

Prevalence of daily hyperglycemia in obese type 2 diabetic men compared with that in lean and obese normoglycemic men: effect of consumption of a sucrose-containing beverage^{1–3}

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ABSTRACT

Background: Hyperglycemia forms a direct and independent risk factor for the development of cardiovascular comorbidities in type 2 diabetes. Consumption of sucrose-sweetened soft drinks might further increase the prevalence of hyperglycemic episodes.

Objective: The objective was to assess glycemic control in type 2 diabetic subjects and healthy lean and obese control subjects under strict dietary standardization but otherwise free-living conditions, with and without the consumption of soft drinks.

Design: Obese type 2 diabetic men ($n = 11$) and lean ($n = 10$) and obese ($n = 10$) normoglycemic male control subjects participated in a randomized crossover study. The subjects were provided with a standardized diet in 2 periods, during which they consumed 250 mL water with or without (control) sucrose (37.5 g) 2 h after breakfast and lunch. Blood glucose concentrations were assessed by continuous glucose monitoring.

Results: In the type 2 diabetic subjects, the mean 24-h glucose concentrations were significantly elevated (9.1 ± 0.6 mmol/L), and hyperglycemia (glucose >10 mmol/L) was evident over $33 \pm 8\%$ (8 ± 2 h) of a 24-h period ($P < 0.01$). Hyperglycemia was rarely present in the normoglycemic lean and obese control subjects ($5 \pm 2\%/24$ h for both). Consumption of 75 g sucrose, equivalent to 2 cans of a soft drink, did not further augment the prevalence of hyperglycemia throughout the day in any group.

Conclusions: Type 2 diabetic subjects taking oral blood glucose-lowering medication experience hyperglycemia during most of the daytime. Moderate consumption of sucrose-sweetened beverages does not further increase the prevalence of hyperglycemia in type 2 diabetic subjects or in normoglycemic lean or obese men. *Am J Clin Nutr* doi: 10.3945/ajcn.2008.27072.

INTRODUCTION

Several large epidemiologic surveys and intervention studies have shown that postprandial hyperglycemia is a direct and independent risk factor for the development of cardiovascular disease in type 2 diabetes (1–3). However, intense glucose-lowering treatment accompanied by hypoglycemia is also associated with an increased risk of cardiovascular disease (4, 5). The rapid postprandial rise in blood glucose concentrations, also referred to as hyperglycemic spikes, seem to be more relevant to the onset of micro- and macrovascular complications than merely elevated fasting blood glucose concentrations (6–8). In

accordance, recent data by Monnier et al (9) suggest that acute fluctuations in plasma glucose induce more oxidative stress than does chronic hyperglycemia. Thus, it is of important clinical relevance to obtain more insight on the prevalence of daily blood glucose excursions. Because the contribution of postprandial glucose increments has been shown to be predominant to the prevalence of overall hyperglycemia in well-controlled type 2 diabetic subjects (10), it is evident that current standards of glycemic control do not provide sufficient information on daily blood glucose excursions (11).

The use of continuous glucose monitoring (CGM) provides an effective strategy for assessing glycemic control throughout the day under free-living conditions (12, 13). In accordance, we applied continuous glucose monitoring to show that postprandial hyperglycemic blood glucose excursions are prevalent throughout the greater part of the day, even in well-controlled, type 2 diabetic subjects using oral blood glucose-lowering medication (11, 14). Consequently, it became evident that, even in the presence of normal hemoglobin A_{1c} values, large perturbations in postprandial blood glucose concentrations can be prevalent throughout the day (10, 15). Consequently, we speculated that hyperglycemic blood glucose excursions might already be present in a healthy population that does not yet show any signs of glucose intolerance. As such, the presence of hyperglycemia throughout the day might represent an early stage in the development of insulin resistance and/or type 2 diabetes. Therefore, in the present study we assessed 24-h glycemic control in healthy lean and obese men and obese type 2 diabetic subjects under strict dietary standardization but otherwise free-living conditions via continuous glucose monitoring.

Dietary practice plays a central role in glycemic control (16). The use of sucrose-sweetened beverages has been shown to be associated with hyperglycemia and the development of insulin

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resistance or type 2 diabetes (17–20). Whether the latter is attributed to the proposed acute effects of sucrose-sweetened beverage consumption (eg, induction of postprandial hyperglycemia and the stimulation of excess energy intake and subsequent development of obesity) remains unresolved. However, limited data are available on the effect of habitual consumption of sucrose-sweetened soft drinks on daily glycemic control under normal, free-living conditions (21). We speculated that sucrose-sweetened soft drink consumption, in addition to a normal diet, further augments the prevalence of hyperglycemia in both type 2 diabetic subjects and normoglycemic lean and obese men.

The present study compared 24-h glycemic control between obese type 2 diabetic subjects and both lean and obese normoglycemic men under strict dietary standardization, but otherwise free-living conditions. Furthermore, by evaluating the glycemic responses to a standardized diet with and without the additional consumption of sucrose-containing beverages, the present study also evaluated the effect of moderate consumption of sucrose-sweetened soft drinks on daily glycemic control.

SUBJECTS AND METHODS

Subjects

A total of 11 obese type 2 diabetic men, 10 age-matched healthy lean normoglycemic men, and 10 age- and body mass index (BMI; in kg/m²)–matched obese normoglycemic men were recruited to participate in this study (Table 1). Exclusion criteria were impaired renal and/or liver function, extreme obesity (BMI > 35), cardiac disease, hypertension, diabetic complications, and exogenous insulin therapy. All subjects were informed about the nature and risks of the experimental procedures before their written informed consent was obtained. The Medical Ethical Committee of the Academic Hospital in Maastricht approved all clinical experiments.

Screening

All subjects underwent a standard 75-g oral-glucose-tolerance test (OGTT). After an overnight fast, the subjects arrived at the

laboratory at 0800 by car or public transportation. Plasma glucose concentrations were measured to determine glucose intolerance and/or type 2 diabetes according to American Diabetes Association guidelines (22). Plasma glucose and insulin concentrations obtained during the OGTT were used to assess whole-body insulin resistance and sensitivity using the homeostasis model assessment of insulin resistance (HOMA-IR) index (23) and the oral-glucose-insulin sensitivity (OGIS) index (24), respectively. Furthermore, the hemoglobin A_{1c} value was measured in basal blood samples. After the OGTT, body weight was measured with a digital balance with an accuracy of 0.001 kg (E1200; August Sauter GmbH, Albstadt, Germany). Body composition was determined by the hydrostatic weighing method. Simultaneously, residual lung volume was measured by the helium-dilution technique with a spirometer (Volugraph 2000; Mijndhardt, Bunnik, Netherlands). Body fat percentage was calculated by using Siri's equation (25). Fat-free mass was calculated by subtracting fat mass from total body weight.

Protocol

Each subject participated in a randomized, double-blind, crossover design. Subjects were studied for ≈40 h under strict dietary standardization but otherwise free-living conditions with a continuous glucose monitoring system (CGMS) (Figure 1). In one period, the subjects received 2 beverages containing only water (control); in the other period, the subjects received a beverage sweetened with sucrose. Measurements were performed in each subject, with a 2-wk interval between periods. Before the start of the first 40-h assessment period, the subjects reported to the laboratory in the afternoon and were given instructions regarding the standardized diet, the consumption of the experimental beverages, and the proper use of the food intake and physical activity questionnaires. All subjects received brief training on the use of the capillary blood sampling method (Glucocard Memory PC; A. Menarini Diagnostics, Firenze, Italy). Next, a microdialysis fiber (Medica, Medolla, Italy) was inserted in the periumbilical region. The microfiber was subsequently connected to a portable CGMS (GlucoDayS; A.

TABLE 1
Characteristics of the subjects¹

	Lean normoglycemic control subjects (n = 10)	Obese normoglycemic control subjects (n = 10)	Obese type 2 diabetic subjects (n = 11)
Age (y)	56 ± 2 (44–62)	52 ± 2 (40–61)	56 ± 2 (47–63)
Body weight (kg)	74.7 ± 1.3 (68–80)	104.9 ± 1.4 ² (98–113)	97.7 ± 2.9 ² (79–115)
BMI (kg/m ²)	23.9 ± 0.5 (20–25)	31.7 ± 0.5 ² (30–35)	31.8 ± 0.6 ² (30–35)
Body fat (%)	20.0 ± 1.6 (15–32)	31.4 ± 1.7 ² (26–41)	31.4 ± 1.0 ² (27–36)
Basal plasma glucose (mmol/L)	5.3 ± 0.1 (4.8–6.0)	5.1 ± 0.6 (5.0–6.1)	9.2 ± 0.4 ^{2,3} (7.8–12.5)
Plasma glucose _{OGTT120} (mmol/L)	4.4 ± 0.3 ² (3.3–6.1)	5.0 ± 0.8 (4.0–6.4)	16.1 ± 0.6 ^{2,4} (13.7–20.4)
Basal plasma insulin (mU/L)	11.6 ± 0.9 (6.2–16.3)	20.0 ± 3.6 ² (10.0–37.0)	18.4 ± 2.1 ² (11.6–34.0)
Hemoglobin A _{1c} (%)	5.5 ± 0.1 (5.0–6.7)	5.7 ± 0.1 (5.4–6.2)	7.4 ± 0.2 ^{2,3} (6.5–8.8)
OGIS ₁₂₀ (mL · min ⁻¹ · m ⁻²)	419 ± 15 (361–479)	337 ± 24 ² (253–385)	272 ± 11 ^{2,3} (219–351)
Diagnosed with type 2 diabetes (y)	—	—	6 ± 2 (1–17)
Medication use	—	—	Metformin, SUDs, and/or TZDs

¹ All values are means ± SEMs; ranges in parentheses. OGTT120, oral-glucose-tolerance test 120 min after ingestion of 75 g glucose; OGIS₁₂₀, oral glucose insulin sensitivity test based on a 120-min OGTT; SUDs, sulfonylurea derivatives; TZDs, thiazolidinediones.

² Significantly different from the lean normoglycemic group, *P* < 0.05 (ANOVA with Scheffe's post hoc test).

³ Significantly different from the obese normoglycemic group, *P* < 0.05 (ANOVA with Scheffe's post hoc test).

⁴ Significantly different from baseline, *P* < 0.01 (paired Student's *t* test).

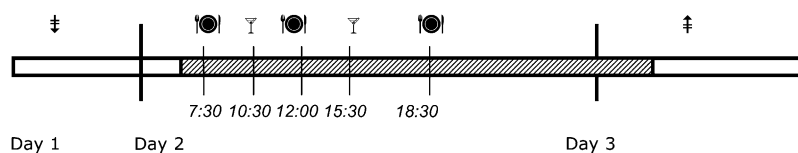


FIGURE 1. Schematic overview of the experimental periods. All subjects reported to the laboratory on day 1, at which time the continuous glucose monitoring device was inserted (⌘). On day 2, all subjects consumed prepackaged meals (Ⓜ) at 0730, 1200, and 1830. At 1030 and 1530, beverages (Ⓝ) containing either placebo or sucrose were ingested. In the afternoon on day 3, the subjects returned to the laboratory, at which time the continuous glucose monitoring device was removed (⌘).

Menarini Diagnostics). The ambulant CGMS is based on the microdialysis principle and allows continuous glucose monitoring for a period of 48 h (26). The glucose sensor, which consists of immobilized glucose oxidase, measures the glucose concentration every minute and stores an average value every 3 min up to 48 h.

Then, the subjects were provided their diet, after which they went home and resumed their normal daily activities. The following day, the subjects consumed their designated meals, drinks, and snacks at the predetermined time points. Before consuming a meal, the subjects provided a capillary blood glucose sample. At 1030 and 1530, the subjects drank either the control or the sucrose beverage. The subsequent day, the subjects reported back to the laboratory, where the CGMS was removed. CGMS data from the second day (from 0700 to 0700) were used for the analyses.

Medication, diet, and physical activity

The type 2 diabetic subjects were either taking oral blood glucose-lowering medication [metformin and sulfonylurea derivatives (SUDs), $n = 5$; metformin, $n = 2$; and thiazolidinediones (TZDs), $n = 1$] or undergoing dietary modulation only ($n = 3$). All subjects had been using the same medication and dietary prescription for ≥ 3 mo. Blood glucose-lowering medication was discontinued 2 d before screening, but continued as normal throughout the entire experimental period. All subjects maintained normal dietary and physical activity patterns throughout the entire experimental period and refrained from exhaustive physical labor and exercise training for ≥ 3 d before each period. Food intake and physical activity questionnaires were collected for 2 d before the test periods to keep dietary intake and physical activity as identical as possible. Food intake and physical activity records were filled in under direct supervision of a certified dietitian, who consulted our subjects throughout the entire experimental period and calculated the daily energy intake and macronutrient composition of the habitual diet in the type 2 diabetic subjects and the lean and obese normoglycemic control subjects.

The evening before each period, all subjects received the same standardized meal (43.8 kJ/kg body wt; 60% of energy as carbohydrate, 28% of energy as fat, and 12% of energy as protein). All meals, snacks, and beverages were provided in preweighed packages and ingested at predetermined time points to ensure fully standardized dietary modulation during the subsequent 40-h test period. The standardized diet (3 meals and 1 snack per day) provided 12.2 MJ/d and consisted of 56% of energy as carbohydrate, 34% of energy as fat, and 10% of energy as protein. The standardized diet was designed based on the individual energy requirements of the obese subjects based on the equations of Harris and Benedict (27) multiplied by a physical activity index of 1.4 for conversion to total energy expenditure. Consequently,

the lean control group received more energy than their individual requirements (9.4 ± 0.4 compared with 12.2 MJ/d, respectively). The energy intake of the lean subjects was kept identical to the obese groups to allow the comparison of glycemic excursions between groups when consuming exactly the same diet. In the morning and afternoon, the subjects ingested a prepacked bottle containing either control or sucrose. Ingestion of the sucrose beverage increased daily energy intake to 13.5 MJ/d. Sucrose beverage consumption changed the macronutrient composition of the diet to 60% of energy, 30% of energy, and 10% of energy.

Beverages

The beverages consisted of 250 mL water with or without (control) 37.5 g sucrose and were ingested in the morning at 1030 and in the afternoon at 1530. The drinks were uniformly flavored with 5 g cream vanilla flavor (Quest International, Naarden, Netherlands) per liter beverage to make the taste comparable in both periods.

Blood sample analysis

Blood (10 mL) was collected into EDTA-containing tubes and centrifuged at $1000 \times g$ and 4°C for 10 min. Aliquots of plasma were immediately frozen in liquid nitrogen and stored at -80°C until analyzed. Plasma glucose concentrations (Uni Kit III; Roche, Basel, Switzerland) were analyzed with the COBAS FARA semiautomatic analyzer (Roche). Plasma insulin was measured by radioimmunoassay (HI-14K; Linco Research Inc, St Charles, MO). To determine the hemoglobin A_{1c} content, a 3-mL blood sample was collected into EDTA-containing tubes and analyzed by HPLC (Bio-Rad Diamat, Munich, Germany).

Statistics and data analysis

The acquired data were downloaded from the CGMS to a personal computer with GlucoDay software (version 3.0.5). Values reported by the CGMS were converted into glucose values by using the self-monitoring blood glucose values. The efficacy and the accuracy of the GlucoDayS has been validated for both type 2 diabetic subjects (26, 28) and healthy subjects (29). CGMS data from the second day (from 0700 to 0700) were used for data analyses and are expressed as means \pm SEMs. All variables were analyzed over the entire 24-h measuring period, postprandially (3 h after meal ingestion) and 2 h after beverage consumption. To quantify and compare the prevalence of hyperglycemia between periods, the amount of time during which glucose concentrations were >10 mmol/L was calculated. Dietary records were analyzed with KOMeet v4.0 with the 2006 NEVO tables (BaS software, Wageningen, Netherlands). Energy expenditure during the intervention day was determined by

TABLE 2

Energy content and macronutrient composition of the habitual and standardized diets

	Habitual diet			Standard diet
	Lean normoglycemic control subjects (<i>n</i> = 10)	Obese normoglycemic control subjects (<i>n</i> = 10)	Obese type 2 diabetic subjects (<i>n</i> = 11)	
Energy intake (MJ/d)	9.4 ± 0.4 ¹	9.7 ± 0.3	9.7 ± 0.5	12.2
Carbohydrate (% of energy)	51 ± 2	51 ± 2	43 ± 4 ²⁻⁴	56
(g)	280 ± 11	295 ± 10	251 ± 26 ²⁻⁴	342
Protein (% of energy)	14 ± 1 ²	18 ± 3 ²	17 ± 2 ^{2,3}	10
(g)	80 ± 6	105 ± 16 ²	101 ± 12 ^{2,3}	75
Fat (% of energy)	35 ± 3	31 ± 3	38 ± 3 ⁴	34
(g)	89 ± 9	80 ± 10	95 ± 7 ⁴	91
Fiber (g)	25 ± 2 ²	38 ± 3 ²	29 ± 3 ⁴	30

¹ Mean ± SEM (all such values)² Significantly different from standard diet, *P* < 0.05 (ANOVA).³ Significantly different from the lean normoglycemic group, *P* < 0.05 (ANOVA with Scheffe's post hoc test).⁴ Significantly different from the obese normoglycemic group, *P* < 0.05 (ANOVA with Scheffe's post hoc test).

using the Compendium of Physical Activities (30). A 2-factor ANOVA with group and treatment as factors was used to compare differences in treatment effects between groups. In case of significant differences between periods, Scheffe's post hoc test was applied to locate these differences. Statistical significance was set at *P* < 0.05. All calculations were performed by using Stat View 5.0 (SAS Institute Inc, Cary, NC).

RESULTS

Energy intake and expenditure

The standardized diet provided 12.2 MJ/d and provided 56% of energy as carbohydrate, 34% of energy as fat, and 10% of energy as protein according to current guidelines for a healthy diet (31–34). Details on the content of the standardized diet are provided in **Table 2** and **Table 3**. Habitual energy intake, as assessed by the dietary intake records, averaged 9.4 ± 0.4, 9.7 ± 0.3, and 9.7 ± 0.5 MJ/d in the lean and obese normoglycemic and type 2 diabetic subjects, respectively (Table 2). Average energy expenditure during the periods did not differ between groups: 138 ± 3, 139 ± 6, and 138 ± 6 kJ · kg⁻¹ · 24 h⁻¹ in the control period and 133 ± 3, 146 ± 7, and 138 ± 5 kJ · kg⁻¹ · 24 h⁻¹ in the sucrose period in the lean and obese normoglycemic and type 2 diabetic subjects, respectively.

TABLE 3

Composition of the standardized diet

Breakfast	Lunch	Dinner	Evening snack
Whole-grain bread, margarine, strawberry jam, ham, paté, orange juice, coffee/tea (no sugar)	Raisin bread, white bread, margarine, chocolate spread, ham, apple, semiskim milk, coffee/tea (no sugar)	Lasagna Bolognese (meat, tomatoes, wheat flour, onion, cheese, vegetable oil, cornstarch, carrots, milk and egg protein, vanilla custard)	Coffee/tea, (no sugar), candy sugar biscuit

Glycemic control

Blood glucose concentrations over 24 h in both the lean and obese normoglycemic control subjects and type 2 diabetic subjects during the control period are illustrated in **Figure 2A**. Average glucose concentrations over the 24-h period are reported in **Table 4**. Repeated-measures ANOVA showed a significant group effect (*P* < 0.01) in 24-h glucose concentration.

Consumption of the standardized diet did not result in any overt hyperglycemic blood glucose excursions in either the lean or obese normoglycemic subjects. In the control period, total postprandial glucose concentrations averaged 6.7 ± 0.5 and 6.5 ± 0.5 mmol/L (average of the sum of the postprandial glucose concentrations after breakfast, lunch, and dinner) in the lean and obese control subjects, respectively. In contrast, consumption of the same diet in the type 2 diabetic subjects resulted in postprandial hyperglycemic episodes with glucose concentrations averaging 10.3 ± 0.7, 8.7 ± 0.7, and 7.5 ± 0.5 mmol/L over the first 3 h after breakfast, lunch, and dinner, respectively (Table 4). Nocturnal and postprandial glucose concentrations after breakfast and lunch were significantly higher in the type 2 diabetic subjects than in the lean and obese normoglycemic control subjects (*P* < 0.05). Despite the provision of a healthy diet and the continued use of oral blood glucose-lowering medication, the prevalence of hyperglycemia was evident for as much as 33 ± 8% (8:00 ± 1:50 h:min) of the 24-h period in the type 2 diabetic subjects (control period). Even in the well-controlled subjects with a blood hemoglobin A_{1c} value <7.0% (*n* = 5), hyperglycemia was experienced for 5 ± 1 h over the 24-h period. In contrast, hyperglycemia was evident in merely 5 ± 2% (1:11 ± 0:24 h:min) and 5 ± 2% (1:12 ± 0:25 h:min) of the 24-h period in the lean and obese normoglycemic control subjects, respectively (**Table 5**; *P* < 0.05). During the night (from 000 to 600), the type 2 diabetic subjects were in a state of hyperglycemia for >2 h, whereas nocturnal hyperglycemia was rarely present in the normoglycemic control subjects (*P* < 0.05; Table 5). Repeated-measures ANOVA showed a significant group effect (*P* < 0.01) on the prevalence of hyperglycemia.

Significant correlations were observed between hemoglobin A_{1c} and the 24-h prevalence of hyperglycemia (*r* = 0.55, *P* < 0.01) and with postprandial hyperglycemia after breakfast (*r* = 0.57, *P* < 0.01) but not after lunch (*r* = 0.30, *P* = 0.1) or dinner (*r* = 0.34, *P* = 0.06). Both HOMA-IR (*r* = 0.52, *P* < 0.01) and OGIS (*r* = -0.40, *P* < 0.05) correlated well with the 24-h prevalence of hyperglycemia.

Sucrose consumption

Consumption of 250 mL of a sucrose-containing beverage twice daily did not change 24-h glucose concentrations relative to the control beverage. In the type 2 diabetic subjects, average 24-h glucose concentrations were significantly elevated when

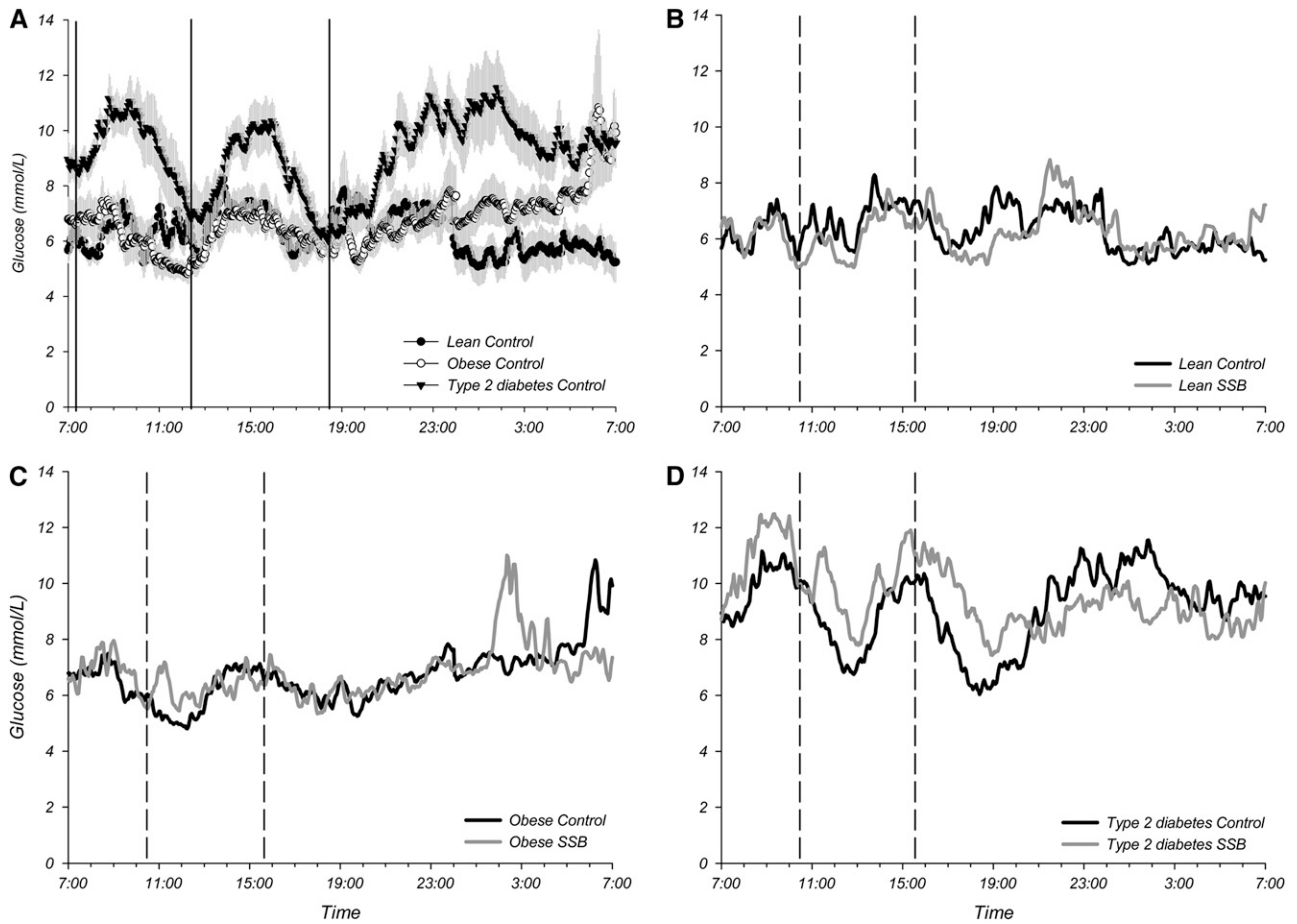


FIGURE 2. A: Mean (\pm SEM) plasma glucose concentrations over a 24-h period during a standardized diet (control) in lean ($n = 10$) and obese ($n = 10$) normoglycemic subjects and obese type 2 diabetic subjects ($n = 11$). B–D: Mean plasma glucose concentrations over a 24-h period during a standardized diet with a sucrose-sweetened beverage (SSB; gray line) or without (control; black line) in lean normoglycemic subjects (B), obese normoglycemic subjects (C), and obese type 2 diabetic subjects (D). The solid lines indicate breakfast (0700), lunch (1230), and dinner (1830). The vertical dashed lines indicate the times of morning (1030) and afternoon (1530) beverage consumption.

compared with both control groups ($P < 0.05$). Repeated-measures ANOVA showed a significant group effect on 24-h glucose concentrations. Postprandial glucose concentrations did not differ in type 2 diabetic subjects in the first 2 h after con-

sumption of the sucrose beverage when compared with the control beverage. In accordance with the control period, type 2 diabetic subjects showed significantly higher glucose concentrations after breakfast, lunch, and dinner in the SSB period

TABLE 4
Postprandial glucose concentrations¹

	24 h	Breakfast	Lunch	Dinner	Nocturnal	Drink 1	Drink 2
Lean normoglycemic control subjects ($n = 10$)	<i>mmol/L</i>	<i>mmol/L</i>	<i>mmol/L</i>	<i>mmol/L</i>	<i>mmol/L</i>	<i>mmol/L</i>	<i>mmol/L</i>
Control beverage	6.3 \pm 0.4	6.3 \pm 0.5	7.1 \pm 0.5	6.9 \pm 0.6	5.6 \pm 0.6	6.5 \pm 0.4	5.9 \pm 0.4
Sucrose beverage	6.1 \pm 0.4	6.0 \pm 0.4	6.5 \pm 0.5	6.4 \pm 0.4	5.9 \pm 0.5	5.7 \pm 0.4	6.5 \pm 0.5
Obese normoglycemic control subjects ($n = 10$)							
Control beverage	6.7 \pm 0.3	6.5 \pm 0.6	6.9 \pm 0.4	6.1 \pm 0.3	6.9 \pm 0.7	5.1 \pm 0.3	6.1 \pm 0.4
Sucrose beverage	6.8 \pm 0.4	6.9 \pm 0.4	6.4 \pm 0.3	6.1 \pm 0.2	7.1 \pm 0.4	6.1 \pm 0.3	6.6 \pm 0.4
Obese type 2 diabetic subjects ($n = 11$)							
Control beverage	9.1 \pm 0.6 ^{2,3}	10.3 \pm 0.7 ^{2,3}	8.7 \pm 0.7 ^{2,3}	7.5 \pm 0.5	10.0 \pm 1.0 ^{2,3}	8.7 \pm 1.1 ^{2,3}	8.7 \pm 0.7 ^{2,3}
Sucrose beverage	9.4 \pm 0.4 ^{2,3}	11.3 \pm 1.1 ^{2,3}	10.0 \pm 0.7 ^{2,3}	8.7 \pm 0.6 ^{2,3}	8.7 \pm 0.5 ^{2,3}	10.0 \pm 0.7 ^{2,3}	10.8 \pm 0.9 ^{2,3}

¹ All values are means \pm SEMs. The postprandial periods were defined as 3 h postmeal and 2 h after beverage consumption, the nocturnal period was defined as the period from 0000 to 0600. The data were analyzed by using repeated-measures ANOVA with group and treatment as factors. No group \times treatment interaction was observed for any of the variables ($P > 0.48$).

² Significantly different from the lean normoglycemic group, $P < 0.05$ (Scheffe's post hoc test).

³ Significantly different from the obese normoglycemic group, $P < 0.05$ (Scheffe's post hoc test).

TABLE 5
Prevalence of hyperglycemia¹

	24 h	Breakfast	Lunch	Dinner	Nocturnal	Drink 1	Drink 2
	<i>h:min</i>	<i>h:min</i>	<i>h:min</i>	<i>h:min</i>	<i>h:min</i>	<i>h:min</i>	<i>h:min</i>
Lean normoglycemic control subjects (<i>n</i> = 10)							
Control beverage	1:11 ± 0:24	0:06 ± 0:03	0:15 ± 0:12	0:10 ± 0:05	0:05 ± 0:05	0:08 ± 0:05	0:01 ± 0:01
Sucrose beverage	0:49 ± 0:22	0:01 ± 0:01	0:04 ± 0:02	0:05 ± 0:03	0:07 ± 0:05	0:01 ± 0:01	0:03 ± 0:02
Obese normoglycemic control subjects (<i>n</i> = 10)							
Control beverage	1:12 ± 0:25	0:17 ± 0:09	0:12 ± 0:10	0:00 ± 0:00	0:22 ± 0:17	0:01 ± 0:01	0:00 ± 0:00
Sucrose beverage	1:06 ± 0:39	0:12 ± 0:06	0:05 ± 0:03	0:02 ± 0:01	0:14 ± 0:08	0:01 ± 0:01	0:02 ± 0:01
Obese type 2 diabetic subjects (<i>n</i> = 11)							
Control beverage	8:00 ± 1:50 ²	1:30 ± 0:17 ²	0:51 ± 0:17	0:25 ± 0:15 ²	2:27 ± 0:41 ²	0:43 ± 0:15 ²	0:32 ± 0:12 ²
Sucrose beverage	8:38 ± 1:43 ²	1:33 ± 0:19 ²	1:23 ± 0:18 ²	0:43 ± 0:12 ²	1:31 ± 0:36 ²	0:52 ± 0:14 ²	1:08 ± 0:15 ²

¹ All values are means ± SEMs. Hyperglycemia was defined as a glucose concentration <10 mmol/L. The postprandial periods were defined as 3 h postmeal and 2 h after beverage consumption, the nocturnal period was defined as the period from 0000 to 0600. The data were analyzed by using repeated-measures ANOVA with group and treatment as factors. No group × treatment interaction was observed for any of the variables (*P* > 0.39).

² Significantly different from the lean and obese normoglycemic groups, *P* < 0.05 (Scheffe's post hoc test).

when compared with the healthy lean and obese control subjects (*P* < 0.05). The prevalence of 24-h hyperglycemia was similar in the sucrose period and averaged 3 ± 2% and 5 ± 2% in the lean and obese normoglycemic control subjects, respectively. In the type 2 diabetic subjects, hyperglycemia was prevalent for 36 ± 6% (8:38 ± 1:43 h:min) of the 24-h period (*P* < 0.05). The latter was similar to the prevalence of hyperglycemia reported in the control period. Analysis of the 2-h postprandial period after consumption of the beverages showed no significant differences between the control and sucrose periods in all groups (Tables 4 and 5).

DISCUSSION

The present study showed that type 2 diabetic subjects receiving standard medical care still experience hyperglycemia during most of the daytime. In contrast, hyperglycemic blood glucose excursions are rarely prevalent throughout the day in healthy lean or obese individuals. Consumption of sucrose-sweetened beverages, equivalent to 2 cans of soft drink per day, does not further induce hyperglycemic or reactive hypoglycemic blood glucose excursions under normal free-living conditions in lean or obese normoglycemic individuals or obese type 2 diabetic subjects.

Postprandial hyperglycemia has been implicated as a risk factor in the development of cardiovascular complications (3, 6). However, recent large clinical trials also report that intense glycemic control (hemoglobin A_{1c} <6.5%) with exogenous insulin and/or oral blood glucose-lowering medication is associated with hypoglycemia and an increased risk of cardiovascular disease (4, 5). In the present study, hyperglycemia is shown to prevail for more than 8 h during the 24-h assessment of glycemic control in the type 2 diabetic subjects. These results were observed despite the fact that we provided a healthy well-balanced diet (Table 2) in type 2 diabetes subjects who continued their use of oral blood glucose lowering medication. Even in the well-controlled subjects with a blood hemoglobin A_{1c} value <7.0%, hyperglycemia was experienced for ≈5 h over the entire 24-h assessment period. This excess postprandial hyperglycemia represents a direct and independent risk of the development of

cardiovascular complications (7, 8, 35) and shows that standard pharmaceutical intervention with oral blood glucose-lowering medication does not provide sufficient protection against postprandial hyperglycemia. The present data confirm previous suggestions that postprandial hyperglycemia is an underestimated problem in type 2 diabetes (11).

In light of these findings, we also assessed the effect of the same standardized diet on 24-h glycemic control in healthy glucose-tolerant lean and obese control subjects. As the prevalence of hyperglycemia in type 2 diabetic subjects seems to be severely underestimated, we hypothesized that postprandial hyperglycemia is experienced more frequently in obese, normoglycemic individuals at risk of developing insulin resistance and/or type 2 diabetes when compared with healthy lean control subjects (36–38). As such, we assumed that the prevalence of postprandial hyperglycemia over a 24-h period might indicate an early stage of reduced glucose tolerance and could represent a more sensitive marker for evaluating the risk of developing insulin resistance and/or type 2 diabetes. However, in contrast with the finding in type 2 diabetic subjects, 24 h hyperglycemia was negligible in both the lean and obese (5 ± 2%) normoglycemic control subjects, despite the fact that all subjects were provided with exactly the same diet. Analysis of the dietary food intake records showed that self-reported daily energy intake was ≈20% lower when compared with calculated energy requirements. Such underreporting is common and has been reported previously (31). The standardized diet was based on the requirements of the obese type 2 diabetic subjects. The lean and obese normoglycemic control subjects ingested exactly the same diet to further strengthen our study design and, as such, to allow a direct comparison of the prevalence of daily hyperglycemia between obese type 2 diabetic subjects and lean and obese normoglycemic control subjects while using the exact same diet. As such, it should be noted that the lean control subjects received more energy than needed based on their calculated requirements. Despite the latter finding, the prevalence of hyperglycemia was negligible in the lean normoglycemic control subjects. Our results suggest that the prevalence of (postprandial) hyperglycemia is associated with the type 2 diabetic state and

does not necessarily represent a good marker for impaired glycemic control and the risk of developing insulin resistance and/or type 2 diabetes in obese normoglycemic subjects. However, it should be noted that the present study only included male subjects. As such, the presented results do not necessarily apply to females. Clearly, more studies are warranted to assess daily glycemic control and the prevalence of daily hyperglycemic blood glucose excursions in oral-glucose-intolerant subjects, subjects with the metabolic syndrome, or subjects very recently diagnosed with type 2 diabetes.

Over the past decade, much media attention has been generated on the proposed health threats associated with the consumption of sucrose-sweetened beverages, especially in relation to the proposed effect of excess caloric intakes on the development of obesity and/or type 2 diabetes (17, 39–41). Although most sucrose-sweetened beverages show a moderate glycemic index, consumption of large amounts of carbohydrate will induce postprandial blood glucose fluctuations in both type 2 diabetic subjects and normoglycemic individuals (17, 19). In the present study, we aimed to assess the effect of moderate consumption of sucrose-sweetened beverages on 24-h glycemic control, consumed under normal free-living conditions. All subjects performed a second experimental trial in which 75 g sucrose (comparable with the consumption of 2 cans of soft drink) was ingested in addition to the standardized diet in the control period. On the basis of data from previous studies in our laboratory (13), we calculated that ≥ 9 subjects per group were required to detect a 0.9-mmol/L difference in glucose concentrations with an α of 0.05 and a power of 0.8. Therefore, relevant increases in blood glucose excursions after sucrose-sweetened beverage consumption should have easily been detected within the applied study design. However, even though total energy intake was 10% greater in the sucrose period, this did not have a substantial effect on average 24-h or postprandial blood glucose concentrations (Table 4). The present findings seem to be corroborated by previous observations by Colagiuri et al (42) and are in line with the current nutritional guidelines on moderate sucrose consumption (43).

The prevalence of postprandial hyperglycemia did not increase after the ingestion of the 2 sucrose-containing beverages in either the type 2 diabetic subjects or the lean or obese normoglycemic control subjects. Consequently, our data indicate that modest consumption of sucrose-sweetened beverages does not further induce hyperglycemia when combined with a healthy diet under normal free-living conditions. Although the consumption of sucrose-sweetened beverages does not induce overt hyperglycemia in either normoglycemic or insulin-resistant subjects, these results do not imply that regular consumption of sucrose-sweetened beverages cannot impose certain health risks. It has been suggested that excess consumption of sucrose-sweetened beverages might lead to a more positive energy balance because of a reduced sense of satiety after consumption of such beverages (17, 39, 41). This could result in weight gain and lead to the development of obesity or type 2 diabetes. However, the proposed relation between habitual sucrose-sweetened beverage consumption and the development of obesity remains a topic of debate (44). Furthermore, more research is warranted to further elucidate the proposed effect of high-sucrose (>15%) diets on disturbances in blood glucose and triglyceride concentrations in type 2 diabetic subjects (45–47).

In conclusion, male type 2 diabetic subjects under standard medical care and treated with oral blood glucose-lowering medication still experience excess hyperglycemia during most of the daytime. In contrast, hyperglycemic blood glucose excursions are not prevalent in lean or obese normoglycemic men. Consumption of sucrose-sweetened beverages equivalent to 2 cans of sucrose-sweetened soft drinks per day does not increase the prevalence of hyperglycemia under normal free-living conditions in healthy lean or obese individuals or in men with type 2 diabetes.

The authors' responsibilities were as follows—RJFM and LJCvL: designed the study; RJFM, BP, CPGB, and TIA: organized and carried out the clinical trials; RJFM, CPGB, and TIA: performed all calculations; and RJFM and LJCvL: performed the statistical analyses and wrote the manuscript. None of the authors had any personal and/or financial conflict of interest with regard to this study.

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