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Research Article Treatment

Dose–response between frequency of interruption of sedentary time and fasting glucose, the dawn phenomenon and night-time glucose in Type 2 diabetes

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Abstract

Aim To explore the dose–response between frequency of interruption of sedentary time and basal glucose (fasting glucose, the dawn phenomenon and night-time glucose) in Type 2 diabetes.

Methods In a randomized three-treatment, two-period balanced incomplete block trial, 12 people with Type 2 diabetes (age, 60.0 ± 3.2 years; BMI, 30.2 ± 1.4 kg/m^2) completed two of three conditions: sitting for 7 h interrupted every 60 min (Condition 1), 30 min (Condition 2), and 15 min (Condition 3) by 3-min light-intensity walking breaks. The activPAL3 and FreeStyle Libre were used to assess physical activity/sedentary behaviour and continuous glucose profile. Standardized meals were provided, and changes in basal glucose of the nights and early mornings before and after treatment conditions were calculated (mean ± SE).

Results After treatment conditions, fasting glucose and duration of the dawn phenomenon were lower for Condition 3 (−1.0 ± 0.2 mmol/l, $P < 0.02$; −3.1 ± 1.3 h, $P = 0.004$) compared with Condition 1 (−0.1 ± 0.2 mmol/l; 1.9 ± 1.2 h). The magnitude of the dawn phenomenon was reduced in Condition 3 (−0.6 ± 0.4 mmol/l, $P = 0.041$) compared with Condition 2 (0.6 ± 0.3 mmol/l). Night-time glycaemic variability (coefficient of variation) was reduced in Condition 3 (−9.7 ± 3.9%) relative to Condition 2 (6.1 ± 4.8%, $P < 0.03$) and Condition 1 (2.5 ± 1.8%, $P = 0.02$). There was no change in night-time mean glucose.

Conclusions Frequent interruptions of prolonged sitting with 3 min of light-intensity walking breaks every 15 min improves fasting glucose, the dawn phenomenon and night-time glycaemic variability, and this might be a simple therapeutic intervention to improve glucose control.

Introduction

Basal hyperglycaemia, including high fasting glucose, the dawn phenomenon and night-time glucose, could be indicative of insulin resistance and pancreatic β-cell deficiency, which are two important underlying mechanisms in Type 2 diabetes [1–3]. Basal hyperglycaemia influences daily glucose and HbA_{1c} control [2,4]. It makes a greater contribution to overall hyperglycaemia in people with HbA_{1c} > 68 mmol/mol (8.4%), whereas postprandial glucose is a main contributor in people with HbA_{1c} < 56 mmol/mol (7.3%) [5]. Consequently, basal hyperglycaemia can lead to vascular complications [6], so good basal glucose control is important. However, high fasting glucose and the dawn phenomenon, defined as a spontaneous elevation of glucose from nocturnal (starting at midnight) nadir glucose to pre-breakfast glucose, have been reported in people with Type 2 diabetes, even with combination therapy of oral anti-diabetes agents [2,7,8]. This suggests that medications might not be enough to address basal hyperglycaemia, and adjunct lifestyle interventions are needed.

There is evidence that sedentary time is associated with high fasting glucose, insulin resistance and metabolic risk profile [9–11]. By contrast, breaks in sedentary time have a beneficial effect on metabolic risk profile and postprandial glucose, and this beneficial effect might extend to basal glucose control [12]. A break in sedentary time is defined as a short period of standing or walking between two periods of sitting [13]. The reduction in postprandial glucose and insulin resistance with light-intensity walking breaks is well established in healthy adults and those with Type 2 diabetes in an experimental laboratory setting [14]. However, experimental evidence to inform the beneficial effect of light-intensity walking breaks in sedentary time on fasting glucose, the dawn phenomenon and night-time glucose is limited. One experimental study showed a reduction in night-time glucose with 3-min light-intensity walking breaks every 30 min compared with uninterrupted sitting (7 h) [15]. However, in real life people very rarely sit all day but rather naturally break sitting on an irregular basis [16], and there is limited consensus on how frequently sitting should be interrupted. It is therefore important to find out if more frequent breaks have a beneficial effect. In other words, the dose–response relationship between frequency of breaks and basal glucose needs to be explored to inform potential therapeutic intervention based on breaking sedentary time. This study aimed to compare the effect of light-intensity walking breaks every 60 min of sitting with light-intensity walking breaks every 30 min and 15 min on fasting glucose, the dawn phenomenon and night-time glucose.

Methods

Study design

This three-treatment, two-period balanced incomplete block trial was approved by the Research Ethics Committees of Glasgow Caledonian University and University of Strathclyde. This study design has been used in pharmaceutical trials, and it reduces trial duration, participant burden, attrition rate and intra-subject effect, thus increasing the reliability of data and precision of study [17]. The study is registered as a clinical trial (Clinicaltrials.gov Identifier: NCT02738996). It was conducted in accordance with the Declaration of Helsinki. Eligible participants provided signed, written informed consent.

Participants completed two of the following three treatment conditions: sitting interrupted by 3 min light-intensity walking breaks every 60 min (Condition 1), 30 min (Condition 2) or 15 min (Condition 3).

Participants and recruitment

Participants were recruited between January and June 2017 from diabetes support groups in Glasgow. Eligibility criteria included self-reported Type 2 diabetes, age ≥ 35 years and BMI ≥ 25 kg/m^2. Exclusion criteria were insulin therapy, pregnancy, liver and renal diseases, cancer, alcohol and substance abuse, mobility issues and diabetes-related complications such as foot ulcer, foot deformity, peripheral neuropathy and peripheral arterial diseases.

Randomization

Until the first treatment condition day, participants were blinded to trial condition order. The order was assigned using block randomization sequence produced by SPSS.

Experimental protocol

The total duration of the experimental protocol was 15 days: 4 days of pre-experimental monitoring, 1 day of first treatment condition, 5 days of wash-out period, 1 day of second treatment condition and 4 days of post-experimental monitoring. Participants resumed their habitual diet and physical activity during the pre-experimental monitoring, wash-out and post-experimental monitoring periods, and refrained from alcohol, smoking and moderate to vigorous physical activity (MVPA) throughout the study. To ensure compliance with protocol, they were reminded at each visit.

Pre-experimental monitoring period (visit 1)

Participants visited the university laboratory at Glasgow Caledonian University or University of Strathclyde. A researcher recorded participants' demographic information and medication history. Participants were fitted with a continuous glucose monitoring (CGM, Abbott FreeStyle Libre) and activPAL3 activity monitor (PAL Technologies, Glasgow, UK). They were provided with a FreeStyle Libre reader to scan glucose every 8 h, a sleep diary to record bedtime and waking time, and a 24-h dietary recall form to record medication and dietary intake during study period. Participants then completed their normal daily living behaviour for 4 days.

First treatment condition (visit 2)

After an overnight fast (starting at 22:00 h), participants reported to the laboratory at 08:00 h. Participants remained seated for 1 h to achieve a steady state. The internet, a personal computer and books were provided for entertainment. A standardized breakfast, consisting of 50–53.7 g carbohydrate, 9.1–12.6 g fat, 14.7–22.4 g protein and 1.4–1.7 MJ energy, was consumed at 09:00 h. One of the following treatment conditions commenced after breakfast according to the randomization order:

1. Condition 1. Participants performed 3 min of light-intensity walking on level ground every 60 min at a pace of 10 m in 11 s (3.2 km/h), and timing and supervision were done by the researcher to ensure full adherence to the treatment condition as per protocol. Participants then sat for 60 min, and this was repeated until the end of treatment condition (16:00 h). There were six bouts (18 min) of walking.

2. Condition 2. The procedure was identical to Condition 1, but participants walked for 3 min every 30 min of sitting. There were 12 bouts (36 min) of walking.

3. Condition 3. The procedure was the same as above two conditions except that 3 min of walking was introduced every 15 min of sitting. Participants performed 23 bouts (69 min) of walking.

Participants consumed a standardized lunch with 75 g carbohydrate, 14.5 g fat, 28 g protein and 2.2 MJ energy at 12:36 h. Participants were also provided with a ready-meal dinner, consisting of 50.1–55.6 g carbohydrate, 7.3–12.3 g fat, 20.1–30.1 g protein and 1.4–1.8 MJ energy, and a snack, consisting of 10–13.1 g carbohydrate, 0.3–0.6 g fat, 0.3–2.6 g protein and 0.2–0.3 MJ energy, to consume at home after treatment condition. Dinner was consumed between 18:00 h and 21:00 h, and the snack between 16:30 h and 22:00 h. On treatment condition days, participants were only allowed to have meals they were provided with. Participants refrained from caffeine in addition to alcohol, smoking and MVPA.

<H2>Wash-out period
A 5-days of wash-out period was introduced between two treatment conditions to avoid the potential carryover effect.

<H2>Second treatment condition (visit 3)
Procedures, diet and meal time were identical to the first treatment condition except that participants performed another of the three treatment conditions, which was not performed on the first treatment condition day.

<H2>Post-experimental monitoring period (visit 4)
After 4 days of post-experimental monitoring, participants visited the laboratory to remove the CGM and activPAL3. This was the end of the trial period.

<H2>Physical activity and sedentary behaviour monitoring
Participants wore the activPAL3 using hypoallergic dressing and waterproof plastic tubing. This is a validated device that accurately records the start and duration of physical activity, and sedentary bouts and walking cadence for 2 weeks [18]. This device estimates energy expenditure (metabolic equivalents, MET). activPAL3™ software (version 7.2.32) was used to download the data.

activPAL data for 3 days before each treatment condition were used to calculate baseline daily sedentary time, standing time and walking time after sleeping time was excluded using the sleep diary and activPAL file. Baseline energy expenditure during 3 days before the treatment condition and energy expenditure on treatment condition day were computed using the 24-h activPAL data.

Continuous glucose monitoring

Participants wore the CGM providing interstitial glucose records every 15 min for 2 weeks. The sensor was inserted into the subcutaneous tissue on the back of upper arm. The interstitial glucose value recorded using this well-tolerated consumer grade device is as accurate as the capillary blood glucose [19]. The accuracy is not influenced by type of diabetes, HbA_{1c}, age and BMI [19]. The reader and FreeStyle Libre software (version 1.0) were respectively used to retrieve the data wirelessly every 8 h and to download the glucose data.

Glucose outcome measures were changes in fasting glucose, magnitude and duration of the dawn phenomenon, night-time mean glucose and night-time glycaemic variability [coefficient of variation (CV%) = (SD/mean) × 100] of the nights and early mornings before and after treatment conditions. Changes in glucose variables were calculated by subtracting glucose values before treatment conditions from glucose values after treatment conditions. The CGM glucose value just before the start of breakfast was defined as fasting glucose (pre-breakfast glucose) [20]. The dawn phenomenon was calculated by subtracting nocturnal (starting at midnight) nadir glucose from pre-breakfast glucose [8]. The time interval between nocturnal nadir glucose and pre-breakfast glucose was defined as the duration of the dawn phenomenon [8]. If all nocturnal glucose values were greater than the pre-breakfast glucose value, the dawn phenomenon and duration of the dawn phenomenon were recorded as zero [8]. The period between bedtime and waking time reported in the sleep diary was defined as night-time. Night-time mean glucose and glycaemic variability (CV%) were calculated using glucose values during this period.

Statistical analyses

Sample size calculations were based on a previous study [21]. Allowing for a statistical power of 80%, a 0.05 probability level and a correlation of 0.5 between repeated measures, we estimated that 12 participants would be needed to detect a 24% change in glucose based on the effect size observed in this previous study [21]. There were no inclusion or exclusion criteria regarding missing glucose values. Across all treatment conditions, 3.5% of night-time glucose values (54 of 1527 glucose points) were missing, and within-individual mean substitution was applied. Within-individual mean substitution might underestimate standard errors (SE), however, this method has been shown to be effective and accurate to deal with ≤ 10% of missing data [22].

Multilevel mixed-effects linear regression allowing repeated measures for the same individuals was used to assess changes in glucose variables between conditions. Model 1 was adjusted for age (years), sex, BMI (kg/m^2), carbohydrate intake (g/day) and energy expenditure (MET × h/day) on

treatment condition day, and Model 2 was additionally adjusted for anti-diabetes medication dose (mg/day), sedentary time (h/day) and walking time (h/day) on treatment condition day. All variables were added as continuous variables except for gender. Differences in baseline participant characteristics were assessed with multilevel mixed-effects linear regression. To locate differences between conditions, pairwise comparisons were performed using *post hoc* Fisher LSD tests. Statistical analyses were conducted using IBM SPSS Statistics software (version 24.0). Data are expressed as mean ± SE unless otherwise indicated, and *P* ≤ 0.05 was considered statistically significant. No adjustment was applied for multiple comparisons.

Results

Twelve participants (eight men, four women; mean duration of diabetes, 5.2 ± 0.8 years; mean age, 60.0 ± 3.2 years; mean BMI, 30.2 ± 1.4 kg/m^2) were randomized and completed trial conditions. Baseline participant characteristics before treatment conditions are displayed in Table 1, and no significant differences between conditions were observed.

Table 2 shows the changes in glucose variables in three treatment conditions. Fasting glucose was significantly lowered in Condition 3 (−1.0 ± 0.2 mmol/l, *P* < 0.02), but not after Condition 2 (−0.6 ± 0.2 mmol/l, *P* = 0.12) compared with Condition 1 (−0.1 ± 0.2 mmol/l). Moreover, the duration of the dawn phenomenon was significantly reduced in Condition 3 (−3.1 ± 1.3 h, *P* = 0.004), but not in Condition 2 (−0.1 ± 1.4 h, *P* = 0.37) in comparison with Condition 1 (1.9 ± 1.2 h). Compared with Condition 2 (0.6 ± 0.3 mmol/l), there was significant reduction in the magnitude of the dawn phenomenon after Condition 3 (−0.6 ± 0.4 mmol/l, *P* = 0.041). In addition, Condition 3 (−9.7 ± 3.9%) significantly reduced night-time glycaemic variability (CV%) compared with Condition 2 (6.1 ± 4.8%, *P*<0.03) and Condition 1 (2.5 ± 1.8%, *P*=0.02).

A reduction in fasting glucose and the duration of the dawn phenomenon in Condition 3 (−1.0 ± 0.2 mmol/l, *P* < 0.02; −3.0 ± 2.1 h, *P* < 0.03) relative to Condition 1 (−0.1 ± 0.2 mmol/l; 1.9 ± 1.6 h) was observed, independent of medication, sedentary time and walking time (Model 2). Moreover, there was a consistent reduction in the magnitude of the dawn phenomenon and night-time glycaemic variability (CV%) in Condition 3 (−0.6 ± 0.4 mmol/l, *P* < 0.01; −6.1 ± 3.8%, *P* < 0.04) compared with Condition 2 (0.8 ± 0.3 mmol/l; 5.2 ± 3.2%). No difference in night-time mean glucose was observed in both Model 1 and Model 2.

Discussion

The main finding of this study is that interrupting prolonged sitting frequently (at least every 15 min) improves basal glucose control in Type 2 diabetes. Lower fasting glucose, the magnitude and duration of the dawn phenomenon, and night-time glycaemic variability (CV%) were observed if the previous day sedentary time was interrupted more frequently.

In this study, no change in fasting glucose after Condition 2 is in agreement with the previous finding in overweight and obese adults with Type 2 diabetes with standing and walking breaks every 30 min [23]. To date, only one experimental study has shown a reduction in night-time mean glucose with 3-

min walking breaks every 30 min in comparison with uninterrupted sitting (7 h) [15], but our study did not observe the difference in night-time mean glucose between treatment conditions. The lowering of night-time glycaemic variability (CV%) after more frequent breaks (Condition 3) is similar to the reduction in 22 h glycaemic variability reported previously [15]. The lower glycaemic variability and basal glucose with frequent walking breaks might contribute to reducing risks of vascular complications [6,24].

Basal glucose control is one of the main therapeutic goals of diabetes management. However, most anti-diabetes agents, such as prandial glucose regulators, α-glucosidase inhibitors and incretins, are designed to reduce postprandial glucose, and increasing the sulphonylurea dose is not ideal to control basal glucose because of the risk of hypoglycaemia [2]. Among oral anti-diabetes agents, metformin is effective in reducing fasting glucose and insulin resistance. However; basal glucose is not adequately controlled by metformin or a combination of oral anti-diabetes agents [2,7,8]. In addition to anti-diabetes agents, at least 150 min of MVPA per week is recommended to improve glucose control and pancreatic β-cell function, and to reduce insulin resistance [25]. However, adherence to exercise is often suboptimal in people with Type 2 diabetes.

This study found that light-intensity walking breaks improved basal glucose. The mechanism for this is unclear. However, frequent interruption of sedentary time every 15 min could be considered in addition to the current treatment regimen. A feasibility study conducted in overweight and obese adults discovered that breaks in sedentary time (3-min break every 30 min vs. 6-min break every 60 min vs. 12-min break every 120 min) reduce sedentary time and improve physical activity, with greater compliance with more frequent breaks [26]. But, the feasibility and clinical relevance of walking breaks in free-living conditions in Type 2 diabetes should be tested in future studies.

This study has a number of strengths. First, the reference condition (Condition 1) and light-intensity walking (3.2 km/h) on level ground were relatively closer to habitual sedentary and activity patterns observed in Type 2 diabetes [16,27]. Second, this is the first study to compare the effects of different frequencies of walking breaks on basal glucose, especially the dawn phenomenon, although postprandial metabolic responses to different frequencies of standing breaks have been investigated previously [28]. Third, analyses were adjusted for different confounding variables, which might influence glucose homeostasis. Finally, the activPAL3 and CGM allowed relatively long duration of sedentary behaviour/physical activity and interstitial glucose monitoring.

This study also has some limitations. First, the study had a small sample size and might be underpowered to detect some of the changes in glucose variables. The small sample size (n = 10) and controlled laboratory settings had been used in previous studies [28,29]. We therefore suggest future definitive randomized controlled trials with larger sample size in free-living settings. Second, usual glucose control, such as fasting glucose and HbA$_{1c}$ levels, were not assessed to consider as inclusion or exclusion criteria for the selection of participants. Regular light-intensity walking breaks in sedentary time could have greater beneficial effects on glucose control in individuals with higher baseline fasting glucose and insulin resistance [30]. The dose–response of frequency of breaks might be more prominent in these individuals, and should be evaluated in future studies. Third, an acute effect rather than longer-term exposure of light-intensity walking breaks was investigated in this study. Fourth, the dinner before treatment conditions was not standardized. Fifth, standardized meals provided were not adjusted for the body weight and daily energy requirements of each

participant. Sixth, the difference in sedentary time, physical activity time, energy expenditure and timing of activity breaks in relation to meals could influence the effect of breaks. Future studies should compare different frequencies of breaks when these factors are matched. Finally, the dose–response of breaks on insulin resistance could not be assessed directly due to lack of insulin measurement. Nonetheless, lower fasting glucose and the dawn phenomenon in response to Condition 3 could reflect improved insulin sensitivity [1–3]. Observational and experimental studies have already reported that breaks in sedentary time improve insulin homeostasis [10,14].

In conclusion, this study demonstrates the dose–response of frequency of light-intensity walking breaks on basal glucose. The introduction of short frequent breaks in sedentary time could be an effective approach to improve fasting glucose, the dawn phenomenon and night-time glycaemic variability. Longer-term exposure to light-intensity walking breaks every 15 min of sitting added to current treatment regimen might produce sustainable clinical effect in Type 2 diabetes, and this should be explored in long-term studies.

Competing interests

None declared.

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Table 1 Baseline participant characteristics before treatment conditions

Participant characteristics	Overall	Condition 1	Condition 2	Condition 3
No. of participants (*n*)	12	8	8	8
Male : female (*n*)	8 : 4	7 : 1	5 : 3	5 : 3
Age (years)	60.0 ± 3.2	60.3 ± 4.1	60.4 ± 4.2	59.5 ± 3.8
BMI (kg/m^2)	30.2 ± 1.4	29.9 ± 1.8	30.5 ± 1.8	30.4 ± 1.8
Duration of diabetes (years)	5.2 ± 0.8	5.4 ± 1.0	4.9 ± 1.1	5.2 ± 1.1
Systolic blood pressure (mmHg)	139.6 ± 3.1	139.1 ± 2.9	140.8 ± 2.9	138.9 ± 2.9
Diastolic blood pressure (mmHg)	80.9 ± 1.9	81.3 ± 2.3	81.2 ± 2.3	80.2 ± 2.2
Smoking status, *n* (%)				
Non-smoker	11 (91.7)	7 (87.5)	8 (100)	7 (87.5)
Smoker	1 (8.3)	1 (12.5)	0 (0.0)	1 (12.5)
Medications, *n* (%)				
Metformin	7 (58.3)	5 (62.5)	5 (62.5)	4 (50.0)
Metformin + Gliclazide	4 (33.3)	2 (25.0)	3 (37.5)	3 (37.5)
Statin	5 (41.7)	3 (37.5)	3 (37.5)	4 (50.0)
Calcium channel blocker	2 (16.7)	2 (25.0)	1 (12.5)	1 (12.5)
Angiotensin converting enzyme inhibitor	2 (16.7)	2 (25.0)	2 (25.0)	0 (0.0)
Angiotensin receptor blocker	2 (16.7)	1 (12.5)	1 (12.5)	2 (25.0)
β blocker	1 (8.3)	1 (12.5)	1 (12.5)	0 (0.0)
Anti-diabetes medication dose				
Metformin (mg/day)	1227.3 ± 152.4	1214.3 ± 170.9	1187.5 ± 159.9	1285.7 ± 147.1
Gliclazide (mg/day)	80.0 ± 0.0	80.0 ± 0.0	80.0 ± 0.0	80.0 ± 0.0
Sedentary and activity time (h/day)*				
Sedentary time	10.2 ± 0.5	10.3 ± 0.7	10.2 ± 0.6	10.2 ± 0.6
Standing time	3.8 ± 0.4	3.6 ± 0.4	4.1 ± 0.4	3.7 ± 0.4
Walking time	1.5 ± 0.2	1.6 ± 0.2	1.5 ± 0.3	1.6 ± 0.2
Energy expenditure (MET × h/day)†	33.4 ± 0.3	33.6 ± 0.3	33.3 ± 0.3	33.4 ± 0.3
Basal glucose‡				
Fasting glucose (mmol/l)	6.8 ± 0.4	6.2 ± 0.5	6.7 ± 0.5	7.4 ± 0.4
The dawn phenomenon (mmol/l)	1.7 ± 0.2	1.5 ± 0.3	1.5 ± 0.3	1.9 ± 0.3
Duration of the dawn phenomenon (h)	5.6 ± 0.8	5.3 ± 0.9	5.9 ± 0.9	5.7 ± 0.9
Night-time mean glucose (mmol/l)	6.2 ± 0.6	6.1 ± 0.8	6.2 ± 0.8	6.5 ± 0.8
Night-time glycaemic variability (CV%)	12.9 ± 3.2	14.4 ± 5.7	9.1 ± 1.5	12.8 ± 2.1

Data are means ± SE or *n* (%).

CV, coefficient of variation.

*Sedentary and activity time during three days before treatment conditions.

†Energy expenditure during three days before treatment conditions.

‡Basal glucose of the nights and early mornings before treatment conditions.

There were no significant differences in age, BMI, duration of diabetes, systolic blood pressure, diastolic blood pressure, sedentary and activity time, energy expenditure and basal glucose between treatment conditions.

Table 2 Change in glucose variables

Glucose	Condition 1 (*n* = 8)	Condition 2 (*n* = 8)	Condition 3 (*n* = 8)
Model 1			
Fasting glucose (mmol/l)	−0.1 ± 0.2*	−0.6 ± 0.2	−1.0 ± 0.2
The dawn phenomenon (mmol/l)	0.3 ± 0.4	0.6 ± 0.3*	−0.6 ± 0.4
Duration of the dawn phenomenon (h)	1.9 ± 1.2*	−0.1 ± 1.4	−3.1 ± 1.3
Night-time mean glucose (mmol/l)	−0.9 ± 0.4	−1.2 ± 0.3	−0.5 ± 0.4
Night-time glycaemic variability (CV%)†	2.5 ± 1.8*	6.1 ± 4.8*	−9.7 ± 3.9
Model 2			
Fasting glucose (mmol/l)	−0.1 ± 0.2*	−0.6 ± 0.2	−1.0 ± 0.2
The dawn phenomenon (mmol/l)	0.2 ± 0.4	0.8 ± 0.3*	−0.6 ± 0.4
Duration of the dawn phenomenon (h)	1.9 ± 1.6*	−0.1 ± 0.4	−3.0 ± 2.1
Night-time mean glucose (mmol/l)	−1.1 ± 0.3	−1.1 ± 0.3	−0.3 ± 0.4
Night-time glycaemic variability (CV%)	−0.3 ± 3.5	5.2 ± 3.2*	−6.1 ± 3.8

Data are marginal means ± SE.

Model 1 was adjusted for age, sex, BMI, carbohydrate intake and energy expenditure.

Model 2 was additionally adjusted for anti-diabetes medication dose, sedentary time and walking time.

*Significantly different compared with Condition 3 ($P < 0.05$).

†CV, coefficient of variation.