Benefits for Type 2 Diabetes of Interrupting Prolonged Sitting With Brief Bouts of Light Walking or Simple Resistance Activities

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OBJECTIVE

To determine whether interrupting prolonged sitting with brief bouts of light-intensity walking (LW) or simple resistance activities (SRA) improves postprandial cardiometabolic risk markers in adults with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

In a randomized crossover trial, 24 inactive overweight/obese adults with T2D (14 men 62 ± 6 years old) underwent the following 8-h conditions on three separate days (with 6–14 days washout): uninterrupted sitting (control) (SIT), sitting plus 3-min bouts of LW ($3.2 \text{ km} \cdot \text{h}^{-1}$) every 30 min, and sitting plus 3-min bouts of SRA (half-squats, calf raises, gluteal contractions, and knee raises) every 30 min. Standardized meals were consumed during each condition. Incremental areas under the curve (iAUCs) for glucose, insulin, C-peptide, and triglycerides were compared between conditions.

RESULTS

Compared with SIT, both activity-break conditions significantly attenuated iAUCs for glucose (SIT mean $24.2 \text{ mmol} \cdot \text{h} \cdot \text{L}^{-1}$ [95% CI 20.4–28.0] vs. LW 14.8 [11.0–18.6] and SRA 14.7 [10.9–18.5]), insulin (SIT $3,293 \text{ pmol} \cdot \text{h} \cdot \text{L}^{-1}$ [2,887–3,700] vs. LW 2,104 [1,696–2,511] and SRA 2,066 [1,660–2,473]), and C-peptide (SIT $15,641 \text{ pmol} \cdot \text{h} \cdot \text{L}^{-1}$ [14,353–16,929] vs. LW 11,504 [10,209–12,799] and SRA 11,012 [9,723–12,301]) (all $P < 0.001$). The iAUC for triglycerides was significantly attenuated for SRA ($P < 0.001$) but not for LW (SIT $4.8 \text{ mmol} \cdot \text{h} \cdot \text{L}^{-1}$ [3.6–6.0] vs. LW 4.0 [2.8–5.1] and SRA 2.9 [1.7–4.1]).

CONCLUSIONS

Interrupting prolonged sitting with brief bouts of LW or SRA attenuates acute postprandial glucose, insulin, C-peptide, and triglyceride responses in adults with T2D. With poor adherence to structured exercise, this approach is potentially beneficial and practical.

Lifestyle interventions, including exercise, are the recommended front-line therapy in the management of type 2 diabetes (T2D), even after the commencement of hypoglycemic agents. Current guidelines stipulate that, in addition to 150 min/week of moderate-vigorous aerobic exercise, individuals with T2D should engage in resistance exercises at least 2–3 days/week (1). However, despite the known benefits, particularly for glucose metabolism and insulin sensitivity, meeting prescribed

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exercise guidelines can be challenging, and many with T2D remain physically inactive (2).

Furthermore, fewer opportunities now exist in modern societies for incidental (nonexercise) physical activity. Rapidly advancing technological innovations in transportation, communications, workplaces, and home entertainment have created environments conducive to prolonged periods sitting—sedentary behaviors, defined as any waking, sitting, or reclining behavior with low-energy expenditure (<1.5 METs) (3,4). Sedentary behaviors are ubiquitous and increase the risk of T2D, cardiovascular disease, and premature mortality, even when the influence of moderate-vigorous or leisure-time physical activity is controlled for (5,6). Therefore, in addition to increasing purposeful exercise, decreasing sitting time has the potential to reduce the burden of T2D.

There is observational and experimental evidence that sitting time with brief interruptions can be associated with a more favorable cardiometabolic risk profile and postprandial metabolism than is an equivalent amount of sitting time accumulated in longer, uninterrupted bouts (7,8). In overweight/obese adults at risk for T2D, interrupting sitting time with 2-min walking bouts every 20 min reduced glucose and insulin responses (24–30%), irrespective of whether the bouts were of light or moderate intensity (9). However, it is not known whether such metabolic benefits extend to those with T2D.

Moreover, limited consensus exists on how prolonged sitting time should be interrupted. Experimental studies to date have only examined the utility of intermittent standing or ambulatory bouts, which may have differing levels of metabolic stimulus, practicality, or health efficacy. As an alternative, resistance-type activities use the larger muscle groups and markedly increase muscle activity (>20-fold compared with sitting [10]), potentially providing a potent stimulus for increased energy expenditure and for glucose uptake. They can also be performed in a fixed position with minimal disruption to work tasks or leisure pursuits.

We examined, compared with uninterrupted sitting (SIT), the effects of interrupting sitting time with brief bouts of light-intensity walking (LW) or simple resistance activities (SRA) on postprandial metabolic responses in adults with T2D. We hypothesized that postprandial blood glucose, insulin, C-peptide, and triglyceride levels during sitting would be attenuated by brief intermittent bouts of physical activity, irrespective of modality.

RESEARCH DESIGN AND METHODS

Participants

Enrollment Process and Screening (Visit 1)
Overweight/obese (BMI ≥25 but <40 kg/m^2) men and women (aged 35–75 years) diagnosed with T2D (diet or metformin controlled, ≥3 months' duration [based on American Diabetes Association diagnostic criteria] [11]) were recruited from local community advertisements and the Baker IDI Diabetes Clinic. All participants were required to be inactive (i.e., currently sitting ≥5 h/day and not meeting physical activity guidelines of ≥150 min/week of moderate-intensity exercise for >3 months). Other exclusion criteria were as follows: HbA$_{1c}$ <6.5 or ≥9%, taking insulin or any other hypoglycemic agents, pregnancy, pre/perimenopausal, current smoker, employment in a nonsedentary occupation, major systemic illness, known physical activity contraindications (including the presence of cardiovascular disease, unstable angina, or symptoms of cardiac failure at screening visit), or major illness or physical problems (acute or chronic) limiting ability to perform the light-intensity physical activities.

After initial telephone screening, all potentially eligible participants attended a medical screening at our laboratory that included the following: anthropometric measurements, resting blood pressure, resting 12-lead electrocardiogram, blood biochemistry (liver or renal function and HbA$_{1c}$), and a physical examination performed by the study physician (N.D.C.). Participants also underwent initial orientation to the SRA and treadmill walking during this visit to ensure the activity interventions could be undertaken safely and consistently.

Study Design

This randomized crossover trial was undertaken at the Baker IDI Heart and Diabetes Institute between October 2013 and November 2014 and was approved by the Alfred Human Research Ethics Committee. Eligible participants provided written informed consent and attended the laboratory on five separate occasions: medical screening visit, familiarization visit, and three trial condition visits in a randomized order: *1*) SIT, *2*) LW, and *3*) SRA.

Randomization and Masking
Trial condition order was randomly assigned by a third party using computer-generated random numbers and sealed envelopes (block randomization and balanced block sizes), stratified by sex. Study personnel were blinded to the condition order until the night prior to the first trial condition. Participants were blinded to trial condition order up until commencement of the second trial visit. Pathology technicians were kept blinded to trial conditions.

Study Protocol and Trial Conditions

Familiarization (Visit 2)
Three to five days prior to the first experimental trial condition (visit three), participants attended a familiarization visit and were given further practice with the SRA and treadmill walking. Participants were also familiarized with all study procedures, including weighed food diaries and activity records, objective activity monitoring, and requirements for the restrictive lead-in phase and fasting prior to each trial condition. Prearranged, standardized text messaging or e-mail prompts were used to maximize participant compliance.

Indirect Calorimetry
With the aim of characterizing the interventions, indirect calorimetry was completed either before visit three (n = 11) (during familiarization visit) or after visit five (n = 12) (during a sixth visit) based on participant availability. Participants reported to the temperature-controlled (22–24°C) laboratory at 0700–0800 h after a 12-h overnight fast. After participants voided and were weighed, a TrueOne 2400 metabolic cart (Model QMC; ParvoMedics, Sandy, UT) was used to measure VO$_2$, VCO$_2$, and energy expenditure (kcal · min^{-1}) (based on the Weir equation [12]) over an ~75-min period. (See Supplementary Table 1 for additional data handling and calibrations details.) During this time, participants completed a protocol divided into two sequential parts (outlined below), each part capturing periods of quiet sitting, interspersed with either a 3-min bout of LW or SRA, in a randomized order:

Part 1: 20-min sitting quietly → 3-min activity LW-1/SRA-1 → 10-min sitting quietly → 3-min LW-1/SRA-1 → metabolic cart recalibrated → commence part 2. Part 2: 15-min sitting quietly → 3-min activity LW-2/SRA-2 → 10-min sitting quietly → 3 min LW-2/SRA-2 → 15-min sitting quietly → protocol finishes.

Trial Conditions (Visits 3–5)

Figure 1 shows the overall study protocol. Since an acute exercise session may enhance insulin action for up to 48 h (13), a 6- to 14-day washout period between trial conditions was used to eliminate potential carryover effects. Participants were asked to refrain from structured moderate-vigorous physical activities (i.e., no physical activity beyond activities of daily living), caffeine, and alcohol for 48 h prior to each experimental condition.

During the washout period between experimental conditions, participants resumed their habitual diet and physical activity patterns. From visit two (familiarization visit) until visit five (final trial condition), participants wore accelerometers (GTX3+; ActiGraph, Pensacola, FL) during waking hours for objective measurements of sedentary time and physical activity. The 1-min epoch activity data were processed to derive average sedentary (<100 cpm), light-intensity (100–1,951 cpm), and moderate-vigorous (≥1,952 cpm) activity time on valid (≥10 h) days (14).

For minimizing of any potential diet-induced variability during testing conditions, medication times were standardized and food intake was strictly controlled starting from the night before each trial visit. Meals were standardized between conditions and were individualized to meet daily estimated energy requirements (Schofield equation [15], 1.5 physical activity factor) and a target macronutrient profile of 12–15% energy from protein, 55–58% energy from carbohydrate, and 29–31% energy from fat. For accommodation of dietary preferences, participants were able to select from a range of meal options, and each meal provided 33% estimated energy requirements (mean ± SD 823 ± 124 kcal/meal). Breakfast options included bran-based cereal, fruit salad, ham-and-cheese croissant, and juice. Lunch options included a salad and meat bread roll and commercially available drink. An evening meal pack, consisting of a commercially available drink, snack, and microwave meal, were also provided for participants to prepare at home on the evenings prior to experimental conditions.

After a 12-h overnight fast, participants reported to the laboratory at 0715 h. After voiding and being weighed, they remained seated while an indwelling catheter was inserted into an antecubital vein and fasting samples collected before (−1 h) and after (0 h) a 60-min steady-state period (Fig. 1). Each experimental condition commenced upon starting the breakfast meal, with the time taken to consume (<20 min) replicated in subsequent conditions. At 3.5 h, participants consumed lunch (<20 min). Postprandial blood samples were collected at 30-min intervals (immediately prior to physical activity bouts on activity days) over each 7-h condition.

Participants consumed water ad libitum during the first trial condition and were then instructed to replicate the volume consumed in subsequent trial conditions. Standardized lavatory visits incorporated into the protocol minimized unscheduled physical activity; however, additional lavatory visits were permitted. Participants complied with the respective trial condition protocols under direct supervision from research staff.
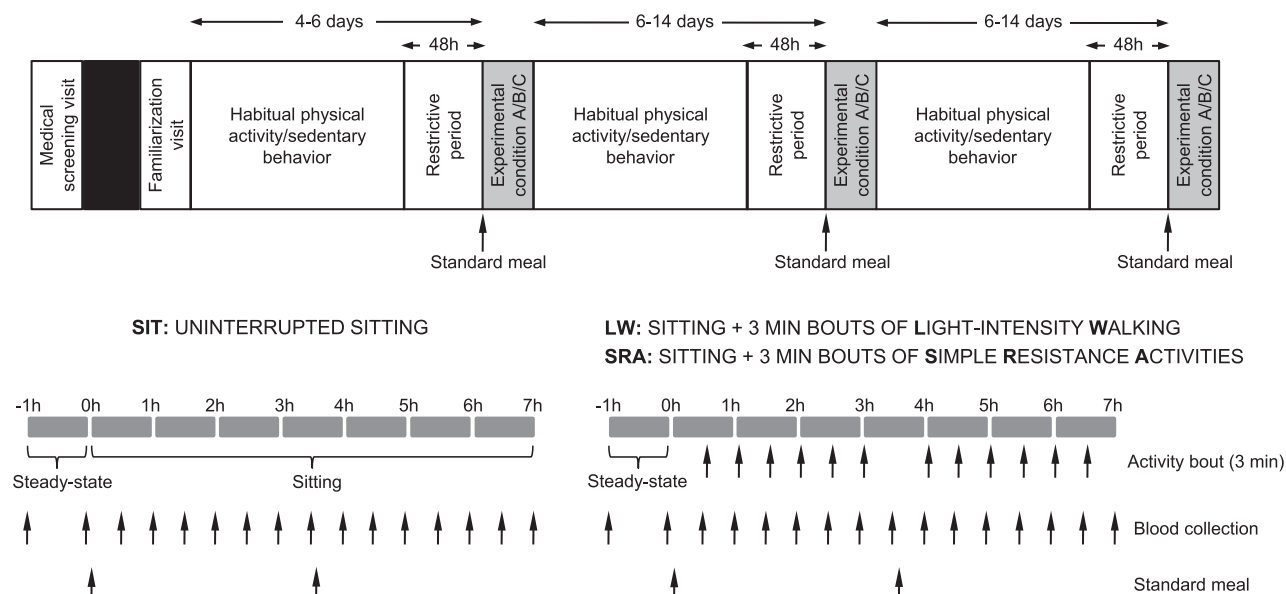

Figure 1—Study design and protocol for treatment conditions. Participants visited the laboratory on five separate occasions. The 3 trial conditions were completed in a randomized order separated by a 6- to 14-day washout. Blood was collected half-hourly, 2 min prior to each activity bout. Each standardized meal (mean ± SD 822.9 ± 124.3 kcal/meal) constituted 33% of participants' daily estimated energy requirements (Schofield equation [15], physical activity factor 1.5) with a target macronutrient profile of 55–58% energy from carbohydrate, 12–15% energy from protein, and 29–31% energy from fat.

The three trial conditions were as follows.

SIT. Participants sat upright in a comfortable chair throughout the experimental period and were instructed to minimize excessive movement, only rising from the chair to void.

LW. Participants rose from the seated position every 30 min throughout the experimental period (except during the lunch meal) and completed a 3-min bout of LW on a treadmill (zero gradient, 3.2 km · h^{-1}) and then returned to the seated position. This procedure was undertaken on 12 occasions (i.e., 36 min total light-intensity activity).

SRA. Participants underwent a protocol identical to that of the LW condition, except that participants completed 3-min bouts of SRA (total: 36 min) instead of LW. The 3 min was divided into a total of nine 20-s movement segments, alternating between body weight half-squats, calf raises, gluteal contractions, and knee raises. The interchange between movements was to provide rest for the corresponding muscle groups between each movement segment, allowing for continual muscle activation over the 3-min period. To ensure appropriate movement standardization, tempo, and correct form, participants mimicked a standardized, preprepared video recording (practiced in visits one and two). Range of motion (knee/hip angle 45–90° for half-squats/knee raises) was tailored to participants' ability, as assessed during visit one.

Participants had access to television, DVDs, books, magazines, and internet services during the trial conditions. Activity intensity during the trial conditions was monitored using heart rate monitoring (RS400; Polar Electro Oy, Kempele, Finland) and the Borg rating of perceived exertion (RPE) (range: minimum–maximum 6–20) scale. The mean differences for heart rate (immediately postactivity bout minus preactivity; mean ± SEM) for the LW and SRA activity-break conditions were 17 ± 1.2 bpm (range 8–31) and 19 ± 1.0 bpm (range 10–30) and for mean RPE were 9 ± 0.3 points (range 7–12) and 10 ± 0.3 points (range 7–13), respectively.

Biochemical Analysis

Code-labeled samples were sent to an independent National Association of Testing Authorities (NATA)/The Royal College of Pathologists of Australasia (RCPA)-accredited laboratory on the day of testing for the determination of glucose, insulin, and C-peptide levels. Plasma glucose (fluoride/oxalate) was measured using a hexokinase method. Serum insulin and C-peptide were measured using a chemiluminescent microparticle immunoassay (Architect ci16200; Abbott Diagnostics, Santa Clara, CA). Plasma triglycerides (from EDTA tubes, stored at −80°C) were analyzed using a COBAS Integra 400+ analyzer (Roche Diagnostics, Indianapolis, IN).

Statistical Analyses

Coprimary outcomes were changes in net incremental area under the curve (iAUC) (trapezoidal method) for plasma glucose and insulin. Sample size calculations were based on a previous trial conducted in our laboratory (9) using similar methodology in overweight/obese adults (24–30% and 23% decrease in glucose and insulin, respectively), an effect similar in magnitude to that which may be observed after a single bout of moderate-intensity cycling in patients with T2D (16). Therefore, we estimated that 17 paired observations would be needed to achieve 90% power to detect the smallest expected effect size (Cohen $d = 0.84$) in the primary outcome variables between the interventions (control vs. breaks in sitting, two sided, 5% level). For accommodation of potential withdrawals, 24 participants were randomized. Across all trial conditions and participants, 3% of outcome values (34 of 1,152 data points) were missing and treated as such in subsequent analyses.

After recent recommendations on data analysis of crossover trials (17), generalized linear mixed models (with random intercepts were used to evaluate the differential effects of the experimental conditions on the selected outcomes using Stata 12 (StataCorp LP). All models were adjusted for potential confounders explaining residual outcome variance (age, sex, and BMI), preprandial values (iAUC only), and period effects (treatment order). Sex-by-condition interaction tests were performed for each of the iAUC outcome measures. Residuals were examined for serial correlation, heteroscedasticity, and normality. Substantial departures from model assumptions were not observed. A two-tail probability level of 0.05 was adopted. Data are expressed as mean ± SEM or mean (95% CI) unless otherwise stated.

RESULTS

Of the 29 participants who attended screening, 24 were randomized and completed all trials (Fig. 2). There were no dropouts after randomization. There were 14 men and 10 women of mean ± SD age 62 ± 6 years with BMI 33.0 ± 3.4 kg/m^2, HbA$_{1c}$ 7.2 ± 0.7% (55.1 ± 8.0 mmol · mol^{-1}), estimated glomerular filtration rate 87 ± 8 mL/min per 1.73 m^2, total cholesterol 4.36 ± 0.83 mmol · L^{-1}, fasting triglycerides 1.9 ± 0.1 mmol · L^{-1}, fasting HDL cholesterol 1.1 ± 0.3 mmol · L^{-1} and LDL cholesterol 2.5 ± 0.8 mmol · L^{-1}, systolic blood pressure 123 ± 14 mmHg, diastolic blood pressure 77 ± 9 mmHg, and diabetes duration 6.8 ± 5.1 years and with $n = 23$ taking metformin, $n = 15$ taking statins, and $n = 16$ taking antihypertensive therapy (included $n = 16$ taking an ACE inhibitor or angiotensin II receptor blocker, $n = 5$ a calcium channel blocker, $n = 11$ a thiazide diuretic, and $n = 2$ a β-blocker). Aside from BMI (men 31.5 kg/m^2 vs. women 35.2 kg/m^2, $P = 0.0051$) and baseline (fasting) insulin levels (men 70.6 pmol · L^{-1} vs. women 106.4 pmol · L^{-1}, $P = 0.0035$), there were no significant differences in sex-related baseline parameters or medications.

Anthropometric, biochemical, dietary, and accelerometer-derived physical activity data before each of the respective trial conditions are presented in Table 1. Apart from preprandial C-peptide (adjusted for in statistical models), there were no significant differences between trials for any of these measurements.

Based on indirect calorimetry measurements ($n = 23$) (Supplementary Table 1), compared with 15 min sitting quietly, a bout of LW and SRA increased mean energy expenditure (kcal · min^{-1}) by 73 ± 5% and 121 ± 7%, respectively. A bout of SRA, compared with a bout of LW, elicited a significantly greater increase (relative to 15 min sitting quietly) in mean VO$_2$ (0.13 ± 0.01 L · min^{-1}), VCO$_2$ (0.08 ± 0.01 L · min^{-1}), and energy expenditure (0.58 ± 0.06 kcal · min^{-1}) (all $P < 0.001$); however, the opposite effect was observed for respiratory exchange ratio (VCO$_2$/VO$_2$) (−0.02 ± 0.01; $P < 0.05$).
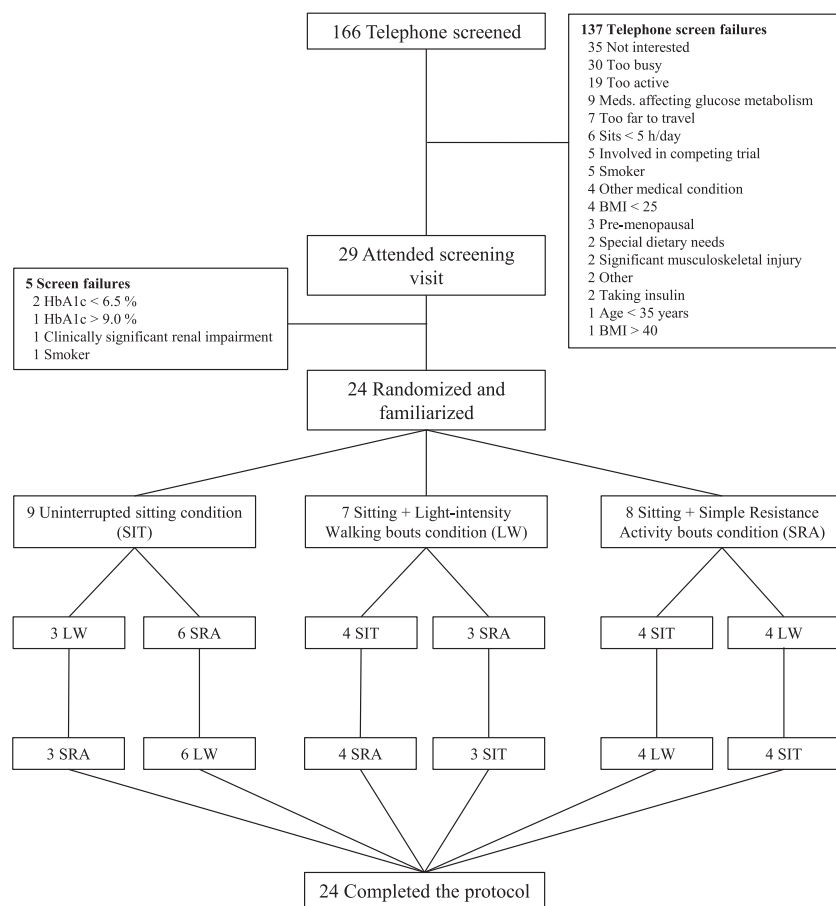
Figure 2—Consolidated Standards of Reporting Trials (CONSORT) flow diagram. Meds., medications.

Figure 3 shows mean glucose, insulin, C-peptide, and triglyceride concentrations during each of the trial conditions. Net 7-h iAUC during both of the activity-bout conditions was significantly (all $P < 0.001$) attenuated compared with SIT for glucose (SIT mean 24.2 mmol $\cdot$ h $\cdot$ L^{-1} [95% CI 20.4–28.0], LW 14.8 [11.0–18.6], and SRA 14.7 [10.9–18.5]), insulin (SIT 3,293 pmol $\cdot$ h $\cdot$ L^{-1} [2,887–3,700], LW 2,104 [1,696–2,511], and SRA 2,066 [1,660–2,473]), and C-peptide (SIT 15,641 pmol $\cdot$ h $\cdot$ L^{-1} [14,353–16,929], LW 11,504 [10,209–12,799], and SRA 11,012 [9,723–12,301]). The iAUC for triglycerides was attenuated significantly for SRA compared with SIT ($P < 0.001$) but not for LW (SIT 4.8 mmol $\cdot$ h $\cdot$ L^{-1} [3.6–6.0], LW 4.0 [2.8–5.1], and SRA 2.9 [1.7–4.1]). Differences between SRA and LW were only significant for triglyceride levels ($P = 0.048$). Meal-specific effects (3.5-h iAUC per meal) are displayed in Supplementary Table 2.

A significant sex-by-condition interaction effect was observed for the mean difference in glucose net iAUC between conditions SIT and LW (Supplementary Fig. 1), indicating that, while LW resulted in significantly lowered glucose net iAUC for both sexes, the magnitude of the glucose attenuation for LW versus SIT was greater (↓58% vs. ↓26%) in women than in men (mean iAUC difference in lowering between women and men −6.8 mmol $\cdot$ h $\cdot$ L^{-1} [95% CI −13.46 to −0.14; $P = 0.045$]). The sex-by-condition interaction for SRA versus SIT trended similarly (↓53% vs. ↓31%) but was nonsignificant (−4.6 mmol $\cdot$ h $\cdot$ L^{-1} [−11.17 to 1.98; $P = 0.17$]). No significant sex-by-condition interactions were observed for any other outcomes.

CONCLUSIONS

This study demonstrates, for the first time in inactive overweight/obese men and women with T2D, that interrupting prolonged sitting with brief bouts of either LW or SRA effectively attenuates postprandial glucose (mean change ↓39%), insulin (LW ↓36%, SRA ↓37%),

and C-peptide (LW ↓27%, SRA ↓30%) responses. Despite the novel modality and relative increase in energy expenditure for the SRA bouts compared with LW, glucose, insulin, and C-peptide responses were comparable between the two conditions. Triglyceride levels tended to be lower for both activity types; however, only the iAUC reduction for SRA (↓40%) was statistically significant.

This study builds on hypotheses generated from epidemiological observational research on the metabolically beneficial correlates of breaking up sitting time and recent experimental trials demonstrating the acute metabolic benefits of interrupting prolonged sitting with light- (18) and moderate-intensity (9) bouts of ambulation. Our findings extend upon this work by providing new insights regarding the potential efficacy of this novel, lifestyle-based treatment strategy (interrupting prolonged sitting) in adults with T2D; the potential efficacy of an alternative, simple, and practical form of sitting interruption (brief bouts of SRA); and that 3-min light activity bouts every 30 min (versus, for example, ~2 min walking breaks every 20 min [9,18], 5-min walking or standing bouts every 30 min [19], or 15-min postmeal walking bouts [16,20]) may also be a useful prescription target.

Our findings are consistent with a recent study of similar design in overweight adults showing reduced glucose and insulin responses from brief interruptions to sitting, irrespective of activity bout intensity (9). They are also consistent with recent findings in postmenopausal women at high risk of T2D (19), which showed metabolic benefits with both walking and standing bouts for 5 min every 30 min. Furthermore, Peddie et al. (18) demonstrated that, in healthy normal-weight adults, interrupting prolonged sitting with intermittent bouts of walking (1 min and 40 s every 30 min) was more effective than a single 30-min bout of moderate-vigorous walking in reducing postprandial glycemia. This is consistent with other experimental studies (21–23) suggesting that the manner in which physical activity (or sitting time) is accumulated may differentially influence postprandial glucose handling. Indeed, van Dijk et al. (16) recently showed in adults with T2D that, compared with prolonged sitting, both a 45-min bout of moderate exercise and three 15-min bouts of

Table 1—Anthropometric, biochemical, physical activity, and dietary values during the preexperimental period

	SIT	LW	SRA
Weight (kg)	90.4 ± 2.1	90.4 ± 2.1	90.3 ± 2.1
Preprandial levels*			
Plasma glucose (mmol · L^{-1})	8.0 ± 0.3	8.1 ± 0.3	8.1 ± 0.3
Serum insulin (pmol · L^{-1})	87.0 ± 9.5	83.5 ± 9.5	86.0 ± 9.5
Serum C-peptide (pmol · L^{-1})	974 ± 58	924 ± 58§	984 ± 58
Plasma triglycerides (mmol · L^{-1})	1.7 ± 0.2	1.9 ± 0.2	1.8 ± 0.2
Accelerometer data†			
Daily wear time (min)			
Habitual period	822 ± 21	877 ± 22	841 ± 21
48-h restricted period	863 ± 18	870 ± 18	869 ± 18
Sedentary time (min/day)			
Habitual period	559 ± 19	570 ± 19	535 ± 19
48-h restricted period	552 ± 19	569 ± 19	563 ± 19
Physical activity time (min/day)			
Light intensity			
Habitual period	275 ± 14	299 ± 14	278 ± 14
48-h restricted period	306 ± 15	296 ± 15	302 ± 15
Moderate-vigorous			
Habitual period	7 ± 1	8 ± 1	9 ± 1
48-h restricted period	5 ± 1	5 ± 1	5 ± 1
Diet‡			
Total energy intake (kcal/day)	2,069 ± 80	2,079 ± 80	2,094 ± 80
Total carbohydrate (energy %)	46.7 ± 1.1	46.9 ± 1.1	47.1 ± 1.1
Total fat (energy %)	31.3 ± 1.0	31.8 ± 1.0	31.9 ± 1.0
Total protein (energy %)	18.6 ± 0.6	17.8 ± 0.6	17.8 ± 0.6

Data are means ± SEM. *Preprandial values based on average of two time points (−1 and 0 h) immediately before the first meal. †Accelerometer data collected during habitual (free-living) days and the 48-h period preceding the trial condition. ‡Dietary intakes were assessed from weighed/measured food records during the 48-h period before the trial condition, using dietary analysis software (FoodWorks; Xyris Software, Highgate Hill, Queensland, Australia). §LW significantly different from SIT and SRA ($P < 0.05$).

light-intensity activity over a day of sitting were effective in lowering postprandial glucose and insulin responses. Remarkably, the shorter, more frequent activity bouts used in our study appear to have resulted in comparable, if not greater, reductions in glucose and insulin responses. This difference in magnitude change could be due to sex, participant attributes, or methodological differences or the longer sitting duration used by van Dijk et al. Nonetheless, our findings and those of van Dijk et al. underscore the potential metabolic importance of increasing intermittent physical activity across a day of prolonged sitting for glycemic control in patients with T2D.

These findings hold clinical and public health relevance for three key reasons. First, postprandial excursions in glucose, insulin, and triglycerides can trigger oxidative stress, elevated inflammatory cytokines, reduced nitric oxide bioavailability, and endothelial dysfunction (24,25). This dysmetabolic profile represents a direct and independent risk factor for the development of diabetic and cardiovascular complications in patients with T2D, even in those receiving oral blood glucose medications (26,27). Second, patients with T2D are more likely to be physically inactive (28) and overweight/obese and have reduced exercise tolerance, with uptake of public health exercise recommendations remaining a persistent challenge at the population level (29–31). Third, our findings provide evidence for two novel lifestyle-based treatment strategies (LW and SRA bouts) with a degree of metabolic efficacy (postprandial lowering of glucose and insulin) indirectly comparable with an acute 45-min bout of moderate exercise followed by a day of prolonged sitting in T2D patients (16). This is an important finding given the intermittent nature and low intensity of the activity bouts performed by our participants.

Responsible mechanisms remain unclear and will require further study. However, the inherent nature of sitting clearly does not lend itself to skeletal muscle contractile activity, increased energy expenditure, or augmented blood flow/shear stress (32). Therefore, it may be hypothesized that the reduction in glucose levels during the brief activity bout conditions, consistent with prior mentioned studies of similar design, are the result of localized increases in contractile-mediated (insulin-independent) glucose uptake. Moreover, the concurrent reductions in insulin levels with physical activity suggest less of a reliance on insulin-mediated glucose uptake, with concomitant reductions in C-peptide levels (a marker of endogenous insulin secretion) further reinforcing this notion. Other possible mediators associated with increased postural alterations and light muscle activity may include hemodynamic changes (i.e., increased blood volume, tissue perfusion, and capillary permeability [33–35]), as well as modulation of intracellular signaling changes (i.e., AMPK, translocation/turnover of GLUT4, and calcium-activated proteins [36]), increased muscle insulin sensitivity, or changes in sympathetic nervous system activity. It is also possible that the effects of simply standing up more regularly could have significantly contributed to the observed metabolic effects (19), potentially via combinations of hemodynamic, hemodilutional, or minimal muscle contractile activity. While these mechanistic possibilities could not be ascertained from our study design, they should be examined in future research in populations with T2D. This could involve longer stabilization periods in the standing position, prior to each activity bout, to account for any potential additive metabolic effect of the physical activity itself. Moreover, it remains to be determined whether different activity bout modalities provide unique physiological benefits and to what extent they inhibit the adverse consequences of prolonged sitting. Future studies should examine the optimal frequency, duration, and intensity of activity bouts to determine the specific translational potential for the management of T2D.

The nonsignificant reduction in triglyceride iAUC during the LW condition is consistent with the intermittent walking (1 min and 40 s every 30 min) condition of Peddie et al. (18) in healthy normal-weight adults, who notably also demonstrated a significant lowering in
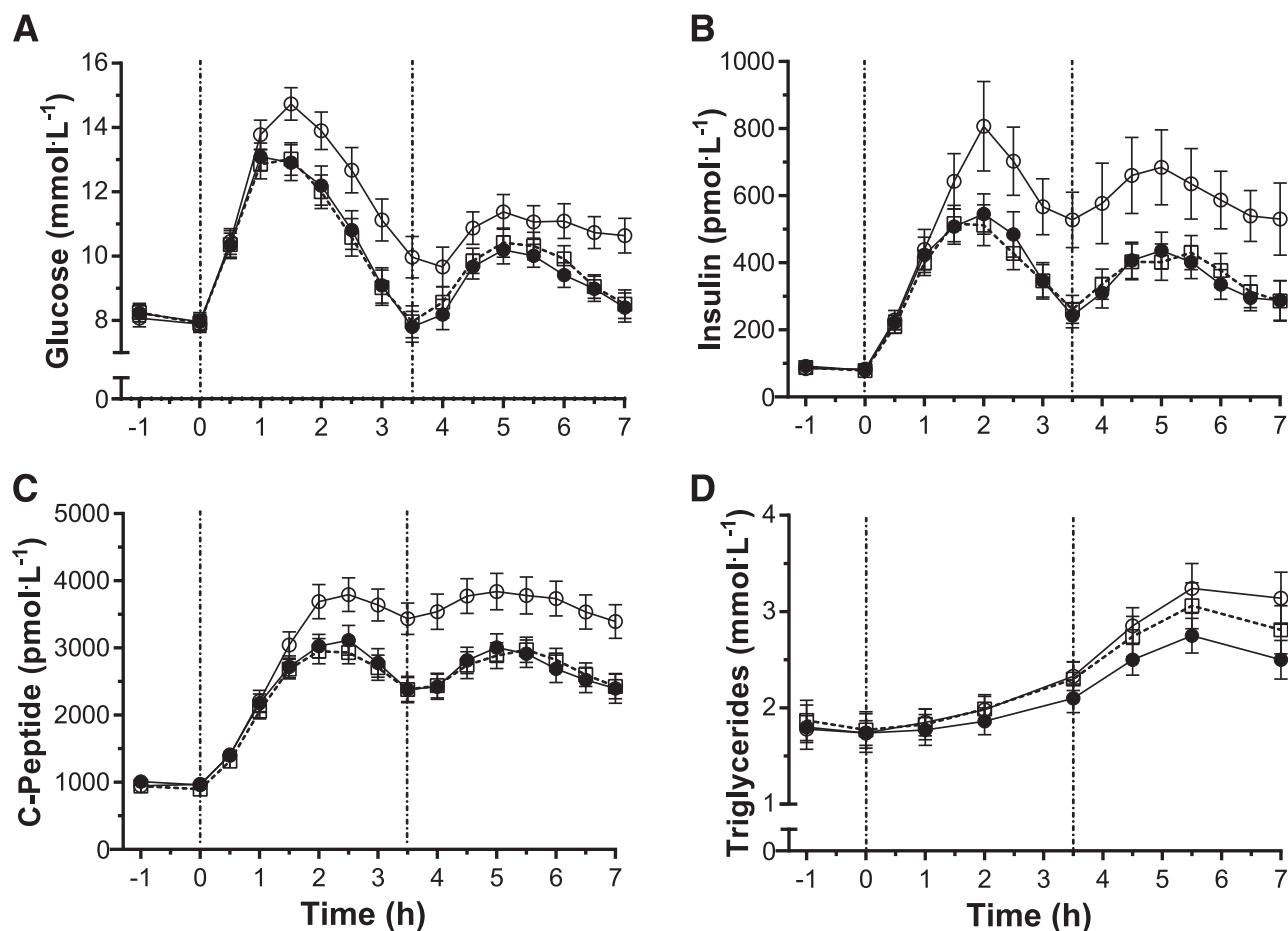
Figure 3—Fasting and postprandial plasma glucose (*A*), serum insulin (*B*), serum C-peptide (*C*), and plasma triglyceride (*D*) concentrations measured during SIT (○) and sitting interrupted with 3-min LW (□) or SRA (●) bouts. Vertical dashed lines indicate timing of the breakfast (0 h) and lunch (3.5 h) meals. Data are presented as mean ± SEM.

triglycerides with a single 30-min bout of moderate-vigorous walking. However, the significant triglyceride reduction during the resistance activity condition in our study is a novel finding and a first in patients with T2D. Plausible reasons for the comparatively lower triglyceride levels with both walking and resistance activities may be due to our trial condition or activity bouts being of longer duration than some previous studies, which is broadly consistent with studies that have observed reductions in triglycerides the next day after using both intermittent and continuous walking interventions (37,38); the less natural modality (subjective comments from participants not reported), increased activity stimulus (intensity and energy expenditure), and lower respiratory exchange ratio during the SRA bouts (indicating a relative increase in lipid oxidation); differences in the participants studied (healthy vs. overweight/obese patients with T2D);

or the nutritional composition (i.e., higher glucose-to-fat ratio) of test meals.

In light of epidemiological findings documenting sex differences in the associations of television-viewing time with cardiometabolic biomarkers (39,40), our findings offer some initial experimental insights suggesting that (postmenopausal) women with T2D may derive greater reductions in postprandial glucose than men by interrupting their sitting time with LW. Although we suspected that the greater glucose reductions may be related to increases in activity intensity, we did not observe significant increases in heart rate, oxygen consumption, or perceived exertion for women compared with men. Differences in adipose and lean body mass or other biological disparities between men and women with T2D could be the potential basis for these findings. Future studies should continue to elucidate sex-specific effects.

Key strengths of our study include the focus on both men and women with overt T2D, the well-described and standardized trial condition lead-in periods (as illustrated by minimal variance in confounder variables such as diet, physical activity, and fasting metabolic levels during trial condition lead-in periods) through the use of weighed food records and objectively measured physical activity, standardized calorimetric assessment of the two modes of activity bout, the strict behavioral supervision and standardized feeding of a typical Western diet during experimental conditions (as opposed to less ecologically valid test drinks), full retention of participants and minimal data loss, and the collection of regular blood time points during trial visits for more robust time course and iAUC calculations.

The present trial also has some limitations that future studies could address. First, the acute nature of the

current study precludes extrapolations about longer-term exposures to the particular conditions that we examined. It is presently unknown whether our approach is beneficial over a longer period of time or whether the putative benefits can be sustained in ways that have previously been shown in longer-term trials that included aerobic exercise (41). Second, although this well-controlled study has offered insights into the metabolic consequences of prolonged sitting and the incorporation of alternate modes of intermittent activity bouts, generalizability to free-living settings is less certain and may not always reflect habitual behaviors. For example, in the workplace, other factors such as stress and workload may also play a role in glycemic homeostasis. Third, the exploratory sex analyses in this study should be interpreted with caution, given the limited sample size, which may have increased the risk of type 1 errors. Finally, the standardized Western dietary feeding profiles (42) used during this trial, while arguably more reflective of real-world scenarios, will inevitably vary in daily life settings (e.g., macronutrient profile, glycemic index, meal frequency, and size). Although our specific focus was on standardized meal responses to the sedentary and activity patterns, such dietary variations and their interactions with physical activity are an integral piece of the puzzle and will require further examination.

Pragmatically, both activity conditions were easily tolerated and well accepted by our T2D participants (based on subjective comments collected at the end of each trial condition [data not shown]), and it appears the beneficial metabolic effects of interrupting prolonged sitting can be achieved with different modes of light-intensity activity. In this regard, both LW and SRA bouts may have application irrespective of individual ability or workplace or home context encountered. For example, SRA bouts require no specialized equipment, only small amounts of space, and could be easily performed behind a work desk or at home with minimal disruption to work tasks or leisure pursuits, whereas light walking may be more convenient and socially acceptable in certain contexts. Longer-term engagement in either mode of activity bout may also elicit differing physiological effects (e.g., increased muscle strength, bone density,

and physical function) that are presently unknown. Taken together, while this study provides a first piece of experimental evidence on the potential benefits of interrupting prolonged sitting in T2D patients, further mechanistic studies and interventions in larger samples in ecologically relevant, free-living, and workplace environments, using a broader range of participants (including premenopausal women and patients with less well-controlled T2D [e.g., patients with poorly controlled diabetes on insulin or sulfonylurea dependent, with β-cell dysfunction and increased risk of experiencing hypoglycemia]), will be informative in developing more specific public health guidelines for the management of T2D.

In conclusion, interrupting prolonged sitting with brief LW or SRA bouts significantly attenuates postprandial glucose, insulin, C-peptide, and triglyceride responses in adults with T2D. With the ubiquity of sedentary behaviors and the low adherence to structured exercise, these two approaches are practical strategies that may contribute toward reducing the risk of diabetes complications and cardiovascular complications. The efficacy and sustainability of our particular approach should be tested in larger and longer-duration trials, as has been done for aerobic exercise interventions in the T2D context (41). Nonetheless, our findings contribute complementary initial experimental evidence to further inform the existing, albeit broad, T2D exercise recommendations to "increase daily movement through unstructured activity to gain additional health benefits" (1). Thus, in addition to the essential promotion of purposeful moderate-vigorous and leisure-time physical activity, it seems prudent and nonmaleficent (primum non nocere) that health care professionals consider promoting the message, or providing prescriptive advice to T2D patients, to also regularly interrupt prolonged sitting time.

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