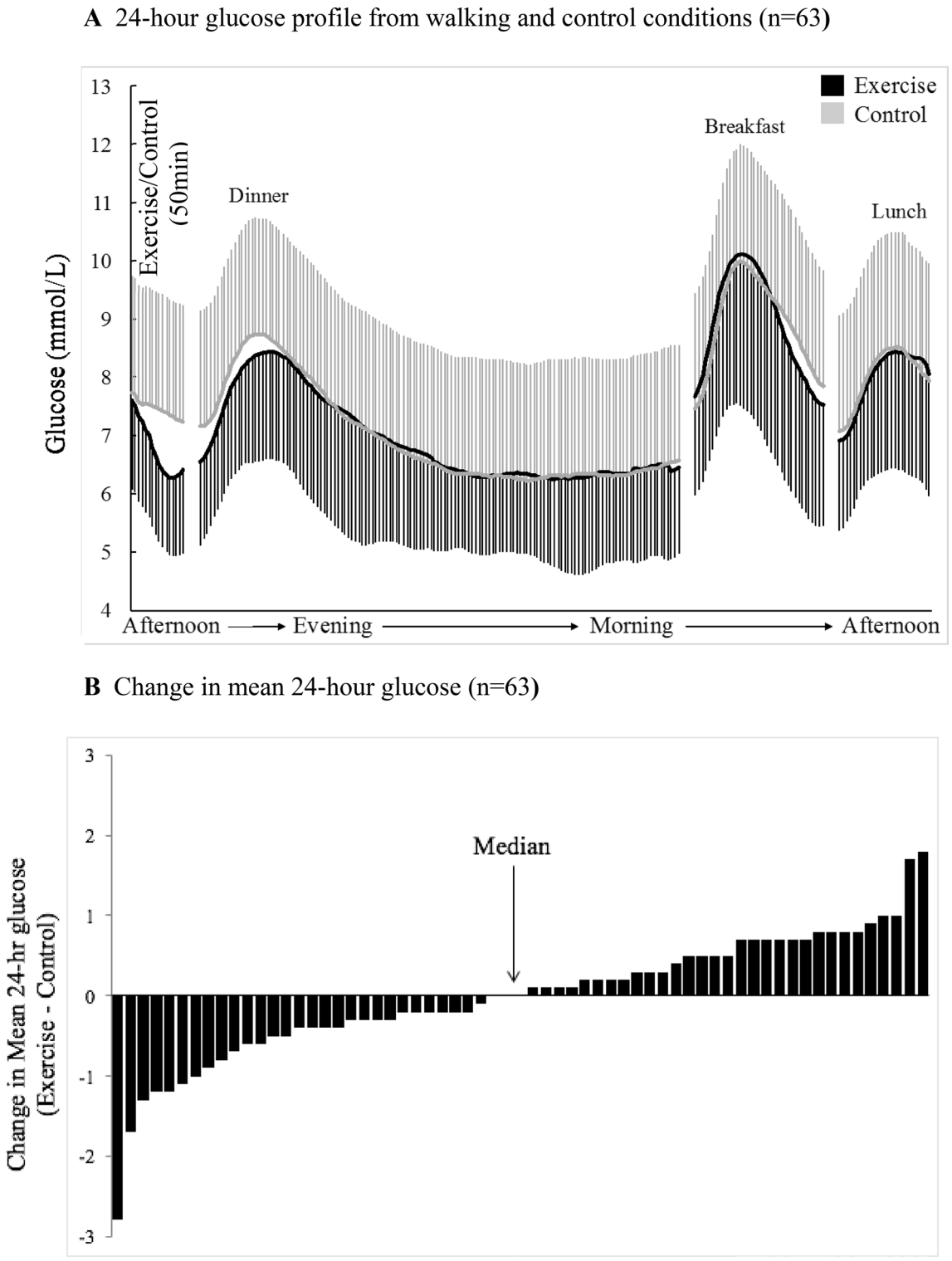

Fig. 2 **a** 24-h glucose profile from walking and control conditions ($n=63$). **b** Change in mean 24-h glucose ($n=63$)

Discussion

To our knowledge, this is the largest study to examine the acute effect of exercise on 24-h CGM glucose profiles in individuals with T2D. Contrary to our hypothesis and most previous morning exercise studies with smaller samples sizes [5], there was no effect of walking before dinner on CGM outcomes measured in the 24 h following exercise.

Table 3 Continuous glucose monitoring outcomes

	EX	CON	Estimated treatment effect (95% CI)	*P* value
Mean 24-h glucose (mmol/L)			0.03 (−0.17, 0.22)	0.778
Period 1	7.4 ± 1.5	7.3 ± 1.4		
Period 2	7.6 ± 1.8	7.6 ± 1.8		
MAGE (mmol/L)			−0.34 (−0.79, 0.11)	0.137
Period 1	4.2 ± 1.8	4.5 ± 2.2		
Period 2	3.7 ± 1.4	4.1 ± 1.8		
Fasting glucose (mmol/L)	7.3 ± 1.6	7.0 ± 1.7	0.23 (−0.07, 0.53)	0.126
Mean 2-h post-dinner glucose (mmol/L)			−0.18 (−0.50, 0.14)	0.264
Period 1	7.9 ± 1.5	7.8 ± 1.3		
Period 2	8.0 ± 1.5	8.4 ± 2.2		
Mean 2-h post-breakfast glucose (mmol/L)	9.4 ± 2.4	9.3 ± 2.5	0.10 (−0.26, 0.46)	0.582
Mean 2-h post-lunch glucose (mmol/L)	8.2 ± 2.1	8.1 ± 2.2	0.02 (−0.40, 0.43)	0.938
Mean 2-h post-meals glucose (mmol/L)	8.5 ± 1.8	8.5 ± 1.9	−0.02 (−0.25, 0.21)	0.876
Proportion (%) of time > 10 mmol/L	4 [0–17]	7 [0–18]	0.90 (0.64, 1.28)	0.564
Experienced glucose < 4 mmol/L			0.20 (0.07, 0.56)	0.003
Period 1	4/37 (10.8%)	10/26 (38.5%)		
Period 2	1/26 (3.8%)	5/37 (13.5%)		
Proportion (%) of time in range (4–10 mmol/L)	95 [83, 100]	91 [77, 98]	1.28 (0.89, 1.82)	0.177
Glucose change during 50 min of exercise or seated rest (mmol/L)	−1.8 ± 1.8	−0.3 ± 1.6	−1.56 (−2.18, −0.95)	< 0.001

MAGE: mean amplitude of glycemic excursion, Ex: exercise condition, CON, control condition. Results presented as mean ± standard deviations, as median [interquartile range] or count with percentage. Descriptive summaries were broken down by time period if period effect was statistically significant in the regression analysis. Treatment effects estimated from linear mixed effects model were expressed as mean difference or odds ratio for EX vs. CON. *P* value determined from linear mixed effects model adjusted for time period

Although the mean difference between conditions was minimal, the variability in response to the same bout of exercise was large, with changes in 24-h mean glucose ranging from −2.8 to +1.8 mmol/L.

The exercise volume and intensity in our study is similar to previous smaller studies that have shown significant reductions in CGM-derived glucose. For example, Manders et al. [14] compared the effect of single bouts of cycling on glucose profiles in participants who had a mean HbA1c of 54 mmol/mol (7.1%). Cycling was performed in the morning for either 30 min at 70% of maximum workload (high intensity), or 60 min at 35% of maximum workload (low intensity). They found that mean 24-h glucose was 9.4 mmol/L following the control condition but 7.8 and 8.8 mmol/L following the low-intensity and high-intensity conditions, respectively [14]. A potential explanation for the absence of changes in CGM-derived glucose outcomes in the E-PAraDiGM protocol may be related to the timing of exercise, which was performed 3–5 h after lunch and 20 min before the evening meal. For example, 8 out of the 10 subgroups included in the meta-analysis by MacLeod et al. [5], including the study by Manders et al. [14] completed exercise soon after breakfast (1–2.5 h after), and two studies did not specify time since breakfast. A subsequent study showed improvements in glycemic control when exercise was performed either before or after breakfast [15]. Further support for the idea that exercise timing may have led to the absence of changes in CGM-derived variables comes from a study in older adults who did not have diabetes, which found improvements in mean 24-h glucose when 45 min of exercise was performed at 10:30 AM but not when performed at 4:30 PM [16].

One of the strengths of our study was the provision of all meals and snacks during the 2 days for both the EX and CON conditions. In previous studies, a variety of different nutritional approaches have been used, including asking participants to replicate their usual diet [17–19], prescribing a diet [20], providing standardized meals [15, 21, 22] or combinations thereof [21, 23]. Providing a standardized diet can help to minimize confounders such as dietary compensation that can occur following exercise in free-living situations. However, it is possible that our prescribed energy intake introduced a bias. For example, we may have provided participants less food than they typically would eat under free-living conditions (or provided healthier alternatives). Indeed, greater mean 24-h glucose was observed on the washout day when individuals resumed their normal daily activities compared to the

CON day. Studies have shown that greater plasma glucose concentrations before exercise as well as exercising after a meal both lead to greater reductions in glucose during or shortly after exercise [24–26].

Consequently, our protocol may have been expected to lead to a reduced glucose-lowering effect of exercise. Nonetheless, we did observe a significant reduction in glucose during the 50 min of EX versus CON, but this did not translate in reductions over 24 h.

Participants included in the E-PAraDiGM protocol were likely more active than the average persons living with T2D. For example, average step count of participants on the washout day was 6783, which is ~2000 steps higher than the average based on previous reports in people with T2D [27]. This may have had affected insulin sensitivity on the control day compared to participants who are more sedentary and may help to explain why there were no observed differences in CGM variables between EX and CON. Participants also had 1139 fewer steps on the day following the EX condition compared to CON ($P=0.059$), suggesting potential compensation following exercise. However, we found no association between steps per day or the scores from the Godin Leisure-Time Exercise Questionnaire and the difference between EX and CON of 24-h glucose outcomes.

The study is strengthened by the randomized design, tight control of diet between trials and the relatively large sample size. However, there are some limitations that should be considered. First, of the 80 randomized participants, complete data were available on only 63 participants. We only studied a single dose of exercise and therefore, it is unclear if the walking session performed was insufficient to elicit a glucose-lowering effect. In this regard, the same walking speed was selected for each participant and not individualized to their fitness level. These decisions were made to enhance the external validity of the findings, as many guidelines encourage individuals with T2D to walk for exercise. CGM data also indicated a time period effect, with higher glucose on day 5 compared to day 2 (regardless of randomization order). There is no readily apparent explanation for this, as we performed further exploratory analyses to examine whether day of the week or site may have impacted the results and did not detect any evidence of these factors influencing glucose responses to exercise.

In conclusion, we found that a single bout of walking performed before dinner did not result in changes in most CGM outcomes over 24 h, with the notable exception of a decrease in glucose during exercise itself. Overall, the variability in responses was large. The E-PAraDIGM protocol was feasibly implemented across multiple sites and could be implemented in other settings to compare responses among participants with different characteristics or in response to other exercise interventions.

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Author contributions JLR, CRC, MEF, AMC, AF, NDK, RAD, DRF, GS, KB, FEG and MCD collected the data. JLR, ER, JMM, JEY, RJS, MJG, JSW, CMP, MJ, RM, NGB and JPL provided substantial contributions to the conception or design of the work. JLR, NGB and JPL drafted the article, and all others revised it critically for important intellectual content. TL and JS designed and performed the statistical analyses. All authors provide final approval of the submitted version and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Conflict of interest JEY has received in-kind research support from Animas Canada, Dexcom Canada and Abbott Nutrition Canada. JPL is a scientific advisor and shareholder with Metabolic Insights Inc., a start-up company developing a noninvasive metabolic monitoring device. JPL is a volunteer chief scientific officer for the not-for-profit Institute for Personalized Therapeutic Nutrition (www.therapeuticnutrition.org).

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (University of Alberta Health Research Ethics Board: Pro00059779, The University of British Columbia Clinical Research Ethics Board: H1600377, Conjoint Health Research Ethics Board at the University of Calgary: REB16-1049, University of Manitoba Health Research Ethics Board: HS20322, Hamilton Integrated Research Ethics Board: 1695, Comité d'éthique de la recherche du CIUSSS de l'Estrie-CHUS: #MP-31-2017-1601) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Data availability The datasets generated during and/or analyzed during the current study are not publicly available as participants did not provide consent to this form of data sharing. Aggregated data and additional analyses are available from the corresponding author on reasonable request.

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