The Acute Effects of Interval- Vs Continuous-Walking Exercise on Glycemic Control in Subjects With Type 2 Diabetes: A Crossover, Controlled Study

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Context: Glycemic control improves with physical activity, but the optimal exercise mode is unknown.

Objective: The objective of the study was to determine whether interval-based exercise improves postprandial glucose tolerance and free-living glycemia more than oxygen consumption- and time duration-matched continuous exercise.

Design: This was a crossover, controlled study with trials performed in randomized order.

Setting: The study was conducted in hospitalized and ambulatory care.

Patients: Patients diagnosed with type 2 diabetes mellitus (n = 10, no withdrawals) participated in the study.

Interventions: Subjects performed three 1-hour interventions: 1) interval walking (IW; repeated cycles of 3 min of slow and fast walking); 2) continuous walking (CW); and 3) control (CON). Oxygen consumption (VO_2) was measured continuously to match mean VO_2 between exercise sessions (~75% VO_2peak).

Main Outcome Measures: A mixed-meal tolerance test (MMTT; 450 kcal, 55% carbohydrate) with stable glucose isotopic tracers was provided after each intervention, and glucose kinetics were measured during the following 4 hours. Free-living glycemic control was assessed for approximately 32 hours after the MMTT using continuous glucose monitoring.

Results: VO_2 was well matched between the exercise interventions. IW decreased the mean and maximal incremental plasma glucose during the MMTT when compared with the CON (mean 1.2 ± 0.4 vs 2.0 ± 0.5 mmol/L, $P < .001$; maximal 3.7 ± 0.6 vs 4.6 ± 0.7 mmol/L, $P = .005$) and mean when compared with CW (1.7 ± 0.4 mmol/L, $P = .02$). No differences in the mean or maximal incremental plasma glucose values were seen between the CW and CON. The metabolic clearance rate of glucose during the MMTT was increased in the IW compared with CW ($P = .049$) and CON ($P < .001$). Continuous glucose monitoring mean glucose was reduced in IW compared with CW for the rest of the intervention day (8.2 ± 0.4 vs 9.3 ± 0.7 mmol/L, $P = .03$), whereas no differences were found between IW and CW the following day.

Conclusions: One interval-based exercise session improves glycemic control in type 2 diabetes mellitus subjects when compared with an oxygen consumption- and time duration-matched continuous exercise session. **(*J Clin Endocrinol Metab* 99: 3334–3342, 2014)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received March 25, 2014. Accepted May 21, 2014.
First Published Online June 6, 2014

Abbreviations: CGM, continuous glucose monitoring; CON, control; CW, continuous walking; HR, heart rate; IW, interval walking; MCR, metabolic clearance rate; MMTT, mixed-meal tolerance test; Ra_{ENDO}, endogenous rates of glucose appearance; Ra_{MMTT}, exogenous rates of glucose appearance from the MMTT; Rd, rate of glucose disappearance; RPE, rate of perceived exertion; T2DM, type 2 diabetes mellitus; VO_2, oxygen consumption; VO_2max, maximal oxygen consumption rate; VO_2peak, peak oxygen consumption rate.

It has been known for many years that peripheral tissue glucose disposal is increased and blood glucose is lowered in subjects with type 2 diabetes mellitus (T2DM) after an exercise session under carefully controlled, laboratory conditions (1). Under free-living conditions, recent work has shown reduced glycemia over the day after an exercise bout in T2DM subjects (2, 3). However, the type and mode of exercise that results in the best improvement is unknown.

Interval training interventions with alternating periods of low- and high-intensity improve glycemic control more than training interventions with constant intensity (4, 5). Changes in several variables, such as improved body composition (6), fitness level (7), mitochondrial capacity (8), insulin sensitivity (9), and vascular function (10), may be responsible for this. However, in T2DM subjects, less is known about the acute effect of a single interval exercise session on glycemic control. Gillen et al (11) found reduced hyperglycemia in T2DM subjects for 24 hours after a single high-intensity interval exercise session but did not make a comparison with a noninterval exercise session. Interestingly, a single high-intensity, noninterval exercise session has been found to result in inferior improvements in glycemic control when compared with a low-intensity, noninterval exercise session (12). Thus, results are ambiguous and because no crossover, controlled trial comparing an interval-based vs a continuous exercise session in T2DM subjects has been conducted, it is not clear whether interval-type or continuous-type exercise is the better for improving glycemic control.

We have previously shown that 4 months of free-living interval-walking (IW) training improves glycemic control more than energy expenditure- and time duration-matched continuous-walking (CW) training in T2DM subjects (13). If this superior training effect of IW is also evident after a single IW session is not known. Because regular physical activity is necessary for maintained improvements in glycemic control (14, 15), T2DM subjects are recommended to exercise at least three times weekly, with no more than 2 days in a row without exercise (16). As such, T2DM subjects will ideally spend most of their life within 2 days after an exercise session and consequently, the acute effects of exercise interventions are clinically important. Thus, the acute effects of all exercise interventions need to be investigated.

In this study, the aim was to determine the differential effect of a single IW session vs an oxygen consumption- and time duration-matched CW session on glycemic control in T2DM subjects, under controlled as well as free-living conditions. Moreover, the aim was to assess underlying differences in glucose kinetics. We hypothesized that an IW session would decrease daytime glycemic levels and lower postprandial hyperglycemia more than a CW session due to increased peripheral glucose disposal.

Materials and Methods

Subjects

Subjects with T2DM (16) were recruited and underwent a medical screening. Exclusion criteria were the use of exogenous insulin; use of β-blocking agents; smoking; pregnancy; evidence of liver, renal, or cardiopulmonary disease; and diseases contraindicating physical activity (17). Subjects filled out a baseline physical activity questionnaire (18) and underwent a medical screening including an oral glucose tolerance test, a dual-energy X-ray absorptiometry scan (Lunar Prodigy Advance; GE Healthcare), a graded walking oxygen consumption rate (VO_2) peak test (13, 19, 20) with a portable indirect calorimetric system (Cosmed K4b^2), and a treadmill-based (Technogym Runrace) maximal oxygen consumption rate (VO_2max) test [walking with incremental inclination (13)] using a stationary indirect calorimetry system (Cosmed Quark). The peak oxygen consumption rate (VO_2peak) test consisted of three 3-minute stages, during which subjects on flat ground walked with slow, moderate, and fast speed, respectively, and VO_2peak was calculated as the mean oxygen consumption during the last 1 minute of the fast stage, as originally described (19). Conversely, the VO_2max test consisted of 1-minute stages until exhaustion, and VO_2max was calculated as the mean oxygen consumption during the 20 consecutive seconds with the highest oxygen consumption.

Finally, familiarization to the exercise sessions was performed at the screening, which took place 1–2 weeks prior to the first trial. Written informed consent was obtained from all subjects. The study was approved by the Ethical Committee of the Capital Region of Denmark and registered at www.clinicaltrials.gov (NCT01987258).

Trials

Three trials were performed in a randomized, counterbalanced order. Trials were identical except for the following interventions: 1) 1 hour of IW, 2) 1 hour of oxygen consumption-matched (CW), and 3) no walking (CON). The intervention days were separated by 1–2 weeks, and subjects were instructed to pause antidiabetic medication and avoid vigorous physical activity and alcohol from 48 hours before the intervention day until after each trial. In each trial, total activity monitoring [Actiheart; CamNtech (a triaxial accelerometer (21)], continuous glucose monitoring (CGM; Guardian Real-Time with Enlite glucose sensor; Medtronic), and online diet recordings (www.madital.dk, based on reference 22) were performed for 3 full days with the intervention day being the middle day. The subjects were instructed to eat the same food the day prior to the intervention day in all three trials and otherwise to maintain a normal, free-living behavior with respect to dietary intake.

Intervention day

At 8:00 AM, after an overnight fast ($\geq$8 h), body weight was measured by standard procedures and bilateral antecubital venous lines for tracer infusion and blood sampling were placed. A primed (20 μmol/kg multiplied by fasting glucose divided by 5 mM), continuous (0.3 μmol/kg·min) infusion of [6,6-$^2H_2$]glucose

tracer was initiated. Subjects remained in a supine position for a 1-hour tracer loading period. The intervention was then begun with both IW and CW performed on a treadmill with 1% incline [except for one subject who, due to unpleasantly high walking speeds (corresponding to 7.6 km/h at 1% incline during fast IW), walked with 7% incline during both CW and IW (corresponding to 6.2 km/h during fast IW)]. Breath-by-breath indirect calorimetry (Cosmed Quark) was applied throughout the sessions. The goal was to match overall oxygen consumption in IW and CW, with IW consisting of alternating slow and fast intervals (3 min each) aiming at 54% and 89% of VO_2peak, respectively, and with the CW intensity aimed at 73% of VO_2peak, as previously found (13). Walking speed was adjusted to ensure correct intensities. Heart rate (HR) was monitored throughout the sessions (Cosmed; wireless HR monitor). The rate of perceived exertion (RPE) during and after the exercise interventions (and during both slow and fast intervals in IW) was assessed using a Borg Scale (23).

After the intervention, the subjects recovered in a chair. During CON, the subjects also sat on the chair during the intervention. Forty-five minutes after the cessation of the intervention, the subjects were moved to a bed and a 4-hour standardized liquid mixed-meal tolerance test (MMTT; 300 mL, 450 kcal; macronutrient composition: 15% protein, 55% carbohydrate, 30% fat) spiked with 2 g of [U-$^{13}C_6$]glucose tracer was begun. After the cessation of the MMTT, subjects left the laboratory for free-living activity, CGM and diet record monitoring during the following approximately 32 hours.

Blood sampling and analyses

Blood was sampled at the intervention day at baseline and during (in the IW intervention during both slow and fast intervals) and after the intervention and every 15 minutes throughout the MMTT (samples for tracer enrichment analyses were obtained only until 3 h into the MMTT). Glucose and lactate were measured immediately (ABL 7 series; Radiometer). Tracer (NaF plasma tubes) and glucagon [EDTA plasma tubes coated with aprotinin (50 kIU/mL) and dipeptidyl peptidase-4 inhibitor (0.01 mmol/L diprotin A; Sigma)] samples were immediately placed on ice and subsequently centrifuged (2000 × *g*, 15 min, 4°C). Insulin (serum tubes) samples were left at room temperature for 30 minutes before centrifugation. Samples were stored at −80°C until analysis. Stable isotope tracer analyses were performed using liquid chromatography mass spectrometry by a hexabenzoyl derivative method, as previously described (24). Glucagon concentrations were measured by a RIA (Millipore), in line with the manufacturer's instructions. Insulin was measured by an electrochemiluminescence immunoassay (E-Modular; Roche).

Calculations

VO_2 and HR during the slow and fast intervals in the IW intervention were measured during the last 1 minute in each of the 3-minute intervals. The total VO_2 and HR during the IW and CW interventions were measured during the entire duration of the interventions. Glucose values during the MMTT were analyzed as absolute values and as values incremental to the subject's baseline glucose. Endogenous rates of glucose appearance (Ra_{ENDO}), exogenous rates of glucose appearance from the MMTT (Ra_{MMTT}), and rates of glucose disappearance (Rd) were calculated using non-steady-state assumptions as previously described (25, 26). The glucose metabolic clearance rate (MCR) was calculated as the Rd divided by the plasma glucose concentration.

Statistics

Variables only relevant to the exercise trials were compared using Student's two-tailed paired *t* tests. Variables relevant to all trials were compared using one-way repeated-measures ANOVA, and where significant interactions arose, Bonferroni post hoc tests were applied to identify significant differences between trials. All statistical analyses were performed by Prism version 6 (GraphPad). Results are reported as mean ± SEM. Statistical significance was accepted with $P < .05$.

Results

Subjects

Ten T2DM subjects participated in the study. Baseline characteristics are given in Table 1.

In addition to the CGM, all variables were obtained for all subjects. Due to failure of the CGM sensor in at least one trial, the CGM data analyses included only seven subjects. Therefore, analyses of the corresponding activity and diet recordings included only the same seven subjects.

No differences in physical activity, dietary intake, or CGM-derived glycemic control were seen between trials the day before the intervention day. Nor were there dif-

Table 1. Baseline Characteristics

Characteristics	Values
n	10
Sex, M/F	7/3
Age, y	60.3 ± 2.3
Time since diagnosis, y	6.0 ± 0.9
MLTPAQ, kcal/d	243 ± 44
Medication, n	
Diet only	2
Metformin	7
Sulfonylureas	2
DPP4 inhibitors	1
Fitness variables	
VO_2max, mL O_2 per kg/min	30.4 ± 3.1
VO_2max, mL O_2 per min	2633 ± 294
VO_2peak, mL O_2 per min	2058 ± 157
VO_2peak, % of VO_2max	80.6 ± 3.8
Body composition	
Body mass, kg	85.9 ± 3.6
BMI, kg/m^2	28.3 ± 1.1
Lean body mass, kg	58.8 ± 3.2
Body fat content, %	32.6 ± 2.2
Glycemic control	
Fasting glucose, mmol/L	7.1 ± 0.4
Fasting insulin, pmol/L	80.0 ± 11.1
Two-hour OGTT glucose, mmol/L	12.2 ± 1.4
HbA1c, mmol/mol	46 ± 2 (6.3% ± 0.2%)

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; MLTPAQ, Minnesota Leisure Time Physical Activity Questionnaire (18); OGTT, oral glucose tolerance test. Data are mean ± SEM.

ferences in body weight between the trials (85.3 ± 4.2 vs 84.9 ± 4.1 vs 84.8 ± 4.2 kg for IW, CW, and CON, respectively; $P > .05$ for all).

Interventions

Mean VO_2 during exercise (Figure 1) was not different between IW and CW (1634 ± 126 vs 1641 ± 133 mL/min, $P = .69$), whereas during slow and fast (1284 ± 84 and 1985 ± 160 mL/min) IW intervals, VO_2 was lower and higher compared with CW, respectively (both $P < .001$ vs CW). VO_2 during IW and CW was at all times higher than during the CON intervention (297 ± 13 mL/min, $P < .001$ for all). Mean HR during exercise (Figure 1) was not different between IW and CW (115.2 ± 2.8 vs 115.0 ± 3.5 bpm, $P = .92$), with the HR being lower (104.1 ± 2.7 bpm, $P < .001$) and higher (127.7 ± 3.3 bpm, $P < .001$) during slow and fast IW compared with CW. HR during IW and CW was at all times higher than during the CON intervention (62.1 ± 3.1 bpm, $P < .001$ for all). The mean RPE during exercise was lower during slow (11.1 ± 0.3 a.u., $P = .001$) and higher during fast (13.8 ± 0.5 a.u., $P = .049$) IW compared with CW (13.0 ± 0.4 a.u.). The total RPE of the intervention was not different between IW and CW (12.8 ± 0.4 vs 12.9 ± 0.5 a.u., $P = .80$). The mean walking speed was lower during IW compared with CW (4.68 ± 0.26 vs 5.04 ± 0.27 km/h, $P < .001$), with the slow IW intervals being slower (3.40 ± 0.24 km/h, $P < .001$) and fast IW intervals being quicker (5.97 ± 0.29 km/h, $P < .001$) than CW. Finally, blood lactate concentrations during the intervention were higher in IW (2.1 ± 0.2 mmol/L, no difference between slow and fast IW) compared with CW (1.4 ± 0.1 mmol/L, $P < .001$), and both IW and CW resulted in higher lactate concentrations than CON (0.9 ± 0.1 mmol/L, $P < .001$ and $P = .002$, respectively).

Mixed-meal tolerance test (Table 2)

Fasting blood glucose concentrations (Figure 2A) did not differ between the intervention days ($P > .05$ for all). No changes were seen during the CON intervention, whereas blood glucose levels declined equally during both exercise interventions ($P = .02$ and $P = .006$ vs within trial baseline values for IW and CW, respectively). The mean and maximal glucose concentrations during the MMTT were lower in IW compared with CON ($P = .007$ and $P = .01$, respectively), whereas CW did not differ significant from the two others (mean: $P = .24$ vs IW and $P = .33$ vs CON; maximal: $P = .28$ vs IW and $P = .49$ vs. CON). The mean incremental glucose concentrations during the MMTT (Figure 3A) were lower in IW compared with both CON ($P < .001$) and CW ($P = .02$), with no difference between CON and CW ($P = .38$). Maximal incremental glucose concentrations during the MMTT (Figure 3B) were lower in IW than in CON ($P = .005$) and numerically lower than in CW (3.7 ± 0.6 vs 4.3 ± 0.6 mmol/L, $P = .07$), again with no difference between CW and CON ($P = .67$).

Ra_{ENDO} (Figure 2B) was higher in IW and CW during both the intervention ($P < .001$ for both) and the MMTT ($P = .046$ and $P = .008$, respectively) compared with CON, with no differences between IW and CW ($P > .99$). Ra_{MMTT} (Figure 2C) was higher in IW compared with CON ($P = .02$), whereas Ra_{MMTT} in CW did not differ significantly from either IW or CON ($P = .80$ and $P = .18$, respectively). Rd (Figure 2D) was higher during the MMTT in both IW and CW compared with

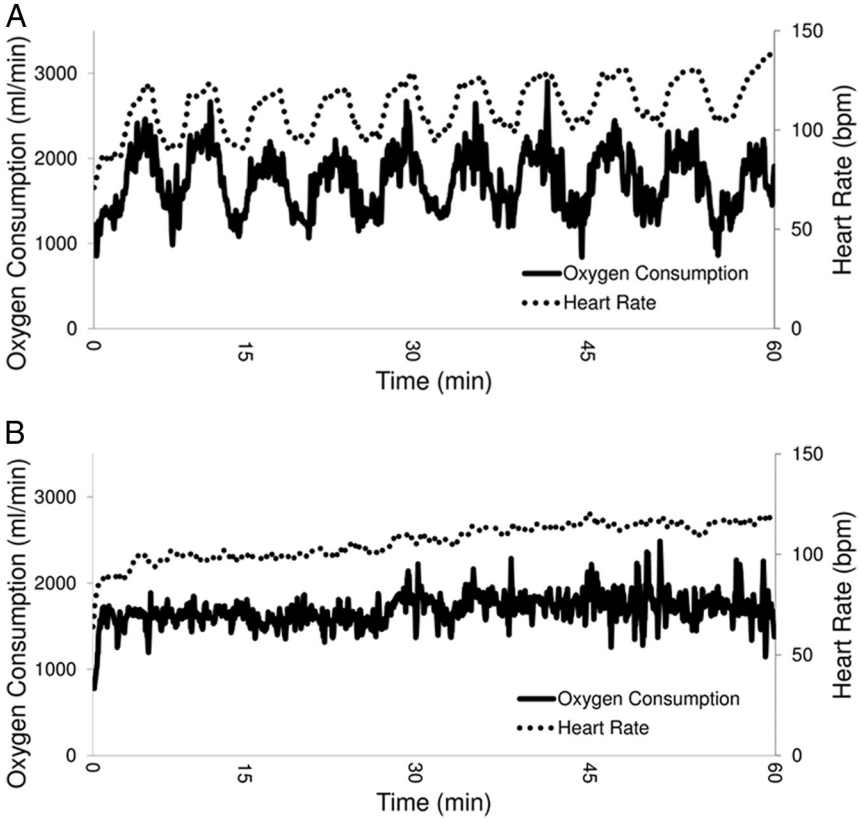

Figure 1. Subjects with T2DM underwent three interventions in a randomized, counterbalanced order: 1) 1 hour of IW (repeated cycles of 3 min of slow and fast walking); 2) 1 hour of oxygen consumption-matched CW; and 3) CON. VO_2 and HR were measured continuously throughout the interventions, and representative profiles of these variables are shown for IW (panel A) and CW (panel B).

Table 2. MMTT Variables

	CON	CW	IW	CON vs CW	CON vs IW	CW vs IW
Glucose						
Fasting glucose, mmol/L	7.9 ± 0.5	7.6 ± 0.6	7.5 ± 0.5			
Mean intervention glucose, mmol/L	7.9 ± 0.6	6.8 ± 0.5	6.8 ± 0.4	$P = .008$	$P = .008$	
Mean MMTT glucose, mmol/L	9.9 ± 0.9	9.3 ± 0.8	8.7 ± 0.7		$P = .007$	
Maximum MMTT glucose, mmol/L	12.5 ± 1.0	11.9 ± 0.9	11.2 ± 0.8		$P = .01$	
Mean incremental glucose, mmol/L	2.0 ± 0.5	1.7 ± 0.4	1.2 ± 0.4		$P < .001$	$P = .02$
Max incremental glucose, mmol/L	4.6 ± 0.6	4.3 ± 0.6	3.7 ± 0.6		$P = .005$	$P = .07$
Glucose kinetics						
Mean intervention Ra_{ENDO}, mg/kg·min	2.33 ± 0.14	3.04 ± 0.18	3.14 ± 0.16	$P < .001$	$P < .001$	
Mean MMTT Ra_{ENDO}, mg/kg·min	1.50 ± 0.11	1.77 ± 0.14	1.70 ± 0.09	$P = .008$	$P = .046$	
Mean MMTT Ra_{MMTT}, mg/kg·min	1.54 ± 0.11	1.81 ± 0.13	1.96 ± 0.22		$P = .02$	
Mean MMTT Rd, mg/kg·min)	2.89 ± 0.13	3.42 ± 0.18	3.56 ± 0.26	$P = .002$	$P < .001$	
Mean MMTT glucose MCR, mg/kg·min	0.27 ± 0.02	0.33 ± 0.02	0.37 ± 0.03	$P = .002$	$P < .001$	$P = .049$
Insulin						
Fasting insulin, pmol/L	79.9 ± 10.5	73.0 ± 9.4	75.3 ± 9.6			
Postintervention insulin, pmol/L	80.4 ± 10.5	48.2 ± 5.1	47.4 ± 5.0	$P = .001$	$P < .001$	
Mean MMTT insulin, pmol/L	333.5 ± 59.2	315.6 ± 57.0	284.7 ± 46.6			
Glucagon						
Fasting glucagon, pg/mL	97.7 ± 11.5	96.4 ± 9.4	103.3 ± 12.1			
Postintervention glucagon, pg/mL	80.2 ± 8.2	107.2 ± 9.1	113.5 ± 12.2	$P = .001$	$P < .001$	
Mean MMTT glucagon (0–180 min), pg/mL	93.9 ± 6.1	102.4 ± 8.2	105.4 ± 7.3	$P = .09$	$P = .02$	
Mean MMTT glucagon (0–30 min), pg/mL	107.9 ± 8.6	130.9 ± 11.3	134.5 ± 10.8	$P = .004$	$P = .001$	
Mean MMTT glucagon (30–180 min), pg/mL	84.6 ± 5.5	83.3 ± 5.8	86.1 ± 7.2			

Data are mean ± SEM. Bonferroni-corrected statistical comparisons between trials are indicated in separate columns, with crude *P* values reported if $P < .10$.

CON ($P < .001$ and $P = .002$, respectively). Glucose MCR during MMTT was greater in IW compared with both CON and CW ($P < .001$ and $P = .049$, respectively), and higher in CW compared with CON ($P = .002$).

Fasting serum insulin levels (Figure 2E) did not differ between the intervention days ($P > .05$ for all). After the interventions, the insulin levels were lower during IW and CW compared with CON ($P < .001$ and $P = .001$, re-

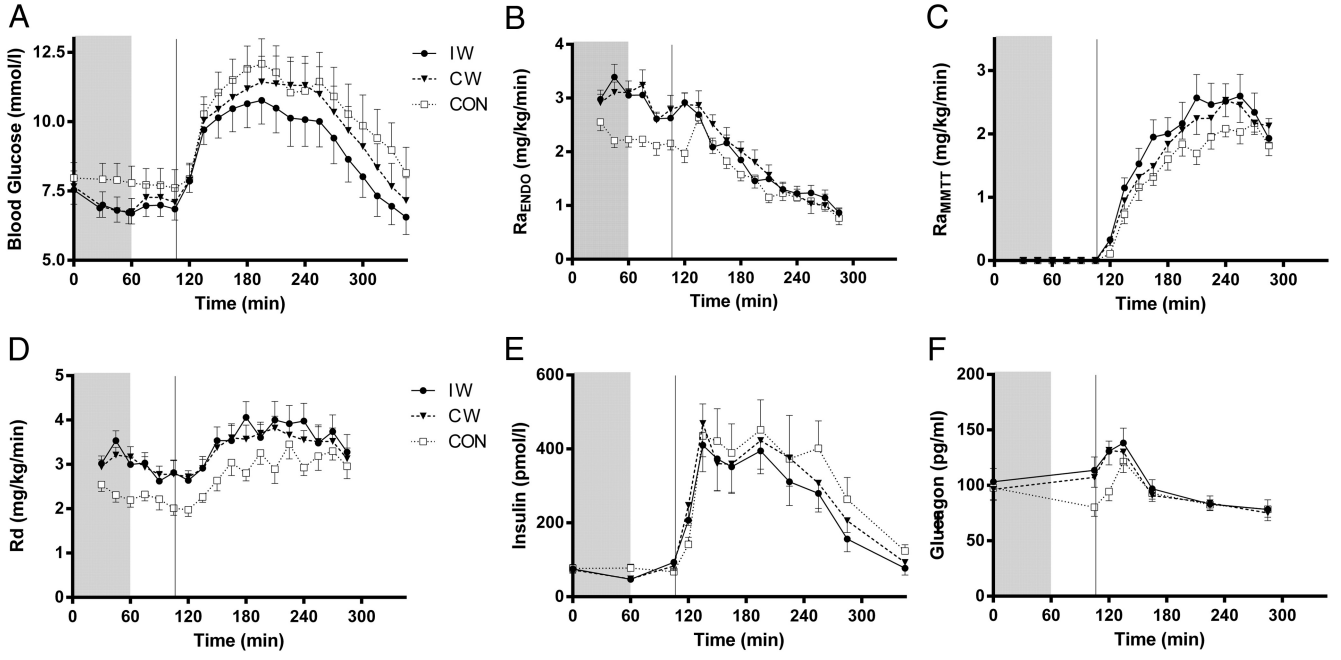

Figure 2. Subjects with T2DM underwent three interventions in a randomized, counterbalanced order: 1) 1 hour of IW (repeated cycles of 3 min of slow and fast walking); 2) 1 hour of oxygen consumption-matched CW; and 3) CON. An MMTT with stable glucose isotope tracers was started 45 minutes after cessation of the intervention. Profiles of blood glucose levels (panel A), Ra_{ENDO} (panel B), Ra_{MMTT} (panel C), Rd (panel D), insulin (panel E), and glucagon (panel F) concentrations are shown. The shaded area indicates the intervention (t = 0–60 min), whereas the solid vertical line indicates start of the MMTT (t = 105 min). For statistical analyses, see text and Table 2.

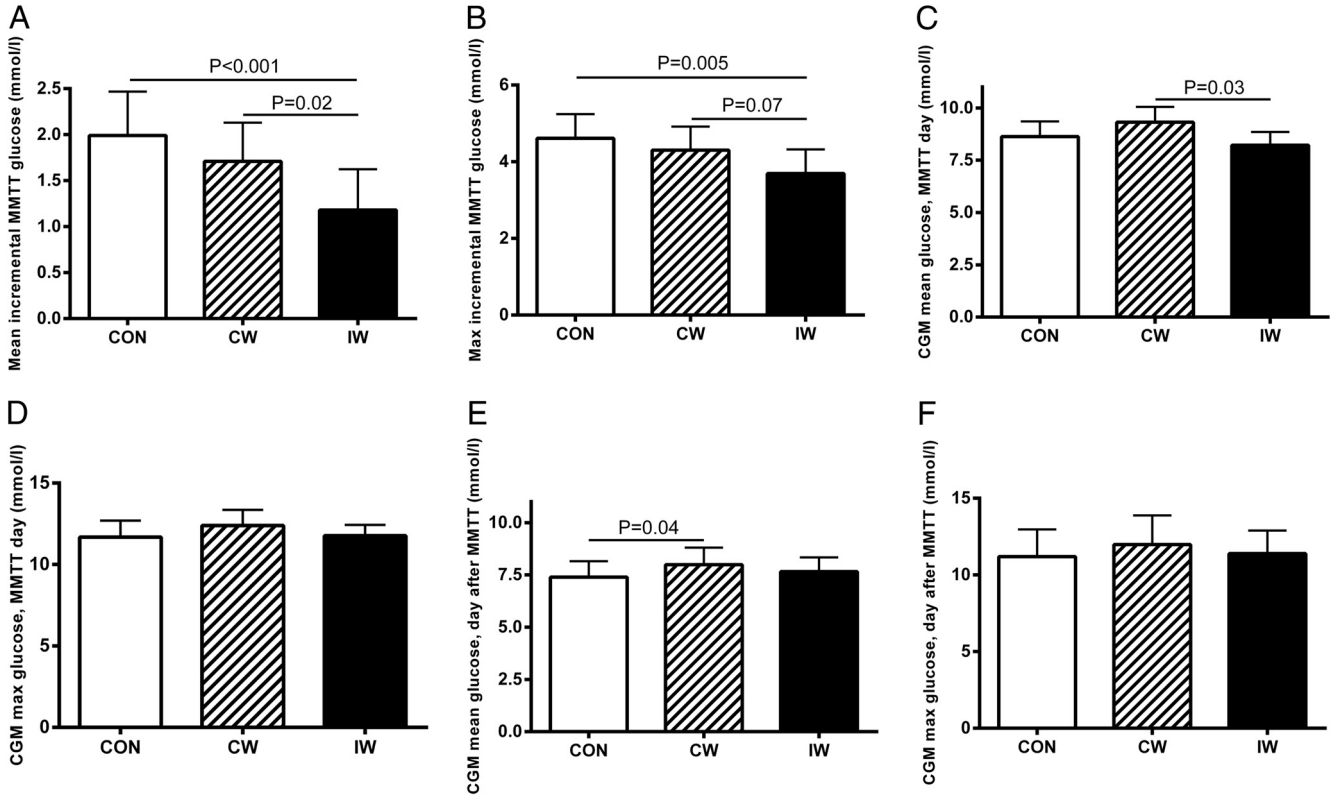

Figure 3. Subjects with T2DM underwent three interventions in a randomized, counterbalanced order: 1) 1 hour of IW (repeated cycles of 3 min of slow and fast walking); 2) 1 hour of oxygen consumption-matched CW; and 3) CON. An MMTT was started 45 minutes after cessation of the intervention and mean (panel A) and maximum (panel B) incremental glucose levels during the MMTT are shown. Free-living glycemic control was subsequently assessed using continuous glucose monitoring (CGM). Mean (panel C) and maximum (panel D) CGM glucose levels of the remaining part of the intervention day and mean (panel E) and maximum (panel F) CGM glucose levels the day after the intervention day are shown. Data are presented as mean ± SEM. Differences were analyzed by a one-way, repeated-measures ANOVA, with significant differences indicated by Bonferroni-corrected crude *P* values.

spectively) with no differences between IW and CW. The insulin levels were not different between trials immediately before or during the MMTT ($P > .05$ for all). No differences in the insulin levels were found between IW and CW at any time.

Fasting plasma glucagon levels (Figure 2F) did not differ between the intervention days ($P > .05$ for all). Glucagon was increased after exercise in both IW and CW compared with CON ($P < .001$ and $P = .001$, respectively). Levels remained higher in IW and CW until 30 minutes into the MMTT (75 min after cessation of the intervention), compared with CON ($P < .05$ for all time points), after which glucagon levels did not differ between trials. No differences were seen between IW and CW at any time.

The insulin to glucagon ratio was not different at baseline or at any time point between any of the trials.

Free-living glycemia

On the day of the intervention (from the end of MMTT to midnight), mean CGM glucose levels (Figure 3C) were lower in IW (8.2 ± 0.4 mmol/L) vs CW (9.3 ± 0.7 mmol/L, $P = .03$), but neither IW nor CW were different compared with CON (8.6 ± 0.7 mmol/L, $P = .84$ and $P = .24$, respectively). On the day after the intervention, the mean CGM glucose levels (Figure 3E) were not different between IW (7.7 ± 0.7 mmol/L and CON (7.4 ± 0.8 mmol/L, $P = .39$), whereas the CW glucose levels (8.0 ± 0.8 mmol/L) were greater than CON ($P = .04$). No differences between trials were seen for minimum or maximum (Figure 3, D and F) CGM glucose levels on either the day of or the day after the intervention, nor were differences in time duration with hyperglycemia (CGM glucose values > 10.0 mmol/L) (12, 27) seen between any of the trials. During the free-living period of the intervention day (after the MMTT), total energy intake was numerically lower in IW (1213 ± 160 kcal) vs CW (1586 ± 258 kcal, $P = .08$), whereas CON (1338 ± 218 kcal) did not differ from the other trials. Total energy intake was not different between trials on the day after the intervention, nor were there any trial differences in macronutrient composition or Actiheart-derived energy expenditure on either day.

Discussion

The most important finding of this study is that a single aerobic interval-walking session more greatly reduced

postprandial blood glucose levels in T2DM subjects, when compared with a continuous-walking session matched with regard to oxygen consumption, time duration, and perceived exertion. Furthermore, day-long free-living glucose levels were lower after the interval walking when compared with continuous walking. These findings highlight the importance of considering exercise mode and not just exercise volume and mean intensity when implementing physical activity in diabetes care.

Studies that have investigated metabolic outcome after short-term or single-session interval-type interventions have in general reported robust improvements in glycemic control and insulin sensitivity in both healthy and T2DM subjects (5, 11, 28–30). These studies have, however, not compared the interval-type interventions with matched continuous type interventions; thus, until now, the additional benefit of interval-type exercise could not be precisely concluded. One single study previously compared a single interval-type exercise session with an energy expenditure-matched continuous type session, showing that only the continuous-type intervention resulted in greater improvements in insulin sensitivity (31). The study was, however, performed in healthy, young individuals and the interventions were of very short duration (four × 30 sec sprints vs a single energy expenditure matched extended sprint with a mean duration of ~200 sec) and anaerobic by nature (postintervention mean lactate between 7 and 11 mmol/L), limiting the comparability to our study. Thus, our crossover, controlled design allows us to conclude that a single aerobic interval-exercise session is superior to continuous exercise for improving glycemic control in T2DM subjects.

Both 1-hour exercise sessions increased Rd during the MMTT as compared with rest; and, interestingly, glucose MCR during the MMTT was greater after IW than after CW. This may theoretically be due to both insulin-dependent and insulin-independent mechanisms, between which our study design does not allow us to distinguish. Although insulin sensitivity has been found to be massively up-regulated in T2DM subjects after short-term interval-based training regimens (5), this has not been investigated immediately after single-session interval-type interventions in humans. In rodents, however, it has been found that whereas no major differences in the improvements in insulin sensitivity after continuous and interval-type exercise are seen, insulin-independent glucose disposal is markedly higher after interval-type exercise (32). Whether this is also true in humans should be investigated in future studies.

The increased Ra_{MMTT} in IW vs CON is interesting and may potentially be explained by differential gastric emptying rates or a larger glucose concentration gradient between the gut and the circulation in IW compared with CON because blood glucose levels were lower during the MMTT after IW. Moreover, exercise has been shown to increase sodium glucose cotransporter 1-mediated glucose uptake in the intestine (33). Thus, increased Ra_{MMTT} in IW may be due to the increased facilitated intestinal glucose absorption. That being said, the isotope tracer-derived estimates of ingested nutrient appearance based on peripheral blood sampling do not allow us to control for differences in hepatic glucose uptake, which may be altered by exercise. As such, from our study design, it is not possible to define the mechanisms for group differences in Ra_{MMTT}.

By using CGM, we found that the improved glucose tolerance immediately after IW was continued throughout the intervention day under free-living conditions. The blood glucose curve during the MMTT (Figure 2A) indicates that the immediate beneficial effect of IW on glycemic control compared with CW was sustained toward the end of the MMTT, and although our CGM data should be carefully interpreted due to a low number of subjects, this is in agreement with a conclusion that IW improves free-living glycemia after the cessation of the MMTT. The mechanisms to explain this are beyond the scope of this study, but we did observe a numerically lower (yet statistical insignificant) energy intake in IW compared with CW, which potentially may have contributed to the differences seen in free-living glycemia. Although some evidence suggests that low- vs high-intensity exercise differentially modulate appetite hormones (34, 35), it is unknown whether such differences exist between interval and continuous exercise.

In addition to increased glucose MCR, no beneficial effect on glycemic control during the MMTT after CW compared with CON was found. Based on visual interpretations from Figure 2, A–D, one may argue that the lack of significant differences is due to low power, particularly because this outcome was not expected and is not in agreement with previous findings (1, 2, 12, 36). However, our subjects had a high VO_2max compared with other T2DM cohorts (37, 38), and they reported that they were fairly active. As such, the CW intervention might have provided an insufficient exercise stimulus that was rather similar to their habitual activity habits. Thus, it is possible that a less active T2DM group would have profited more from the CW intervention. The deterioration in free-living glycemic control the day after the CW intervention was even more unexpected. Bearing the low subject number in mind, however, these results must be carefully interpreted.

Our data support the results from Gillen et al (11), who found that an interval-exercise session improved free-living CGM-derived glycemia in T2DM subjects. However,

a study from Manders et al (12), comparing the effects of energy expenditure-matched high- vs low-intensity (70 vs. 35% VO_2max) continuous exercise sessions, found that only the low-intensity session improved free-living CGM-derived glycemia over the 24 hours after the exercise. Although purely speculative, a potential explanation for the discrepancy between our study and the study by Manders et al is given by Kjaer et al (39), who found that a high-intensity exercise session increases glucose levels in T2DM subjects due to the increased secretion of glucagon and catecholamines, thereby increasing Ra_{ENDO}. Assuming that the high-intensity exercise session in the study by Manders et al was sufficiently high to elicit large increases in glucagon and catecholamine levels, this might explain the sustained elevation in glucose levels after the high- but not the low-intensity exercise session. Although we did not measure catecholamines, we found no differences in plasma glucagon or Ra_{ENDO} between IW and CW, suggesting that no differences in catecholamine levels between IW and CW existed.

Overall, this study has shown that an aerobic interval-type exercise session improves both postprandial and free-living glycemic control in T2DM subjects compared with an oxygen consumption- and time duration-matched continuous exercise session. This highlights the importance of considering exercise mode and not just the exercise volume and/or mean intensity when implementing physical activity in diabetes care. Whether it is the greater peak exercise intensity or the cyclic exercise pattern that induces the greater beneficial effect of IW over CW on glycemic control remains to be evaluated in future studies.

Acknowledgments

This study was primarily funded by DD2 (The Danish Centre for Strategic Research in type 2 Diabetes) supported by the Danish Agency for Science (grants 09–067009 and 09–075724 to B.K.P.). The project partners are listed on the project website, www.DD2.nu. This study was further supported by grants from the Augustinusfonden (K.K.) AP Møller Fonden (K.K.) and Aase og Ejnar Danielsens Fond (K.K.). The Centre of Inflammation and Metabolism (CIM) is supported by a grant from the Danish National Research Foundation (DNRF55). The Centre for Physical Activity Research (CFAS) is supported by a grant from Trygfonden. CIM is part of the UNIK Project: Food, Fitness & Pharma for Health and Disease, supported by the Danish Ministry of Science, Technology, and Innovation. The Copenhagen Muscle Research Centre is supported by a grant from the Capital Region of Denmark.

KK conceived the idea, performed the experiments, analyzed the data and wrote the manuscript. CSC performed the experiments and reviewed/edited the manuscript. BKP conceived the idea and reviewed/edited the manuscript. TPS conceived the idea, analyzed the data, reviewed/edited the manuscript and, as the guarantor, takes responsibility for the contents of the manuscript. All authors read and approved the final version of the manuscript.

Gerrit van Hall (Clinical Metabolomics Core Facility, Department of Infectious Diseases and CMRC, Rigshospitalet, Faculty of Health Sciences, University of Copenhagen), Ruth Rovsing, Hanne Villumsen and Sine H. Knudsen (all Rigshospitalet) are acknowledged for their technical assistance.

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This work was supported by Augustinusfonden, AP Møller Fonden, Aase og Ejnar Danielsens Fond.

Disclosure Summary: The authors have nothing to disclose.

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