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Glycemic control during consecutive days with prolonged walking exercise in individuals with type 1 diabetes mellitus

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ABSTRACT

Aims: Despite its general benefits for health, exercise complicates the maintenance of stable blood glucose concentrations in individuals with type 1 diabetes. The aim of the current study was to examine changes in food intake, insulin administration, and 24-h glycemic control in response to consecutive days with prolonged walking exercise (~8 h daily) in individuals with type 1 diabetes.

Methods: Ten individuals with type 1 diabetes participating in the worlds' largest walking event were recruited for this observational study. Simultaneous measurements of 24-h glycemic control (continuous glucose monitoring), insulin administration and food intake were performed during a non-walking day (control) and during three subsequent days with prolonged walking exercise (daily distance 40 or 50 km).

Results: Despite an increase in daily energy (31±18%; $p<0.01$) and carbohydrate (82±71g; $p<0.01$) intake during walking days, subjects lowered their insulin administration by 26±16% relative to the control day ($p<0.01$). Average 24-h blood glucose concentrations, the prevalence of hyperglycemia (blood glucose >10 mmol/L) and hypoglycemia (blood glucose <3.9 mmol/L) did not differ between the control day and walking days ($p>0.05$ for all variables). The prolonged walking exercise was associated with a modest increase in glycemic variability compared with the control day ($p<0.05$).

Conclusion: Prolonged walking exercise allows for profound reductions in daily insulin administration in persons with type 1 diabetes, despite large increments in energy and carbohydrate intake. When taking such adjustments into account, prolonged moderate-intensity exercise does not necessarily impair 24-h glycemic control.

Key words: type 1 diabetes mellitus; physical activity; exercise; walking; glycemic control; insulin

1. INTRODUCTION

Regular exercise has been associated with many health benefits, including cardiorespiratory fitness, muscle strength, cardiovascular and metabolic health, and increased life expectancy. Such health benefits are even more important for persons with type 1 diabetes, as this population is characterized by an increased prevalence of cardiovascular complications and premature death. Therefore, exercise is an important cornerstone in the management of type 1 diabetes [1-3].

Despite its general benefits for health, exercise has been associated with an increased risk for developing hypoglycemia [4, 5]. Such exercise-induced hypoglycemia may develop during and immediately after exercise, and even the day after performing exercise [5]. Several factors contribute to the occurrence of exercise-induced hypoglycemia. In persons with type 1 diabetes, the increase in blood glucose disposal during and following exercise is not compensated by a physiological reduction in circulating insulin concentrations. The resulting (relative) excess in circulating insulin concentrations inhibits the hepatic glucose output and stimulates the insulin-dependent blood glucose disposal [6]. Consequently, blood glucose concentrations further decline and hypoglycemia may develop. This process is further potentiated by the impairment in glucose counter-regulatory responses after exercise that is often present in individuals with type 1 diabetes [6, 7]. Since severe hypoglycemia has been associated with severe complications, such as cardiac dysrhythmia, seizure, coma and even death, preventing exercise-induced hypoglycemia is of utmost importance.

Two important strategies are well-recognized for the prevention of exercise-induced hypoglycemia, i.e. reductions in insulin administration and supplementation of carbohydrates before and after exercise [2, 8]. These strategies will, at least partly, correct for the relative insulin excess resulting from exercise. Accurate predictions of adequate adjustments in insulin

administration and dietary carbohydrate needs are difficult, and under- or over adjustment may potentially induce or worsen hypo- or hyperglycemia before and after exercise [9]. The optimal adjustments required to achieve stable blood glucose concentrations may vary dependent on the characteristics of the exercise performed (e.g. type, intensity, duration, and timing of exercise) [10]. Therefore, much research has focused on blood glucose responses to different exercise characteristics, along with the optimization of insulin administration and carbohydrate intake in preparation or in response to exercise [9, 11-15]. Despite the incremental knowledge in this area, only limited information is available regarding the impact of prolonged endurance-type exercise (>2 h duration) on blood glucose control. Such information is essential given the growing number of people with type 1 diabetes engaging in prolonged endurance-type exercise or leisure time physical activity (e.g. day hiking, cycling tours, or athletic events).

In the current observational study, we assessed changes in 24-h blood glucose concentrations, physical activity, dietary intake, and insulin administration in individuals with type 1 diabetes in response to consecutive days of prolonged moderate-intensity walking exercise (~8 h/day). For this purpose, we conducted simultaneous measurements with continuous glucose monitoring devices, physical activity monitors, and food and insulin records in 10 individuals with type 1 diabetes participating in the worlds' largest walking event, i.e. the Nijmegen Four Day Marches. We hypothesized that large adjustments in insulin administration and carbohydrate intake are required to prevent exercise-induced impairments in glycemic control.

2. METHODS

2.1 Subjects

A total of 10 individuals with type 1 diabetes volunteered to participate in this study. Subjects were recruited after registration for the 'Nijmegen Four Day Marches' walking event (an annual 4-day walking event in the Netherlands). The characteristics of the subjects are listed in **Table 1**. A written informed consent was obtained from all subjects before the start of the study. The study was approved by the Medical Ethical Committee of the Radboud University Nijmegen Medical Centre, and was conducted in accordance with the Declaration of Helsinki.

2.2 Study design

All individuals participated in this observational study, comprising simultaneous measurements of 24-h glycemic control, insulin administration, food intake, and physical activity (**Figure 1**). These variables were assessed the day before the 'Nijmegen Four Day Marches' walking event (control assessment), and over the course of this 4-day walking event (walking assessment). Upon registration for the walking event, participants selected to walk a daily distance of 40 or 50 km. In 2013, the walking event took place from July 16th to July 19th. All subjects were monitored at the same time.

2.3 Study protocol

The study was conducted over a 6-day period (**Figure 1**). On day 1 of the study period, subjects reported to the research laboratory in the afternoon. A venous blood sample was drawn for the assessment of HbA1c content, and subjects completed a short screening questionnaire on their

diabetes and training status. Subsequently, subjects were given instructions on the use of the combined food and insulin records, and subjects were equipped with a blinded continuous glucose monitoring (CGM) device (iPro2®, Medtronic Inc, Northridge, CA, USA) and a physical activity monitor. Day 2 was the day before the first walking stage, which served as the control day. From day 3 until day 6 of the study period, the 4-day walking event took place. During the walking event, subjects daily completed a 40 or 50 km walking stage. Directly prior to the start, and after the finish of each walking stage, subjects briefly reported to the onsite research laboratory for the registration of start and finish times. The combined food and insulin records, the CGM devices, and the physical activity monitors were returned on day 6 of the study period, after subjects completed the final stage of the walking event. As this study had an observational character, subjects were given no advice regarding adjustments in food intake and insulin administration. During the study period, subjects only received feedback on their blood glucose concentrations by self-monitoring, as the CGM measurements were conducted in a blinded fashion.

2.4 Dietary / Insulin records

Participants were instructed to report all the foods and drinks ingested over the 6-day period in the designated records. Participants were encouraged to report the food and drinks immediately upon consumption. Besides dietary intake, participants also reported the frequency and dose of the administered insulin in the records. Participants using an insulin pump reported the basal insulin infusion rates and administration of insulin boluses, whereas individuals on multiple daily injections reported the administration of long- (basal insulin) and short-acting (bolus) insulin

analogues. During the 6-day study period, the dietary/insulin records were reviewed on completeness and clarity by the research staff at least every other day.

2.5 Physical activity

Participants were equipped with a physical activity monitor (SenseWear Pro3 Armband, Body Media, Pittsburgh, PA) that was worn around the right upper arm. The sampling frequency was 32 Hz and data from the physical activity monitor were stored in 60-second epochs. The physical activity monitor measured physical activity 24 h per day throughout the 6-day study period. Physical activity data were used to assess the daily step count, the daily sedentary time, and the duration of breaks during the walking stages.

2.6 Continuous glucose monitoring

A subcutaneous glucose sensor (Enlite®, Medtronic Inc, Northridge, CA, USA) was inserted in the periumbilical region and connected to a continuous glucose monitoring recorder (iPro2®, Medtronic Inc, Northridge, CA, USA). The Enlite glucose sensor in combination with a Medtronic iPro recorder has been shown to generate accurate glucose readings for of at least 6 days [16]. Moreover, the previous generation of Medtronic glucose sensors has been shown to provide accurate glucose readings during exercise in patients with type 1 diabetes [17, 18].

In addition to the blinded CGM device, all participants received a handheld blood glucose meter (Glucocard X Meter, Arkray, Kyoto, Japan) for measuring capillary blood glucose concentrations. Participants were instructed to measure their capillary blood glucose concentrations six times daily throughout the entire 6-day study period. After returning the CGM device, data were uploaded to a laptop computer using the web-based Carelink® software

(Medtronic Inc, Northridge, CA, USA), and glycemic profiles were calibrated using the self-monitored capillary blood glucose concentrations.

Twenty-four-hour glycemic control derived from the glycemic profiles was expressed as average 24-h blood glucose concentration, time spent in hyperglycemia and hypoglycemia, high blood glucose index (HBGI) and low blood glucose index (LBGI), and glycemic variability. Based on the ADA/EASD guidelines for glycemic control [1, 19], the prevalence of hyperglycemia and hypoglycemia were defined as total time during which glucose concentrations were above 10 mmol/L and below 3.9 mmol/L, respectively. The HBGI and LBGI, as described by Clarke and Kovatchev [20], are summary indices reflecting the risk for hyperglycemia and hypoglycemia, respectively. Glycemic variability, which reflects acute glucose fluctuations, was assessed by the standard deviation of the average 24 h glucose concentration (SD) and by continuous overlapping net glycemic action (CONGA) as described by McDonnell et al. [21]. With this method, the difference between each glucose reading and the glucose reading n hours previously is calculated. The CONGAn is the standard deviation of these differences. We used CONGA1 and CONGA2 based on 1 and 2 h time differences, respectively.

2.7 Statistical analysis

Daily dietary intake, exogenous insulin use, physical activity and glycemic control were calculated over 24-h periods (00:00 h to 00:00 h). Therefore, only data obtained on day 2 until day 5 were used for analysis. The day prior to the walking event (day 2) served as the control situation, whereas the average of the first three days of the walking event (day 3-5; **Figure 1**) represented the ‘walking’ days. One subject (subject #7) failed to report dietary intake correctly, and as such, dietary records were analyzed for 9 subjects. One subject (subject #7) felt hindered

by the physical activity monitor armband, after which the armband was removed. Consequently, data obtained by the physical activity monitor were analyzed for 9 subjects. The CGM device failed to record CGM data in one of the subjects (subject #4), and as such, CGM data were analyzed for 9 subjects. Paired Student's t-tests (normally distributed data) or Wilcoxon signed rank tests (skewed data) were applied to compare data obtained during the control and walking days. Data are presented as mean±SD or median (IQR).

3. RESULTS

3.1 Walking characteristics

All subjects successfully completed the walking event. One subject completed a daily walking distance of 50 km, whereas the other nine subjects completed a daily walking distance of 40 km. The walking stages started in the early morning at 5:26±0:35 h and were completed in the afternoon at 15:01±1:00 h. The total duration of the breaks during each walking stage, as assessed by the physical activity monitor, was 1h21min±0h44min. As such, the net walking time was 8h12min±0h41min, representing an average walking speed of 5.0±0.3 km/h.

3.2 Physical activity

As expected, the average step count was markedly higher during the walking days (55,490±7,482 steps/day), compared with the control day (11,315±3,664 steps/day, $p<0.001$). In accordance, the amount of time spent in sedentary behavior (including sleep) was lower during the walking days (59±3% of the time) compared with the control day (88±6% of the time; $p<0.01$).

3.3 Energy and carbohydrate intake

With an average daily energy intake of 9.9±2.2 MJ during the walking days, the daily energy intake was 31±18% higher compared with the control day (7.6±1.0 MJ; $p<0.01$). The average intake of carbohydrate, protein, and fat was respectively 224±35 g, 69±16 g, and 61±16 g during the control day, and 306±79 g, 83±21 g, and 83±20 g during the walking days. As such, the average intake of carbohydrate, protein, and fat was respectively 82±71 ($p<0.01$), 13±21 ($p=0.09$), and 21±24 g ($p<0.05$) higher during the walking days compared with the control day.

3.4 Insulin administration

The daily insulin use is shown in **Figure 2**. Despite a profound increase in energy and carbohydrate intake, the use of bolus insulin was 49±25% lower during the walking days compared with the control day (10.0±6.7 verus 19.8±8.8 IU, respectively; $p<0.01$). The use of basal insulin, however, did not differ between the control day and walking days (22.5±7.9 and 21.7±8.1 IU, respectively; $p=0.19$). Altogether, the total insulin use (basal plus bolus) was 26±16% lower during the walking days compared with the control situation (31.7±12.4 versus 42.3±14.6, respectively; $p<0.01$).

3.5 24-h Glycemic control

Markers of 24-h glycemic control are shown in **Figure 3**. With a mean difference of 0.5±1.7 mmol/L, average 24-h blood glucose concentrations were not significantly different between the control day and walking days (8.1±2.7 mmol/L and 8.7±1.7 mmol/L, respectively; $p=0.36$). Compared with the control day, prolonged walking exercise was not associated with an increased prevalence of hyperglycemia and hypoglycemia (**Figure 3B** and **3C**, respectively). Consequently,

the time spent in the glycemic target zone (3.9 to 10 mmol/L) did not differ between the control day and walking days (**Figure 3D**). These results are further supported by the lack of difference in risk indices for both hyperglycemia (HBGI) and hypoglycemia (LBGI). The HBGI values were 6.1 (5.2 to 11.9) and 7.6 (6.5 to 11.6), whereas the LBGI values were 5.1 (4.4 to 8.4) and 4.4 (3.2 to 9.3) during the control and walking days, respectively ($p>0.05$ for both variables).

3.6 Glycemic variability

Despite the absence of differences in the prevalence of hyperglycemia and hypoglycemia, the walking days were associated with a higher glycemic variability compared with the control day, as illustrated by the higher CONGA1 (**Figure 4B**; $p<0.05$) and CONGA2 (**Figure 4C**; $p<0.05$) values. These observations suggest that the amplitude and/or frequency of glucose changes were more pronounced during the walking days compared to the control situation.

4. DISCUSSION

In this observational study, we assessed changes in 24-h glycemic control, physical activity, dietary intake, and exogenous insulin administration in individuals with type 1 diabetes in response to consecutive days with prolonged walking exercise (>8 h daily). We observed a profound reduction (49%) in bolus insulin administration during the walking days, despite increments in daily energy intake and amount of carbohydrate consumed. These self-initiated adjustments in insulin administration and food intake appeared sufficient to maintain the level of glycemic control observed during the control day.

The majority of research investigating the impact of exercise in persons with type 1 diabetes is limited to exercise durations for up to 2 hours per session [22, 23]. As such, most information on glycemic control during and after prolonged physical activity (>2 h) can be considered as 'anecdotal evidence'. Here we monitored glycemic control and food intake in relatively well-trained persons with type 1 diabetes participating in the world's largest walking event, i.e. the 'Nijmegen Four Day Marches' comprising consecutive days with prolonged walking exercise (40 or 50 km/day; ~8 h/day). The distances were covered at an average walking speed of 5.0±0.3 km/h (~3 mph), which can be considered moderate intense (~3.5 MET [24]). The daily step count of 55,490±7,482 steps during the walking days was more than 5-fold higher than the 10,000 steps/day often advocated for general health purposes [25]. We observed large reductions in daily insulin requirements (26±16%) during the walking days despite a large increase in the amount of carbohydrate consumed (82±71 g). These findings illustrate the major impact of prolonged walking exercise on insulin sensitivity and blood glucose disposal.

Despite the demanding nature of the walking event, we observed no noteworthy changes in 24-h glycemic control in participants with type 1 diabetes. Thus, the self-initiated adjustments in

insulin administration and carbohydrate intake appeared to be sufficient to prevent an impairment in 24-h glycemic control. The reduction in daily insulin administration (26±16%) was mainly attributed to the reduction in bolus insulin administration (49±25%). The latter tends to be in line with recent experimental evidence. In this regard, Campbell and colleagues [9] demonstrated a lower risk for hypoglycemia in individuals with type 1 diabetes after largely reducing the insulin boluses administered with the meals before (25% reduction) and after (50% reduction) 45 min of vigorous exercise. It should be noted that those reductions in bolus insulin administration appeared to be adequate to prevent early (<8h post-exercise), but not late-onset hypoglycemia [9]. In the current study, participants reduced their bolus insulin administration throughout the entire 24-h period, which seemed to be adequate to prevent exercise-induced impairments of hypoglycemia. Recent evidence suggests that the combined reduction of basal and bolus insulin administration on the exercise day provides superior protection against hypoglycemia compared to reductions in bolus insulin administration alone [15]. Our participants, however, did not change their basal insulin administration. As such, the combined reduction of basal and bolus insulin administration in preparation or response to exercise may require more attention amongst individuals with type 1 diabetes, healthcare providers and (bio)medical scientists.

Although most markers of 24-h glycemic control did not change in response to prolonged walking exercise (**Fig 3**), we observed a modest increase in glycemic variability during the walking days relative to the control day (**Fig 4B and 4C**). This observation suggests that prolonged walking exercise induces an increase in the amplitude and/or frequency of glucose excursions throughout the day. This greater variability is not surprising when considering the higher frequency of food/carbohydrate intake associated with the prolonged walking exercise,

thereby inducing a higher frequency of glucose fluctuations. It could also be speculated that the anticipation to changing glucose levels is complicated by prolonged exercise. For example, the insulin-to-carbohydrate ratio required to maintain euglycemia is strongly altered during and following exercise [26]. Inadequate adjustment of pre- and post-exercise insulin use could result in exaggerated up- or downward glucose excursions [9]. This prompts the need for an insulin correction bolus or carbohydrate supplement to prevent either hyper- or hypoglycemia. Thus, suboptimal anticipation to prolonged exercise might induce unnecessary glucose excursions, thereby increasing the level of glycemic variability. It would be relevant to investigate whether direct feedback on changing blood glucose concentrations, as provided by real time CGM, can be used to prevent the deterioration in glycemic variability [27]. In this regard, feedback-controlled closed-loop insulin delivery might even further support the stability of blood glucose concentrations during and following prolonged exercise [28].

In the current study, we monitored self-selected adjustments in insulin administration and food intake in relatively well-trained individuals with type 1 diabetes participating in the worlds' largest walking event. The results of this observational study give an indication of the adjustments in insulin administration and food intake required to prevent impairments in glycemic control induced by prolonged exercise. Hence, this study provides some early support to develop more comprehensive guidelines for individuals with type 1 diabetes aiming to engage in prolonged endurance-type exercise or leisure time physical activity. Inherent to the unique setting of the present study, we should also recognize some limitations. The relatively small sample size which was overrepresented by women, may impede the robustness and generalizability of our findings. It should also be noted that the required adjustments in insulin administration and food intake associated with prolonged exercise may be influenced by personal

and environmental factors such as training status, habitual physical activity, mental stress, baseline level of glycemic control, type of insulin treatment, and climate. Moreover, the exercise modality, as well as the exercise intensity and duration may ultimately dictate the magnitude and timespan of adjustments in insulin requirements and food intake.

In conclusion, prolonged walking exercise allows for profound reductions in daily insulin administration in persons with type 1 diabetes, despite large increments in energy and carbohydrate intake. When taking such adjustments into account, prolonged exercise does not necessarily impair 24-h glycemic control.

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COMPETING INTERESTS

The authors report no potential conflicts of interest relevant to this article.

AUTHOR RESPONSIBILITIES

The authors' responsibilities were as follows: JWvD designed the study, collected the data, researched the data, and wrote the manuscript. TME designed the study, collected the data, contributed to the discussion, and revised the manuscript. JN collected the data, researched the data, and contributed to the discussion. THS collected the data and contributed to the discussion. MTH collected the data and contributed to the discussion. DHT designed the study, collected the

data, contributed to the discussion, and revised the manuscript. LJCvL designed the study, contributed to the discussion, and revised and edited the manuscript.

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Table 1: Participants' characteristics

N (male/female)	10 (1/9)
Age (y)	45 ± 13
BMI (kg/m^2)	24.2 ± 3.6
Pump / Multiple injections	4 / 6
Diabetes duration (y)	26 ± 11.3
HbA1c (%)	7.9 ± 1.2
HbA1c (mmol/mol)	63 ± 13
Exercise training* (h/week)	7.2 ± 3.9

Data are means±SD or frequencies. * Exercise training refers to all structured exercise over the last month prior to the walking event.

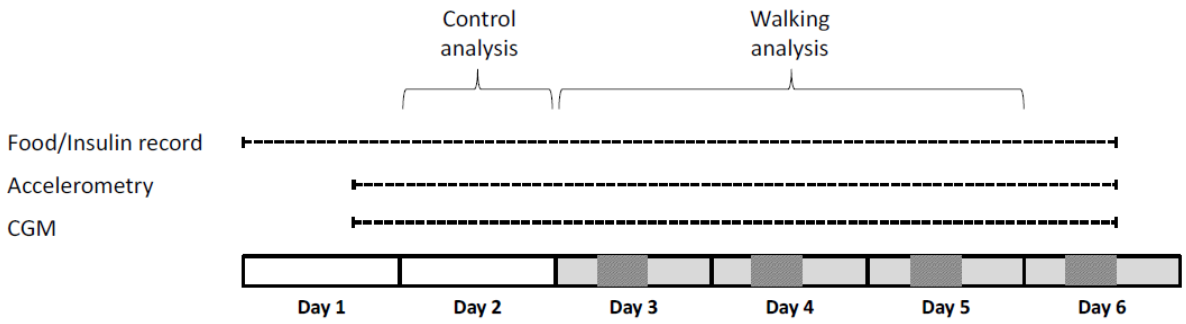
FIGURE LEGENDS

Figure 1: Schematic overview of the study design. The grey shaded boxes represent the walking days, the hatched areas represent the walking stages.

Figure 2: Daily insulin use during the control day and subsequent walking days. Daily insulin use is expressed as total insulin use (**panel A**), basal insulin use (**panel B**), and bolus insulin use (**panel C**). The grey lines represent individual cases, the black lines represent means±SD. * Significantly different compared with sedentary condition ($p<0.01$).

Figure 3: Twenty-four hour glycemic control assessed during the control day and subsequent walking days. Twenty-four hour glycemic control is expressed as (**panel A**) average 24-h blood glucose concentrations, (**panel B**) the prevalence of hyperglycemia (blood glucose >10 mmol/L), (**panel C**) the prevalence of hypoglycemia (blood glucose <3.9 mmol/L), and (**panel D**) time in the glycemic target zone of 3.9 – 10 mmol/L. The grey lines represent individual cases, the black lines represent means±SD (**panel A and D**) or medians±IQR (**panel B and C**).

Figure 4: Glycemic variability assessed during the control day and subsequent walking days. Glycemic variability is expressed as SD of average 24-h blood glucose concentrations (**panel A**), CONGA1 (**panel B**), and CONGA2 (**panel C**). * Significantly different compared with sedentary condition ($p<0.05$).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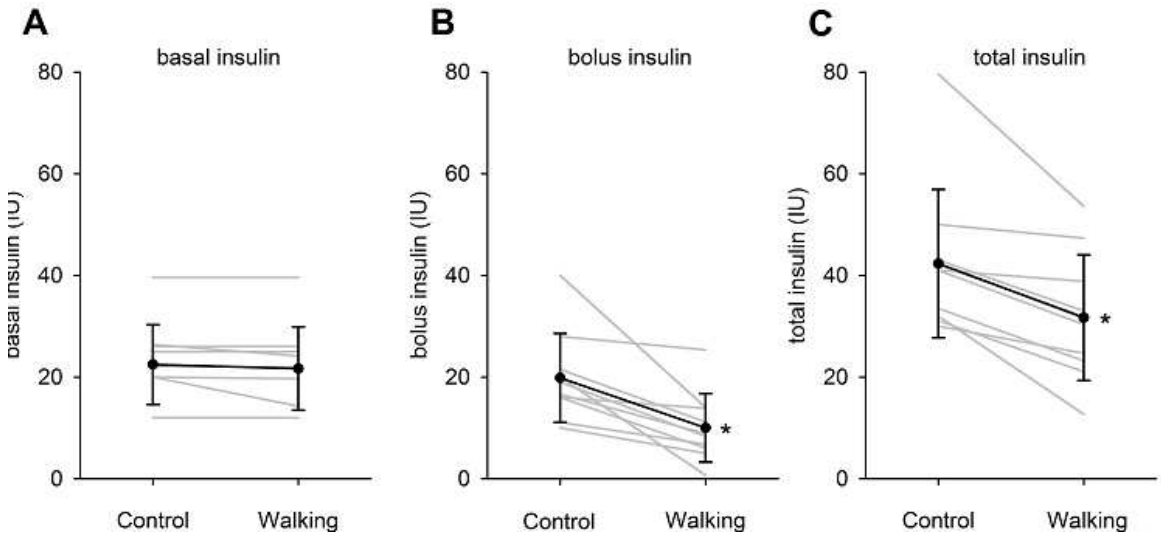
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Walking
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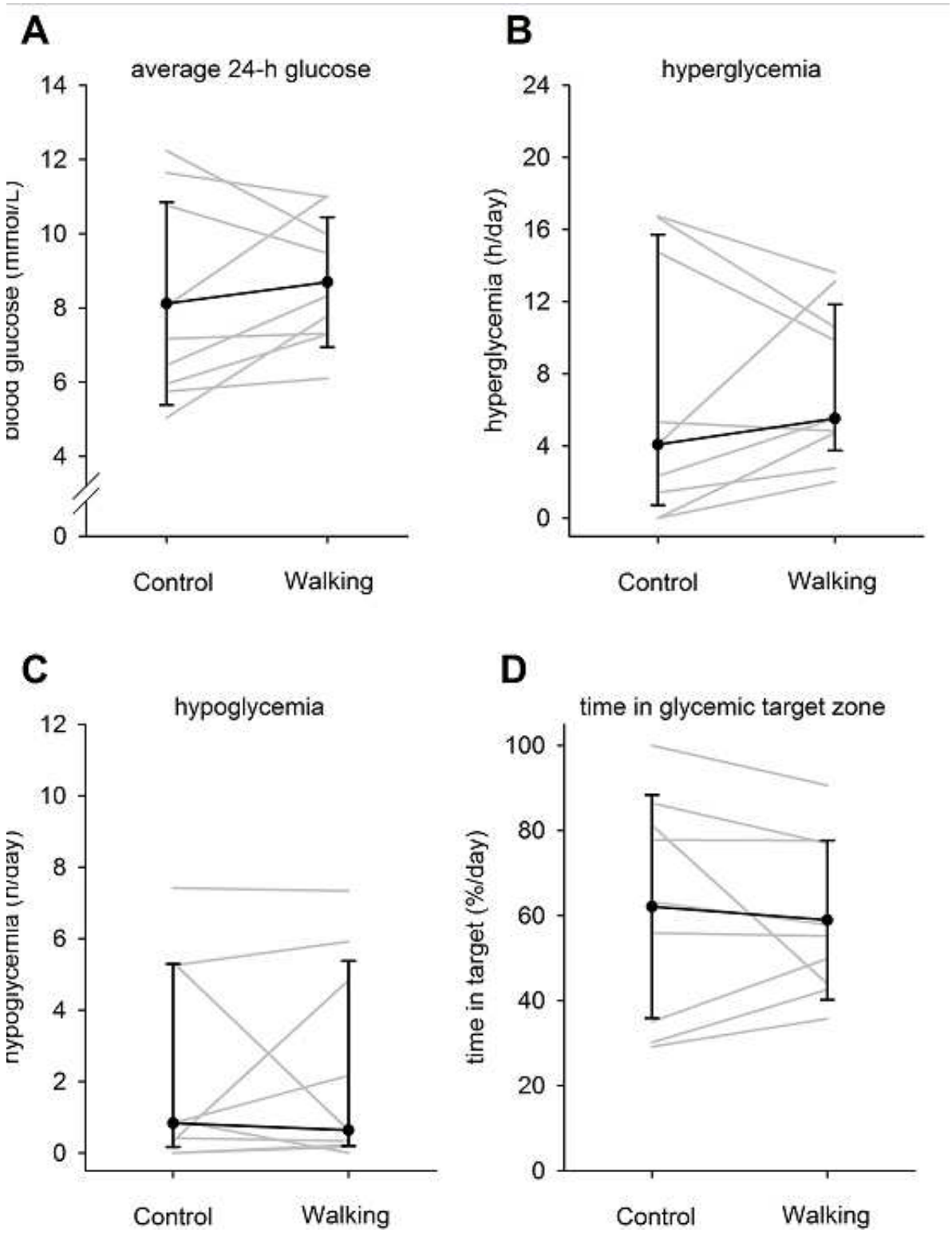
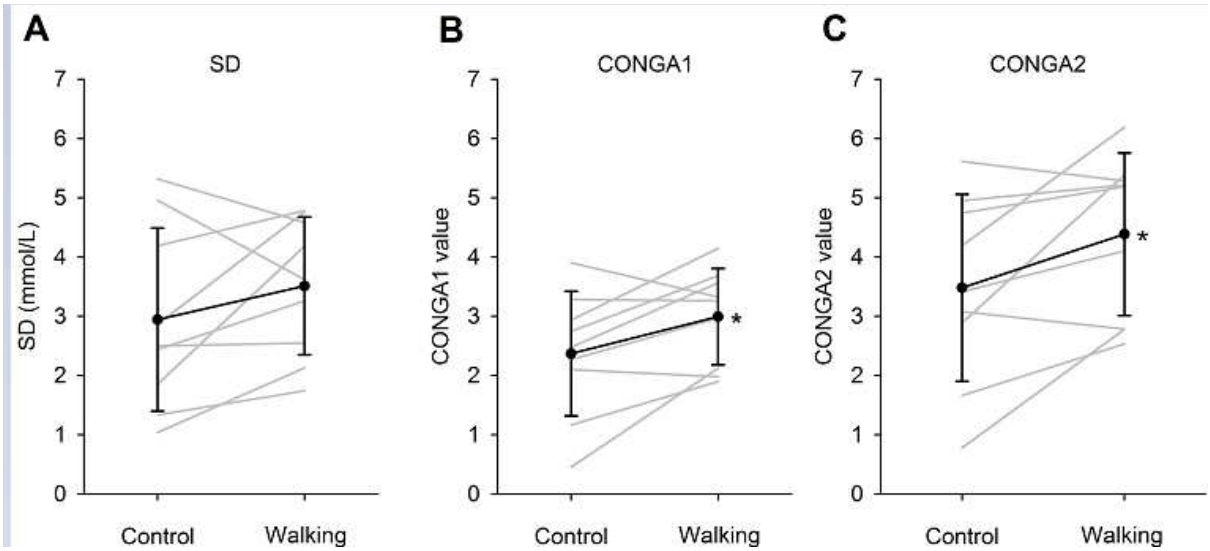

A
average 24-h glucose
blood glucose (mmol/L)
14
12
10
8
6
4
0
Control
Walking
B
hyperglycemia
hyperglycemia (h/day)
24
20
16
12
8
4
0
Control
Walking
C
hypoglycemia
hypoglycemia (n/day)
12
10
8
6
4
2
0
Control
Walking
D
time in glycemic target zone
time in target (%/day)
100
80
60
40
20
0
Control
Walking


A
SD
SD (mmol/L)
7
6
5
4
3
2
1
0
Control
Walking
B
CONGA1
CONGA1 value
*
C
CONGA2
CONGA2 value
*