Original Article

Effect of Eucaloric High- and Low-Sucrose Diets With Identical Macronutrient Profile on Insulin Resistance and Vascular Risk

A Randomized Controlled Trial

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The long-term impact of dietary carbohydrate type, in particular sucrose, on insulin resistance and the development of diabetes and atherosclerosis is not established. Current guidelines for the healthy population advise restriction of sucrose intake. We investigated the effect of high- versus low-sucrose diet (25 vs. 10%, respectively, of total energy intake) in 13 healthy subjects aged 33 ± 3 years (mean ± SE), BMI 26.6 ± 0.9 kg/m^2, in a randomized crossover design with sequential 6-week dietary interventions separated by a 4-week washout. Weight maintenance, eucaloric diets with identical macronutrient profiles and fiber content were designed. All food was weighed and distributed. Insulin action was assessed using a two-step euglycemic clamp; glycemic profiles were assessed by the continuous glucose monitoring system and vascular compliance by pulse-wave analysis. There was no change in weight across the study. Peripheral glucose uptake and suppression of endogenous glucose production were similar after each diet. Glycemic profiles and measures of vascular compliance did not change. A rise in total and LDL cholesterol was observed. In this study, a high-sucrose intake as part of an eucaloric, weight-maintaining diet had no detrimental effect on insulin sensitivity, glycemic profiles, or measures of vascular compliance in healthy nondiabetic subjects. *Diabetes* 55:3566–3572, 2006

Insulin resistance is a key feature of type 2 diabetes and precedes the onset of glucose intolerance (1–3). Insulin resistance is also an independent risk factor for atherosclerotic vascular disease (4–6). Factors that reduce the degree of insulin resistance may reduce the likelihood of developing diabetes or atherosclerosis.

Changing dietary patterns and reduced levels of exercise are associated with the dramatic increase in prevalence of diabetes in developed countries. Western diets are characterized by excess energy intake and increased levels of both sugar and fat (7). Increased consumption of refined sugar, including fizzy drinks, may contribute to the increased risk of diabetes (8). Combined lifestyle intervention, including caloric restriction and increased physical activity, particularly with weight loss, can improve the degree of insulin sensitivity and reduce the risk of future diabetes and vascular disease (9–12). The relative importance of different aspects of this approach is unclear. In particular, while there is evidence regarding the effect of different dietary caloric balances and macronutrient profiles, there is a lack of evidence regarding aspects of carbohydrate quality.

Cross-sectional, longitudinal, and case-control studies demonstrate no consistent association between dietary carbohydrate type and risk of diabetes (13,14). Interventional studies in animal models, however, strongly link high-fructose and -sucrose diets to decreased insulin sensitivity and hyperlipidemia, as well as obesity. However, these diets are either hypercaloric, which leads to obesity, or have grossly elevated contents of fructose or sucrose (up to 70–80% of total caloric intake) (15). These results therefore cannot be extrapolated to humans taking more palatable levels of sucrose or fructose. Studies in human subjects show variable effects with alterations of dietary sucrose intake when using simple measures of insulin sensitivity (16). One small study in seven subjects without diabetes demonstrated that a high–glycemic index diet (25% sucrose) was associated with detrimental effects on insulin sensitivity compared with a low–glycemic index diet (1.2% sucrose) over 4-week dietary periods (17). It is often assumed that a high-sucrose diet will have a high glycemic index but certain high-sucrose foods may have comparable glycemic indexes to starchy foods (e.g., a carbonated orange drink and a mashed potato). Further studies in type 2 diabetes have shown either no effect or a detrimental effect of increased dietary sucrose, but these studies have been either small or of short duration (18–20).

Recently, a number of low-carbohydrate high-fat diets (including the Atkins diet) have been proposed as a substitute for challenging modifications in lifestyle, but the long-term impact of such diets on cardiovascular and diabetes risk is still under investigation and debate (21–

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Received for publication 15 February 2006 and accepted in revised form 23 August 2006.

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DOI: 10.2337/db06-0220

22). A meta-analysis has also highlighted that weight loss associated with such diets is associated more with caloric restriction than reduced carbohydrate content (23). It could be inferred that the same relationship holds for changes in insulin sensitivity. The concept of carbohydrate quality is also attracting attention, and a focus on glycemic index forms the basis of an alternative dietary approach (24–26). A more conventional and proven approach is to advocate a balanced macronutrient profile, in conjunction with caloric restriction and other lifestyle measures, in both weight-reduction and weight-maintenance diets.

Traditionally, dietary sugar or sucrose content is the major focus of carbohydrate-based dietary guidelines. The term "sugars" is conventionally used to describe mono- and disaccharides. "Sugar," by contrast, is used to describe purified sucrose (table sugar), as are the terms "refined sugar" and "added sugar" (27). In 2003, the World Health Organization/Food and Agriculture Organization issued guidelines for prevention of chronic disease in terms of macronutrient balances, and although acknowledging a lack of evidence, included a recommendation to restrict free sugars to <10% of total caloric intake (7). The American Heart Association adopted a similar approach commenting on the potential detrimental effects of a high-sucrose content diet with expected adverse effects when content exceeded >20% of total energy intake (28). Such effects included a fall in HDL levels, a rise in triglycerides, and decreased vitamin and mineral content. In the U.K., the Department of Health recently suggested reducing mean added sugar intake from 12.7 to 11% (29).

To inform dietary guidelines and develop advice regarding the impact of varying sucrose intake, we performed a randomized controlled trial of 10 and 25% sucrose diets (as percent of total energy intake). The diets were isocaloric and weight maintaining with matched macronutrient profiles. (Specifically, the total carbohydrate quantity was the same in the trial diets, and the form of carbohydrate was varied.) We examined the effect of these two diets on the primary outcome variable of insulin resistance, assessed using the isoglycemic-hyperinsulinemic clamp combined with isotope dilution techniques in healthy male volunteers. We also assessed 24-h glycemic profiles, serum lipids, and vascular compliance.

RESEARCH DESIGN AND METHODS

Fourteen healthy male volunteers were recruited (female subjects were excluded to avoid the effect of the menstrual cycle on study end points). Before commencing the study, a brief clinical history and examination was carried out to ensure that those selected did not have significant obesity (BMI >35 kg/m^2) or cardiac, hepatic, or renal disease. Other exclusion criteria included a history of diabetes, blood pressure >140/80 mmHg, or hyperlipidemia (LDL >3.0 mmol/l and triglycerides >2.0 mmol/l). All patients gave written informed consent, and the protocol for the study was approved by the research ethics committee of The Queen's University of Belfast and the Administration of Radioactive Substances Advisory Committee.

Habitual dietary intake was assessed at baseline using a 4-day food diary (including at least one weekend day). Thereafter, volunteers were assigned to a randomized crossover trial consisting of a 6-week period of either low- or high-sucrose intake, followed by a second 6-week period on the complementary diet. The dietary periods were designed to meet projected isocaloric needs (estimated by multiplying basal metabolic rate by an appropriate activity factor [30]) and were separated by a 4-week washout phase during which volunteers returned to their usual diet. Volunteers were advised to maintain their usual level of physical activity throughout the study. Subjects were randomized in blocks of four using a random-number generator to ensure that equal numbers of volunteers received high- or low-sucrose diets during the first phase. Anthropometric measurements (weight, height, and waist and hip circumference), fasting blood samples (plasma glucose, insulin, C-peptide, HbA_{1c}, renal function, and lipids), and blood pressure were taken at the beginning and end of each diet period. Blood pressure was measured using an oscillometric device (Omron Healthcare U.K., Milton Keynes, U.K.) and taken as the average of the second and third readings after 30-min supine. Insulin resistance, vascular compliance, and 72-h continuous subcutaneous glucose monitoring were assessed in the last week of each dietary period.

Diets. A 7-day cyclic menu plan was formulated for both sucrose diets using the dietary analysis program WISP (weighed intake software program; Tinuviel Software, Warrington, U.K.). The low- and high-sucrose diets provided 10 versus 25% of total dietary energy as sucrose, respectively (sucrose derived from both solid food and beverages). Diets were otherwise identical in their macronutrient and fiber intakes, both providing ~55% energy from carbohydrate, 30–35% energy from fat, 10–15% energy from protein, and 18 g/day fiber.

Volunteers attended daily, or on alternate days, throughout the intervention and were supplied with all appropriate foodstuffs (preweighed into daily portions) for their particular diet. At each visit, the nutritionist discussed concerns and assessed dietary compliance. Throughout the study, caloric intake was adjusted if body weight (measured twice weekly) increased or decreased on two successive occasions. Foods, ad libitum, included noncaloric beverages (water, diet cola, black tea, and coffee) and seasoning. Alcohol was not permitted. Representative menus for a single day for the high- and low-sucrose diets are shown in Table 1. The energy distribution between the different meals was similar for both diets.

Assessment of insulin action. At the end of each dietary period, insulin sensitivity was assessed by a two-step euglycemic-hyperinsulinemic clamp, as previously described (32). A cannula was inserted into the left arm for infusions and in the right arm for samples. The right hand was placed in a temperature-controlled plexiglass box (55°C) to arterialize the venous blood. A primed-continuous infusion of high-performance liquid chromatography–purified [3-^{3}H]glucose was administered during a 2-h equilibration period (−120 min to zero time). The initial tracer prime was adjusted, based on fasting plasma glucose (22). A two-step sequential, continuous infusion of insulin was commenced: 0.4 mU · kg^{-1} · min^{-1} (zero time to 120 min) then 2.0 mU · kg^{-1} · min^{-1} (120–240 min). Plasma glucose was measured at 5-min intervals on a bedside analyzer (Beckman Glucose Analyzer 2; Beckman, High Wycombe, U.K.) and maintained at the desired fasting concentration by an exogenous infusion of 20% wt/vol glucose. Exogenous glucose was prelabeled with [3-^{3}H]glucose to match the predicted basal plasma glucose specific activity as described (32), with the modification that the primed-continuous tracer infusion was reduced to 50% of the basal rate after 20 min and to 25% of the basal rate after 140 min of insulin infusion (to maintain tracer steady state).

Analytical techniques. Arterialised venous blood was used for all analyses in the glucose clamp studies. Plasma for measurement of glucose specific activity was deproteinized with barium hydroxide and zinc sulfate by the method of Somogyi (32). Aliquots of tracer infusate and labeled exogenous glucose infusion were spiked into nonradioactive plasma and processed in parallel to allow calculation of [3-^{3}H]glucose infusion rates. Serum insulin was measured by enzyme-linked immunosorbent assay (Abbot Imx; Abbott Laboratories, Berkshire, U.K.). Glucose was measured using an automated glucose oxidase method using a Beckman Glucose Analyzer 2. Commercial kits were used to estimate C-peptide (Dako Diagnostics, Ely, U.K.) and nonesterified free fatty acids (Wako Chemicals, Neuss, Germany).

Calculations. The nonsteady state equations of Steele et al. (33), as modified by De Bodo et al. (34), were used to determine the glucose appearance (R_a) and disappearance (R_d), assuming a pool fraction value of 0.65 and an extracellular volume of 190 ml/kg. This was measured over three 30-min time periods: before insulin infusion (−30 to 0 min), during the final stages of the low-dose insulin infusion (90–120 min), and during the final stages of the high-dose insulin infusion (210–240 min). The [3-^{3}H]glucose infusion rates were calculated as the sum of the tracer infused continuously and the tracer in the labeled exogenous glucose infusion. Rates of endogenous (hepatic) glucose production were then calculated by subtraction of the exogenous glucose infusion rates required to maintain euglycemia from isotopically determined rates of glucose appearance.

Continuous glucose monitoring system. A continuous glucose monitoring system developed by MiniMed (CGMS; MiniMed, Northrodge, CA) was used to monitor the concentration of interstitial fluid glucose for 48–72 h using a subcutaneous sensor and was calibrated with a standard glucometer.

Arterial stiffness. Arterial stiffness was determined using pulse-wave analysis (model SCOR-Px; PWV Medical, Sydney, Australia), as described previously (35,36). All volunteers rested for 15 min in the supine position, and measurements were taken immediately following determination of brachial artery blood pressure. The right radial artery blood pressure waveform was recorded using a tonometer and calibrated according to the brachial systolic and diastolic pressures. Analysis of the central aortic waveform obtained using the SphygmoCor software identified the outgoing and reflected pressure waves (augmentation), occurring during systole. The augmentation index

TABLE 1
Sample menus for a typical day on each intervention diet

Meal	10% sucrose diet (13.3 mJ)	25% sucrose diet (13.4 mJ)
Breakfast	Cornflakes (60 g) Semiskimmed milk (167 g) Sugar (10 g) White bread, toasted (31 g) Strawberry jam (20 g) Orange juice (200 g)	Cornflakes (35 g), bran-based cereal (3 g) Semiskimmed milk (160 g) Sugar (15 g) Pineapple juice (200 g)
Lunch	White bread (150 g) Cooked ham (70 g) Mayonnaise (40 g) Yogurt with fruit purée (175 g)	Wholemeal bread (72 g) Cooked ham (69 g) Mayonnaise (32 g) Yogurt with fruit purée (175 g) Carbonated orange drink (330 g)
Dinner	Potatoes, boiled (450 g) Broccoli, boiled (85 g) Carrots, boiled (80 g) Chicken breast in crumbs, baked (90 g) Gravy, reconstituted (160 g)	Potatoes, boiled (400 g) Broccoli, boiled (85 g) Carrots, boiled (80 g) Chicken breast in crumbs, baked (90 g) Gravy, reconstituted (70 g) Carbonated orange drink (330 g)
Additional snacks	Semiskimmed milk (80 g) Chocolate biscuit bar (48 g) Chocolate candy bar (52 g) Plain potato chips (55 g) White bread, toasted (72 g) Polyunsaturated margarine (15 g)	Semiskimmed milk (80 g) Smartie-type sweets (80 g) Chocolate nut bar (60 g) Vanilla fudge (40 g) Milk chocolate (68 g) Apple (170 g) Polyunsaturated margarine (15 g)

(expressed as a percentage) was defined as the ratio of augmentation to pulse pressure and was used to estimate overall systemic arterial stiffness (37). The timing of the reflected waveform (a measure of the transit time between the ascending aorta and the first main reflectance site) was also identified and therefore used to indirectly estimate aortic pulse-wave velocity and, hence, aortic stiffness (38). Arterial waveforms were also recorded by consecutively applanating the carotid and radial arteries gated to a three-lead electrocardiogram to enable calculation of pulse-wave velocity as previously described (39).

Statistical methods. Statistical analysis was as recommended by Hills and Armitage (40), enabling comparison of the effects of the treatment to be adjusted for period effects. Results are described as means ± SE. Variables that were nonnormally distributed are described as median (lower quartile, upper quartile) and were logarithmically transformed before analysis. Where parameters were assessed at the baseline and end of each period, ANCOVA was used with baseline values as covariates. The power of the study, calculated from previous clamp data, gave a 90% chance of detecting a 10% change in insulin action at the 5% level of significance.

RESULTS

Both study diets were well tolerated (one subject left for reasons unrelated to the study). The clinical and anthropometric characteristics of the volunteers are given in Table 2. Volunteers were adult males who were, on average, overweight (mean BMI 26.6 ± 0.9 kg/m^2) but were normotensive with normal fasting lipid profiles and indexes of glycemia. Simple fasting measures of insulin sensitivity (insulin and homeostasis model assessment of insulin resistance) indicated that the subjects were moderately insulin resistant. The habitual dietary intake data (Table 3) suggested that mean consumption of macronutrients was comparable with intakes reported for the adult population of the U.K. (41). Within the group, the total dietary energy provided by sucrose (preintervention) ranged from 2 to13%. Daily intervention intakes of energy and macronutrients during the high- and low-sucrose diets are displayed in Table 3. Diets were matched for energy, macronutrient profile, and fiber intake (Table 4).

Weight and physical activity remained constant throughout the study. While no formal instrument to compare physical activity was used, as weight and energy consumption were the same after each diet, it can be assumed that the level of physical activity between the dietary periods was equivalent.

Clamp studies. Serum insulin levels in the fasting state and during each infusion period were the same during both dietary periods. Plasma glucose was maintained at a constant level by exogenous glucose infusion with a coefficient of variation <5% as the plateau for each clamp (glucose infusion rates at plateau after 25 and 10% sucrose were 13.9 ± 1.6 vs. 15.4 ± 2.9 μmol · kg^{-1} · min^{-1}, respectively, after low-dose insulin and 47.5 ± 3.5 vs. 42.5 ± 3.0 μmol · kg^{-1} · min^{-1} after high-dose insulin

TABLE 2
Baseline clinical and anthropometric characteristics (n = 13)

Age (years)	33.3 ± 3.0
Height (m)	1.80 ± 0.02
Weight (kg)	86.0 ± 3.4
BMI (kg/m^2)	26.6 ± 0.9
Blood pressure (mmHg)	127/69 ± 3/3
Waist circumference (cm)	91.9 ± 3.0
Waist-to-hip ratio	0.88 ± 0.02
Fasting plasma glucose (mmol/l)	4.8 ± 0.1
Fasting insulin (mU/l)	10.2 (5.4–11.0)
HbA_{1c} (%)	5.7 ± 0.1
HOMA-IR	1.99 (1.21–2.36)
Total cholesterol (mmol/l)	4.53 ± 0.27
LDL cholesterol (mmol/l)	2.78 ± 0.27
HDL cholesterol (mmol/l)	1.26 ± 0.05
Triglycerides (mmol/l)	1.03 (0.70–1.29)

Data are means ± SE or median (interquartile range). HOMA-IR, homeostasis model assessment of insulin resistance.

TABLE 3
Habitual daily energy and nutrient intakes of the volunteers at baseline

Energy (mJ/d)	10.4 ± 0.8
Carbohydrate (total energy %)	45 ± 3
Starch	28 ± 2
Sucrose	7 ± 1
Protein (total energy %)	16 ± 1
Fat (total energy %)	35 ± 2
Saturated fat	13 ± 1
Monounsaturated fat	11 ± 1
Polyunsaturated fat	6 ± 1
Alcohol (total energy %)	4 ± 2
Fiber (g/day)	17 ± 1

Data are means ± SE. $n = 13$.

infusion; Fig. 1). Endogenous glucose production was similar in the fasting state and similarly suppressed after low- and high-dose insulin infusion on the 25 and 10% sucrose diets (Figs. 2 and 3). Peripheral glucose utilization was no different after either low- or high-dose insulin infusion on the 25 and 10% sucrose diets. Serum nonesterified fatty acids were suppressed similarly after 25 and 10% sucrose diets (Table 5).

Hemodynamic studies. Blood pressure, central augmentation pressure, augmentation index corrected to heart rate of 75 bpm, time to reflectance, and pulse-wave velocity were not changed by diet (Table 6).

Metabolic profiles. Fasting plasma glucose, serum insulin, and interstitial glucose levels over 24 h did not change with alteration of dietary sucrose content (Table 7). Total and LDL cholesterol were higher after 25% sucrose compared with 10% sucrose. HDL cholesterol and fasting triglycerides were similar on the two diets.

DISCUSSION

This study demonstrates that a high-sucrose diet, with 25% of total energy intake from sucrose, has no detrimental

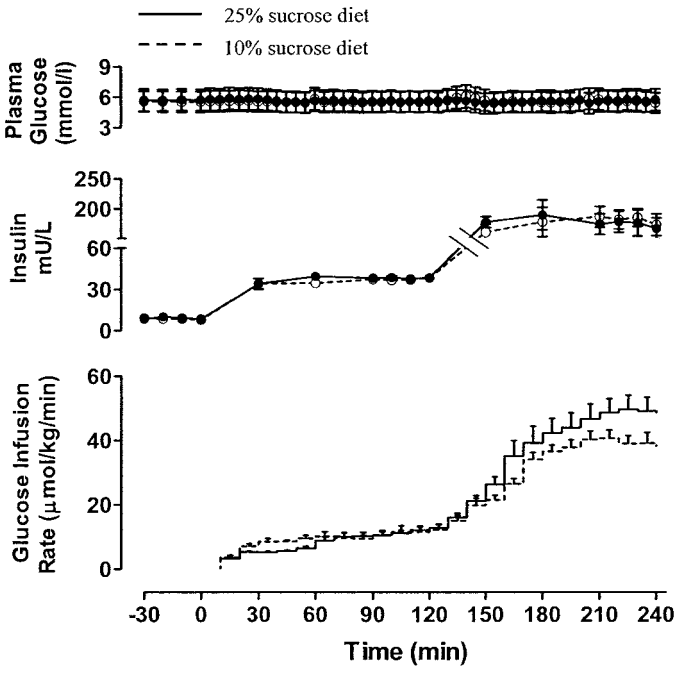

FIG. 1. Plasma glucose, serum insulin, and glucose infusion rates during euglycemic-hyperinsulinemic clamp. Data are means ± SE.

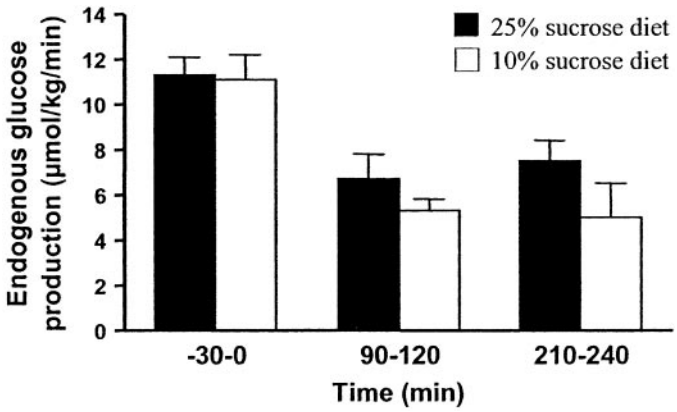

FIG. 2. Suppression of endogenous glucose production during euglycemic-hyperinsulinemic clamp. Data are means ± SE.

effect on insulin resistance or measures of vascular risk in healthy nondiabetic subjects. Evidence-based dietary guidelines are urgently required to tackle the global epidemic of diabetes. The absence of specific evidence in relation to sucrose has resulted in a lack of clear guidelines from some groups and variation in recommendations by others. Average sugar intake is much higher in the U.S., where 15% of men and 21% of women aged 19–50 years have a sucrose intake >25% (42). In the present study, we chose to compare a sucrose intake of 25%, which is a level substantially above recommended intakes and a level some guidelines consider may be detrimental to health, with a 10% intake, which compares with the lowest recommended restriction, while keeping total carbohydrate content constant.

Evidence from animal studies has generally shown that increased sucrose intake has a detrimental effect on insulin sensitivity and cardiovascular risk factors. However, the levels of sucrose intake in these studies, of up to 60–70% of dietary energy intake as sucrose or fructose, have generally been at a level that is nonphysiological and, for most human subjects, unpalatable. Furthermore, the diets studied were in many cases hypercaloric, making interpretation of the relative impact of sucrose intake and weight gain impossible (15). Human studies have produced conflicting findings. Interventional studies have shown variable effects on insulin sensitivity, and, in many, the method of assessing insulin resistance has been suboptimal but the study period relatively short and the sample size small (43).

TABLE 4
Intervention intakes of energy and macronutrients during the high- and low-sucrose diets

	10% sucrose diet	25% sucrose diet
Energy (mJ/day)	13.3 ± 0.2	13.3 ± 0.2
Carbohydrate (total energy %)	55 ± 0.04	55 ± 0.03
Starch	34 ± 0.4	17 ± 0.3
Sucrose	10 ± 0.02	25 ± 0.02
Protein (total energy %)	12 ± 0.2	11 ± 0.1
Fat (total energy %)	33 ± 0.2	33 ± 0.1
Saturated fat	11 ± 0.5	15 ± 0.3
Monounsaturated fat	10 ± 0.1	9 ± 0.2
Polyunsaturated fat	7 ± 0.5	5 ± 0.3
Fiber (g/day)	18 ± 0.03	18 ± 0.02

Data are means ± SE.

TABLE 5
Serum nonesterified fatty acid levels at basal state and after low-dose insulin infusion (0.4 mU · kg^{-1} · min^{-1}) plateau at 90–120 min and high-dose insulin infusion (2.0 mU · kg^{-1} · min^{-1}) plateau at 210–240 min

Time (min)	10% sucrose diet	25% sucrose diet	*P*
−30 to 0	744 ± 63	698 ± 52	NS
90–120	486 ± 51	489 ± 46	NS
210–240	239 ± 28	277 ± 34	NS

Data are means ± SE. NS, not significant.

A strength of the present study is the randomized controlled design and rigorous dietetic supervision. Due to the wide interindividual but low intraindividual variation in the degree of insulin resistance in normal subjects, a two-period crossover design separated by a washout period was chosen with each subject acting as their own control (44). The 6 weeks of dietary intervention per assessment period compares favorably with other relevant human studies; however, it is not possible to predict the effect of a high-sucrose intake over a more prolonged period. Although it is impossible to measure compliance with the diets under study, volunteers were reviewed every 2–3 days throughout the dietary periods and were questioned regarding palatability and compliance with the food that was provided for the duration of the study. In addition, the absence of any change in weight is further evidence of careful dietary planning and supervision.

The primary outcome measure of insulin resistance was assessed using the reference standard technique of the hyperinsulinemic-isoglycemic clamp combined with isotope dilution techniques. The sensitivity to insulin varies widely in different insulin-responsive tissues, and abnormalities of these responses may occur separately in insulin-resistant states. There was no significant effect of altering dietary sucrose content on either fasting hepatic glucose production or its suppression during low-dose insulin infusion, which are both measures of hepatic insulin action. This result suggests no abnormality of hepatic insulin action, which is recognized to be an early feature of type 2 diabetes (3). The high-dose insulin infusion results in maximally stimulated glucose uptake and reflects skeletal muscle or peripheral insulin sensitivity. We found no difference in peripheral insulin resistance between the two dietary periods. The study was powered to exclude a 10% difference in insulin action, which is a level assumed likely to have a clinically relevant impact. The results in fact showed a trend toward an increase in insulin sensitivity with the high-sucrose diet, although this was not statistically significant. No plausible biological mechanism exists to explain why a high-sucrose diet might improve insulin sensitivity, and it is likely that this finding is due to chance. Furthermore, we found no difference in fasting levels of serum nonesterified fatty acid concentrations during the dietary periods and a comparable degree of suppression during hyperinsulinemia, indicating no detrimental effect on adipose tissue insulin action.

TABLE 6
Effect of sucrose diets on hemodynamic variables

	10% sucrose diet	25% sucrose diet	*P*
Blood pressure (mmHg)	125/71 ± 3/2	122/71 ± 3/2	NS
Augmentation (mmHg)	3.0 ± 1.7	2.2 ± 1.5	NS
Aortic augmentation index (%)	−0.4 ± 4.1	0.8 ± 3.9	NS
Time to wave reflection (ms)	167 ± 8.0	171 ± 7.0	NS
Brachial pulse-wave velocity (ms)	8.4 ± 0.4	8.5 ± 0.3	NS

Data are means ± SE. NS, not significant.

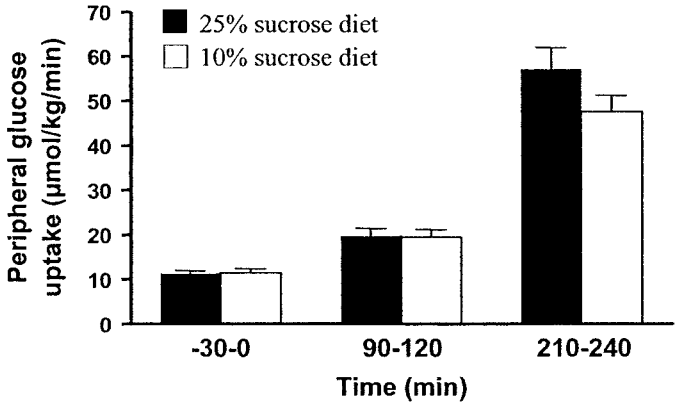

FIG. 3. Peripheral glucose uptake during euglycemic-hyperinsulinemic clamp. Data are means ± SE.

The premise of this study is that a high-sucrose diet may alter the risk of type 2 diabetes and cardiovascular disease. Although the primary outcome of the study was assessment of insulin resistance, a feature of both conditions, it is possible that other mechanisms may link high-sucrose intake to cardiovascular disease. We also used the noninvasive technique of pulse-wave analysis to assess arterial stiffness, which is increasingly being recognized as an important determinant of cardiovascular risk (45). Stiffening of the arterial tree increases the velocity and amplitude of reflected pulse waves from the periphery, with the result that larger waves return to the aorta

TABLE 7
Effect of sucrose diets on metabolic variables

	10% sucrose diet	25% sucrose diet	*P*
Weight (kg)	85.8 ± 3.6	86.2 ± 3.6	NS
Mean interstitial glucose levels (mmol/l)	5.9 ± 0.2	6.1 ± 0.7	NS
Fasting plasma glucose (mmol/l)	5.6 ± 0.1	5.6 ± 0.1	NS
Fasting serum insulin (mU/l)	8.6 ± 1.2	9.6 ± 1.4	NS
Total cholesterol (mmol/l)	4.01 ± 0.80	4.62 ± 0.8	<0.01
LDL cholesterol (mmol/l)	2.25 ± 0.25	2.78 ± 0.30	<0.01
HDL cholesterol (mmol/l)	1.2 ± 0.06	1.2 ± 0.06	NS
Triglycerides (mmol/l)	0.92 (0.66–1.17)	0.95 (0.66–1.58)	NS

Data are means ± SE or median (interquartile range). NS, not significant.

earlier. This augments central systolic pressure, which increases left ventricular workload and, thus, myocardial oxygen demand. In the present study, we found no difference in markers of arterial stiffness, such as augmentation pressure/index, time to reflectance, or brachial pulse-wave velocity. It should be noted that this study was powered for the primary outcome of insulin sensitivity; although in a smaller cohort, we have previously shown (39) that acute elevation of plasma glucose is associated with significant adverse changes on pulse-wave analysis. In this study, continuous monitoring of interstitial glucose levels using a continuous glucose monitoring system showed no difference in 24-h or postprandial glycemic exposure.

A rise in total and LDL cholesterol and a trend toward increased triglycerides were observed during the 25% sucrose diet compared with the 10% sucrose diet. Although the mean changes were relatively modest and levels remained within normal ranges, it is possible that more marked abnormalities could arise in subjects with hyperlipidemia at baseline. Other studies have demonstrated increased triglyceride levels with sucrose contents >20%; however, the LDL increase is more unusual (46). A similar change in lipoprotein profiles has been noted in high-fructose diets in man (47). Fructose is the more lipogenic component, as it bypasses a major rate-controlling step in glycolysis (48). The food selection that was necessary to achieve the balance resulted in a change in fat quality but no change in total fat quantity. The high-sucrose diet had 29% higher energy content from saturated fat and 29% lower polyunsaturated fat than the low-sucrose diet. We hypothesize that this alteration in saturated fat intake may have contributed to the rise in LDL cholesterol rather than by a direct effect of sucrose.

An important limitation of this study must be recognized. The subjects were a defined group without significant metabolic or clinical abnormality. They were of male sex, white Western-European origin, relatively young (on average), and did not have diabetes or significant hyperlipidemia. All these factors can alter baseline insulin sensitivity and may influence interventional responses. In addition, the caloric intakes were controlled rather than ad libitum to allow conclusions to be drawn regarding carbohydrate quality itself rather than the complicating factor of differing energy intakes and balances. Outside such study conditions, differing diet quality could have differing effects on satiety and food intake, which may be mediated via leptin and other adipokines, and could result in different energy intakes, balance, and weight change; all of which could impact insulin sensitivity (49). Certainly, in children, increased servings of sugar-sweetened drinks were associated with obesity in a prospective observational study (50). Furthermore, although 24-h glycemic profiles and insulin clearance were similar on the high- and low-sucrose diets, we did not directly assess insulin secretion or postprandial metabolic changes. It is, however, possible that a high-sucrose diet could have detrimental effects on insulin secretion and postprandial glucose and lipid metabolism, particularly in established type 2 diabetes where these are recognized to be important features. The conclusions from these data regarding effects of a high-sucrose diet on insulin secretion and postprandial metabolism must therefore be limited to the described healthy group taking an eucaloric diet.

In conclusion, a high-sucrose intake as part of a balanced, eucaloric, weight-maintaining diet had no detrimental effect on insulin sensitivity in healthy nondiabetic subjects compared with a low-sucrose diet. These results suggest that important pathogenic processes that precede diabetes and vascular disease are not significantly worsened by sucrose itself. These findings should be incorporated in dietary guidelines for the prevention of diabetes and cardiovascular disease. It is likely that other dietary factors, such as caloric excess, and lifestyle factors, such as physical inactivity and weight gain, may be more important determinants of insulin action than carbohydrate type. The results of this study cannot be extrapolated to established type 2 diabetes, and further information regarding the impact of severe restriction of sucrose intake in low-carbohydrate weight-reduction diets is also needed.

ACKNOWLEDGMENTS

This study was supported by an unrestricted research grant from The Sugar Bureau and Suikerstichting, the Netherlands. R.N.A.B. was in receipt of an R&D Fellowship from the Northern Ireland Department of Health and Social Services Research and Development Office.

We are grateful to Dr. C. Patterson, The Queen's University of Belfast, for statistical advice, to Dr. C. Mercer, Department of Medicine, The Queen's University of Belfast, for carrying out nonesterified fatty acid assays, and to Mr. Brian Sheridan and the staff at Belfast Link Laboratories for carrying out insulin and C-peptide assays.

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