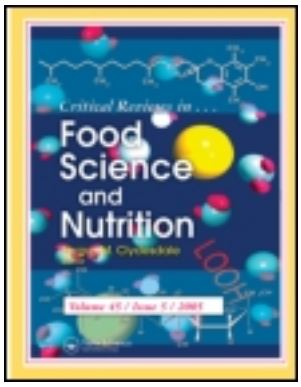

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The Effects of Sucrose on Metabolic Health: A Systematic Review of Human Intervention Studies in Healthy Adults

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The Effects of Sucrose on Metabolic Health: A Systematic Review of Human Intervention Studies in Healthy Adults

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We systematically reviewed interventions substituting sucrose for other macronutrients in apparently healthy adults to assess impact on cardiometabolic risk indicators. Multiple databases were searched to January 2012 and abstracts assessed by 2 reviewers. Twenty-five studies (29 papers) met inclusion criteria but varied in quality and duration. Weaknesses included small subject numbers, unclear reporting of allocation, unusual dietary regimes, differences in energy intake, fat composition or fibre between conditions, unhealthy subjects, heterogeneity of results, and selective reporting. Insufficient data were available to draw reliable conclusions except with regard to the substitution of sucrose for starch, where effects on plasma lipids were inconsistent, mostly explicable by other factors, or nonsignificant. Based on fewer studies, there was little evidence for significant effects on plasma glucose or insulin. Sucrose substitution for starch up to 25% energy does not appear to have adverse effects on cardiometabolic risk indicators in apparently healthy adults. Furthermore, there is no consistent evidence that restricting sucrose in an isoenergetic diet would affect risk indicators, except perhaps in people with certain preexisting metabolic abnormalities. Larger, high-quality studies, lasting several months and studying a wider range of outcomes, are needed in order to provide evidence on which to base public health initiatives.

Keywords Sugar, glucose metabolism, lipid metabolism, macronutrient, diet recommendation

INTRODUCTION

Current dietary guidelines for improving cardiometabolic risk indicators and reducing the risk of cardiovascular disease (CVD) have tended to focus on restricting saturated fat consumption and replacing fat with carbohydrate (Krauss et al., 2000). However, there is increasing interest in the role of dietary carbohydrate type (and by implication sugars intake) in preventing or promoting disorders of lipid and carbohydrate metabolism, including metabolic syndrome and type 2 diabetes (noninsulin-dependent diabetes mellitus (NIDDM)) as well as CVD (Parks and Hellerstein, 2000; Hellerstein, 2002; Fried and Rao, 2003; Stanhope and Havel, 2010; Tappy et al., 2010). This review focuses on the potential adverse metabolic effects of sucrose, the main contributor to total sugar intakes worldwide.

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Most dietary recommendations define sugars in terms of their origin (added sugars, free sugars, or simple sugars) rather than their chemical structure (sucrose, fructose, glucose, etc.). In the United States, the Institute of Medicine suggested a maximum intake level of 25% energy from added sugars in the 2002 Dietary Reference Intakes, on the ground of preventing nutritional deficiencies (Institute of Medicine, 2002). The 2005 Dietary Guidelines for Americans recommended a much more conservative level, limiting discretionary calories (including both sugars and solid fat) to 13% of energy requirement (US Department of Health and Human Services, 2005), while the American Heart Association proposed limiting sugar calories to 140 kcal/day for men or 100 kcal/day for women, which equates to a mere 5% of energy requirement (Johnson et al., 2009). In Europe, the European Food Safety Authority (EFSA) Panel on Dietetic Products, Nutrition and Allergies (NDA) (2010) concluded that there are insufficient data to set an upper limit for (added) sugar intake, although most European countries aspire to

follow the recommendations of the World Health Organisation (<10% of energy from "free sugars"; WHO/FAO, 2003). Dietary reference values for the UK adult population relate to so-called "nonmilk extrinsic sugars" (NMES; comprising added sugars, fruit juice, and 50% proportion of dried and cooked fruit) and suggest that these should provide no more than 10% of total energy intake (Department of Health, 1991). Currently, mean NMES intake in Britain is 12% of energy among adults and 15% among children (Department of Health, 2011) and two-thirds is sucrose (8–10% of energy; Gibson, unpublished). Across Europe, estimated average intakes of sucrose range from 8% in Nordic countries to 15–17% of energy in southern countries (Elmadfa, 2009). In the United States, an estimated 15% of total energy intake is derived from "added sugars" (Marriott et al., 2010) with a higher proportion among adolescents (21.4%; Welsh et al., 2011). However, according to food supply statistics, sucrose contributes only around 44% of total caloric sweetener volume in the United States, due to the widespread use of high fructose corn syrup (HFCS; Marriott et al., 2009).

Sucrose is a disaccharide that is efficiently hydrolyzed (by sucrase) in the intestinal mucosa to its constituent monosaccharides. It has been established that glucose stimulates fructose uptake in a dose-dependent manner (Rumessen and Gudmand-Hoyer, 1986) and that monosaccharides derived from sucrose are essentially absorbed at a similar rate to glucose:fructose mixtures (Tappy et al., 2010). However, whereas glucose elicits a glycaemic and insulinaemic response that stimulates its uptake into cells, fructose is mainly metabolized in the liver via an insulin-independent pathway not regulated by energy supply. There it may be converted into trioses that can be used for the de novo synthesis of triglycerides (TG) and cholesterol (Frayn and Kingman, 1995; Hellerstein, 2002). Thus, sucrose has the potential to influence both insulin sensitivity and lipid metabolism and there may be interconnectivity between the two. For example, according to Daly, hypertriglyceridemia (HTG) has long been known to be associated with insulin resistance (IR) in metabolic syndrome, although it is not clear whether HTG is caused by IR, or IR caused by HTG; there are plausible mechanisms for both (Daly et al., 1997). However, much of the evidence for adverse effects of sucrose comes from studies on animals fed excessive amounts of sugars, or else relates to human subjects with existing metabolic disorders such as type 1 or type 2 diabetes, or hyperlipidemia. Regarding the animal data, Daly has commented "overall, there is no conclusive or consensual evidence to show that humans respond similarly (to rodents) to sucrose- or fructose-rich diets at the doses used in human studies" (Daly, 2003). Moreover, to date there has been much less evidence that diet-induced HTG occurs in normal healthy subjects or with amounts of sucrose more typical of Western diets (<20% energy from sucrose; Frayn and Kingman, 1995; Fried and Rao, 2003).

Among the current uncertainties, therefore, is the dose limit, that is, "What amount of sucrose can be included in diets without adverse effects on lipid profile and carbohydrate metabolism?" Length of study is also important in interpreting outcome data. If the observed effect is transient, it may be less important; on the other hand, if it is cumulative, it may be missed in short-term studies. Alteration in levels of other dietary constituents as a result of the intervention may be contributing to adverse effects (e.g., a high intake of saturated fatty acids (SFAs) or low intake of essential fatty acids, fibre, antioxidants, or an increase in energy intake). Finally, as noted above, adverse effects may be strongly influenced by individual factors, such as IR, obesity, genetic factors, and lifestyle (Hellerstein, 2002). While analysis of these factors is beyond the scope of the present review, we have sought to interpret studies in their context.

The most robust type of evidence addressing the research question consists of studies in which there was a deliberate change in the sucrose component of diet under controlled or semicontrolled conditions in normal adults. Relevant outcomes were cardiovascular risk factors relating to lipid and carbohydrate metabolism, in particular TG, LDL, HDL cholesterol, and glucose and insulin responses. Effects on uric acid, gut hormones, appetite, and satiety were considered beyond the scope, as was the vast literature on sugars and bodyweight. Very short term studies lasting less than 3 days and mechanistic studies involving acute effects were also excluded unless they followed a period of adaptation.

METHODS

We conducted a systematic search using Medline and EMBASE and the Cochrane Library of systematic reviews to build the bibliographic database. Search strategy and terms were as follows:

Sucrose$ AND (starch OR fat OR protein) AND (lipid$5 OR lipoprotein$1 OR triglyceride$1 OR insulin OR glucose OR glucose tolerance OR HOMA OR blood pressure OR hypertension OR cardiac OR cardiovascular OR coronary OR metabolic syndrome) AND (replace$4 OR substitut$3 OR isocaloric$4).

The electronic search was complemented by a hand search of relevant cross-references. Search results were imported into a bibliographic database (Endnote © Thomson Reuters; www.endnote.com) and then sifted for eligibility; 2 reviewers independently read abstracts using inclusion/exclusion criteria in Table 1. Copies of potentially relevant papers were obtained from the web, requested from authors, or purchased from libraries. The process of identifying pertinent articles and major reasons for exclusion are shown in the flowchart (Figure 1).

Details of each study were entered into a spreadsheet based on PICOS principles for research questions (Liberati et al., 2009) with fields for Population, Intake/exposure (sucrose), Comparators (e.g., starch, fat), Outcome measures, Study design, and in addition Results, Conclusions, and Comments (including confounders). Table 2 gives a summary for the area with the most comprehensive evidence, namely, studies where sucrose was substituted for starch. This table is ordered by sucrose dose to make it easier for the reader to see an effect. Tables 3–5 summarize the studies and describe the population, dose,

Table 1 Inclusion and exclusion criteria

	Inclusion criteria	Exclusion criteria
A	Intervention studies or experimental studies involving 2 or more conditions where subjects are asked to increase or decrease intake of sucrose in exchange for other caloric sources	Observational studies, recommendations, guidelines. Studies on fructose/other sugars/HFCS unless a sucrose group was also included
B	Measured outcomes relating to lipid and carbohydrate metabolism, blood pressure, CVD risk	Effects on kidney function, body weight, gut hormones, satiety
C	Human studies	Animal studies, in vitro studies
D	Studies with healthy human populations, including overweight but otherwise healthy	Studies on subjects with diabetes or NIDDM or hyperlipidemia (unless normal subjects were also included and reported separately).
E	English language	Not in English language
F	Published since 1970	Published before 1970
G	Experimental period lasting 3 days or more	Single meal studies, studies shorter than 3 days

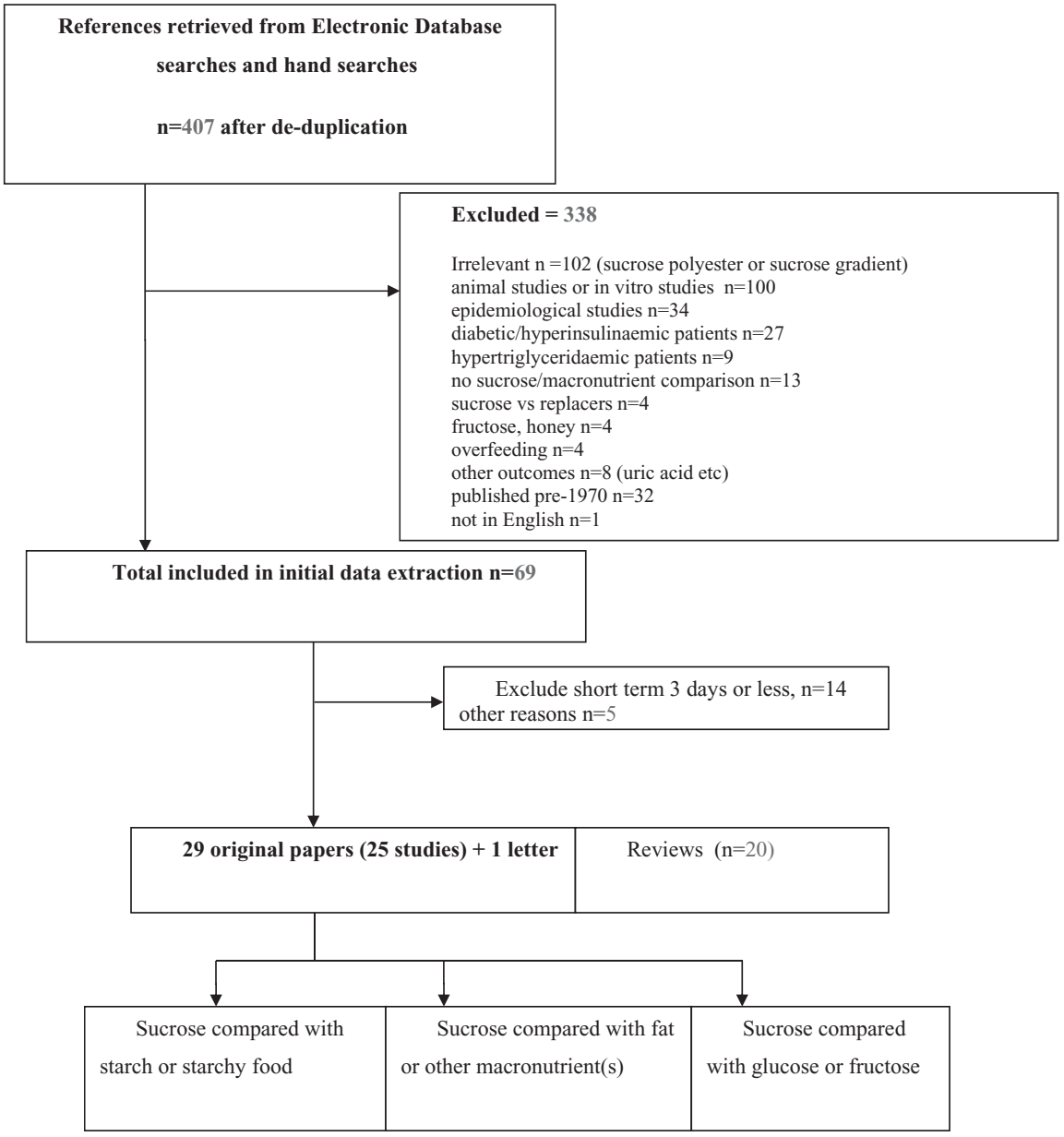

Figure 1 Flowchart of search and exclusion process.

Table 2 Studies on the metabolic effects of isocaloric substitution of sucrose for starch (ordered by sucrose dose)

Study	Sucrose dose[a]	Duration	TG[b]	TC[b]	LDL[b]	HDL[b]	Glucose[b]	Insulin[b]	Comments
(Grande et al., 1974)	18.6% and 22.6%	14 days	NSD	NSD					Sucrose supplementation (500 kcal/day) for 2 weeks. Starch fed as wheat flour or leguminous seeds.
(Marckmann et al., 2000)	23%	14 days	+15%	+8%	+9%	NSD			Data not corrected for differences between groups (e.g., body weight, saturated fat). Sucrose diet higher in saturated fat. TG, TC, and LDL remained within normal range.
(Raben et al., 2001)	23%	14 days	NSD				NSD	NSD	Same study as Marckmann et al. (2000). TG differences were not significant once corrected for differences between groups (e.g., body weight).
(Mann and Truswell, 1972)	23%	14 days	NSD	NSD				NSD	Subjects young men with neurological conditions. Diets 55% energy as CHO, 30% as fat.
(Black, 2006)	25%	6 weeks	NSD	+15%	+24%	NSD	NSD	NSD	Test group had higher saturated fat intake. TC and LDL increased but remained within normal range.
(Kiens, 1996)	25%	30 days					NSD	NSD	Study was of high versus low GI diets. 46% energy as CHO. Sucrose included in high GI diet.
(Fraser et al., 1981)	"12.5% above basal"	3 weeks	NSD	Leafs and grains lower	Leafs and grains lower	NSD			Sugar intake not stated but assumed to be ~25%. Comparison with starches from 3 different vegetable types, leafs, grains, and roots.
(Dunnigan et al., 1970)	31.5%	4 weeks	NSD	NSD			+6%	NSD	Subjects were patients, most with neurological disorders. All had normal carbohydrate tolerance, 3 had elevated cholesterol or TG. Diets 45% energy from CHO, 40% from fat.
(Reiser et al., 1979a, 1979b, 1980)	33%	6 weeks	+33%	+7%			+2%	+23%	Gorging feeding pattern: 90% energy at dinner. Diets 43% energy as CHO, 42% as fat.
(Yudkin et al., 1986)	37%	2 weeks	NSD	NSD		−16%			Experiment 1—Diets 54% energy as CHO, 34% as fat.
(Albrink et al., 1986)	36% and 52%	11 days	Higher	Higher	Higher	Lower			Test diets 70% energy from CHO, 15% energy from fat. 36% and 52% energy from sucrose compared with 0% and 18% energy from sucrose.
(Naismith et al., 1974)	39%	14 days	+13%	+8%					Experiment 1—Diets 49% energy as CHO, 38% as fat. TG and TC remained within normal range.
(Surwit et al., 1997)	42%	6 weeks	NSD	NSD			NSD		Weight loss diets 71% energy as CHO, 11% as fat.
(Behall et al., 1980)	43%	4 weeks	NSD	NSD					Diets 51% energy as CHO, 36% as fat.
(Wu et al., 1975)	45%	11–13 days	+13%	NSD					Most subjects grossly obese.
(Nestel et al., 1970)	52–64%	7 days	Increase						Diets ~70% energy as CHO, 10% fat. Increase in TG "modest" in normal subjects. No group statistics.

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

[a]Test dose of sucrose used (% energy).

[b]Comparison of sucrose group with starch group at the end of feeding period (fasting measurement) except where stated.

Table 3 Details of studies comparing sucrose with starch (in alphabetical order by first author)

Reference	Sample size	Males	Females	Age (years)	Study length	Study type	Sucrose%	Substitute/ comparator	Sucrose% in comparator/control
(Albrink et al., 1986)	24	24	0	22–35	1 week on normal diet, 10 days high/low fibre, 4 days normal diet, 10 days high/low fibre	Parallel groups, factorial design (4 sucrose levels each with low/high fibre crossover)	0, 18, 36, 52	Starchy foods	36% and 52% sucrose compared with 0% and 18% sucrose
(Behall et al., 1980)	12	0	12	19–25	4 weeks normal, 4 weeks sucrose or starch with 4-week washout	Crossover	43	Wheat starch	8%
(Black et al., 2006)	14	14	0	Mean 33	6 weeks low/high sucrose, 4 weeks normal diet, 6 weeks high/low sucrose	Randomized crossover, repeated measures	25	Starchy foods	10%
(Dunnigan et al., 1970)	9	6	3	37–62	2 weeks normal diet, 4 weeks sucrose, 4 weeks sucrose-free	Crossover, repeated measures	31.5	Wheat, potato, and maize starch	0%
(Fraser et al., 1981)	16	16	0	Mean 24–26	3 weeks on each diet: sucrose/grains/roots/leaves	Crossover, repeated measures, latin square design	12.5% above basal	(1) Grains (wheat, corn, oats); (2) leafy vegetables + sucrose, (3) roots + sucrose (all 400 kcal)	Not stated
(Grande et al., 1974)	12	12	0	18–26	17 days control, 2 weeks on each diet. Then 10 days control, 2 weeks on each diet.	Randomized crossover, repeated measures	22.6 and 18.6	Experiment (1) wheat flour/or fruit/or vegetables. Experiment (2) wheat flour/dry peas and beans/chickpeas	6% and 3%
(Kiens et al., 1996)	7	7	0	Mean 24, 20–30	30 days low/high GI, 2–3 weeks normal diet, 30 days low/high GI	Randomized crossover, repeated measures	25	Starch (low GI)	1%
(Mann and Truswell, 1972)	9	9	0	30–40	2 weeks on each diet	Crossover, repeated measures	23	Starchy foods (rice and potatoes)	0%
(Marckmann et al., 2000) (see also Raben studies)	20	0	20	21–52	2 weeks each diet with 2–6 week washout between	Randomized crossover, repeated measures. Ad libitum.	23	(1) Starchy foods, (2) high fat diet (see also Table 5)	<3%
(Naismith et al., 1974)	23	23	0	Not stated	Experiment 1: 7 days normal diet, 14 days high sucrose, 14 days normal. Experiment (2) overfeeding study 3 weeks 160% energy (not relevant)	(1) Repeated measures no control (2) parallel design with control	39	Starchy foods	105 g/day (13%)
(Nestel et al., 1970)	6	6	0	19–49	7 days high starch, 7 days high sucrose or reverse	Crossover, repeated measures	52–64	Starchy foods	14–19% within 70% CHO diet
(Raben et al., 1997)	20	0	20	Mean 39	3-day stabilization diet, 2 weeks on high sucrose, fat, and starch, each separated by 2–6 weeks, according to the subjects' menstrual cycle	Randomized crossover, repeated measures. Ad libitum.	23	(1) Starchy foods, (2) high fat diet (see also Table 5)	2%
(Raben et al., 2001)	18	0	18	Mean 39	3-day stabilization diet, 2 weeks on high sucrose, fat, and starch, each separated by 2–6 weeks	Randomized crossover, repeated measures. Ad libitum. Same study as Raben (1997)	23	(1) Starchy foods, (2) high fat diet (see also Table 5)	2%
(Reiser et al., 1979a)	19	10	9	35–55, mean 42	6 weeks diet, 4 weeks normal, 6 weeks diet	Crossover, repeated measures	33	Wheat starch	2.5%
(Reiser et al., 1979b)	19	10	9	35–55, mean 42	6 weeks diet, 4 weeks normal, 6 weeks diet	Crossover, repeated measures	33	Wheat starch	2.5%
(Reiser et al., 1980)	19	10	9	35–55, mean 42	6 weeks diet, 4 weeks normal, 6 weeks diet	Crossover, repeated measures	33	Wheat starch	2.5%
(Surwit et al., 1997)	60	0	60	mean 41	6 weeks on either high or low sucrose	Parallel control, with subjects matched for BMI, age and menstrual status	42	Starch and aspartame	4%
(Yudkin et al., 1986)	Experiment (1) 14	14	0	38–62, mean 51	Experiment (1) 2 weeks normal diet, 2 weeks increase sucrose, 2 weeks normal	Repeated measures	37	Other CHO, mainly starch	17%
(Wu et al., 1975)	17	5	12	19–55	2 weeks low sucrose, 2 weeks high sucrose	Repeated measures	45	Starchy foods	5%

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

Table 4 Details of studies comparing sucrose with glucose or fructose (in alphabetical order by first author)

Reference	Sample size	Males	Females	Age (years)	Study length	Study type	Sucrose%	Substitute/ comparator	Sucrose% in comparator/control
(Aeberli et al., 2011)	29	29	0	20–50	3 weeks supplemental beverages (6 conditions) with 4-week washouts between.	Randomized crossover, repeated measures	19 (80 g+ base)	Fructose, glucose (80 g) in 600 ml beverages	7.4% sucrose in high fructose, 8.8% in high glucose condition
(Bossetti et al., 1984)	8	4	4	20–32, mean 27	2 weeks fructose/sucrose, 2 weeks rest, 2 weeks fructose/sucrose	Crossover, repeated measures	~15	Fructose	Not stated
(Lock et al., 1980)	18	18	0	31–62	1 year	Repeated measures	16	Glucose	40 g (6%)
(Fry, 1972)	19	19	0	mean 25 (21–41)	6 weeks normal diet, 14 weeks sucrose-free, 12 weeks on normal diet	Repeated measures	~12.5	Glucose syrup	<5 g/day (<0.7% energy)
(Roberts, 1973)	18	18	0	21–40 (mean 25)	4 weeks normal, 14 weeks sucrose-free, 24 weeks normal	Repeated measures	10–13	Glucose syrup	<1%
(Hayford et al., 1979)	8	8	0	19–24	10 days on each of 4 diets	Randomized crossover, repeated measures	45 and 65	Corn syrup (glucose)	<1%
For study by Brynes et al., see Tables 5 and 8.									

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

comparison, and design of each study. These tables are ordered alphabetically by first author for ease of referencing. Tables 6–8 give the main study results and the authors' conclusions.

RESULTS

Twenty-nine papers on 25 different studies were identified as potentially relevant and data were extracted. Of these, 7 (5 studies) included both sexes, 17 were on men only, and 5 (3 studies) were on women only. Study descriptions are in Tables 3–5 and the results are in Tables 6–8.

All studies intended to involve healthy subjects, although some subsequently identified individuals with high fasting TG or who were "carbohydrate-sensitive" (Nestel et al., 1970; Reiser et al., 1979a,b, 1980). One included healthy subjects with one or more CVD risk factors (Brynes et al., 2003) and several included overweight, obese, or post-obese individuals. These are included in the review as they represent approximately two- thirds of the general adult population; however, it is likely that some would have some degree of IR and/or mild hyperlipidemia.

The duration of each experimental period ranged from 4 days to 1 year with most studies being around 14–28 days. Four were carried out in a metabolic ward or hospital environment, but most were on free-living subjects given prepared diets of known composition that were isocaloric and intended to be weight maintaining (eucaloric). Two noneucaloric studies in women are included in this review but discussed separately: one was isocaloric but hypocaloric (designed to achieve weight loss; Surwit et al., 1997), while the Danish study allowed the prescribed diets ad libitum (Raben et al., 1997; Marckmann et al., 2000; Raben et al., 2001).

Results of all pertinent studies are described in the following section, with effects on lipids distinguished from effects on carbohydrate metabolism. The latter section includes only studies in which carbohydrate content was held constant as this is the major determinant of blood glucose and insulin responses.

Effects of Sucrose on Blood Lipids (Isocaloric Studies)

Most studies compared sucrose versus starch/starchy foods (Tables 4 and 6), while a few compared sucrose versus glucose/corn syrup or fructose (Tables 4 and 6). The remainder involved substitutions of mixed or unspecified composition, where the control was a normal Western diet (Tables 5 and 8).

Studies Involving Sucrose Substitution for Starch

Studies where sucrose was substituted for starch provided the majority of studies and allowed some insight as to the effect of sucrose dose on metabolic end points (Table 2).

Studies Using Sucrose Intakes Above the Normal Range (>30% Energy)

A high level of sucrose in the context of a high carbohydrate diet was shown in a number of early studies to modestly increase TG responses, although frequently with considerable variation between subjects. For example, when eucaloric 70% carbohydrate diets either very high in sucrose (52–64% sucrose energy) or starch (14–19% sucrose) were given to 6 men for 7 days each, all subjects showed a greater rise in (fasting) TGs with sucrose but large increments were seen only in 4 men with hyperlipidemia, while the effects in the 2 normal subjects were modest (Nestel et al., 1970). TG concentration was also significantly related to body mass index (BMI) and the insulin response.

Using slightly lower levels of total carbohydrate, Wu et al. also found significantly raised TG (+12.6%) and VLDL-TG (+22%) among 17 overweight subjects fed a high sucrose diet (45%) compared with 5% sucrose for 10–14 days, although there was no effect on cholesterol (Wu and Shreeve, 1975). By contrast, among 23 free-living healthy young men consuming a high sucrose diet (39% or 300 g sucrose) for 14 days and then returning to their normal diet for another 14 days (13% sucrose or 105 g), there were significant increases in total cholesterol (TC) (8%), TG (13%), and phospholipids (10%) on the sucrose diet (all $p < 0.01$), which returned to baseline on resumption of the normal diet (Naismith et al., 1974). Adopting a similar protocol, 14 young male volunteers were asked to double their normal sucrose consumption for 14 days and then return to their normal diet for another 14 days (Yudkin et al., 1986). Sucrose intakes in the 2 periods averaged 37% and 17% energy, respectively. In this study, the change in TG (+10%) with higher sucrose intake was not significant but there was a significant fall (−16%) in HDL-C. However, a second experiment intended to demonstrate that HDL levels rose when high consumers of sucrose reduced intake from approximately 22% sucrose to 9% was unsuccessful in that subjects did not compensate for the sucrose and energy reduction. As a result it is not possible to determine whether the null result for HDL (and fall in TG) in the second experiment was attributable to the reduction in sucrose or an approximately 10% energy reduction, or both.

In the only study investigating the impact of a range of levels of sucrose, Albrink et al. (1986) compared the effect of providing 0, 18, 36, or 52% of energy as sucrose (in very low fat/ high carbohydrate diet) for 10 days after a normal Western high fat diet (39% fat, 40% carbohydrate; Albrink and Ullrich, 1986). This design enabled comparison of sucrose/starch substitution at different doses and also substitution of fat by carbohydrate mixtures (see later section). There were 6 men in each group and the design included a crossover high/low fibre condition within each level of sucrose. In terms of the sucrose-for-starch substitution, TG concentration at day 11 was higher on the 3 sucrose-containing diets (when combined) than on the 0% sucrose diet ($p < 0.01$) and higher on the high sucrose diets (36% and 52% sucrose combined) compared with the 18% sucrose diet. The authors estimated, from regression analysis, that for every 10% increase in sucrose energy there was a 11 mg/dl TG

Table 5 Details of studies comparing sucrose with fat or mixed/control diet (in alphabetical order by first author)

Reference	Sample size	Males	Females	Age (years)	Study length	Study type	Sucrose%	Substitute/ comparator	Sucrose% in comparator/control
(Aeberli et al., 2011)	29	29	0	20–50	3 weeks (each condition) with 4-week washouts between.	Randomized crossover, repeated measures	19	Baseline diet 48% CHO, 36.5% fat, 15% protein	~10%
(Albrink et al., 1986)	24	24	0	22–35	1 week on normal diet, 10 days high/low fibre, 4 days normal diet, 10 days high/low fibre	Parallel groups, factorial design (4 sucrose levels each with low/high fibre crossover)	0, 18, 36, 52	Baseline diet 17% protein, 39% fat, 40% CHO	8%
(Anderson et al., 1973)	9	9	0	18–22	3–5 days control, 4–5 days at 40%, then up to 65 days at 80%	Repeated measures control/40%/80% sucrose.	40 and 80	Control diet 17:43:40 (protein: fat: CHO)	Not stated
(Brynes et al., 2003)	22	22	0	Mean 45	24 days on each of 4 diets: high MUFA/high sucrose/low GI/high GI	Randomized crossover, repeated measures. Ad libitum	22	Fat (MUFA), also low GI and high GI	~ 8% (45–50 g)
(Erkkilä et al., 2007)	37	6 and 7	9 and 12	Mean 48 and 35	8 weeks high sucrose	Repeated measures	~15	Fat (mainly)	7–9%
(Mann and Truswell et al., 1972)	51	51	0	36–55	22 weeks experimental diets: low sucrose versus control	Randomized parallel control	13 (base/control)	Fat/protein (control diet)	2–3% (on low sucrose)
(Marckmann et al., 2000) (see also Raben studies)	20	0	20	21–52	2 weeks each diet with 2–6 week washout between	Randomized crossover, repeated measures. Ad libitum.	23	(1) Starchy foods (see also Table 3), (2) high fat diet	<3%
(Raben et al., 1997)	20	0	20	Mean 39	3-day stabilization diet, 2 weeks on high sucrose, fat, and starch, each separated by 2–6 weeks, according to the subjects' menstrual cycle	Randomized crossover, repeated measures. Ad libitum	23	(1) Starchy foods (see also Table 3), (2) high fat diet	2%
(Raben et al., 2001)	18	0	18	Mean 39	3-day stabilization diet, 2 weeks on high sucrose, fat, and starch, each separated by 2–6 weeks	Randomized crossover, repeated measures. Ad libitum. Same study as Raben (1997).	23	(1) Starchy foods (see also Table 3), (2) high fat diet	2%

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

Table 6 Results of studies comparing sucrose with starch (in alphabetical order by first author)

Reference	Sucrose%	Outcomes	Result	Authors conclusion	Comments
(Albrink et al., 1986)	0, 18, 36, 52%	TGs, TC, LDL, HDL	Sig. higher TG levels, TC and LDL for the 36% and 52% sucrose diets than for both the 0% and 18% sucrose diets. No apparent difference in HDL between sucrose diets.	High sucrose (>36%) has detrimental effects on TGs, although fibre may offer some protection from HTG.	Normal diet ~2800 kcal, intervention diet 3000 kcal.
(Behall et al., 1980)	43%	TG, TC, HDL, LDL, VLDL	NSD in TG, TC, or lipoproteins between sucrose and starch diets. In response to a sucrose test meal FFA rose higher and decreased sooner on sucrose diet than on starch diet.	No differences due to diet overall. For oral contraceptive users, TG levels were slightly, but not significantly, higher on the sucrose diet.	The only study on young women. Designed to assess interaction between oral contraceptive (OC) use and CHO type on metabolism.
(Black et al., 2006)	25%	Insulin sensitivity, fasting and 24 hr glucose and insulin, TC, LDL, HDL, and TGs, pulse wave velocity, BP	NSD in fasting insulin, endogenous glucose production or peripheral glucose utilization during clamp. NSD in 24 hr glucose or insulin profiles. NSD on hemodynamics (BP and pulse wave velocity), NEFAs, HDL, or TGs. Sig. difference in TC and LDL that were higher on 25% sucrose.	Increasing sucrose intake from 10 to 25% has no effect on insulin sensitivity or glucose activity, but may affect some lipid markers.	Controlled for total CHO, protein, fat, and fibre but not SFA (which was 15% and 11% energy in high and low sugar conditions, respectively) and PUFA, which may account for lipid differences.
(Dunnigan et al., 1970)	31.5%	TGs, cholesterol, blood glucose, insulin, and glucose tolerance test ($n = 7$), NEFAs ($n = 4$).	Sig. higher fasting glucose on sucrose diet ($p < 0.001$). NSD on plasma insulin or glucose tolerance test, or TGs, cholesterol, and NEFAs. One subject had higher cholesterol, one lower cholesterol, and one lower TGs on sucrose diet (all sig.).	CHO tolerance and serum lipids not affected by the substitution of sucrose for starch, except in the case of blood glucose.	Study took place on a hospital ward. 3 subjects had elevated lipids. All had normal CHO tolerance.
(Fraser et al., 1981)	12.5% above basal	TC, HDL, LDL, VLDL, and TGs	Sig. higher TC and LDL ($p < 0.01$) in sucrose group versus grains (−9 and −8 mg/dl). Leafy vegetables (less valid comparison) had lower VLDL and TC.	Whole grains and leafy vegetables may both be associated with lower cholesterol than an isocaloric amount of sucrose.	Controlled for fat content (42%). Minor variations between control and experimental diets for macronutrients (<5% total energy).
(Grande et al., 1974)	22.6% and 18.6%	Cholesterol, phospholipids, and TGs	NSD between diets in TGs, cholesterol, or phospholipids.	Sucrose supplementation (500 kcal/day) for 2 weeks does not cause higher fasting TC, phospholipids, or TG than isocaloric quantities of starch fed as wheat flour or leguminous seeds.	More cholesterol and slightly more saturated fat on sucrose diet. 1 MJ more energy consumed on sucrose and fat. More fibre in starch diet

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Table 6 Results of studies comparing sucrose with starch (in alphabetical order by first author) *(Continued)*

Reference	Sucrose%	Outcomes	Result	Authors conclusion	Comments
(Kiens et al., 1996)	25%	Fasting and post-prandial glucose, insulin, and TGs, 24 hr profiles on day 4 and 29 or 30, muscle glycogen and TGs, peripheral glucose disposal	Initially blood [glucose] and plasma [insulin] were lower during part of the day with the LGI than with the HGI diet, but after 30 days this difference diminished. FFAs rose on low GI diet. Sig. lower post-prandial insulin and glucose at lunch on low GI at 3 days. Sig. higher glucose infusion rate (insulin sensitivity) on high GI versus low GI. Sig. lower muscle glycogen and muscle TG at the end of low GI diet compared with at the end of high GI diet.	High sucrose/high GI diet may increase insulin sensitivity. Whole body insulin action may be impaired in low GI diets possibly because of higher FFAs. There may also be some effect on post-prandial metabolic markers, but not fasting markers after 30 days.	Diets differed in PUFA and fibre (7.3 g fibre on high GI vs. 19 g on low GI diet). Diets controlled and delivered to subject homes.
(Mann and Truswell, 1972)	23%	TGs, cholesterol, fatty acids, glycaemic stimulus, insulin, and lipaemic response	NSD on TGs, cholesterol, or FFAs at the end of each diet. After lunch, sig. increase in glycaemic stimulus ($p < 0.05$) and insulin response ($p < 0.001$) on starch diet, but lower lipaemic response ($p < 0.05$), due to faster clearing of ingested TG.	At physiological levels of sucrose ingestion, there is no benefit of replacing sucrose with starch on insulin, TGs, lipids. and FAs.	Subjects were staying on a metabolic ward but had no metabolic problems.
(Marckmann et al., 2000) (see also Raben studies)	23%	TC, LDL, HDL, TGs, Factor VII, Fibrinogen	Sucrose period associated with ~10% higher LDL, higher TGs (~20% fasting and ~50% nonfasting) compared with starch. 10% higher nonfasting factor VIIc than high starch period. NSD in HDL.	High sucrose diets might be more atherogenic and thrombogenic than high starch diets. Fructose component may stimulate hepatic VLDL production and impair clearance.	Ad libitum. Starch group had lower EI, higher fibre and weight loss. Sucrose group had higher (absolute) fat intake and cholesterol than starch group, which may be a confounder.
(Naismith et al., 1974)	39%	TGS, cholesterol, phospholipids, free and esterified cholesterol	Experiment (1) TC (8%), TGs (13%), and phospholipids (10%) all increased on sucrose diet (all $p < 0.01$), before returning to baseline on normal diets. In 10 subjects, TC (15%, $p < 0.01$) and esterified cholesterol (26%, $p < 0.02$) increased on the high sucrose diet.	The increase in plasma lipids is due to sucrose itself rather than any accompanying increase in energy intake.	Examined hypothesis that high TG with high sucrose diet was due to increased energy intake.
(Nestel et al., 1970)	52–64%	TGs, insulin response, rate of FFA incorporation, and FFA turnover	Sig. higher TGs with sucrose versus starch, but TG effects were modest in the (2) normolipidaemic subjects. FFA turnover was about the same on both diets but given the higher TG pool total FFA in TG was higher on sucrose. Insulin response to intra-venous GTT was higher on sucrose diet.	All subjects showed a rise in TGs with sucrose but large increments were seen only in those with hyperlipidemia. TG also associated with BMI.	Normal subjects reached a peak TG concentration on day 5; declining 12% by day 7.

(Raben et al., 1997)	23%	Body weight, fat mass, EI and EE, noradrenaline (NA) and adrenaline (A), PA, HR, BP, hunger/palatability ratings	EI, body weight and fat mass were stable on high sucrose (and high fat) diets but fell on starch diet (high fibre) ($p < 0.05$). 24-hr EE was higher on sucrose ($p < 0.05$). Sympathoadrenal activity (adrenaline and noradrenaline) was increased on sucrose diet compared with other 2 diets but no adverse effect on BP or HR. Satiety was higher on starch, palatability highest on sucrose $p < 0.05$.	A high sucrose diet does not have detrimental effects on body weight or composition, or on BP. It does seem to increase sympathoadrenal activity, probably due to the higher EI and fructose component.	EI higher on sucrose (10.3 MJ) and fat (10.1 MJ) compared with starch (9.1 MJ) $p < 0.05$. Lack of change in fat mass despite +ve fat balance likely due to higher free-living PA than that observed in the respiration chamber.
(Raben et al., 2001)	23%	Plasma glucose and lactate, serum insulin, TGs, NEFAs, glycerol, glucagon, glucose-independent insulinotropic polypeptide, and glucose-like peptide-1	The high sucrose diet induced faster but lower glucose peak and sig. lower total and incremental AUCs than did the high fat and high starch diets. There were no significant differences in the insulin AUCs although initial rise was steeper with sucrose diet. Weight loss on high starch ($p < 0.05$). Post-prandial TG and total AUC were higher with high sucrose diets than with the high starch diet. Post-obese had sig. lower fasting TGs and AUCs on all diets.	Sucrose does not reduce insulin sensitivity. IR (homeostasis model assessment) did not differ between diets. Lower GI of sucrose than starch probably explains lower glucose response. Higher lactate levels after lunch and supper likely due to fructose content. Post-obese women seem to have better insulin sensitivity and lipid storage capacity than normal.	Composition of diets: sucrose and starch: 59% CHO, 28% fat, and 13% protein. High fat diet: 2% sucrose, 41% CHO, 46% fat, and 13% protein (22 g fibre). EI lower on high starch (9.1 vs. 10.3 MJ; $p < 0.05$), and higher for post-obese on high sucrose ($p < 0.0001$) and high fat ($p < 0.001$).
(Reiser et al., 1979a)	33%	Serum lipids, TGs, FFAs, TC, and lipoproteins	Lipids (10.5%), TGs (33%), and cholesterol (7.4%) all increased with sucrose diet and time (all $p < 0.01$). NSD on body weight, lipoproteins, or FFAs. TGs, cholesterol, and lipoproteins showed a significant sex effect—men had higher levels than women.	Increasing sucrose from 0 to 30% energy sig. increases lipids, TGs, and cholesterol, but not lipoproteins or FFAs compared with starch. Men and those with high TG may be more sensitive to CHO.	10% energy taken at breakfast and 90% at dinner. Feeding 90% of energy at one meal may have exaggerated sucrose effect.
(Reiser et al., 1979b)	33%	Fasting insulin/glucose, plus (after sucrose load test) insulin:glucose ratios, and insulin and glucose response	Sig. higher fasting insulin on sucrose diet (+23.8%, $p < 0.01$) but glucose effect was very small (+2.4%, $p < 0.025$). In a subpopulation of subjects with high fasting lipoproteins, there was an exaggerated insulin response to sucrose.	Increasing sucrose from 0 to 30% energy sig. increases insulin and glucose compared with starch, suggesting reduced insulin sensitivity on the sucrose diet. Some people may be more susceptible.	Feeding 90% of energy at one meal may have exaggerated sucrose effect.

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Table 6 Results of studies comparing sucrose with starch (in alphabetical order by first author) *(Continued)*

Reference	Sucrose%	Outcomes	Result	Authors conclusion	Comments
(Reiser et al., 1980)	33%	Glucose-independent insulinotropic polypeptide, insulin, and glucose response to 2 g/kg body weight of sucrose	Sig. higher glucose-independent insulinotropic polypeptide at 0.5 ($p < 0.001$) and 1 hr ($p < 0.05$), higher insulin at 1 hr ($p < 0.05$) and higher fasting glucose ($p < 0.05$) on sucrose diet.	Increasing sucrose from 0 to 30% energy sig. increases GIP response, and this may mediate the increase in insulin without a blood glucose increase when fed sucrose.	Same population and protocol as other Reiser studies.
(Surwit et al., 1997)	42%	Fasting glucose, Thyroid hormones, TC, LDL, HDL, and TGs	NSD between high and low sucrose groups for plasma glucose, fasting lipid measures, or thyroid hormones. The low sucrose groups exhibiting larger reductions over time for TC and LDL but started from a higher base; the meaning of this is questionable (say authors).	No adverse effects on weight loss, glycaemic or lipidaemic profiles, or behavioral outcomes when comparing a high sucrose diet to an isoenergetic low sucrose diet; both diets low in fat and hypocaloric.	Diets provided were low fat (11%) high CHO (71%) and aimed at weight loss, which was accomplished.
(Wu et al., 1975)	45%	TGs, VLDL, TC.	Sig. increase in TGs (12.6%) and VLDL (22–23%) on high sucrose diet ($p < 0.05$). Individually the change in VLDL_TG did not correspond to change in plasma TG. No sig. effect on cholesterol. VLDL kinetics show NSD in TG removal between diets.	A high sucrose diet may have a detrimental effect on lipid profile, but its effect on TG turnover is unclear. There was a fractional decrease turnover rate (k) in conjunction with modest expansion in VLDL pool and no overall change in turnover rate (V)	Lack of difference in TG removal may be due to measurement in the postabsorptive state, not fed state.
(Yudkin et al., 1986)	37%	HDL, TG	Doubling sucrose intake from normal resulted in a sig. fall (16%) in HDL but NSD in TG (+10%). However, decreasing sucrose did not show reverse, possibly due to susceptibility.	Increase in sucrose was associated with fall in mean HDL (in 11/14 subjects). In experiment 2, (sucrose reduction) TG fell, possibly due to energy reduction.	

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

Table 7 Results of studies comparing sucrose with glucose/fructose (in alphabetical order by first author)

Reference	Sucrose%	Outcomes	Result	Authors conclusion	Comments
(Aeberli et al., 2011)	19%	TC, LDL, HDL, TG, LDL particle size and distribution, fasting glucose, IR, C-reactive protein, BP	NSD in TC, LDL, HDL, or TG. LDL particle size (LDL1) lower on high sucrose and high fructose but not high glucose. No increase in small dense LDL. NSD in fasting glucose (slight rise compared with baseline).	High sucrose and high fructose beverage conditions showed similar effects on LDL particle size. High glucose condition did not.	More data required on significance of LDL particle size.
(Bossetti et al., 1984)	~15%	TC, TGs, LDL, HDL, LDL:HDL, insulin, glucose, insulin:glucose ratio	NSD on any outcome on either diet at 7 or 14 days. HTG subject had increased TGs on sucrose diet.	Physiological amounts of sucrose have the same effect on metabolic outcomes as fructose.	EI determined by food diary before experiment, so difficult to determine exact%sucrose.
(Lock et al., 1980)	16%	TG, TC	In subjects whose weight remained unchanged there was a sig. (8%) fall in TC ($P < 0.025$) and phospholipid-P ($P < 0.025$) in the glucose-syrup period but TG did not change.	Changes in some blood lipids may be attributed to the isoenergetic replacement of table sucrose by glucose syrup.	Longest study. Suggests small but sig. beneficial effects on TC of replacing sucrose with glucose.
(Fry, 1972)	~12.5%	GTT every 3 weeks	Sig. higher blood glucose at 0.5 hr on normal sucrose diet ($p < 0.001$), but lower at 1 and 1.5 hr ($p < 0.05$). NSD on AUC (mean of last 3 GTTs on each diet).	There is a change in glucose tolerance when changing from a sucrose-free to sucrose-containing diet. Post-prandial glucose curve may be flatter with glucose than sucrose but NSD in AUC.	Subjects were men in British Antarctic survey
(Roberts, 1973)	10–13%	TG, cholesterol, and phospholipids	Overall NSD in TG during low sucrose diet. However 10% fall for high TG group ($p < 0.01$) (not correlated with body weight changes). NSD for low TG group. TC fell during sucrose-free diet in the high TC group, but rose in the low TC group. NSD in phospholipids.	Sucrose reduced diets may lower TGs in those with high levels at baseline, which seems to be an effect of sucrose restriction rather than weight loss (but see comment). The effect on cholesterol is less clear.	The sig. reduction in the high TG group should be viewed with caution (Mann et al., 1973) and may be regression to mean (no control group). Does not constitute evidence of a sucrose effect on TG, independent of weight loss.
(Hayford et al., 1979)	45% and 65%	TG, 24 hr TG (AUC)	Fasting TG increased on 65% CHO diet versus 45% CHO but NSD between sucrose and corn syrup. However 24-hr TG concentration was higher on sucrose diet versus corn syrup (112 vs. 91 mg/dl at 45%; 129 vs. 94 mg/dl at 65%).	High sucrose diet at 45% or 65% energy induces higher 24 hr TG response than corn syrup diet of equivalent composition.	

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

Table 8 Results of studies comparing sucrose with fat or other mixed diet (in alphabetical order by first author)

Reference	Sucrose%	Outcomes	Result	Authors conclusion	Comments
(Aeberli et al., 2011)	19%	TC, LDL, HDL, TG, LDL particle size and distribution, fasting glucose, IR, C-reactive protein, BP	NSD in TC, LDL, HDL, or TG versus baseline diet. Decrease in LDL particle size (LDL1) on high sucrose diet but no increase in small dense LDL. Fasting glucose rose slightly. No change in high sensitivity C-reactive protein or IR. No change in BP. No significant change in energy intake.	Sugar-sweetened beverages (80 g in 600 ml) for 3 weeks showed no effects on conventional risk markers but changes in other putative atherogenic risk markers.	Only study to show adverse effects of moderate sucrose (as beverage) in healthy young men. Requires replication. More data required on significance of LDL particle size.
(Albrink et al., 1986)	0, 18, 36, 52%	TGs, TC, LDL, HDL	Compared with the control diet (40% fat) no sig. increase in TGs at the end of the 11-day study. Total and LDL-C fell on the 0% and 18% sucrose. HDL-C fell on the 36% and 52% sucrose.	Differential effects on cholesterol above 35% sucrose as compared with below 19% sucrose	Normal diet approximately 2800 kcal, intervention diet 3000 kcal
(Anderson et al., 1973)	40% and 80%	TGs, oral and intravenous GTT, fasting glucose and insulin	Increased TGs 50–100% (on 80% sucrose diet) TG not reported on 40% sucrose. Oral GTT better on 40% sucrose than control diet ($p < 0.05$). Continued to improve with the 80% diet (time effect $p < 0.01$). No change in fasting plasma glucose, lower fasting insulin.	High sucrose diet improves oral glucose tolerance.	Control diet was 3025 kcal and sucrose was 2800 kcal.
(Brynes et al., 2003)	22%	TC, TC:HDL, HDL, LDL, TG, NEFA, glucose, insulin, IR	NSD between diets in fasting lipids, glucose, insulin, or IR after 24 days. Total AUC for TG did not differ between the 3 CHO diets. High fat (MUFA) diet had better glycaemic outcomes but worse lipidaemic outcomes compared with high sucrose diet.	High sucrose diet had post-prandial responses intermediate between low GI and high GI diets. High GI diet (but not high sucrose diet) was associated with reduced insulin sensitivity.	Ad libitum diet in free-living environment. About 250 kcal more consumed on high fat diet.
(Erkkilä et al., 2007)	~15%	TG, LDL, HDL, BP, insulin, glucose, IR	NSD on any outcome. Moderate sucrose consumption does not affect lipid responses and was not modified by the e2 allele.	Poorly controlled, subjects changed diet individually, and sig. increase in energy on an addition of sucrose not compensated by decrease in fat.	
(Mann and Truswell et al., 1972)	13% (baseline control)	TC, TGs, and VLDL	22% reduction of serum TGs on low sucrose diet ($p < 0.01$) was correlated with weight loss. Effect mostly due to those with high baseline TGs (30%) and minimal for those with normal range TGs. Similar reduction of prebeta lipoproteins (VLDL) on the low sucrose diet in subjects with high TGs at baseline.	Free-living with diet instruction. Study essentially about sucrose removal and weight loss. Weight loss ($p < 0.01$) in low sugar group may explain TG reduction $R = 0.31$, $p < 0.005$.	8 subjects had hyperlipidemia and showed more reduction in TG, more were in the low sucrose group.

(Marckmann et al., 2000)	23%	TC, LDL, HDL,TGs, Factor VII, Fibrinogen	Compared with high fat period, sucrose period was associated with lower HDL and higher TGs.	Fructose component may stimulate hepatic VLDL production and impair clearance.	Ad libitum. Same study as Raben (1997, 2001). See also results for starch/sucrose (Table 3)
(Raben et al., 1997)	23%	Body weight, fat mass, EI and EE, noradrenaline and adrenaline, PA, HR, BP, hunger/palatability ratings	EI, body weight and fat mass were stable on high sucrose and high fat diets but fell on starch diet (high fibre) ($p < 0.05$). Sympathoadrenal activity was increased on sucrose diet compared with fat or starch but no adverse effect on BP or HR. Palatability highest on sucrose diet $p < 0.05$.	A high sucrose diet does not have detrimental effects on body weight or composition, or on BP. It does seem to increase sympathoadrenal activity, probably due to the higher energy intake and fructose component.	EI higher on sucrose (10.3 MJ) and fat diets (10.1 MJ) compared with starch (9.1 MJ) $p < 0.05$. Yet energy balance maintained on fat and sucrose diet (negative on starch diet) Possibly higher free-living PA explains this.
(Raben et al., 2001)	23%	Plasma glucose and lactate, serum insulin, IR, TGs, NEFAs, glycerol, glucagon, glucose-independent insulinotropic polypeptide, and glucose-like peptide-1	The high sucrose diet induced faster but lower glucose peak and significantly lower total and incremental AUCs than did the high fat (and high starch) diets. There were no significant differences in the insulin AUCs although initial rise was steeper with sucrose diet.. Higher fasting TG on high CHO diets (vs. high fat) disappeared when adjusted for energy, diet composition, and weight change. Post-prandial TG responses differed, peaking 1 hr after meal on fat diet but rising slowly over the day on high sucrose diet. Incremental AUC for TGs higher on fat diet but total AUC NSD for sucrose and fat diets.	Sucrose does not reduce insulin sensitivity. Lower GI of sucrose than starch probably explains lower glucose response. Higher lactate levels after lunch and supper likely due to fructose content. Post-obese women seem to have better insulin sensitivity and lipid storage capacity than normal weight.	Composition of diets: sucrose and starch: 59% CHO, 28% fat, and 13% protein. High fat diet: 2% sucrose, 41% CHO, 46% fat, and 13% protein (22 g fibre). EI lower on high starch (9.1 vs. 10.3 MJ; $p < 0.05$), and higher for post-obese on high sucrose ($p < 0.0001$) and high fat diet ($p < 0.001$).

NSD = no significant difference; Sig. = significant; AUC = area under curve; EI = energy intake; EE = energy expenditure; GTT = glucose tolerance test; PA = physical activity; HR = heart rate; BP = blood pressure; PWV = pulse wave velocity; FFA/NEFA = free/nonesterified fatty acids; TG = triglycerides; TC = total cholesterol; LDL = LDL cholesterol; HDL = HDL cholesterol; GI = glycaemic index; CHO = carbohydrate; MUFA = monounsaturated fatty acids; VLDL = VLDL cholesterol.

increase at the end of the study. Compared with baseline TG values of 100–120 mg/dl, this is equivalent to a 10% rise. Total and LDL-C was higher on the 36% and 52% sucrose than on the 0 and 18% sucrose diets (Albrink and Ullrich, 1986).

Finally, in the only study on young women included in this review, Behall et al. investigated the metabolic effects of a 43% energy from sucrose diet (compared with an 8% sucrose, 43% wheat starch diet) and whether there was an interaction with oral contraceptive use among 12 university students (Behall et al., 1980). Both diets supplied protein, fat, and carbohydrate in the ratio 13:36:51 (percentage energy) and each diet was fed for 4 weeks in a crossover design with a 4-week washout period between. There was no effect of diet type on TG, TC, or individual lipoproteins (HDL, LDL, VLDL). However, post-prandial free fatty acid (FFA) levels measured after a high sucrose meal peaked faster and declined sooner with the sucrose diet condition.

Thus, while these studies provide some evidence for an increase in plasma lipids, especially TG in men over the short term (1–2 weeks), the effect is modest and not consistent across studies. Furthermore, intake in these protocols is at least 3 times the mean estimated intake of normal adults.

Studies using sucrose intakes within normal range (30% energy or less)

In a longer-term study, Dunnigan et al. found no significant effects overall after a 4-week moderately high sucrose diet (31% of total energy) on plasma lipids (TC or serum TG) compared with a sucrose-free, high starch diet (Dunnigan et al., 1970). Both diets in this crossover study contained 45% of energy from CHO; 40% from fat; and 15% from protein, and subjects were 9 middle-aged men and women hospitalized for neurological disability. Overall, this study suggests that serum lipids are not altered (over a period of weeks) by the substitution of starch for sucrose and vice versa within the normal range of sucrose intakes in a Western diet of modest total carbohydrate content.

Similarly, Mann and Truswell (1972) investigated the effects of isocalorically replacing starch with a physiologic amount of sucrose (23% energy) among 9 men on a metabolic ward fed a diet with 55% energy from CHO (protein:fat:CHO of 15:30:55). After 14 days on each diet, there were no differences in fatty acids, cholesterol, or TG (Mann and Truswell, 1972). However, in 5 subjects studied post-prandially, there was a higher lipaemic response after the sucrose, compared with the starch meal (rice and potatoes). The authors suggested that the higher insulin response to starch (see later section) improved lipid clearance from the circulation. Overall this study suggests that normal sucrose intake may increase post-prandial TG levels, possibly due to reduced clearance, while it does not alter basal lipid profiles.

Two studies in the review (Grande et al., 1974; Fraser et al., 1981) compared supplementary sucrose with other mixed carbohydrate foods, including legumes and vegetables. A randomized crossover study in 12 healthy young men found that 500 kcal of sucrose in a background diet (36% fat) had a similar effect on serum cholesterol, phospholipids, and TG to isocaloric supplements of refined wheat flour, fruits, and leguminous seeds, over 2 weeks (Grande et al., 1974). Only the vegetable diet resulted in lower lipid levels. The amounts of sucrose in this experiment were moderately high but not excessive (19–23% sucrose) whereas the comparison diets contained 2–6% sucrose (a 16% difference). Similarly, Fraser et al. (1981) investigated the effects of sucrose versus wholegrain starchy food added as 400 kcal supplement (12.5% energy) to a standard controlled diet (42% fat) for 3 weeks each to 16 healthy young men (Fraser et al., 1981). There were also 2 other conditions involving partial substitution of sucrose with root vegetables or leafy vegetables. The sucrose diet was associated with a small elevation in TC and LDL (9 mg/dl and 8 mg/dl; $p < 0.01$) compared with the wholegrain diet but no significant change in TG or HDL, while leafy vegetables plus 200 kcal sucrose condition resulted in lower total and VLDL cholesterol. However, higher fibre intakes in these conditions may have confounded the association. Taken together, these studies fail to provide good evidence of a significant detrimental effect of sucrose on lipid metabolism, at least over 2–3 weeks, although they do raise the possibility of small post-prandial changes of uncertain significance.

In contrast to the studies quoted above, a series of papers in the late 70s by Reiser and colleagues from the Carbohydrate Nutrition Laboratory, Beltsville/University of Maryland, USA suggested that high sucrose diets could produce deleterious changes in lipid profiles over 6 weeks. Effects of a controlled diet rich in sucrose (30% energy) compared with a low sucrose diet (<3% energy) for 6 weeks each were studied in 19 men and women. The diets were identical in protein, fat, and total carbohydrate content (15:42:43). During the high sucrose period, plasma TGs were 33% higher, total lipids were 10% higher, and TC were 7.4% higher than in the starch period. There was no difference in levels of FFA or other lipoproteins (alpha or HDL-C, and beta or LDL-C) between diet types (Reiser et al., 1979a).

However, one major problem with the interpretation of these studies is that 9 out of 19 subjects (7 of whom were men) were discovered to have high fasting TG levels (>150 mg/100 ml); these same individuals had markedly higher lipid and insulin responses, skewing the results. Using data given in the paper (Reiser et al., 1979a), it can be estimated that the rise in TG levels for the normal individuals was of the order of 22% (compared with 45% for the HTG subjects) and the rise in TC was approximately 4% (compared with 11% in TG subjects) after 6 weeks.

Two other factors may have contributed to the magnitude of the sucrose effect on metabolism. These are the gorging pattern (90% of the sucrose was administered at dinner after an 8 hr fast since breakfast) and the high intake of dietary cholesterol (562 mg/day). Together with the heterogeneous responses between healthy and less healthy individuals identified above this may limit the extent to which these studies are generalizable to normal dietary patterns and healthy people. However, they

do suggest that diets including high levels of sucrose (30% energy) may be associated with adverse changes in blood lipid levels that are accentuated in adults with underlying metabolic abnormalities.

More recently, another 6 week randomized controlled study using levels of sucrose consistent with modern European diets, Black et al. (2006) fed a group of 14 healthy young men a diet containing 25% or 10% sucrose energy (starch replacing sucrose). The high sucrose diet resulted in no significant differences in HDL or TG, or measures of vascular compliance (blood pressure, arterial stiffness). IR, as measured by the gold standard method, was also unaffected (see the next section). Although total and LDL cholesterol were significantly higher on the 25% sucrose diet ($p < 0.01$), this was in comparison to the unexpected fall in LDL cholesterol on the 10% sucrose diet. Furthermore, the high sucrose diet was significantly higher in SFAs (15% energy vs. 11%) and lower in polyunsaturated fatty acids (PUFA; 5% vs. 7%). Overall, this study suggests that a diet of 25% sucrose under controlled conditions has little impact on metabolism of healthy young men who were mildly overweight (mean BMI 26 kg/m^2).

The above studies fed under controlled isocaloric conditions fail to demonstrate a consistent or meaningful adverse effect of sucrose at a level up to 25% energy in healthy young adults, although this cannot be extrapolated to adults with dyslipidemia or diabetes. Nor can it be assumed to be the same in ad libitum conditions, or in the context of underfeeding or overfeeding, discussed later.

Studies Involving Sucrose Replacing Fat or a Combination of Nutrients

Some studies involved manipulating the sucrose content of the diet without controlling which other macronutrients were substituted (Tables 5 and 8). For example, in a study primarily designed to look at glycaemic effects, Anderson et al. (1973) tested the effects of increasing sucrose to 40% of energy for 4–5 days and then to 80% of energy up to 65 days among 9 normal young men whose normal diet contained 43% fat, 40% carbohydrate energy. On the 80% sucrose diet (substituting both fat and carbohydrate), TG levels rose by 50–100%, although no lipid data were given at the 40% sucrose level. The unphysiological level of sucrose at which effects were observed means that results from this study are of limited value to the research question.

In a parallel control study of much longer duration, the impact of reducing sucrose intake (from about 13% to about 2%) over 22 weeks was explored among 51 free-living men aged 36–55 years (Mann et al., 1972). Fasting TG levels fell by 22% overall, but this was mainly in those with high baseline TG; there was a minimal drop among those with normal values. There was no significant effect on serum cholesterol (−4%). Weight loss occurred due to a significantly reduced energy intake and was correlated with the reduction in lipids, begging the question as to whether the negative energy balance or sucrose reduction caused improvement in fasting lipids. The authors took the view that negative calorie balance was the likely cause and speculated that weight loss from restriction of other constituents may have a similar effect.

Most recently, a crossover study to assess the effects of added glucose, fructose, and sucrose in the form of sweetened beverages, additional sucrose for 3 weeks (19% sucrose in total diet) was not associated with any significant change in energy intake or in the traditional lipid profile compared with baseline (10% sucrose). The authors reported a decrease in LDL particle size, attributable to a decrease in the large LDL1 subclass but no significant increase in small dense LDL particles (Aeberli et al., 2011).

Studies Substituting Sucrose for Other Sugars

Five studies in the review compared sucrose with glucose or corn syrup (variable length glucose polymers), one compared sucrose with fructose and one compared fructose, sucrose, and glucose drinks (Tables 4 and 7).

When sucrose was replaced with corn syrup at either 45% or 65% energy for 10 days, there was no effect of carbohydrate type on fasting TG. However, 24 hr plasma TG concentrations measured by continuous blood withdrawal were significantly higher on both sucrose diets (Hayford et al., 1979). In a longer study among young men in the British Antarctic survey team, Roberts examined the effect of substituting virtually all dietary sucrose with glucose for 14 weeks and then restoring sucrose for another 24 weeks (Roberts, 1973). Initial sucrose intake during the run-in period was at the level of 10–13% energy. Weight did not change throughout the study and there was no change in TC overall. TG levels did not change significantly in the men whose initial levels were low (<120 mg/l00 ml) but a 10% reduction was reported among 5 men who had initially high TG levels (>120 mg/100 ml). The author interpreted this as evidence for increased sucrose sensitivity although it might be attributable to regression to the mean (Mann and Truswell, 1973). During the sucrose-restored period, TG initially rose but then slowly subsided toward normal (preintervention) levels. Bearing in mind the small effects observed, this study does not suggest that sucrose produced lipid changes that were either harmful or beneficial.

However, the longest study by far included in this review was a 2-year study of the effect on plasma lipids of replacing table sugar with dried glucose syrup (each diet followed for 1 year; Lock et al., 1980). The normal diet of these 18 men contained approximately 100 g sucrose (16% energy), which was reduced to 40 g (6%). Fasting blood samples were taken every 4 weeks and dietary questionnaires administered every 3 months to monitor compliance in macronutrient composition. In subjects whose weight remained unchanged ($n = 8$) and in those who lost weight ($n = 5$), there was a significant (8%) fall in TC ($p < 0.025$) and phospholipid P ($p < 0.025$), compared with the

16% sucrose period. However, there was no change in fasting TG except in those who gained weight. This study suggests that the elevated fasting TG levels seen in shorter studies may be a transient phenomenon. It also raises the possibility that carbohydrate type may modify some aspects of lipid metabolism (e.g., cholesterol level) over the longer term, although this lacks confirmation from other studies.

In a study comparing sucrose with fructose, Bosetti et al., compared isocaloric diets at a realistic level of consumption (15% energy) using typical American foods for 14 days in a crossover study. There was no change in total TG, TC, LDL cholesterol, or HDL cholesterol concentrations between diet periods. They concluded that there is no difference between sucrose or fructose on various lipid components in the "real world" in normal subjects (Bossetti et al., 1984). Similarly, in a crossover study using fructose, sucrose, and glucose drinks for 3 weeks, lipoprotein concentrations were unchanged on all conditions, and sucrose and fructose results were similar with regard to LDL subclass distribution (Aeberli et al., 2011).

Effects of Sucrose on Glucose and Insulin Levels (Isocaloric Studies)

Elevated fasting plasma insulin is regarded as an early sign of IR and results of this basic measurement correlate moderately well with the euglycaemic clamp technique. Homeostatic model assessment (HOMA), derived from the ratio of fasting insulin and glucose concentrations, is better than fasting insulin per se, but this too reflects the basal state. Most of insulin action occurs in the post-prandial state (Daly, 2003), therefore studies that provide evidence on response to a glucose or sucrose load after habituation to high sucrose diets are also valuable. In comparison to blood lipids, relatively few studies examined the effect of sucrose substitution on blood glucose or insulin.

Studies involving sucrose substitution for starch

An early study using a diet containing >50% sucrose energy for 7 days found that insulin responses (to intravenous glucose) were higher than on the high starch diet (Nestel et al., 1970). However, studies using less extreme intakes have not shown the same results. For example, Dunnigan et al. (1970) found a small but significantly higher fasting blood glucose during the 4-week sucrose period (28% of total energy) compared with the 4-week "sucrose-free," high starch diet (45% carbohydrate; Dunnigan et al., 1970). However, no significant differences were found for fasting plasma insulin or area under curve (AUC) for blood glucose or insulin using the glucose tolerance test. Overall, this study suggests that except for small changes in fasting blood glucose, carbohydrate tolerance was not altered.

When sucrose (at 23% energy) was replaced by starch in a crossover study, there were no differences in fasting insulin after 14 days (Mann and Truswell, 1972). However, post-prandial differences were studied in 5 out of the 9 subjects. On the sucrose diet, there was a significantly lower glycaemic and insulin response compared with the starch diet (provided by rice and potatoes), so this well-controlled study suggests that ingestion of sucrose at a normal physiological level may reduce post-prandial insulin secretion compared with starch. This may be a consequence of the lower glycaemic index (GI) of sucrose compared with the starches used in the intervention.

More recent studies have tended to confirm that diets high in sucrose do not cause greater insulinemia than starch, which is not unexpected given that the fructose component of sucrose is a poor insulin stimulator. In fact on the basis of GI, the effect of sucrose would be predicted to be intermediate between low GI and high GI diets. Indeed, compared with a high GI diet, which appeared to increase IR (PP-HOMA +31%), a diet containing 22% sucrose energy slightly reduced post-prandial HOMA over 24 days (−20%) though not as much as a low GI diet (−43%; Brynes et al., 2003). In the study by Kiens and Richter (1996) in which the high sucrose diet was actually a high GI diet (GI = 90; 25% sucrose), insulin sensitivity was not adversely affected compared with the low GI diet (GI = 66; 1% sucrose). By the end of the 30-day period, fasting blood glucose and plasma insulin were not significantly higher on the high sucrose diet. Post-prandially the high GI/sucrose diet showed higher glucose and insulin responses, while the low GI diets were associated with an increased plasma fatty acid concentration, suggesting that low GI diets may impair whole body insulin action, perhaps because of higher FFAs. However, there was also some evidence of adaptation resulting in a more rapid and larger insulin response over time.

In agreement with these general findings are the Danish studies of Raben, Marckmann, and colleagues who examined diurnal metabolic profiles on day 15, after 2 weeks of (ad libitum) diets high in sucrose or starch. Possibly due to the lower GI of sucrose relative to starch, the sucrose-rich diet appeared to improve glucose metabolism (glucose AUCs were lower and there was no significant difference in insulin AUCs; Raben et al., 2001). These findings are in agreement with other work by Daly et al. on post-prandial metabolism (Daly et al., 1998). Lastly, in the controlled study by Black et al. (2006), the 25% sucrose diet had no effect on glucose tolerance measured by a euglycaemic-hyperinsulinaemic clamp, nor on fasting blood glucose and insulin. Taken together these results suggest that insulin sensitivity is not reduced with 25% sucrose ingestion in place of starch in normal healthy adults. However, variation between studies may be partly explained by the form of starch and by total dietary GI, fibre, and fat content.

In contrast to the above, the only studies suggesting adverse effects of sucrose on glucose and insulin levels are those of Nestel, who found higher insulin response (statistics not given) on a very high (>50%) sucrose diet, and the series of studies from Reiser and colleagues from the Beltsville Laboratory. The latter reported fasting insulin levels to be 23% higher after 6 weeks on a 30% versus 3% sucrose diet, accompanied by a much smaller change in fasting glucose (+2.4%), and therefore a higher insulin to glucose ratio (Reiser et al., 1979b). While

the study did not examine insulinaemic or glycaemic responses to the diets directly, it did assess the response to a sucrose load (2 g/kg) after adaptation to the diets. Subjects required more insulin to achieve equivalent levels of blood glucose when they consumed sucrose than when they consumed starch, suggesting that they were less insulin-sensitive on the sucrose diet. However, data presented show that this was only apparent among the 9 subjects who were hypertriglyceridaemic or potentially carbohydrate-sensitive, while the normal subjects showed no significant effect of diet on their insulin response to the sucrose load. A subsequent paper (Reiser et al., 1980) reported evidence for a possible mechanism for the hyperinsulinaemic response to a sucrose load in sucrose-adapted individuals, showing that secretion of the enteric hormone glucose-dependent insulinotropic polypeptide (GIP; an insulin secretagogue) was higher in the sucrose condition. However, as the paper did not distinguish between carbohydrate-sensitive and normal subjects, it is not clear to what extent this applied to the latter. As noted in the previous section on lipid outcomes, the gorging pattern of sucrose delivery in this study may have exaggerated the metabolic effects.

Studies on Substituting Sucrose for Other Sugars

Only 3 studies in the review include data on the glycaemic responses of sucrose compared with other sugars and none indicated significant differences in metabolic response. In an early study of sucrose versus glucose among men living on an Antarctic Base camp (Fry, 1972), the AUC for blood glucose was the same for both diets although the pattern of response was slightly different; blood glucose levels were slightly higher at 30 min for sucrose but declined more rapidly. Bosetti et al. (1984) comparing sucrose with fructose found no differences in fasting glucose or insulin, or the ratio of insulin to glucose, at 7 or 14 days at the modest levels used (15% energy), while the study of Aeberli found that fasting glucose was similar for the sucrose, fructose, and glucose conditions.

Studies Involving Sucrose Replacing Fat or a Combination of Nutrients

Three studies examined outcomes related to glucose and/or insulin response (Tables 5 and 8). One metabolic ward study in healthy young men aged 18–22 years found that a supraphysiologic level of sucrose over a relatively short time period resulted in an improvement of glucose tolerance. Increasing sucrose content to 40% for 4–5 days improved both oral and intravenous glucose tolerance compared with a control/normal diet (17:43:40 protein:fat:CHO; Anderson et al., 1973). Glucose tolerance continued to improve with the 80% sucrose diet administered for up to 65 days, an effect accompanied by a reduction in fasting plasma insulin. The authors suggested that high CHO diets may increase insulin sensitivity in these normal individuals, possibly by enhancing activity of the important glycolytic and pentose phosphate pathway enzymes in various tissues. They contrasted their results in normal men with those in HTG patients, in whom abnormalities of lipid and glucose metabolism frequently occur together, suggesting that these may not be causally related but rather separate manifestations of a more basic underlying abnormality (Anderson et al., 1973). Another study using a much more modest increase in sucrose intake (by 40 g/day) coupled with a reduced fat intake to maintain energy balance had no effect on fasting plasma glucose, serum insulin, or insulin responses over 8 weeks (Erkkilä et al., 2007). The third study (Brynes et al., 2003) is described in the section "ad libitum studies."

Overall, the studies included in our review do not provide evidence of any consistent difference between sucrose and starch or other carbohydrates in respect of the basic markers of insulin sensitivity. Short-term studies of post-prandial and diurnal metabolism offer a more precise means of assessing metabolic effects using more sophisticated assessment methods such as the hyperinsulinaemic, euglycaemic clamp. These also suggest that 24 hr AUC for insulin may be comparable but patterns of response may differ (Daly et al., 1998). As yet there is no evidence to determine which feature (post-prandial elevation or 24 hr AUC) has more influence on metabolic health over the longer term (Daly, 2003).

Ad libitum studies

One of the questions raised by ad libitum and noneucaloric studies is whether the outcomes observed are attributable to altered energy intake. In a series of papers from the same Danish study of 20 women, Raben et al. (1997, 2001) and Marckmann et al. (2000) investigated the effects of 3 diets (high fat, high sucrose, high starch) each fed for 2 weeks in a crossover design with 2 or more weeks washout period in between. The sucrose diet (23% sucrose energy) and starch diets (2.5% sucrose energy) were matched for total carbohydrate (59%) and fat (29%) but the high sucrose diet was higher in SFA and dietary cholesterol and lower in fibre (20 g vs. 31 g). Energy intake was lower (−1.2 MJ/day) on the starch diet resulting in a slight (0.7 kg) weight loss overall, although whether this (and the differences in fatty acid composition) are consequences of the switch in carbohydrate source is a moot point. The high sucrose diet resulted in higher TG levels (20% higher fasting and 50% higher nonfasting) and 10% higher LDL-cholesterol levels compared with the starch diet (Marckmann et al., 2000). However, the difference in fasting TG levels was found to be nonsignificant after correction for the unintended differences in body weight and energy and nutrient intake between the groups (Raben et al., 2001). The authors commented that a high sucrose diet may lead to an undesirable lipid profile possibly due to fructose effects on TG production in the liver, on VLDL production and clearance. This study is one of few to investigate effects on clotting factors and found a 10% increase in nonfasting Factor VIIc but no significant effect on fibrinogen. After 14 days on the high sucrose diet, 24 hr energy expenditure as well as post-prandial plasma adrenaline

and noradrenaline concentrations were significantly increased compared with the other two diets, although with no untoward effect on blood pressure (Raben et al., 1997). In this case, the subjects were in energy balance on the sucrose diet and the improved lipid profiles on the starch diet could be due at least in part to a (spontaneous) reduction in energy intake in that phase.

By contrast, the ad libitum crossover study of Brynes et al. (2003) found no difference in fasting glucose or HOMA between low GI/High GI or high sucrose diets at day 24, although there were post-prandial differences. Subjects in this study were middle-aged men who were healthy but at slightly increased risk because of overweight, high waist circumference, or high cholesterol levels and the high sucrose diet contained approximately 22% energy from sucrose. The high sucrose diet had effects intermediate between that of the low GI and high GI diets but only the high GI diet appeared to increase post-prandial IR. Although instructed to maintain weight, men tended to lose weight on the low GI diet (−0.27 kg) and gain weight on the other diets and this may have influenced the results.

Hypocaloric Diets

Surwit et al. (1997) studied the effect on metabolic parameters of a high sucrose (43%) diet compared with an isocaloric low sucrose (4%) diet in a hypocaloric context for 6 weeks among 60 overweight women. The diets were very low in fat and high in carbohydrate (protein, fat, CHO ratios = 19:11:71) and both provided approximately 4606 kJ/day. Both groups had similar fasting plasma glucose levels, achieved a similar weight loss, and showed a decrease in percentage body fat, blood pressure, resting energy expenditure, and plasma lipids. Thus, as long as a low fat, low calorie diet can be adhered to, a high sucrose content (>40%) does not appear to adversely affect weight loss, metabolic rate, or plasma lipids. The findings of this study and the ad libitum studies above would suggest that metabolic effects may be more strongly related to energy balance than carbohydrate type and in the eucaloric (weight maintaining) or hypocaloric situation there are few adverse effects of sucrose.

DISCUSSION

Limitations of the Data

Studies demonstrated a high degree of heterogeneity in design and quality. Most were on small numbers of subjects (only 7 studies used more than 20 adults) and, given the variation in response between individuals, may have been underpowered. Thus, for example, most studies involving both men and women did not distinguish results by gender. Second, there were few studies (3) reporting specifically on women, and only one was both isocaloric (between diet groups) and eucaloric (weight maintaining) and this found no effect on plasma lipids (Behall et al., 1980). The ad libitum and hypocaloric studies have been included because they offer insights into the possible impact of changing dietary composition in the real world, although confounding effects have to be borne in mind in interpreting the findings. Lack of control over diet composition is also a more general issue for studies involving real foods. Thus in some cases, manipulation of sucrose content also allowed carbohydrate, protein, or fat content to differ between treatment groups, while in others diets were matched in regard to macronutrient composition (fat:protein:carbohydrate) but differed in regard to SFA, PUFA, or fibre content. Thus, some of the observed effects could be due to confounding by other dietary constituents. In our view the evidence is too poorly defined and heterogeneous to derive reliable conclusions on any sucrose substitution except that with starch.

Limitations of the Review Process

By excluding studies lasting less than 3 days, the protocol omitted studies of post-prandial and 24 hr metabolism, except where these were investigated as part of a longer study (i.e., adapted individuals). Nevertheless, results from included studies suggest that there may be subtle differences in the time course of post-prandial response to sucrose compared with other macronutrients. The clinical significance of transient elevations in plasma lipids and glycemia/insulinemia and the levels associated with increased risk of metabolic disease remain uncertain and their discussion beyond the scope of the current review.

Studies specifically on fructose were also outside the scope of the search strategy, but it is apparent from the large number of recent reviews on fructose that these studies may have implications for sucrose, which is the major source of dietary fructose worldwide. Some groups have hypothesized that high fructose consumption results in increased visceral adiposity, lipid dysregulation, and also IR (Stanhope and Havel, 2010) and that fructose has similar effects to sucrose (Stanhope et al., 2009), while others conclude that evidence of adverse effects is lacking at normal dietary fructose levels (Livesey, 2009) and that excess calories are more important (Tappy et al., 2010). It has been suggested that there is limited evidence for adverse effects of fructose at intakes <50 g/day or 10% of energy for a 2000 kcal diet (Livesey and Taylor, 2008), equivalent to 100 g sucrose or sucrose at 20% of energy intake.

Validity

By focusing on human intervention studies in adults without diagnosed CVD, diabetes, or NIDDM, we have tried to avoid what we consider a major threat to validity, that of drawing conclusions based on subjects with preexisting metabolic abnormality. However, in a number of studies subjects had elevated blood lipids at the start of the study (Dunnigan et al., 1970; Nestel et al., 1970; Mann et al., 1972; Wu and Shreeve, 1975; Reiser et al., 1979a, 1979b, 1980; Behall et al., 1980),

were overweight or obese (Nestel et al., 1970; Wu and Shreeve, 1975; Behall et al., 1980; Black et al., 2006), or were moderately insulin resistant (Black et al., 2006). Hence, whether the conclusions of this review are indeed applicable to the "normal" disease-free population of young- and middle-aged adults with a range of body weights is debatable. Such factors and others such as genetics and lifestyle may modify the response to dietary change (Hellerstein, 2002). Nevertheless, there appeared to be heterogeneity in subject response even among apparently healthy individuals. One of the most reproducible findings was that increases in plasma TGs tended to be correlated with baseline levels. This raises the question as to whether subjects with high baseline levels should be excluded from analysis in studies or whether they should be considered as part of the normal distribution. It is our view that results for all subgroups should be reported separately where power permits. This was mostly followed, although in a few studies (and also in some reviews) there was evidence of possible reporting bias where conclusions were based on selected subgroups.

A further cause of confounding that affects interpretation and generalizability is weight loss or gain and energy deficit or excess during the study. Energy balance may be as (or even more) important than diet composition in promoting hyperlipidemia and IR, but whether diets high in sugar always result in higher energy intakes compared with diets high in starch or fat is not established; thus we have considered it legitimate to discuss ad libitum studies, with caveats.

Probably the major consideration in evaluating the generalizability of findings is the realism of the sucrose levels used in interventions. Very high sucrose intakes (exceeding 30% energy) were associated with elevations in plasma TG and/or VLDL in most studies (Nestel et al., 1970; Anderson et al., 1973; Naismith et al., 1974; Wu and Shreeve, 1975; Reiser et al., 1979a; Hayford et al., 1979; Albrink and Ullrich, 1986; Yudkin et al., 1986). However, two studies in women showed no effect (Behall et al., 1980; Surwit et al., 1997). Protocols involving diets with less than 30% energy from sucrose tended to show no significant effect on fasting TGs (Dunnigan et al., 1970; Mann and Truswell, 1972; Roberts, 1973; Grande et al., 1974; Lock et al., 1980; Fraser et al., 1981; Bossetti et al., 1984; Albrink and Ullrich, 1986; Brynes et al., 2003; Black et al., 2006; Aeberli et al., 2011). Those that did report adverse effects included a 22-week study on men (Mann et al., 1972) and the ad libitum studies of women by Marckmann et al. (2000) and Raben et al. (2001) in which confounding due to weight change and differences in diet composition make it difficult to draw conclusions.

Evidence for TC and LDL were similarly conflicting: 4 studies using >30% sucrose suggested adverse effects (Naismith et al., 1974; Reiser et al., 1979a,b; Albrink and Ullrich, 1986; Yudkin et al., 1986), while 3 did not (Wu and Shreeve, 1975; Behall et al., 1980; Surwit et al., 1997). More moderate levels of sucrose (<30%) were associated with small effects on cholesterol in 5 studies (Roberts, 1973; Lock et al., 1980; Fraser et al., 1981; Marckmann et al., 2000; Black et al., 2006) but not in 7 others (Dunnigan et al., 1970; Mann and Truswell, 1972; Grande et al., 1974; Bossetti et al., 1984; Albrink and Ullrich, 1986; Brynes et al., 2003; Aeberli et al., 2011). Effects on HDL were purportedly adverse in 2 studies at high levels of sucrose (>30%) versus starch (Albrink and Ullrich, 1986; Yudkin et al., 1986) although others found no significant effect (Behall et al., 1980; Marckmann et al., 2000; Black et al., 2006). One study reported changes in components of the atherogenic lipoprotein profile, including LDL particle size, not accompanied by increases in other CVD risk factors (Aeberli et al., 2011). Confirmation of these findings and their significance is awaited as these proposed markers have yet to be shown to be associated with CVD risk by prospective studies in a general population cohort.

In the United States, an estimated 15% of total energy intake is derived from "added sugars" (Marriott et al., 2010). However, intakes are higher among adolescents (mean 21.4%) and, according to NHANES data (1999–2004), 32% of adolescents' diets exceed 25% energy from added sugars. By comparison, population mean intake of sucrose (the main form of added sugars across the world) ranges from 8% to 17% of total energy in Europe (Elmadfa, 2009). In the UK, mean sucrose intake, calculated from National Diet and Nutrition Survey data for 2008–2010, was approximately 8% of energy for adults and 10% of energy for children, or 17% at 95th percentile and 19% at the 97.5th percentile for both age groups. Only 4 out of 2126 individuals consumed >25% energy from sucrose (S. Gibson, unpublished). Thus, current mean intakes are well below the level at which adverse effects on metabolic health were observed in this review. Nevertheless, adults with sucrose intakes >25% will likely have added sugar intakes of >30% and might benefit from reduction, especially if they have preexisting metabolic conditions or central obesity. However, it would be unwise, on the basis of current evidence, to place more emphasis on dietary sugars intake than on physical fitness, weight control, and a healthy balanced diet, which have well-established benefits on cardiometabolic risk factors.

Although relatively few studies examined the effects on blood glucose and insulin, there was little evidence of adverse effects on plasma glucose and some evidence of improved glucose tolerance on diets high in sucrose compared with starch (Kiens and Richter, 1996; Raben et al., 2001; Black et al., 2006). Fasting insulin, which is a better risk indicator than plasma glucose for impaired insulin action or reduced insulin sensitivity, was only found to be higher with the sucrose diet in one study whose subjects were potentially carbohydrate-sensitive (Reiser et al., 1979b), while other studies found no effect or even a beneficial effect (Dunnigan et al., 1970; Mann and Truswell, 1972; Kiens and Richter, 1996; Brynes et al., 2003). Moreover, the large bolus of sucrose (90% of the total given at one meal) in the studies by Reiser et al. is not representative of normal meal patterns.

Strength of Effect

It is important to distinguish between statistical significance and clinical significance. As noted above only around half the

studies reported effects on TG to be statistically significant and for those in healthy adults consuming <30% sucrose, the actual elevation was typically of the order of 10–20%, although not always quantified. This is similar to normal day-to-day variation but the increment indicative of increased risk remains a matter of debate (Parks and Hellerstein, 2000). For cholesterol (total or LDL), differences ranged from nil to 25%, but in some cases this was confounded by higher SFA and cholesterol content in the high sucrose diet.

Conclusions and Further Research Needs

From the studies reviewed, it would appear that a moderate dietary sucrose intake at levels up to 25% of energy appears to have no significant adverse effects on lipid or carbohydrate metabolism in normal healthy adults when substituted for starch, at least in the medium term (several weeks). This conclusion is slightly more conservative than that of Truswell (1994), who concluded that the evidence then available allowed a limit of 30% before effects on lipid parameters became apparent in some studies. However, there is a paucity of evidence for dose levels between 25% and 30% from sucrose and we have been reluctant to dismiss entirely the studies by Reiser et al., despite reservations as to their generalizability to the normal healthy population's eating habits. Insufficient data are available to draw reliable conclusions on the effect of substitution of sucrose for other macronutrients, although evidence of any detrimental effect is limited.

While mean intakes of sucrose in most populations are well below the 25% energy level, data are needed on the distribution of sucrose (and fructose) intakes in order to identify vulnerable groups. On our estimates, less than 0.5% of the UK population are consuming sucrose at this level, but the proportion may be higher in other groups.

New research appears to be focusing on the metabolic effects of fructose as the component purported to be responsible for adverse effects of sucrose. Fructose at high doses has been observed to increase de novo lipogenesis and reduce VLDL-C/TG clearance and more recently to increase ectopic fat accumulation (Stanhope et al., 2009). More studies are needed that directly address possible effects of moderately high intake of sucrose on atherogenic lipoprotein phenotype and other indicators of risk of CVD and metabolic syndrome, including inflammatory markers and endothelial function. Longer-term interventions are needed to establish whether any changes attenuate, persist, or worsen over time and how they are related to IR and visceral adiposity. There is a need to differentiate between subjects at high and low risk and to use healthy adults rather than those in whom metabolism already shows evidence of dysregulation. Studies are especially needed among women of different ages, hormonal status, and body fat distribution. The physical form of sucrose consumed (liquid beverages vs. solid sugary foods), meal size and rate of consumption may be important in relation to post-prandial metabolism, which has not been studied in this review. Finally, intervention studies are desirable to compare the relative impact on CVD risk factors of dietary change with that of changes in body weight and exercise, as these are the two modifiable physiological factors that appear to have greatest impact on response to dietary carbohydrate (Hellerstein, 2002).

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