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Evidence-Based Review on the Effect of Normal Dietary Consumption of Fructose on Blood Lipids and Body Weight of Overweight and Obese Individuals

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Although some investigators have hypothesized that ingestion of fructose from foods and beverages is responsible for the development of hyperlipidemia or obesity, a recent evidence-based review demonstrated that there was no relationship between the consumption of fructose in a normal dietary manner and the development of hyperlipidemia or increased weight in normal weight individuals. Because overweight and obese individuals may exhibit metabolic abnormalities such as insulin resistance, impaired glucose tolerance, hyperlipedemia, and/or alterations in gut hormones involved in appetite regulation, the findings of fructose studies performed in normal weight subjects may not be particularly relevant for overweight or obese subjects. A systematic assessment of the strength and quality of the studies and their relevance for overweight or obese humans ingesting fructose in a normal dietary manner has not been performed. The purpose of this review was to critically evaluate the existing database for a causal relationship between the ingestion of fructose in a normal, dietary manner and the development of hyperlipidemia or increased body weight in overweight or obese humans, using an evidence-based approach. The results of the analysis indicate that there is no evidence which shows that the consumption of fructose at normal levels of intake causes biologically relevant changes in triglycerides (TG) or body weight in overweight or obese individuals.

Keywords Triglycerides, fructose, body weight, obesity, human

INTRODUCTION

Fructose is naturally present in many fruits and is used as an added sweetner in some beverages. The average daily intake of total fructose has increased from 37 g/day in 1978 (Park and Yetley, 1993) to 49 g/day in 2004 (Marriott et al., 2009), predominantly due to increased use of fructose as an added ingredient. Concurrent with the increased use of fructose and other sugars in the diet, there has been an increase in obesity and diseases associated with obesity such as Type II diabetes (referred to henceforth as diabetes) or heart disease. Numerous studies have been conducted in humans to determine whether there is a causal relationship between the consumption of fructose and weight gain or alterations in carbohydrate or lipid metabolism that have been associated with obesity or obesity-releated diseases. A recent evidence-based review conducted to analyze the entire database of studies performed in healthy, normal weight humans indicates that after ingestion of 30–100 g/day fructose, sucrose, glucose, or starch (either in a liquid bolus or in a meal), transient increases in plasma TG occur, that are slightly higher with fructose than other types of carbohydrate (Dolan et al., 2010). There is, however, no evidence which suggests that fasting plasma TG levels are increased after long-term ingestion of up to 133 g/day fructose in women and 136 g/day fructose in men (95th percentile levels of intake). Additionally, there is no evidence which indicates that ingestion of fructose at levels approaching 95th levels of intake is associated with an increase in food intake or body weight in normal weight individuals.

Because a large percentage of the population is overweight or obese, it is of interest to conduct a similar, evidence-based review of studies involving overweight or obese subjects. Therefore, the purpose of this review is to use an evidenced-based

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system to determine if a causal relationship exists between the consumption of fructose in a normal, dietary manner and the development of alterations in lipid metabolism or body weight (BW) gain in overweight or obese individuals**.** Like the previous review (Dolan et al., 2010), this evidence-based review is based on the guidance developed by FDA for an evidence-based review of health claims. The same study criteria were evaluated as described in Dolan et al. (2010) with the exception here, that the population of interest was overweight or obese subjects instead of normal weight subjects.

EVIDENCE-BASED REVIEW

FDA Guidance for Evidence-Based Review

The US Food and Drug Administration (FDA) published guidance for health claim petitioners in January 2009 (FDA-CFSAN, 2009). This guidance was created to help manufacturers determine if claims can be substantiated by the totality of all available, credible evidence.

Based on the guidance provided by FDA (2009), only those studies for which conclusions about a substance/disease relationship can be drawn should be reviewed. Studies should then be evaluated by the following criteria:

- Type (human intervention and observational studies will take priority over other types)
- Methodological quality
- Totality of evidence for and against the claim

In an intervention study, a designated quantity of the substance of interest is provided to subjects either in the form of a conventional food or dietary supplement. According to FDA, human intervention studies are the most reliable category of studies for determining a cause-and-effect relationship because the substance is provided under a controlled environment. Information from a poorly designed intervention study from which no scientific conclusions about the substance/disease relationship can be drawn should not be considered. Intervention studies should undergo an initial evaluation for the following critical elements:

- if the mechanism of action of the substance in a diseased population is the same as that of a non-diseased population; and the disease that is the subject of the claim is the primary endpoint;
- the study included an appropriate control group similar in all aspects to the experimental group (with the exception of the substance);
- the study was designed to measure the independent role of the substance in reducing the disease;
- relevant baseline data were not significantly different between groups;
- appropriate statistical analyses were performed;
- valid biomarkers of disease risk were measured; the length of the study was sufficient; the study included a follow-up assessment of change in intake (if the intervention involved dietary advice) and;
- the study population was relevant for the general U. S. population or the population subgroup identified in the proposed claim.

Each study passing the initial evaluation should then be evaluated for methodological quality (i.e. how well the study was designed and outcomes were determined). A number of factors should be considered during this second phase of the evaluation procedure including:

- whether the studies were randomized, blinded, and/or placebo controlled;
- if inclusion/exclusion criteria and key information on the characteristics of the study population were provided (in order for potential mitigating factors to be identified);
- whether subject attrition was assessed, explained, and reasonable;
- if the study included a mechanism for compliance verification; if statistical analyses were performed on all subjects (including dropouts);
- whether the study measured the actual onset of a disease or a risk factor in its development or whether the onset of the disease was confirmed through medical records or pathology reports (preferred) or less specific methods such as death certificates.

Depending on the degree to which each of these methodological factors is addressed, the study should be given a high, moderate, or low quality rating. Studies that are so deficient in methodological quality that conclusions cannot be drawn about the substance/disease relationship should be eliminated from further review.

In contrast to intervention studies, observational studies measure associations between the substance and disease, rather than the cause and effect between an intervention and an outcome. In the guidance document, FDA states that "because of the limited ability of observational studies to control for variables, they are often susceptible to confounders." Therefore, observational studies are not considered to be as reliable as intervention studies. However, per FDA, "observational studies from which scientific conclusions can be drawn, in some situations, can be support for a substance/disease relationship for a significant scientific agreement (SSA) or qualified health claim" (FDA-CFSAN, 2009).

As part of an evidence-based review system, observational studies should be evaluated for the substance/disease relationship by demonstrating: evidence of intake (i.e. do biological samples (e.g., blood, urine, feces) demonstrate a strong correlation between the intake of the material and the concentration of the substance or metabolite in the sample?); use of scientifically

acceptable and validated dietary assessment methods and; use of a quantifiable amount of the actual material of interest (preferred) versus a whole food containing ingredients other than the material of interest.

Observational studies that pass this initial screening should also be graded for methodological quality (low, moderate, or high) by (1) assessing whether potential confounders of the disease of interest were adjusted for and if (2) food frequency questionnaires were utilized to estimate dietary intake (preferred) rather than single, 24-hour diet recall or diet records.

In the aforementioned guidance document, FDA (2009) stipulates that reports which discuss a number of different studies in limited detail (such as review articles) should only be used to "identify reports of additional studies that may be useful to the health claim review and as background about the substance/disease relationship." The reports should not be used as a source of information for studies performed on the material of interest because "the critical elements of a study must be reviewed to determine whether any scientific conclusions can be drawn from it." Animal and in vitro studies can be used to support a hypothesized mechanism, but cannot be used to draw any conclusions about the relationship between the substance and disease in humans.

After reviewing each study for quality, the totality of the database should be examined to determine if it is credible enough to support a cause and effect relationship. Within each study type (e.g. intervention, prospective cohort, case-control, or cross-sectional), the studies should be reviewed for the number of studies and subjects per group, methodological quality (high, moderate, or low), outcome (e.g. statistically significant beneficial effect, no effect, or adverse effect), consistency, and relevance to the general U. S. population.

In general, observational studies should not be used to rule out the findings from intervention studies because observational studies are only able to identify possible associations and do not demonstrate a cause and effect. However, findings from one intervention study should not rule out consistent findings from several observational studies.

Principles mentioned in this guidance (FDA-CFSAN, 2009) were used to critically examine the existing database on the relationship of normal dietary fructose intake to alterations in lipid and/or glucose metabolism and body weight gain in overweight or obese subjects.

LITERATURE SEARCH AND STUDY SELECTION

Strategy for Literature Search

The first step of the evidence-based review was to develop a means of obtaining all relevant, published literature on the relationship between fructose intake and changes in lipid or carbohydrate metabolism that could potentially lead to hyperlipidemia and/or body weight gain. Literature searches were limited to studies conducted in humans, because the guidance on which this review is based (FDA-CFSAN, 2009) indicates that in vitro and experimental animal studies should not be used to draw any definitive conclusions about the relationship between the substance and disease in humans. The searches were also limited to overweight or obese individuals ingesting fructose in order to determine whether a cause-and-effect relationship existed between fructose intake and changes in lipid or glucose metabolism and/or body weight in this population. Studies in which fructose was administered parenterally were excluded from the search.

A comprehensive search of the published literature was performed in SCOPUS, a registered trademark of Elsevier B.V., and the largest abstract and citation database of research literature and quality web sources and is available by subscription only. The following search string was utilized: [((TITLE-ABS-KEY(fructose AND (glyceraldehyde OR triglyceride OR triacylglycerol OR lipid OR cholesterol) AND (overweight OR over-weight OR obese OR "body mass index" OR bmi OR "body fat" OR adiposity) AND (human* OR subject* OR volunteer* OR patient* OR women OR men OR children OR individual* OR adult* OR adolescent*) AND (oral OR fed OR intake OR meal OR diet*) OR (TITLE-ABS-KEY(fructose AND ("body weight" OR diabetes OR "blood glucose" OR obesity OR insulin) AND (overweight OR over-weight OR obese OR "body mass index" OR bmi OR "body fat" OR adiposity) AND (human* OR subject* OR volunteer* OR patient* OR women OR men OR children OR individual* OR adult* OR adolescent*) AND (oral OR diet* OR fed OR intake OR meal))]. An additional literature search was performed in Pub Med (US National Library of Medicine, Bethesda, MD. Available online at http://www.ncbi.nlm.nih.gov/sites/entrez), using the terms [fructose AND (overweight OR obes*) AND human AND NOT review]. All searches were conducted on February 25 and 26, 2010.

Studies that were utilized for the analysis performed in Dolan et al. (2010) also were scrutinized to identify additional studies that may have included overweight or obese subjects in the overall study population or subsets of overweight or obese subjects, based on currently accepted definitions. For the current analysis, body mass index (BMI) values provided by the World Health Organization (WHO) (2006) were used to define overweight (BMI 25.0–29.9 kg/m^2) and obese ($\geq$30 kg/m^2). BMI values were calculated if they were not provided. Alternate criteria used by authors of the individual studies to classify subjects as overweight or obese (e.g. percentage of body weight above "normal" or "ideal") were analyzed to determine if any of the subjects were overweight or obese. As indicated by Kuczmarski and Flegal (2000), some agencies have considered BMIs ranging from 25–30 kg/m^2 as "desirable," "normal," or "healthy." For Dolan et al. (2010), studies using subjects with BMIs ranging from 25–30 kg/m^2 were included, because the authors of the studies considered the subjects to be within the range of normal, healthy, or ideal weight for their age. Studies using subjects with BMI $\geq$30 kg/m^2 and underlying diseases were excluded from Dolan et al. (2010). For the current analysis, participants with

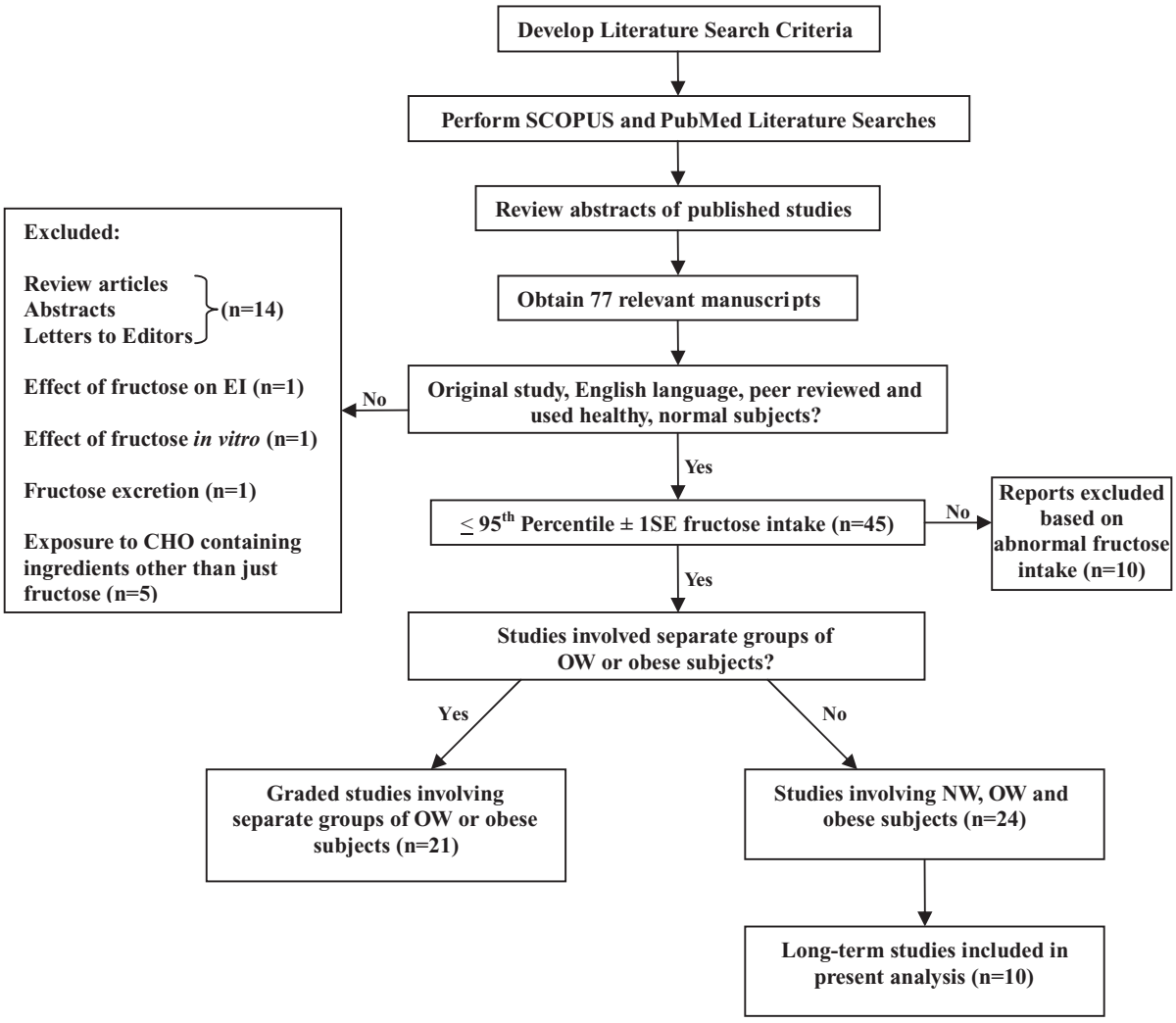

Figure 1 Summary of the decision process for retrieval and inclusion of literature (CHO = carbohydrate; EI = energy intake; n = number of articles; NW = normal weight; OW = overweight; SE = standard error).

underlying disease states (such as diabetes, hyperlipidemia, or heart disease) were included if they met the current criteria for being overweight (BMI = 25.0–29.9 kg/m^2) or obese (BMI ≥30 kg/m^2).

Study Selection Criteria

A review of abstracts of the studies obtained in the searches identified a total of 77 published manuscripts mentioning the clinical effect of fructose consumption on blood lipids or glucose, insulin, body weight, or obesity in obese or overweight subjects (Fig. 1).

The 77 studies identified by the search were obtained, reviewed, and evaluated. The 14 review articles, abstracts, or letters to editors (depicted in Table 1) were used for background information, but were not used as a source of information for studies performed on the material of interest, because according to the FDA review system, the critical elements of a study must be presented in order for one to determine whether any

Table 1 Review articles, abstracts, or letters to the editor identified by the literature search*

Reference
Diaz et al. (2006)
Downes Gastrich et al. (2008)
Fried and Rao (2003)
Havel et al. (2003)
Havel (2005)
Jones (2009)
Segal et al. (1996)
Stanhope et al. (2007)
Stanhope and Havel (2008)
Stanhope and Havel (2009)
Schwarz et al. (1994)
Tappy and Jequier (1993)
Teff et al. (2005)
Zimmermann and Aeberli (2008)

*Used only for background information.

scientific conclusions can be drawn from it. These elements are not present in reviews; therefore the review articles were not evaluated for the effect of fructose on biomarkers of obesity or disease. No additional studies were identified in these reviews that were relevant to the evaluation. An additional eight studies were excluded from the analysis because they examined the energy intake from fructose only (Endres et al., 1989), the effect of body weight on excretion of fructose (Joosen et al., 2008), or the effect of fructose on liver in vitro (Kral et al., 1977), or examined the effect of fruit (or fructose in combination with other carbohydrates) on the study variables (Wolever et al., 1995; Yip et al., 2001; Lofgren et al., 2005; Rodríguez et al., 2005; Crujeiras et al., 2006). Of the remaining 55 references, 26 were previously evaluated in Dolan et al. (2010).

The 55 references were reviewed and the levels of fructose ingested in each study were calculated based on: the quantity (g/day), the percentage of energy, and the percentage of carbohydrate intake. Of these, ten studies involving concentrations of fructose higher than a predetermined cutoff value for normal consumption were rejected from the analysis (Table 2). Data from a recent study published by Marriott et al. (2009) were used to establish the cutoff value, prior to review of any of the other literature. In the Marriott et al. (2009) study, the mean daily intakes of fructose were determined using NHANES 1999–2004 dietary intake data for 25,165 individuals, aged 1 year and older. Groups were classified according to gender and age (9–13, 14–18, 19–30, 31–50, 51–70, and 71+ years). Mean fructose intakes from the highest groups of 95th percentile consumers (plus one standard error) were used as cutoff values. Consumption at percentiles higher than the 95th was not reported in this study. Based on the absolute amount, the percentage of energy intake, and the percentage of carbohydrate intake, the 95th percentile consumption values are 136.1 g/day (in 19–30 year old males), 18.8% (in 19–30 year old females), and 29.2% (in 19–30 year old females), respectively. The 95th percentile fructose consumption (plus or minus one standard error) of males aged 19–22 (as an absolute amount) also is reported (134 ± 12.2 g/day) in the Marriott et al. (2009) study. Because this intake is higher than that of 19–30 year old males, an absolute value of 146 g/day was used as the cutoff value (if the study included 19–22 year old males rather than 19–30 year old males). Using the 95th percentile values (plus one standard error) as intake limits for normal consumption is a reasonable assumption, based on the fact that FDA recognizes 90th percentile intake estimates as upper limits of intake of dietary ingredients when evaluating dietary ingredient notifications. Ninetieth percentile intake estimates are commonly compared to concentrations of dietary ingredients used in safety studies to determine if adverse effects could occur in humans under normal conditions of use. We acknowledge that by limiting our analysis to 95th percentile consumers (plus one standard error) we are omitting data that are pertinent for consumers of fructose at the 96th–100th percentile levels; however, intakes of any food ingredient higher than the 95th percentile would not be considered normal by authoritative bodies.

Study Grading Criteria

A total of 45 studies involving fructose consumption at ≤95th percentile levels were graded according to the following set of criteria, which were developed by the authors based on 1) the criteria developed by the FDA for an evidence-based review of data for health claims; 2) FDA guidelines for the conduct of human studies to demonstrate safety of food ingredients (FDA-CFSAN, 1993); and 3) an understanding of factors that could affect the outcome of studies examining the effect of fructose on human health.

As mentioned previously, the evaluation system used by the FDA is designed to assess the beneficial effects of a dietary ingredient on health, rather than harmful effects. The FDA evaluation system does not provide guidance on the scale that should be used to evaluate studies, point values that should be assigned to certain variables, or the scores associated with low, moderate, or high quality studies. The FDA evaluation system was used to provide a framework for an evidence-based grading process for studies investigating the adverse effects of fructose, which we developed. Because intervention studies are considered to be more reliable than observational studies (FDA-CFSAN, 2009), studies of these two types were evaluated for quality on a different scale.

Intervention Study

The ability of each study to meet the individual factors indentified below as being important criteria was graded on a 2-point scale developed by the authors (minimum = 0; maximum = 2). The factors are based on the FDA criteria for an evidence-based review of human study data, as well as an understanding of the factors which may confound the results of studies examining the effect of fructose ingestion on the parameters measured in the study. The maximum number of points that could be obtained from an intervention study was 40. Based on the total point score, each intervention study was given a low (<20), moderate (20–29), or high quality grade (≥30). In addition to evaluating the strength of each study, we have included a short description of each study meeting the criteria and its interpretation.

I. Subjects
   A. Sufficient number? Studies that used at least ten subjects/group or a number of subjects calculated to be sufficient for uncovering a statistically significant effect were scored higher than others.
   B. Clinically shown to be disease free? Studies that used subjects clinically shown to be free of diseases that could influence outcome such as heart, liver, or kidney disease, hypertriglyceridemia or diabetes were scored higher than those that did not exclude such subjects.
   C. Overweight or obese based on a clinical diagnosis? Studies that classified individuals according to BMI were scored higher than those that classified subjects according to body weight only (or did not provide a rationale for their classification).

Table 2 Intervention studies not meeting inclusion criteria[a]

Fructose (grams/day)	%Total Energy Intake	% CHO Intake	Comments	Reference
300	49.8% (calc avg)	46% (calc avg)	Five subjects with CHTG (three OW) or four normal subjects (one OW) ingested 300 g fru or 300–350 g starch throughout day for 10–38 days. Avg (± SD) BMI = 25.58 ± 1.10 kg/m^2 in CHTG group and 22.9 ± 3.14 kg/m^2 in normal group. Abdominal pain and diarrhea observed with fru. TG fru > TG starch in 3/5 subjects with CHTG (one of which was OW). TG fru = starch in normal subjects. Two of three CHTG subjects that were OW lost weight and the other maintained weight while on fru, and the one OW subject without CHTG lost weight while on fru.	Kaufmann et al. (1966)
300	Cannot determine	50% (calc)	Same results and subjects as reported as in Kaufmann et al. (1966)	Kaufmann et al. (1967)
200	27%	74%	Normal diet plus fru (n = 36) ingested by OW M (avg. BMI (± SEM) 29.0 ± 0.6 kg/m^2) for 2 weeks. Fru ingested throughout the day. EI 2992 kcal/day for fru diet compared to 2414 kcal/day at BL. Ingestion of fru resulted in an increase in BW, liver function enzymes (GGT, AST, ALT), ambulatory BP, fasting TG, INS, and uric acid and a decrease in HDL-C (compared to BL). Nine initial subjects withdrew because of fru-induced diarrhea and abdominal cramping and 10/36 experienced abdominal side effects during treatment.	Perez-Pozo et al. (2009)
168	20%	40% (calc)	Fru or ST added to normal diet of 11 normal (avg. BMI = 24.4 kg/m^2) or 10 HI M (avg. BMI = 25.7 kg/m^2) for 5 weeks, followed by alternate treatment. EI 3260 kcal/day for fru diet and 3220 kcal/day for ST diet. Beneficial effect of fru on glu tolerance in both groups of subjects (compared to ST). HI M had a tendency towards decreased insulin sensitivity after fru. TG and BW not measured.	Reiser et al. (1989b)*
167	20%	40% (calc)	Fru or ST added to normal diet of 11 normal (avg. BMI = 24.4 kg/m^2) or 10 HI M (avg. BMI = 25.7 kg/m^2) for 5 weeks, followed by alternate treatment. EI for both diets was 3240 kcal/day. TG fru > TG ST (especially in HI M).	Reiser et al. (1989a)*
M: 163–176 (169 avg) F: 132–142 (137 avg)[b] M & F calc avg 153	25%	45% (calc)	Diet containing fru (9M, 8F) or glu (7M, 8F) administered over 10 weeks to OW or obese subjects (BMI = 25–35 kg/m^2). Fasting TG increased with glu but not fru (compared to BL). In M, postprandial TG increased with fru but not glu (compared to BL). Similar increase in BW between groups.	Stanhope et al. (2009)*
F: 147.7[c] M: 178.9[c]	30%	55%	Eight obese F (BMI = 34.7 ± 1.0 kg/m^2) and nine obese M (BMI = 34.5 ± 1.0 kg/m^2) were administered a diet based on each individual's energy requirement as estimated by the Mifflin equation, with 30% of the calories from fru or glu in beverage with 3 daily meals. Postprandial TG fru > TG glu (in total population, but not when analyzed according to sex).	Teff et al. (2009)
141 based on basal caloric intake of 1743 kcal/day[d]	25%	45%	Seven OW M (BMI = 26.1 ± 1.0 kg/m^2) with normal fasting TG ingested beverages containing fru or glu (at 25% EI) with 3 meals over 24 hours. TG fru = TG glu.	Stanhope et al. (2008)*
96–150; 135 (calc avg) Avg fru < 136.1[e]	30%	55%	F subjects (some OW, BMI = 19.8 – 26.7 kg/m^2) administered glu or fru at 30% EI in beverage with 3 daily meals providing a mean EI of 1804 ± 129 kcal/day. TG fru > TG glu throughout the day. No effect of fru (compared to glu) on hunger during the study or ad libitum food intake the day after the study.	Teff et al. (2004)*

129.9 (calc. avg) Avg fru < 136.1[f]	25%	52%	7 OW or obese (BMI = 26.8 – 33.3 kg/m^2) PMF (age 50–72 yrs) administered beverages sweetened with fru (at 25% of usual EI) with meals for a period of 10 weeks. All complex CHO was replaced with fru. Compared to BL, ingestion of the fru-containing diet led to decreases in BW, postprandial GLU and INS and increases in fasting GLU, apo B, and postprandial TG. No effect of fru on fasting blood lipids (TC, HDL-C, LDL-C, or TG).	Swarbrick et al. (2008)

*These studies were also discussed in Dolan et al. (2010).

apo B = apoprotein B; avg = average; ALT = alanine aminotransferase; AST = aspartate aminotransferase; avg = average; BL = baseline; BMI = body mass index; BP = blood pressure; BW = body weight; calc = calculated; CDC = Centers for Disease Control; CHO = carbohydrate; CHTG = carboydrate induced hyperglyceridemia; EI = energy intake; F = female; fru = fructose; GGT = *gamma* glutamyl transpeptidase; glu = glucose; GLU = plasma glucose; HDL-C = high density lipoprotein cholesterol; HI = hyperinsulinemic; INS = serum insulin; LDL-C = low density lipoprotein cholesterol; M = male; n = number; OW = overweight; PMF = postmenopausal females; SE = standard error; ST = starch; TC = total cholesterol; TG = triglyceride or triacylglycerol; yrs = years. Calculations were made using the following conversions; 1 g fru = 4 kcal energy; 1 kcal = 4.184 KJ energy; 1 g fru = 16.736 KJ energy.

[a]Inclusion criteria were fru intake <136.1 g/day, <18.8% of energy and <29.2% of CHO intake (for overall population) and <146 g/day (if study used 19–22 year old males); [b]Some F met one inclusion criterion for fru (<136 g/day); [c]Calculation based on BW calculated using avg BMIs for males (34.5 kg/m^2) and females (34.7 kg/m^2) and estimated avg heights from CDC Advance Data (Ogden et al., 2004); and Mifflin equations for males (REE (males) = 10 × weight (107.5 kg) + 6.25 × height (176.4 cm) - 5 × (39 years) + 5) and females (REE (females) = 10 × weight (92 kg) + 6.25 × height (162.8 cm) - 5 × (27 years) - 161) × activity factor of 1.2 (1969.8 kcal for F and 2385 kcal for M); [d]Determined by Mifflin equation (REE (males) = 10 × weight (89.3 kg) + 6.25 × height (cm) - 5 age × (years) + 5; avg height of 176.5 cm estimated from CDC Advance Data (Ogden et al., 2004) × activity factor of 1.3) = 2265 kcal; [e]Rejected because subjects were calorie restricted and given a larger amount of fru than 95th percentile intake for females. Caloric intake was approximately 200 kcal lower than that calculated for avg caloric intake of 19–30 year old females (2033 g/day) and fru intake > 95th percentile ± SE intake for highest group of F (108.2 g/day for 19–30 year old F) as determined by Marriott et al. (2009); [f]Calc based on average basal caloric intake of 2078.04 kcal/d (determined by REE from Harris-Benedict equation and activity factor of 1.5). Harris-Benedict equation: REE = 655 + 9.6 × 75.7 kg (avg. weight) + 1.8 × 161.3 cm (avg. height based on avg. BMI = 29.1 kg/m^2) – 4.7 × 61 yrs (based on range of 50–72 yrs). Rejected because subjects were given a larger amount of fru than 95th percentile intake for highest group of F (108.2 g/day for 19–30 year old F) and approximately two times the 95th percentile intake for 51–70 yr old F (65 g/day) as determined by Marriott et al. (2009).

D. Gender? Studies that used both genders with data analyzed together and separately were scored higher than others.
E. Age (wide or narrow)? Studies that used subjects with a wide range were scored higher than others because the subjects should be selected to reflect the general population.
F. Inclusion/Exclusion criteria (are potential confounders adjusted for)? Studies that excluded subjects whose use of drugs (including alcohol) could alter responses, as well as a history of eating disorders or dieting were scored higher than others. Those studies that also conducted physical examinations and laboratory tests to screen individuals with medically significant abnormalities from the clinical study were scored highest. Laboratory tests should include the following: electrocardiograph, urinalysis, and various tests on blood (e.g. complete blood counts, blood urea nitrogen, serum creatinine, tests of liver function, fasting blood sugar, electrolytes, protein, and albumin) and other tests that may be indicated by the nature of the test material (e.g. blood lipid profiles).

II. Conduct
A. Randomized? Randomized studies were scored higher than others. Methods of randomization should be described and analyses should be presented that demonstrate effectiveness of the methods (FDA-CFSAN, 1993).
B. Blinded? Scoring was as follows: double > single > non-blinded. Studies should be performed blind to avoid selection bias in patient and physician responses.
C. Crossover and/or proper control? Crossover studies that included a proper control group such as sucrose or glucose were scored highest, followed by crossover studies without a control.
D. Appropriate baseline parameters measured? Studies measuring glucose, insulin, blood lipids, and BW parameters at time zero were scored higher than those that did not measure all parameters.
E. Proper risk factor measured? Studies measuring body weight or several biochemical parameters associated with the development of obesity or effect on body weight, food intake, or satiety were scored higher than those only examining one biochemical parameter.
F. Proper statistical analysis? Studies utilizing analysis of variance (ANOVA) or a computer-based statistical program to analyze results were scored higher than those using multiple tests on repeated measured data.

III. Dosing
A. Dose appropriate (also volume appropriate if a liquid)? Studies employing a dose over the 95th percentile limit were rejected; also, studies utilizing large volumes of fructose in solution were graded lower than others, based on findings of Sievenpiper et al. (1998a; 1998b) that the glycemic response to fructose in solution is highly dependent on volume.
B. Given in bolus or throughout the day? Studies administering divided doses were scored higher than bolus dose studies conducted first thing in the morning.
C. Dosing for more than one day? Studies that were performed over multiple days were scored higher than those performed over a single day.
D. Different doses tested? Studies with more than one dose were scored higher than studies with a single dose.
E. Dose administered as liquid only, liquid with meal, or in solid food? Studies which used fructose incorporated into a normal (solid food) diet were scored the highest. Studies providing fructose in liquid form with a meal were scored higher than those providing fructose in liquid only.
F. Diet and beverage (other than water) intake controlled (all diets prepared)? Studies with prepared diets were scored higher than those with ad libitum diets.
G. Diets in studies provide similar amounts of energy? Studies with caloric intake adjusted for energy requirement of individuals (isoenergetic) were scored highest. Studies with equal energy intake in fructose and control diets (isocaloric) were scored higher than those with unequal energy intake.
H. Verification of compliance (intake) conducted in-house and if not, was compliance measured? Studies in which compliance was verified or intake was in-house were scored higher than outpatient studies with no evidence of compliance.
I. Reason for attrition explained? Studies were scored on attrition following: no attrition > explained attrition > unexplained attrition.

Observational Study

The maximum number of points that could be obtained from an observational study was 20. The ability of each study to meet the individual factors identified below as being critical criteria was graded on a 2-point scale (minimum = 0; maximum = 2). The factors are based on the aforementioned FDA criteria for an evidence-based review of human study data, as well as an understanding of the factors that may confound the results of studies examining the effect of fructose ingestion on the parameters measured in the study. Based on the total point score, each observational study was given a low (<10) or moderate (10–20) quality grade.

I. Subjects
A. Sufficient number? Studies in which the number of subjects used was calculated to be sufficient for uncovering a statistically significant effect were scored higher than others.

B. Clinically shown to be disease free? Studies that used subjects clinically shown to be free of diseases that could influence outcome such as heart, liver or kidney disease, hypertriglyceridemia, or diabetes were scored higher than those that did not exclude such subjects.
C. Overweight or obese based on a clinical diagnosis? Studies that classified individuals according to BMI were scored higher than those that classified subjects according to body weight only (or did not provide a rationale for their classification).
D. Inclusion/Exclusion criteria (are potential confounders adjusted for)? Studies that excluded subjects with potential confounders such as a history of use of drugs that could alter responses (including alcohol), as well as eating disorders, or smoking, were scored higher than others.

II. Conduct
A. Study Type (case report, cross sectional, or cohort)? Scoring: cohort > cross sectional > case report.
B. Proper risk factor measured? Studies that measured food intake or satiety were scored higher than studies that only measured a biochemical parameter strongly associated with the development of obesity or BW.
C. Proper statistical analysis? Studies that used multifactorial analysis and analyzed data according to quintiles of fructose intake were scored higher than those which just used regression.

III. Intake
A. Evidence of intake (e.g. fructose, glucose concentration in serum or urine)? Studies with biological evidence of intake were scored higher than those with none.
B. Was the content of the material in the food supply accurately determined? Studies using up-to-date, published nutrient database data were scored higher than those that used older or internally developed databases that were not based on published data.
C. Use of proper dietary assessment methods (24 hour dietary recall or food frequency questionnaire)? Studies utilizing assessment methods were scored higher than those without.

STUDY RESULTS AND DATA REVIEW

Studies Involving Both Normal Weight and Obese Subjects

As shown in Table 3, 20 studies that were previously evaluated in Dolan et al. (2010) used study populations that included both normal weight and overweight individuals. Four studies identified by the new search also included both normal weight and overweight individuals. Because responses were not analyzed according to body weight, one cannot determine from these studies whether responses in overweight subjects (or the few that may have been obese) were different from subjects who were normal weight (or underweight). Nonetheless, a number of these studies involved a substantial percentage of overweight subjects (as defined by BMI $\geq$25 kg/m^2 and $<$30 kg/m^2). Because the literature search identified relatively few studies that met the criteria for fructose intake and examined the effect of fructose on TG, BW or food intake in overweight or obese individuals only, data for the ten studies that involved normal weight, overweight, and obese individuals and measured the aforementioned variables were included in the analysis (Macdonald, 1972; Nikkila and Kekki, 1972; Huttunen, 1976; Huttunen et al., 1976; Makinen and Scheinin, 1976; Hallfrisch et al., 1983a; Hallfrisch et al., 1983b; Crapo and Kolterman, 1984; Swanson et al., 1992; Bantle et al., 2000).

Results of short-term intervention studies in normal weight, overweight, or obese subjects that measured the effect of fructose on TG (Bohannon et al., 1980; Gee et al., 1991; Jeppesen et al., 1995a; Jeppesen et al., 1995b; Singleton et al., 1999; Parks et al., 2008), food intake (Spitzer and Rodin, 1987; Van de Ven et al., 1994), or carbohydrate metabolism only (Reiser et al., 1987; Kim et al., 1988; Heacock et al., 2002; Sir-Petermann et al., 2004) and an observational study in subjects with a large range of body weights (Slyper et al., 2005) indicate that in the short-term, ingestion of 30–100 g/day fructose is associated with either no change or a slight increase in serum TG, a decrease in plasma insulin and glucose, and no change in food consumption or satiety compared to a similar amount of glucose or sucrose.

INTERVENTION STUDIES

The design and results of the 31 intervention studies involving overweight or obese subjects that were graded and discussed in this document are shown in Tables 3–8. The studies were organized according to the study duration, the amount of fructose administered, and the primary endpoints that were measured (e.g. TG, body weight, or food intake) in order to determine if there was a causal relationship between fructose ingestion and biologically relevant changes in the primary endpoints.

Longer Term Intervention Studies: Effect of Fructose on Triglycerides and Body Weight

The design and results of longer-term studies are shown in Tables 3–5. In general, longer term (>1 day) studies in which fructose was ingested with a meal were judged to be of higher quality than those in which fructose was ingested as a bolus, liquid dose. The majority of the long-term studies received moderate quality scores (20–29 points), with two receiving high quality scores ($\geq$30 points) and two receiving a low score ($<$20 points). The longer-term studies tended to be better controlled, screened, and reported and utilized more appropriate statistical methods

Table 3 Studies that used both overweight and normal weight subjects*

Reference/Quality Score**	Body Weight	Dose	Time	Result
	Intervention studies with fructose ingestion with a meal (duration > 1 day)			
Bantle et al. (2000)/ 32 (High)	6 M avg. BMI (<40 yrs): 24.7 ± 0.7 kg/m^2 6 M avg. BMI (≥ 40 yrs): 25.8 ± 1.0 kg/m^2 6 F avg. BMI (<40 yrs): 24.6 ± 1.3 kg/m^2 6 F avg. BMI (≥ 40 yrs): 25.2 ± 1.0 kg/m^2	Fru diet : 85 g/day fru, 17 g/day glu, 3 g/day suc, 20 g/day lac Glu diet: 81 g/day glu, 15 g/day fru, 3 g/day suc, 10 g/day lac	42 days	GLU, INS (postprandial): glu > fru at 2 hrs only BW: fru = glu TG: fru > glu (M only); both decreased over course of study Cholesterol, LDL-C, HDL-C: fru = glu
Crapo and Kolterman (1984)/ 22 (Moderate)	2/11 subjects weighed 22% and 30% more than average	63–99 g/day fru or suc (diet)	14 days	Lactate (fasting), pyruvate, TG, uric acid: fru = suc Total cholesterol (fasting) and HDL-C: suc > fru GLU, INS: suc > fru
Hallfrish et al. (1983a; 1983b)/ 30 (High) and 29 (Moderate)	avg. BMI in 12 normal M: 26.0 kg/m^2 avg. BMI in 12 HI M: 26.9 kg/m^2	Diet with 15% ST (0 g/day fru), 7.5% fru/7.5% ST (approx 50 g/day fru) or 15% fru (approx 100 g/day fru)	5 weeks	TG: fru = fru/ST = ST (normals) TG: fru = fru/ST > ST (HI M) Total cholesterol and LDL-C: fru = fru/ST > ST (combined) HDL-C or FFA: fru = fru/ST = ST (either group or combined) INS: fru = fru/ST = ST (either group or combined) GLU and GIP: fru > fru/ST > ST (combined) Glucagon: fru = fru/ST = ST (either group or combined)
Huttunen et al. (1976); Huttunen (1976); Maikinen and Scheinin (1976)[a]/24 (Moderate)	avg. BMI: 22.6 ± 3.5 kg/m^2; 8/35 subjects with BMI > 25 kg/m^2 and <30 kg/m^2)	Approx. 70 g/day fru Approx. 70 g/day suc Approx. 50 g/day xyl	2 years	BW, TG, GLU, urate, lactate, or pyruvate: fru = suc = xyl
MacDonald (1972)/ 14 (Low)	avg BMI M (calc)[b]: 24.7 kg/m^2; 2/10 M calc. BMI 27 kg/m^2 and 29.9 kg/m^2. avg BMI F (calc)[b]: 22.6 kg/m^2; 2/7 F calc. BMI 25.6 kg/m^2 and 26.3 kg/m^2	fru: 129 g/day (avg); 95–151g/day	5 days	TG: Effect of fru is dependent on the type of fat administered and sex. In M only, after ingestion of sunflower oil, the TG concentration is higher with fru than glu.
Swanson et al. (1992)/ 28 (Moderate)	BW of the 14 subjects was 107% (88–128%) of normal	High fru: 88 g/day fru avg (range 67–134 g/day) Low fru: 5 g/day fru avg (3.8 −7.6 g/day) in isoenergetic diet	28 days	GLU: High fru = low fru (other than Day 1) TG: High fru = low fru (other than Day 1) Peak Lactate: High fru > low fru (until Day 28) Cholesterol and LDL-C: High fru > low fru HDL-C/LDL-C: No effect on ratio
	Shorter-term intervention studies: Effect of fructose on TG			
Bohannon et al. (1980)/ 18 (Low)	2/9 subjects with BMI = 34.6 and 26.4 kg/m^2 7/9 with BMI <25 kg/m^2	100 g fru; 100 g glu; 100 g suc in 250 ml bolus dose	300 min	INS: glu > fru > suc TG: fru > suc > glu EOS TG: fru > BL at 300 min Glucagon: fru > suc > glu GH: glu > suc > fru

Chong et al. (2007)/ 22 (Moderate)	BMI: 22–31 kg/m^2 (avg. 25.3 ± 3.2 kg/m^2)	Approx 60 g fru Approx 60 g glu Based on 80 kg BW (BW not listed) Administered in a drink	360 min	GLU, VLDL-TG, lactate: CO_2 production, CHO oxidation: fru > glu INS, fat oxidation rate and synthesis of NEFA: glu > fru
Jeppesen et al. (1995a)/ 20 (Moderate)	avg BMI: 25.1 ± 1.1 kg/m^2	50 g fru + 40 g fat; 0 g fru + 40 g fat with 40 mg vitamin A in 300 ml liquid	10 hrs	TG: fat + fru > fat–fru. Increase in TG with fru dependent on baseline TG level.
Jeppesen et al. (1995b)/ 21 (Moderate)	avg. BMI: 26.6 ± 3 kg/m^2	5 g fat ± 50 g fru; 40 g fat + 0 g fru; 80 g fat + 0 g fru with 40 mg vitamin A 300 ml liquid bolus	10 hrs	TG: fat + fru > fat–fru. Response of TG to fat + fru similar to 40 g fat.
Parks et al. (2008) 27 (Moderate)	BMI: 18.9–27.3 kg/m^2 (avg. 24.3 ± 2.8 kg/m^2)	85.3 ± 22.3 g glu (100:0); 42.7 ± 11.1 g glu + 42.7 ± 11.1 g fru (50:50); 21.3 ± 5.6 g glu + 64.1 ± 16.7 g fru (25:75)	10 hrs (pre and post lunch)	GLU: 100:0 > 50:50 > 25:75 (fasted, but not fed state) INS: 100:0 > 50:50 > 25:75 (fasted) INS: 100:0 > 50:50 = 25:75 (fed) NEFA: 100:0 = 50:50 = 25:75 (fasted or fed) TG: 50:50 > 100:0; 25:75 = 100:0 (fasted) TG: 50:50 = 25:75> 100:0 (fed) TG: 50:50 = 25:75> 100:0 (overall)
Singleton et al. (1999)/ 16 (Low)	avg. BMI: 25.3 ± 4.5 kg/m^2	108 g cream (plain) 108 g cream + 30 g fru 108 g cream+ 17.5 g glu 108 g cream + 1 g asp	8 hrs	TG: glu = fru > plain (although concentration of fru > glu). Peak TG correlated with BL TG and INS.
Shorter-term intervention studies: Effect of fructose on food intake				
Spitzer and Rodin (1987)/ 21 (Moderate)	Subjects (n = 10) were "9.8 ± 10% overweight" [c]	50 g fru; 50 g glu, 50 g glu + asp (to increase sweetness to fru value), water (control) In 500 ml liquid	2.25 hrs	Food intake at lunch: glu > water > fru
Shorter-term intervention studies: Miscellaneous studies that examined the effect of fructose on carbohydrate metabolism without determining the effect on TG or food intake				
Heacock et al. (2002)/ 25 (Moderate)	BMI: 18.3–29.7 kg/m^2 (avg. 23.3 ± 0.6 kg/m^2)	water or 10 g fru in 60 ml liquid	120 min	GLU: water > fru when fru ingested 30 or 60 min prior to, but not at the same time as food
Kim et al. (1988)/ 19 (Low)	12 normal subjects receiving 75 g/day fru were 91.7–123.1% of ideal BW; 9 diabetics receiving 75 g fru were 88.1–125.5% of ideal BW	75 g fru 75 g glu 75 g suc in 300 ml liquid	180 min	INS: glu > fru = suc No increase over BL with fru
Reiser et al. (1987)/ 19 (Low)	1/15 M 10% above ideal BW, 2/15 M 15–20% above ideal BW, 1/9 females 12% above ideal BW. Majority normal weight	60 g glu (1 g/kg bw) 54 g CS (0.9 g/kg bw) 60 g glu + 105 g fru (1.75 g/kg bw) 54 g CS + 105 g fru 1.75 g fru + water	90 min	INS: glu + fru (highest CHO) > glu > CS + fru> CS = fru

(Continued on next page)

Table 3 Studies that used both overweight and normal weight subjects* *(Continued)*

Reference/Quality Score**	Body Weight	Dose	Time	Result
		Observational Studies		
Slyper et al. (2005)/ 9 (Low)	BMI z score of 32 subjects (−1.18 to 2.64)[d]	Three day food diary		Mean dietary fru intake = 26 g/day (0–73 g/day) No correlation between dietary intake of fru and TG
		New Studies Identified from Search		
		Intervention studies with fructose ingestion with a meal (duration > 1 day)		
Nikkila and Kekki (1972)/ 15 (Low)	Ten subjects with HTG, selected due to history of heart disease, obesity or diabetes ($n = 5$). BW of subjects not provided.	75 or 80 g suc 75 or 80 g fru in isocaloric exchange for ST	10–20 days	Postprandial TG: suc = fru = ST (avg. values) Postprandial TG: suc > fru = ST (individual data)
		Shorter-term intervention studies: Effect of fructose on TG		
Gee et al. (1991)/ 22 (Moderate)	<28 kg/m^2[e] (24.3 ± 1.2 kg/m^2), 6 NIDD subjects	Approx 34.1 g fru or suc in 75 g chocolate	300 min	GLU: suc > fru INS, TG, lactate: fru = glu
		Shorter-term intervention studies: Effect of fructose on food intake		
Van de Ven (1994)/ 20 (Moderate)	BMI range of 24 F subjects: 23– 29 kg/m^2 (average not calculated)	25 g fru + 5 g fiber 25 g fru + 10 g fiber 5 g fru + 5 g fiber 0 g fru + 0 g fiber	30 or 60 min	EI over 24 hr not affected by administration of fru/fiber or PBO 30 or 60 min before lunch
		Shorter-term intervention studies: Miscellaneous studies that examined the effect of fructose on carbohydrate metabolism without determining the effect on TG or food intake		
Sir-Petermann et al. (2004)/ 12 (Low)	BMI: 23.1–37.5 kg/m^2 (avg. 25.6 kg/m^2) in 8 healthy F and 8 F with polycystic ovary syndrome	50 g glu 50 g fru	180 min	GLU, INS: glu > fru (both groups of subjects)

*Data for overweight subjects were not presented separately from normal weight subjects and therefore could not be analyzed. BMI ≥ 25 kg/m^2 is considered overweight. BMI data are presented as range (if available) and/or mean ± SD or SE (as mentioned in the original reference). BMIs were calculated from weights and heights if BMIs were not provided in the original reference. Other criteria of weight are listed in the Table if BMI was not provided or could not be calculated. **Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30). Evaluation system score (quality) for observational studies as described in section entitled "Study Grading Criteria": low (<10) or moderate (10–20).

avg = average; BL = baseline; BMI = weight in kg/square of height in meters; BW = body weight; CHO = carbohydrate; CS = cornstarch; EI = energy intake; F= females; FFA = free fatty acids; fru = fructose; GIP = gastric inhibitory peptide; GLU = plasma glucose; glu = glucose; HDL-C = high density lipoprotein cholesterol; HI = hyperinsulinemic; HTG = hypertriglyceridemia; INS = plasma insulin; LDL-C = low density lipoprotein cholesterol; M = males; min = minutes; NEFA = non-esterified fatty acid; NIDD = non-insulin dependent diabetes mellitus; PBO = placebo; SD = standard deviation; SE = standard error; ST = starch; suc = sucrose; TG = triglyceride or triacylglycerol; VLDL-TG = very low density lipoprotein; xyl = xylitol; yrs = years.

[a] one study with additional references for methodology; [b] BMI calculated based on BW (provided) and avg height estimated from Ogden et al. (2004); [c] according to Metropolitan Life Insurance, 1960 chart; [d] Value > 2 considered overweight (WHO, 1997); [e] Recruitment criterion.

and consumption patterns than shorter-term studies. Concentrations of fructose ingested in the long-term studies ranged from 133 g/day for four days to 12 g/day for eight weeks.

Studies that were Conducted in Normal Weight, Overweight and Obese Subjects (Described in Table 3)

Hallfrisch et al. (1983a; 1983b), conducted a crossover study in groups of twelve men (avg. BMI = 26.9 kg/m^2) with abnormally high insulin responses to a sucrose load (hyperinsulinemics) and twelve men with normal responses (avg. BMI = 26.0 kg/m^2). The results of lipid and glucose analyses are reported in two separate publications, which received scores of high (score = 30) and moderate quality (score = 29), respectively. Each group of subjects was fed diets (15% protein, 42% fat, 43% carbohydrate) containing 0%, 7.5%, or 15% of daily energy intake (38 kcal/kg bw) as fructose for five weeks each. The amount of fructose consumed was approximately 0 g, 50 g, or 100 g/day (based on a 2700 calorie/day diet). Weekly fasting plasma, TG, high density lipoprotein cholesterol (HDL-C), free fatty acid, insulin, glucose, or glucagon in men with normal insulin responses were not altered by the consumption of fructose. In hyperinsulinemics, TG increased in a dose-dependent manner. Fasting blood glucose and gastric inhibitory peptide (GIP), a hormone which stimulates the release of insulin in response to glucose, were higher in the combined population (including hyperinsulinemics) after consumption of either concentration of fructose. The insulin response to a sucrose challenge in both normal individuals and hyperinsulinemics and glucose response to a sucrose challenge in the combined population were higher after ingestion of 100 g fructose than 0 g fructose. Because GIP and glucose response data in subjects without hyperinsulinemia were not analyzed separately from hyperinsulinemic subjects, one cannot conclude that fructose alters any parameter that was measured in this study in subjects that are not hyperinsulinemic, except for the short-term insulin response to a sucrose challenge.

In a moderate quality, crossover study (score = 28), Swanson et al. (1992) examined the effect of ingestion of a prepared diet containing 20% or <3% of dietary energy as crystalline fructose on fasting serum lipids, glucose, or lactate of fourteen healthy, adult subjects (with body weight 88–128% of normal). The diet contained 15% protein, 55% carbohydrate, and 30% fat. The average amounts (and ranges) of fructose ingested in the respective diets were 88 g/day (67–134 g/day) and 5 g/day (3.8–7.6 g/day). The carbohydrate in the low fructose diet was predominantly starch. Fasting serum lipids, glucose, and lactate were measured on Days 1, 7, 14, 21, and 28. Plasma glucose, serum TG, and lactate also were measured postprandially. Over the course of the 28-day study, fasting cholesterol, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) decreased in the low fructose group and remained similar to baseline in the high fructose group. There was no effect of either diet on the ratio of serum HDL-C to LDL-C. There was no difference in fasting serum TG between groups. On the first day of the study only, peak plasma TG was greater in subjects with the high fructose diet (152 ± 18 mg/dl) than the low fructose diet (117 ± 12 mg/dl) and plasma glucose was lower with the high fructose diet (110 ± 7 mg/dl) than the low fructose diet (119 ± 7 mg/dl). Peak serum lactate was higher in the high fructose group than the low fructose group on Days 1, 7, and 14, but not at Days 21 or 28. The results of this study indicate that alterations in lipid and glucose metabolism caused by ingestion of fructose are transient and suggest that short-term studies which show an effect of fructose on lipid metabolism are not predictive of responses that occur after longer term ingestion of fructose.

Bantle et al. (2000) conducted a similar, high quality crossover study (score = 32) in 24 healthy subjects (12 per sex) ingesting prepared, isoenergetic diets (55% carbohydrate, 15% protein, and 30% fat) over a course of 42 days. The average BMI of subjects was approximately 25 kg/m^2. Diets were nearly identical in nutrient composition, with the exception that 17% energy came from crystalline fructose in the high fructose diet and 14% crystalline glucose plus 3% crystalline fructose in the low fructose diet. The quantity of each diet that was provided to each subject was not mentioned; therefore the range of fructose or glucose intakes could not be calculated. However, it is estimated that the subjects ingested approximately 85 g/day fructose and 17 g/day glucose in the high fructose diet and 15 g/day fructose and 81 g/day glucose in the low fructose diet. Throughout the study, fasting or postprandial plasma TG of women was not affected by consumption of either diet. Men ingesting the high fructose diet had significantly greater fasting and postprandial TG concentrations than men ingesting the low fructose diet throughout the study. However, over the course of the study, fasting plasma TG decreased in both groups of men (with respect to baseline). The fructose diet had no significant effect on fasting plasma cholesterol, HDL-C, or LDL-C in either men or women. At the end of the study, body weights of subjects ingesting the high fructose or low fructose diets were approximately 1.3 kg lower than at the beginning of the study. The data indicate that consumption of a high fructose diet does not increase TG levels or body weight with respect to baseline if caloric intake is controlled. In a 24-hour metabolic profile on the last day, with either diet, insulin peaked in the morning, TG in the afternoon (at around 2 pm), and blood glucose at night, suggesting that short-term studies (which are generally conducted for a 3–4 hour period in the morning) are not of adequate duration to assess the effect that consumption of fructose throughout the day has on long-term TG, insulin, and glucose concentrations.

Crapo and Kolterman (1984) performed a moderate quality crossover study (score = 22) in eleven subjects (seven women, four men) in which crystalline fructose was substituted for dietary sucrose (baseline) for a period of 14 days. Two subjects in this study weighed 22% and 30% more than the study average. Meals were prepared on site and provided to subjects based on their typical consumption of energy (1830–3000 kcal/day). The diets contained approximately 55% carbohydrate (of which sucrose or fructose was 24%), 30% fat, and 15% protein. The

approximate amount of sucrose or fructose administered was 63–99 g/day. Fasting TG, lactate, pyruvate, or uric acid were not affected and fasting cholesterol and HDL–C were lower after substitution of sucrose with fructose. There also was no effect of fructose on fasting TG of two subjects that had somewhat elevated plasma TG concentrations at baseline (193 mg/dl and 207 mg/dl, respectively).[1]

In a two-year, moderate quality study (score = 24) examining the effect of sweeteners on tooth caries, 116 subjects were maintained on a diet containing fructose (2.1 kg/month, $n = 35$), sucrose (2.2 kg/month, $n = 33$), or xylitol (1.5 kg/month; $n = 48$) as the only sweetening agent (Huttunen, 1976; Huttunen et al., 1976; Makinen and Scheinin, 1976). Eight of the 35 subjects that received fructose had BMIs between 25 and 30 kg/m^2. The subjects were allowed to consume the diet without restrictions, but were instructed to avoid consumption of sweet fruits and other sweets. Because compliance was not strictly monitored, the amount of each sugar actually ingested could have varied substantially. It is estimated that the participants ingested 70 g/day fructose or sucrose or 50 g/day xylitol. In this study, TG, glucose, urate, lactate or pyruvate concentrations and BW did not differ between groups. This study is not considered to be as reliable as some of the other, better controlled studies that were performed with fructose because blood lipids were not measured between the baseline and five months (an acute effect could have been missed), there was no isocaloric group ingesting no sweeteners (or a noncaloric sweetener) and additional fructose, sucrose, and/or xylitol could have been consumed by the participants.

In a five-day, crossover study that was considered to be low quality for purposes of the assessment (score = 14), ten males and seven females were administered a liquid formula diet (45% carbohydrate, 45% fat, and 10% protein) (Macdonald, 1972). Based on body weights that were provided and estimated heights, the average BMIs of the males and females were 24.7 kg/m^2 and 22.6 kg/m^2, respectively. Two subjects per sex had BMIs between 25 and 30 kg/m^2. The intake of the formula diet was adjusted according to the normal intake of energy prior to the experiment (2100–3350 kcal), in order to keep body weight constant. The fats used were sunflower seed oil or cream, and the carbohydrates were either glucose plus fructose, glucose plus starch, or fructose plus starch. The fructose content provided 18% of the energy requirement for each individual (or 95–151 g/day per person). The results suggest that the effect of fructose or glucose on TG is dependent on the type of fat administered and gender. In either sex, TG decreased with the ingestion of sunflower oil and tended to increase with the ingestion of cream (regardless of the type of carbohydrate co-administered). In males, the TG concentration on Day 4 was reduced (by approximately 10% or 24%) when fructose plus starch or glucose plus starch (respectively) were coadministered with sunflower oil. Conversely, the TG concentration of males on Day 4 was increased (by 13% or 22%) when fructose plus starch or glucose plus starch (respectively) were codamininstered with cream. In females, the response of TG to either fat was not altered by the addition of fructose or glucose.

In a low quality study (score = 15) in ten subjects with hypertriglyceridemia and a history of heart disease, obesity, or diabetes that received 75 or 80 g glucose or fructose in isocaloric exchange for starch for 10–20 days, there was no effect of either fructose or sucrose on average postprandial TG values (Nikkila and Kekki, 1972). When data for individual subjects were analyzed separately, postprandial TG values increased after sucrose, but not fructose. Because body weights were not provided, it is unknown whether all subjects or a subset were obese. Therefore, although this study was conducted in some subjects that were obese, the results should be considered to be relevant for people with hypertriglyceridemia, who may be of normal weight or obese.

Studies that used Overweight Subjects (Described in Table 4)

In a moderate quality study (score = 24), Osei et al. (1987) examined the effect of adding 60 g of fructose to the weight-maintaining ADA[2] diets of 18 overweight or obese patients (predominantly women) had Type II diabetes and were maintained on insulin. BMI was not measured in this study; however, subjects fit the criteria for inclusion because they were 134 ± 3% of ideal body weight.[3] After a baseline period on the ADA diet, the patients ($n = 9$) were either placed on a diet containing non-nutritive sweeteners (NNS, e.g. aspartame or saccharin) or administered the ADA diet plus 60 g crystalline fructose (for an additional 240 kcal/day or approximately 10% of energy) over the course of the 12-week intervention ($n = 9$). Addition of fructose to the diet had no effect on body weight or serum cholesterol, HDL-C, LDL-C, uric acid, or lactic acid levels compared to baseline or to the NNS group. Whereas TG increased in the NNS group (compared to baseline), there was no effect of consumption of fructose on TG. Other changes observed were a decrease in fasting serum glucose in the fructose group (compared to baseline), and an increase in fasting serum glucose in the NNS group (compared to the fructose group). The results showed that the administration of 60 g fructose with meals has no deleterious effects on blood lipids or body weight of obese subjects with Type II diabetes and may actually be preferable to the administration of a diet that contains non-nutritive sweeteners.

Koh et al. (1988) examined the effect of ingestion of a high fructose diet for four weeks on several different indices of metabolism in nine subjects (avg. BMI = 23.4 kg/m^2) with normal glucose tolerance (3 male and 6 female subjects) and nine glucose-intolerant (IGT) individuals (avg. BMI = 27.3 kg/m^2). In this moderate quality, crossover study (score = 25), either fructose or glucose was incorporated (at 15% of energy) into an isocaloric, prepared diet (15–20% protein, 30–35% fat,

[1] It is unknown whether either of these subjects was overweight.

[2] American Diabetes Association.

[3] As defined by Metropolitan Life Insurance Tables (1983).

Table 4 Intervention studies in overweight or obese subjects with fructose ingestion with a meal (duration > 1 day)

Evaluation System Score (Quality)*	Subjects	Dose	Matrix	Time Course	Result	Reference
			Studies that measured TG			
24 (Moderate)	9 (2M, 7F) in fru group 9 (1 M, 8 F) in NNS group BW = 134 ± 3 % of ideal Age: 57 ± 3 yrs All subjects had Type II diabetes Randomized, no CO	0 g fru/day (NNS) 60 g fru/day	NNS diet or diet with 60 g/day crystalline fru added to beverages and cereals Caloric intake was isoenergetic (1600–2800 kcal/day), with 50% as CHO, 15% as protein, 35% as fat	12 weeks	GLU: BL > fru; NNS > fru Glycosylated HB: BL > fru; NNS> fru BW, total cholesterol, HDL-C, LDL-C, apo B100, lactic acid, uric acid = no effect of diet TG: BL = fru, NNS > BL	Osei et al. (1987)
25 (Moderate)	9 NW with normal GT (3M, 6F) avg. BMI: 23.4 kg/m^2 9 OW with IGT (3M, 6F) avg. BMI: 27.3 kg/m^2 Age: 54 ± 6 yrs	45–122 g/day fru 45–122 g/day glu sugar = 15% of calories adjusted for energy requirements	Prepared meals, sugar incorporated into isocaloric diet based on subjects' typical consumption	4 weeks/ sugar	GLU(fasting): fru = glu in normal GT, glu > fru in IGT INS (fasting): glu > fru (both groups) TC, VLDL-C LDL-C, HDL-C and indices of BW: fru = glu (both groups) TG: fru = glu (normal GT) TG: glu > fru in IGT TC, VLDL-C, LDL-C and TG significantly greater and HDL-C significantly lower in IGT than normal GT (regardless of treatment)	Koh et al. (1988)**
28 (Moderate)	31 (17M, 14F) in fru group BW of 7/14 F and 4/17 M > 25 kg/m^2 (OW) based on est. avg height[a] Age: 19–57 yrs Single blind, randomized, no CO	50 g/day fru Study also examined effects of sucralose (data not presented)	Liquid bolus twice daily, along with normal diet	13 weeks	BW, TG: fru = BL (in OW subjects or total subjects)[b]	McLean Baird et al. (2000)**
26 (Moderate)	6 (3M, 3F), obese (BMI: 35 ± 2 kg/m^2) adolescents (15.2 ± 0.5 yrs) Randomized	Low fru (6% energy from fru): 38 g/day avg High fru (24% energy from fru): 149 g/day avg [c]	Prepared, isocaloric diets containing 60% CHO, 25% fat and 15% protein, with 10% or 38% of the CHO (6 or 24% of dietary energy) content from fru[a]	7 days	GLU, INS, C-peptide, TG, free fatty acid, insulin sensitivity or secretion, C-peptide, HDL-C or LDL-C: No comparisons to BL made. The overnight fasting levels of TG, FFA, HDL-C, and LDL-C after fru were within normal ranges.	Sunehag et al. (2008)
			Studies that did not measure TG			
26 (Moderate)	13 (all F) 8 normal BW (BMI: 25 ± 1.0 kg/m^2), 5 obese (BMI: 31 ± 4.0 kg/m^2) Normal BW age:53.1±0.3 yrs Obese age: 52.4±4.8 yrs Randomized, in house	123 g/day fru, glu or suc with 47 g/day fat (normal weight) 133 g/day fru, glu or suc with 50 g/day fat (obese) Administered in 5 meals/day	Fed control diet or diets with 50% excess energy (approximately 914 or 985 kcal/day in normal weight or obese women, respectively) as 54% CHO and 46% fat	4 days/diet	Fat or CHO oxidation or balance: fru = glu = suc Fat storage: fru = glu = suc The net effect of each diet was similar, with 12% of excess energy stored as glycogen and 88% as fat	McDevitt et al. (2000)

(Continued on next page)

Table 4 Intervention studies in overweight or obese subjects with fructose ingestion with a meal (duration > 1 day) *(Continued)*

Evaluation System Score (Quality)*	Subjects	Dose	Matrix	Time Course	Result	Reference
22 (Moderate)	21 obese subjects (6M, 15F), 15-91 pounds over ideal weight BW, Age: not provided No treatment other than fru	36–42 g/day fru as part of a weight loss diet	Based on body weight, each subject consumed a high protein diet of 1100 to 1600 calories/day Vitamin and mineral supplements provided to accommodate reduced intake of milk and green vegetables. Two cups of lettuce salad provided per day to prevent constipation. All meals were home-prepared.	4 weeks	BW: subjects lost an average of 14.5 lbs over the course of the study TC, AP, systolic, diastolic BP: fru <BL Uric acid: fru > BL (at week 1 only) Bilirubin, SGOT (AST), total protein, BUN, creatinine, T4, GLU, calcium, sodium, potassium: fru = BL TG not measured	Wiesner et al. (1979)
24 (Moderate)	53 (19M, 34 F) OW subjects (123.7–128.5% of ideal BW) Age: 22 ± 2 yrs Randomized	36 g fru 36 g glu 36 g gal 0 g CHO	Sugar was 100% of CHO of a hypocaloric diet (a liquid formula providing 560 kcal/day)	14 days	BW: fru = glu =gal = 0 CHO (all groups <BL) GLU, INS: fru = glu =gal = 0 CHO	Rizkalla et al. (1986)

*Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30); **This study was also discussed in Dolan et al. (2010). Data are presented as mean ± SD or SEM (depending on the source). All subjects fasted overnight and met criteria of overweight or obese (BMI = 25.0–29.9 or ≥ 30 kg/m^2, respectively) as defined by WHO (2006) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise. Conversions: Fru: (1 g = 4 kcal); 1 kcal = 4.184 KJ; 1 g fru = 16.736 KJ. apo B100 = apoprotein B100; AP = alkaline phosphatase; avg = average; BL = baseline; BMI = weight in kg/square of height in meters; BW = body weight; BUN = blood urea nitrogen; CHO = carbohydrate; CO = crossover; F = female; FFA = free fatty acid; fru= fructose; gal = galactose; glu= glucose; GLU = plasma glucose; GT = glucose tolerance; HB = hemoglobin; HDL-C = high density lipoprotein cholesterol; IGT = impaired glucose tolerance; INS = plasma insulin; LDL-C = low density lipoprotein cholesterol; M = male; MDA = malondialdehyde; NNS = non-nutritive sweetner (aspartame or saccharin) diet; NW = normal weight; OW = overweight; REE = resting energy expenditure; SD = standard deviation; SEM = standard error of mean; SGOT = serum glutamic oxalic transaminase; TC = total cholesterol; ST = starch; suc = sucrose; lac = lactose; TG = triglycerides; VLDL-TG (or C) = very low density lipoprotein (or cholesterol); yrs = years; T4 = thyroxine. [a] Average height estimated from Ogden et al. (2004); [b]Data were not available in the published manuscript and were obtained from the sponsor of the study; [c]Group with high fru intake was not included because fru intake was greater than cutoff value. It should be noted that the results in the high fru group were not different from the low fru group.

50–55% carbohydrate) based on each subject's typical energy consumption. The amount of fructose or glucose ingested varied from 45–122 g/day. Fasting TG, total cholesterol, very low density lipoprotein cholesterol (VLDL-C), LDL-C and HDL-C, and body weights of subjects receiving fructose or glucose were similar after 4 weeks on either diet. Regardless of treatment, subjects with IGT had greater serum concentrations of TG, VLDL-C, LDL-C, lower concentrations of HDL-C, and higher body weights than subjects with normal glucose tolerance. The results suggest that in overweight individuals with IGT, ingestion of up to 122 g/day fructose has no adverse effects on blood lipids or body weight compared to glucose. Conclusions that can be drawn from the study are limited by the fact that baseline values were not reported and statistical analyses were confined to results that were obtained after ingestion of either fructose or glucose in either normal or IGT subjects. Therefore, it is unknown if TG increased from baseline in the overweight IGT subjects.

In a 13-week, single-blind, randomized study designed to assess the clinical safety of sucralose (a chlorinated sucrose derivative with no caloric value) in humans (which was considered to be of moderate quality (score = 28) for an assessment of the effect of fructose on health), 31 (17 male, 14 female) control subjects received 50 g/day fructose (25 g/day at 10 am and 4 pm in liquid) in addition to their normal diet (McLean Baird et al., 2000). Compliance was assessed by an independent witness. According to the published manuscript, for the overall subject population, there were no changes in biochemical analyses (including TG, urea, and uric acid), BW, physical exams or urinalysis after 13 weeks of consumption of fructose (compared to baseline values). However, data supporting these conclusions were not available in the published manuscript. Because individual data for TG and BW were obtained from the sponsor, responses in seven females and four males with BMI $\geq$25 kg/m^2 that received fructose could be analyzed separately from normal weight individuals. We analyzed the data statistically, using ANOVA with the P value set at <0.05. There was no effect of ingestion of fructose on TG in overweight individuals (compared to the baseline diet or to normal weight individuals). Furthermore, although caloric intake increased by 200 kcal/day with ingestion of fructose, the body weights of either overweight males (86.9 $\pm$ 4.5 kg (SD) at baseline and 88.5 $\pm$ .2.4 kg at end of study) or overweight females (69.8 $\pm$ 1.9 kg at baseline and 70.3 $\pm$ 3.3 kg at the end of the study) ingesting fructose did not increase.

In a moderate quality (score = 26), seven day, randomized, crossover study conducted by Sunehag et al. (2008), six healthy, obese adolescents (three males, three females) were maintained at home on prepared, isocaloric diets containing 60% carbohydrate, 25% fat, and 15% protein, with 10% or 40% of the carbohydrate content (6 or 24% of dietary energy) provided by fructose (low fructose or high fructose diet, respectively). The amount of food provided to each participant was based on the energy intake of each participant the week prior to the test. The total amounts of fructose ingested in the low and high fructose diets averaged 38 and 149 g/day in the low and high fructose groups, respectively. Because the intake level of the high fructose group was higher than the cutoff value of 136.1 g/day, data for this group were not analyzed. Because no baseline values were provided, it is unknown if there was any effect of ingestion of 38 g/day fructose for seven days on TG, free fatty acids (FFA), HDL-C, or LDL-C in the test subjects. However, the TG, FFA, HDL-C, and LDL-C values that were measured after fructose intake (90 $\pm$ 14 mg/ml, 0.5 $\pm$ 0.1 mEq/L, 38 $\pm$ 4 mg/dl, and 82 $\pm$ 4 mg/dl, respectively) were within normal limits for these values (Spraycar, 1995).

In a moderate quality, randomized, in-house crossover study (score = 26) conducted in a whole body calorimeter, the effect of ingestion of an energy balanced (control) diet or a diet with a 50% excess energy on energy balance was assessed in eight normal weight (BMI = 25 $\pm$ 1.0 kg/m^2) and five obese (BMI = 31 $\pm$ 4.0 kg/m^2) women (McDevitt et al., 2000). It should be noted that based on BMI, some of the women in the normal weight group were overweight. The extra amounts of calories, fat, and carbohdydrate ingested by normal weight or obese women were 914 or 985 kcal/day, 57 or 50 g/day, and 123 or 133 g/day, respectively. Basal and sleeping metabolic rates were higher in obese than normal weight women but there was no significant effect of dietary treatment on metabolic rate in either group of women. There were no significant differences between normal weight and obese women in macronutrient oxidation or balances, so data were pooled. Overconsumption of glucose, fructose, or sucrose induced glycogen storage on Day 1 (approximately 100 g), but thereafter stimulated carbohydrate oxidation so that balance was achieved on Days 3 and 4. Fat oxidation was suppressed by a similar degree in subjects ingesting fructose, glucose, or sucrose. There were no significant differences between the various sugars in carbohydrate oxidation, carbohydrate balance, energy balance, fat oxidation, or fat balance. On average, 12% of the excess energy was stored as glycogen and 88% as fat for all dietary conditions (including overconsumption of fat). This study shows that in obese women, ingestion of a high fructose diet did not disproportionally stimulate fat storage compared to glucose or sucrose and that the net effect of overconsumption of sugar on fat balance (regardless of type) was similar to an excess of dietary fat.

Wiesner et al. (1979) conducted a moderate quality study (score = 22) to determine the safety of a weight-reducing diet utilizing fructose (36–42 g/day) as the primary carbohydrate source and protein as the primary caloric source. The diet (a total of 1100 to 1600 calories per day, depending on the initial body weight) was administered over the course of four weeks to 21 obese subjects (6 males and 15 females), who were between 15 and 91 pounds above their desirable weight (Metropolitan Life Insurance Co., 1977). Compared to weight at baseline, subjects lost an average of 14.5 $\pm$ 3 (SE) pounds by week four of the diet. Over the course of the study, there were significant (P <0.05) decreases in serum cholesterol and alkaline phosphatase, and systolic and diastolic blood pressure. Uric acid

concentrations increased during the first week but returned to baseline levels by the end of the study. There was no effect of diet on bilirubin, serum glutamic oxalic transaminase (SGOT), total protein, blood urea nitrogen (BUN), creatinine, thyroxine, glucose, calcium, sodium, or potassium. The authors concluded that the high protein diet containing fructose as the primary carbohydrate source was a safe and effective means of promoting weight loss. However, it should be noted that the effect of fructose on TG was not measured. Furthermore, the extent to which fructose contributed to weight loss is unknown because the diets were designed to promote weight loss.

A moderate quality study (grade = 24) examined the effect of ingestion of 36 g fructose, glucose, or galactose or no carbohydrate for 14 days on body weight, plasma glucose, and plasma insulin in 53 overweight subjects (body weight was 123.7–128.5% of ideal) (Rizkalla et al., 1986). In this study, each sugar provided 100% of the carbohydrate content of a hypocaloric, liquid formula, a weight-loss diet that provided only 560 kcal/day. The fasting plasma insulin and glucose levels decreased in all four groups, with no differences in the magnitudes of the decreases between groups. Each group also lost a similar amount of weight. In conclusion, as part of a calorie-restricted diet, there was no adverse effect of ingestion of 36 g fructose on body weight or plasma glucose or insulin compared to glucose or galactose.

Conclusion from Long-Term Studies Involving Overweight or Obese Subjects

The results of the long-term studies in which concentrations of TG were measured in studies involving overweight or obese subjects are summarized in Table 5 and Fig. 2. Figure 2 includes fasting TG values for all studies involving overweight or obese subjects in which a time course was available (except the Huttunen et al. (1976) study[4]) (Huttunen, 1976; Huttunen et al., 1976; Makinen and Scheinin, 1976). Values for the Huttunen et al. (1976) study are not included in the figure because the first values after the intervention were measured at five months. The corresponding studies for each of the doses administered in Fig. 2 are as follows: 50 g/day: McLean Baird et al. (2000); 60 g/day: Osei et al. (1987); 85 g/day: Bantle et al. (2000); 88 g/day: Swanson et al. (1992).

As shown in Table 5 and Fig. 2, the only long-term studies that have been conducted in strictly overweight or obese subjects that utilized fructose at ≤95th percentile levels of intake were the Osei et al. (1987) and Sunehag et al. (2008) studies, and subsets of the populations of the McLean Baird et al. (2000) and Koh et al. (1988) studies. Of these studies, the only ones that measured TG at more than one time point were McLean Baird et al. (2000) and Osei et al. (1987). As indicated in Fig. 2, TG responses to fructose in overweight and obese subjects are not different from those obtained from studies involving normal and overweight subjects. None of the studies indicate that ingestion of fructose at ≤95th percentile levels of intake leads to increased concentrations of plasma TG. Furthermore, none of the studies in which the body weight was measured showed an adverse effect of fructose consumption on the body weight of normal weight, overweight, or obese individuals. In obese women, ingestion of a high fructose diet did not disproportionally stimulate fat storage compared to glucose or sucrose. The net effect of overconsumption of sugar on fat balance (regardless of type) was similar to an excess of dietary fat.

Also noted in Table 5 and Fig. 2, the average initial TG values of the subjects used in the long-term studies varied widely (from approximately 92 mg/dl to 149.5 mg/dl). Although subjects with higher baseline values tended to have higher fasting concentrations of TG after administration of fructose than those with lower values, the long-term response of TG to fructose ingestion was not augmented in subjects with high baseline TG values.

Shorter-Term Studies: Effect of Fructose on Triglycerides

The only study that was located which examined the short-term effect of ingestion of fructose on TG in overweight or obese subjects (Table 6) was a moderate quality study (score = 20) in five subjects (BMI = 28–51 kg/m^2) with non-insulin dependent diabetes (one man, four women) (Moore et al., 2001). A solution containing 75 g glucose with or without 7.5 g fructose was administered and concentrations of blood lipids were measured up to three hours later. There was no statistically significant effect of fructose on average plasma insulin. The insulin responses in each subject were highly variable—insulin was lower after fructose in the three subjects with the highest plasma insulin levels, not affected by fructose in one subject with an intermediate level, and higher after fructose in the subject with the lowest plasma insulin level. The plasma glucose response was reduced by fructose in all subjects although the reduction was minimal (approximately 3%) in one subject. There was no effect of inclusion of fructose on TG, non-esterified fatty aids (NEFA), or glycerol (compared to ingestion of glucose alone). However, plasma concentrations of lactate increased (with respect to baseline) when fructose was added to glucose. The authors concluded that in diabetic subjects, small amounts of fructose improve the glycemic response to an oral glucose load independently of an increase in insulin, and have no effect on lipolysis.

Shorter-Term Studies: Effect of Fructose on Food Intake or Satiety

The design and results of the four short-term studies which investigated the effect of fructose on food intake or satiety in overweight or obese subjects are depicted in Table 7. All of

[4]The three citations mentioned all pertain to the Turku sugar study and are referred to as the Huttunen et al. (1976) study from this point forward.

Table 5 Triglyceride levels in long-term studies using overweight or obese subjects (fasting unless otherwise noted)

Evaluation System Score (Quality)*	Subjects/Duration	Fast (Y/N)?	Intake	Average Triglyceride (TG) Levels (mg/dl) BL	Peak	EOS	EOS-BL	% Change	Reference
32 (High)	12 M, 12 F (6M, 6F older subjects OW)/6 weeks	Y	85 g/day fru + 17 g/day glu (M)	117.9	119.3	111.2	−6.7	−5.6	Bantle et al. (2000)**
		Y	15 g/day fru + 81 g/day glu (M)	117.9	117.9	84.6	−33.3	−28.2	
		Y	85 g/day fru + 17 g/day glu (F)	103.7	103.7	82.8	−20.9	−20.1	
		Y	15 g/day fru + 81 g/day glu (F)	103.7	103.7	86.3	−17.4	−16.8	
		N [a]	85 g/day fru (M) + 17 g/day glu (M)	111.2	240	111.3	0.1	0.1	
		N [a]	15 g/day fru + 81 g/day glu (M)	80.1	160	80.1	0	0	
		N [a]	85 g/day fru + 17 g/day glu (F)	80	146.8	82.3	2.3	3	
		N [a]	15 g/day fru + 81 g/day glu (F)	89	115.7	86.3	−2.7	−3	
22 (Moderate)	4 M, 7 F (2/11 OW)/2 weeks	Y	63–99 g/day fru	94	ND	84	−10	−10.6	Crapo and Kolterman (1984)**
30 (High)	12 OW M/5 weeks	Y	100 g/day fru	93	ND	92.1	−0.9	−1	Hallfrisch et al. (1983b)**
		Y	50 g/day fru + 50 g/day starch	93	ND	94.7	1.7	2	
		Y	100 g/day starch	93	ND	85.7	−7.3	−8	
24 (Moderate)	116 M/F, 8/35 fru subjects OW/2 yrs	Y	70 g/day fru ($n = 35$)	130	127	111.2	−18.8	−14.5	Huttunen et al. (1976)**
		Y	70 g/day suc ($n = 33$)	133	132	111.2	−21.8	−16	
		Y	50 g/day xylitol ($n = 48$)	135	132	111.6	−18.4	−14	
25 (Moderate)	3 M, 6 F (NW)/4 weeks	Y	45–122 g/day fru	ND	ND	74	ND	ND	Koh et al. (1988)**
		Y	45–122 g/day glu	ND	ND	72	ND	ND	
25 (Moderate)	3 M, 6 F with IGT (OW)/4 weeks	Y	45–122 g/day fru	ND	ND	154	ND	ND	Koh et al. (1988)
		Y	45–122 g/day glu	ND	ND	173	ND	ND	
14 (Low)	10 M, 7 F (2M, 2 F OW)/5 days	Y	40% fru + 60% CS + oil (M)	ND	ND	ND	ND	−10	Macdonald (1972)**
		Y	40% fru + 60% glu + oil (M)	ND	ND	ND	ND	−23	
		Y	40% glu + 60% CS + oil (M)	ND	ND	ND	ND	−24	
		Y	40% fru + 60% CS + double cream (M)	ND	ND	ND	ND	13	
		Y	40% fru + 60% glu + double cream (M)	ND	ND	ND	ND	−5	
		Y	40% glu + 60% CS + double cream (M)	ND	ND	ND	ND	22	
		Y	40% fru + 60% CS + oil (F)	ND	ND	ND	ND	−32	
		Y	40% fru + 60% glu + oil (F)	ND	ND	ND	ND	−18	
		Y	40% glu + 60% CS + oil (F)	ND	ND	ND	ND	−31	
		Y	40% fru + 60% CS + double cream (F)	ND	ND	ND	ND	10	
		Y	40% fru + 60% glu + double cream (F)	ND	ND	ND	ND	1	
		Y	40% glu + 60% CS + double cream (F)	ND	ND	ND	ND	−4	
28 (Moderate)	17 M, 14 F (all subjects)/13 weeks	Y	50 g/day fru	135.6	135.6	106.4	−29.2	−22	McLean Baird et al. (2000)[b]**
28 (Moderate)	4 OW M[c], 7 OW F/13 weeks	Y	50 g/day fru	125.5	140.6	103.2	−22.3	−17.8	McLean Baird et al. (2000)[b]
15 (Low)	10 subjects with HTG/10–20 weeks	N	75–80 g/day fru	ND	ND	256	ND	ND	Nikkila and Kekki (1972)
	BW of subjects not provided (some obese)	N	Isocaloric amount of ST	ND	ND	266	ND	ND	
24 (Moderate)	9 NIDD (2M, 7F) in fru group	Y	60 g/day fru	92	96	92	0	0	Osei et al. (1987)
	9 NIDD (1M, 8F) in NNS group/2 weeks	Y	0 g/day fru (NNS)	146	240	240	94	64	
28 (Moderate)	3M, 3 F (obese)/1 week	Y	34–42 g/day fru	ND	ND	90	ND	ND	Sunehag et al. (2008)
28 (Moderate)	7 M, 7 F (some OW)/	Y	5 g/day fru (avg)	90.8	90.8	81	−9.8	−11	Swanson et al. (1992)**
	4 weeks	Y	88 g/day fru (avg)	103.2	103.2	85.4	−17.8	−17	
		N[d]	5 g/day fru (avg)	116.6	116.6	113.9	−2.7	−2	
		N[d]	88 g/day fru (avg)	149.5	149.5	116.6	−32.9	−22	

*Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30); **Data from these studies were also discussed in Dolan et al. (2010). Additional information about study provided in Table 3.

avg = average; BL = baseline; CS = corn starch; EOS = end of study; F = females; fru = fructose; glu = glucose; HTG = hypertriglyceridemia; IGT = impaired glucose tolerance; M = males; N = no; NIDD = non-insulin dependent diabetes mellitus; ND = not determined; NNS = non-nutritive sweetener; OW = overweight; ST = starch; suc = sucrose; Y = yes; yrs = years. TG reported in mmol/L were multiplied by 89 to achieve TG in mg/dl. TG values are fasting unless indicated otherwise. [a] values over a 24-hour period, which included consumption of meals; [b]Data for TG were not available in the published manuscript and were obtained from the sponsor of the study; [c]all four males had higher than normal TG at baseline; [d]values after consumption of breakfast.

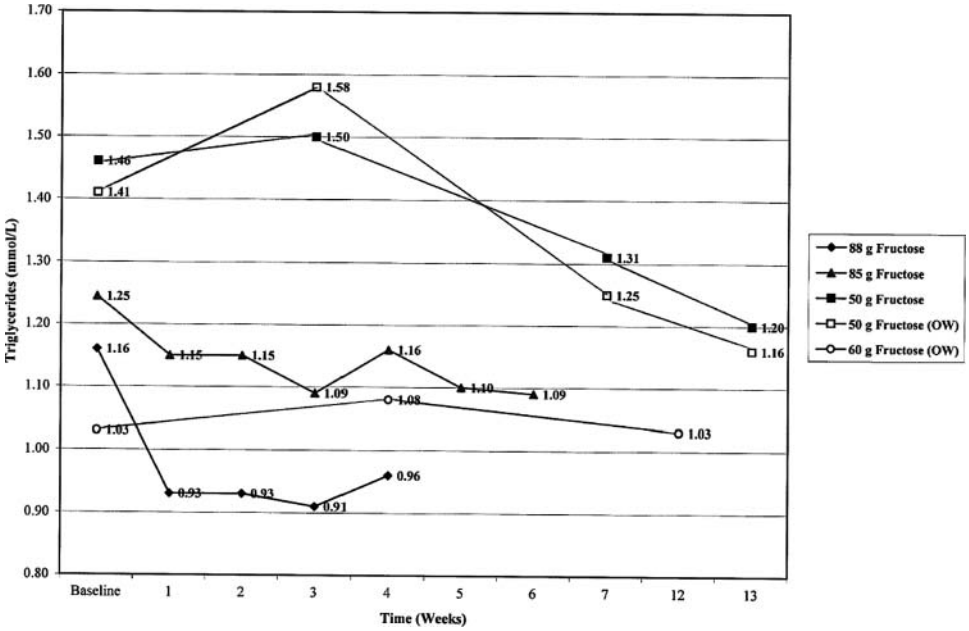

Figure 2 Fasting triglyceride levels in studies involving overweight or obese subjects that provided time course data.

these studies received scores within the moderate quality range (score = 22–28).

Results of a moderate quality study (score = 26) conducted by Rodin (1990) show that ingestion of 50 g fructose in a 500-ml drink 38 minutes prior to a buffet lunch resulted in lower food intake in eight, normal weight subjects (four per sex) and six obese females than either 50 g glucose or 0.25 g aspartame, even though plasma glucose and insulin were lower after consumption of fructose than glucose. Regardless of treatment, food intake was higher in obese than normal weight individuals. Free fatty acids declined in all treatment groups (regardless of weight). Normal weight or obese subjects given the fructose preload also consumed less fat, compared to water or aspartame. The results of the study indicated that the consumption of fructose prior to a meal has a beneficial, rather than a harmful effect on food intake of obese subjects (compared to glucose or aspartame).

In a moderate quality randomized, double-blind crossover study (score = 26), twenty-eight, non-diabetic obese men (BMI $= 32.5 \pm 0.6$ kg/m^2) were administered 50 g glucose, 50 g fructose, 50 g whey protein, or 25 g whey protein plus 25 g fructose (all as a bolus in milk). In these subjects, plasma glucose and insulin were greater with glucose than fructose and plasma GLP-1 and cholecystokinin were similar with glucose or fructose over a two-hour period. There was no difference in hunger ($P = 0.755$) or food intake ($P = 0.121$) of an ad libitum meal offered four hours after administration of glucose, fructose, or whey (with or without fructose). From this study, the authors concluded that in obese men, fructose and glucose beverages had similar effects on appetite and associated regulatory hormones, independent of the effect on blood glucose or insulin (Bowen et al., 2007).

A similar result was found in a moderate quality (score = 28), randomized, single-blind crossover study conducted in overweight and obese patients with type II diabetes (average

Table 6 Short-term studies (<24 hours) investigating the effect of a bolus dose of fructose on triglycerides in overweight or obese subjects

Evaluation System Score* (Quality)	Subjects/Study Design	Dose/Matrix	Time Course	Result	Reference
20 (Moderate)	5/group (1M, 4F) Type II diabetics BMI: 28–51 kg/m^2 Age: 34–57 yrs Single blind, crossover	75 g glu ± 7.5 g fru liquid bolus (vol unknown), no isocaloric control	To 180 min	GLU: glu > glu + fru INS, NEFA, TG: glu = glu + fru Lactate: glu + fru > fru at 60 and 120 min. No difference at 180 min. NEFA, glycerol: both groups <BL Lactate: glu + fru > BL TG: both groups = BL	Moore et al. (2001)

All subjects fasted overnight and met criteria of overweight or obese (BMI = 25.0–29.9 or ≥ 30 kg/m^2, respectively) as defined by WHO (2006) unless indicated otherwise. BL = baseline; BMI = body mass index; F = female; fru= fructose; glu = glucose; GLU = plasma glucose; INS = plasma insulin; M = male; NEFA = non-esterified fatty acid; TG = triglycerides; vol = volume; yrs = years. *Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30).

Table 7 Effect of short term (<1 day) consumption of fructose on food intake of overweight or obese subjects

Evaluation System Score* (Quality)	Subjects/Study Design	Dose/Matrix	Time Course	Result	Reference
		Studies with a bolus dose administered in water			
26 (Moderate)	4/sex/group (NW) 6 obese F (avg. 140.5% OW) Age: 22-50 yrs Randomized	50 g fru 50 g glu 0.25 g asp Unflavored, unsweetened water 500 ml bolus, followed 38 min later with identical, preweighed lunch	To 48 min	GLU: glu > fru = asp = water (NW or obese) INS: glu > fru > asp = water (NW or obese) Caloric or fat intake at meal: water = asp = glu > fru (NW or obese; especially M) Total EI: fru = glu = asp = water (obese); glu > fru, asp, water (NW) Caloric intake: obese > NW subjects. Obese and NW subjects selected less fat when administered fru compared to water or asp.	Rodin (1990)
26 (Moderate)	28 M BMI: 32.5 0 ± 0.6 kg/m^2 Age: 57.0 ± 1.6 yrs Randomized, double-blind crossover	50 g fru, 50 g glu, 50 g whey, or 25 g fru + 25 g whey, with water and milk (1% fat) (provided as a 390 to 410 ml liquid bolus) Beverages were matched to sweetness with NCS Ad lib meal offered 4 hours after ingestion of beverage	To 4 hr	GLU: glu > fru > whey = whey/fru INS: glu > whey = whey/fru > fru Ghrelin: glu = fru = whey = whey/fru (to 120 min); glu = fru = whey/fru > whey (at 240 min) GLP-1: whey > glu = fru = whey/fru Cholcyst: whey > whey/fru > fru = glu EI (test meal), hunger: glu = fru = whey = whey/fru Satistfaction/Fullness: whey > fru	Bowen et al. (2007)
28 (Moderate)	10 OW or obese nondiabetics (6M, 4F)[a] BMI: 27–37.3 kg/m^2 (avg. 30.9 kg/m^2) Age: 44–69 yrs 10 OW or obese NIDD diabetics (6M, 4F) BMI: 25.3–36.2 kg/m^2 (avg. 30.2 kg/m^2) Age: 44–71 yrs Randomized, single-blind crossover	0 g glu or fru (vehicle), 75 g fru or 75 g glu (provided as a 240 ml liquid bolus) Beverages were matched to sweetness with noncaloric lemon flavoring Ad lib meal offered 3 hours after ingestion of beverage	To 4 hr	Fasting GLU: glu > fru = vehicle (both groups of subjects) GLU (after meal): vehicle > fru = glu (both groups of subjects) Fasting INS: glu > fru = vehicle (nondiabetics); glu > fru > vehicle (diabetics) Fasting GLP-1: glu > fru > vehicle (nondiabetics); glu = fru > vehicle (diabetics) Fasting GIP: glu > fru = vehicle (both groups) Fullness: fru = glu > vehicle (both groups) Hunger, Food intake: vehicle > fru = (glu both groups) Food intake: nondiabetics > diabetics (regardless of treatment). No difference in macronutrient preference between groups.	Vozzo et al. (2002)
		Studies with a bolus dose administered with other nutrients			
22 (Moderate)	10 NW (0–2% avg % OW) 9 obese (47–48% avg % OW) Predominantly F Age: 24–38 yrs No crossover	Study 1: 50 g fru, 50 g glu, 500 ml liquid bolus Study 2: 40 g fru (with food), 40 g glu (with food) Breakfast with 15 g sugar followed by snack with 25 g sugar (preload) Identical, pre-weighed lunch offered 2.25 hours after preload	To 155 min	Study 1: GLU, INS: glu > fru; responses in obese > NW Food intake at lunch: glu > fru (both weight groups) Calories consumed by obese (but not NW) correlated with INS levels Study 2: GLU, INS, food intake at lunch: fru = glu. GLU, INS higher in obese than NW. No correlations between INS or food intake in either weight group	Rodin et al. (1988)

All subjects fasted overnight and met criteria of overweight or obese (BMI = 25.0–29.9 or ≥ 30 kg/m^2, respectively) as defined by WHO (2006) unless indicated otherwise.
asp = aspartame; CHO = carbohydrate; Cholcyst: = cholecystokinin; EI = energy intake; F = female; fru= fructose; GLU = plasma glucose; glu = glucose; GIP = gastric inhibitory peptide; GLP-1 = glucagon-like peptide; hr = hours; INS = plasma insulin; M = male; min = minutes; NCS = noncaloric sweetener; NIDD = non-insulin dependent diabetes mellitus; NW = normal weight; OW = overweight; std = standard; suc = sucrose; TCI = total caloric intake; yrs = years.
[a] 9/10 had impaired glu tolerance.
*Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30).

BMI = 30.2 kg/m^2) and non-diabetic subjects (average BMI = 30.9 kg/m^2) with impaired glucose tolerance (Vozzo et al., 2002). In both groups of subjects, plasma glucose, insulin, and gastric inhibitory peptide (GIP) concentrations were greater two to three hours after ingesting a beverage containing 75 g glucose than 75 g fructose. However, in either group, there was no difference in feelings of fullness or hunger or for food intake of an ad libitum meal offered three hours after administration of either sugar. From this study, the authors concluded that in overweight or obese subjects with Type II diabetes or impaired glucose tolerance, fructose and glucose had equivalent short term satiating efficiency.

When 40 g fructose or glucose were incorporated into the breakfast meals of groups of ten normal weight or nine obese subjects, plasma glucose and insulin responses and intake of food, fat, protein, or carbohydrate ingestion at a lunch offered 2.25 hours were similar and not influenced by weight (Rodin et al., 1988). Compared to normal weight subjects, obese subjects had greater plasma glucose or insulin responses to either sugar. When 50 g fructose or glucose were given as a 500 ml liquid preload (instead of in breakfast food), serum glucose and insulin and food intake were lower in the fructose group than the glucose group in both normal weight and obese subjects. In obese, but not normal weight subjects, food intake correlated with insulin levels 15 or 30 min after the liquid preload. The results of this moderate quality study (score = 22) showed that there is no differential effect of addition of a moderate amount of fructose or glucose to a mixed meal on blood glucose, insulin, or food intake in either normal weight or obese people. When fructose is provided as the only nutrient, it can suppress food intake in both obese and normal weight individuals. In obese, but not normal weight subjects, this effect may be related to decreased serum insulin.

In conclusion, the majority of the short term (<1 day) studies that have been performed with a bolus dose of 40–75 g fructose or glucose prior to food consumption indicate that fructose had no effect on food consumption, energy intake, or satiety of overweight or obese subjects compared to glucose.

Shorter-Term Studies: Miscellaneous Studies that Examined the Effect of Fructose on Carbohydrate Metabolism without Determining the Effect on TG or Food Intake

The effect of short-term fructose ingestion (from 2 to 6 hours in duration) on carbohydrate metabolism of overweight or obese subjects has been measured in six studies that do not provide any information about TG, satiety, or food intake. The design and results of these studies are summarized in Table 8. The grades of these studies are associated with moderate quality (20–29 points).

The studies summarized in Table 8 generally show that plasma glucose and insulin concentrations are lower in non-diabetic, overweight, or obese subjects ingesting 47–100 g fructose after an overnight fast (compared to sucrose or glucose), regardless of whether the sugars were administered in liquid (with or without fat) or in solid food (Simonson et al., 1988; Schwarz et al., 1989; Paquot et al., 1996; Van Gaal et al., 1999; Tittelbach et al., 2000). These studies received scores of 21, 23, 20, 26, and 20, respectively.

In a moderate quality study (score = 20), Simonson et al. (1988) found that overweight subjects with non-insulin dependent diabetes, obese non-diabetic subjects and subjects of normal weight exhibited higher plasma glucose and insulin concentrations up to 240 minutes after exposure to 75 g glucose than 75 g fructose. Compared to other groups, diabetic subjects exhibited higher plasma glucose concentrations in response to either fructose or glucose. Whereas the plasma insulin response to glucose was highly variable between subject groups, the plasma insulin response to fructose for all groups was consistent. These data indicate that in overweight subjects with or without diabetes (as well as in normal weight subjects), fructose exhibits a beneficial effect on blood glucose regulation.

In a moderate quality study (score = 21) comparing the effect of ingestion of 30 g sucrose or fructose in a bolus oral dose or with food, Vessby et al. (1990) noted that the insulin and glucose responses to 30 g fructose were less than 30 g sucrose when the sugars were administered as a bolus liquid to either healthy overweight subjects (avg. BMI = 28.2 kg/m^2) or overweight subjects with non-insulin-dependent diabetes (avg. BMI = 28.2 kg/m^2). When 30 g of either sugar was administered in a breakfast meal to overweight subjects with non-insulin-dependent diabetes (avg. BMI = 30.4 kg/m^2), the insulin responses to both sugars were similar, but the glucose response to sucrose was higher than fructose. In normal weight, non-diabetic subjects ingesting a meal containing 30 g of either sugar, the glucose and insulin responses were similar. The results of the study indicate that in overweight subjects with or without non-insulin-dependent diabetes, the effect of 30 g fructose on blood glucose regulation was either similar or beneficial to that of 30 g sucrose.

A moderate quality study (score = 21) performed in 8 normal weight subjects and 15 obese (BMI >30 mg/kg^2) subjects (8 with and 7 without non-insulin-dependent diabetes) demonstrated that endogenous glucose production (which was higher at baseline in obese subjects with non-insulin diabetes compared to other groups) remained constant in all groups of subjects after administration of 47.3–50.4 g fructose over a period of three hours (Paquot et al., 1996). In normal weight and obese subjects without diabetes, the stimulatory effect of fructose on carbohydrate oxidation and the inhibitory effect on lipid oxidation were similar. However, both responses were blunted in obese subjects with diabetes, resulting in increased non-oxidative carbohydrate disposal and non-oxidative fructose disposal. Because carbohydrates other than fructose were not studied, it is unknown if the effect of fructose on carbohydrate and lipid oxidation in diabetics was unique compared to other carbohydrates. Nonetheless, this study shows that the short-term metabolic effects of ingestion of approximately 50 g fructose are similar in normal weight subjects and obese subjects without non-insulin-dependent diabetes.

Table 8 Miscellaneous short term (<1 day) studies that examined the effect of fructose on carbohydrate metabolism in overweight or obese subjects without determining the effect on TG or food intake

Evaluation System Score* (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
			Liquid bolus dose (not with meal)			
20 (Moderate)	9 obese ND (2M, 7F) BW: 135% of ideal[a] Age: 60 ± 4 yrs 10 subjects with NIDD (6M, 4 F) BW: 116% of ideal[a] Age: 60 ± 4 yrs Also 9 NW controls of similar age	75 g fru 75 g glu	300 ml liquid bolus	To 240 min	GLU: glu > fru for all groups INS: glu > fru for for all groups EE: fru > glu for all groups CHO oxidation: fru > glu for all groups Decrease in Lipid oxidation: fru = glu for all groups FFA: fru > glu (obese), fru = glu (NIDD or controls) The thermic response to fru in obese and NIDD groups was similar to that of similar aged–controls	Simonson et al. (1988)
20 (Moderate)	13 OW or obese F BMI: > 28.0 kg/m^2 Age: 40 ± 11 yrs	100 g fru 100 g glu	Liquid bolus[b]	To 180 min	GLU, INS: glu > fru EE, RQ: fru > glu CHO oxidation: fru > glu Fat and protein oxidation: glu > fru NE excretion: fru > glu	Van Gall et al. (1999)
26 (Moderate)	14 obese subjects (7M, 7F), 120% – 150% above ideal weight Age:18–40 Crossover study	50 g fru 50 g glu	Bolus in skim milk[b] containing 73.8 g of total CHO, 16.7 g protein, 0.9 g fat Subjects administered an EB or NEG diet for 6 days prior to treatment and exercised for 40 min just before treatment	To 180 min	GLU, INS: glu > fru (after either diet) EE: fru = glu (after either diet) CHO and fat oxidation: fru = glu (after NEG diet) CHO oxidation: fru > glu (after EB diet) Fat oxidation: glu > fru (after EB diet) Hunger: glu = fru (after either diet)	Tittlebach et al. (2000)
21 (Moderate)	8 (4M, 4F) NW (avg BMI: 23.7 kg/m^2) 8 obese (4M, 4F) with NIDD (avg BMI: 31.5 kg/m^2) 7 obese (all F) without NIDD (avg BMI: 34.3 kg/m^2) Age: 23.1 ± 0.8 yrs (NW), 55.5 ± 3.0 yrs (obese with NIDD), 44.1 ± 4.1 yrs (obese without NIDD) No crossover	47.3 - 50.4 g fru (divided) 15.8 - 16.8 g fru (300 mg/kg fru/FFM) once per hour for 3 hours Responses compared to BL or obese subjects	Radiolabelled glucose (30 μg/kg/min) or glucagon (3 ng/kg/min) infused, followed by ingestion of radiolabeled fru once per hr for 3 hr	To 180 min	NEFA: fru <BL (all subject groups) GLU: fru > BL (all subject groups) Endogenous glucose production: fru = BL (all subject groups)	Paquot et al. (1996)
			With a meal			
23 (Moderate)	10 normal BW F (BMI: 20.5 ± 0.6 kg/m^2) and 13 obese F (BMI: 30.2 ± 0.7 kg/m^2) Age: 18–40 yrs	75 g fru 75 g glu	390 ml liquid meal containing 35 g protein, 23 g lipid plus 75 g sugar, and 7 g decaffeinated coffee diluted in water	To 6 hr	GLU, INS: glu > fru to 180 min (both subject groups) FFA: fru = glu (obese > normal BW) Lactate, energy expenditure, CHO oxidation, RQ: fru > glu (both subject groups) Lipid oxidation: glu > fru (both subject groups)	Schwarz, et al. (1992)

(Continued on next page)

Table 8 Miscellaneous short term (<1 day) studies that examined the effect of fructose on carbohydrate metabolism in overweight or obese subjects without determining the effect on TG or food intake *(Continued)*

Evaluation System Score* (Quality)	Subjects	Dose	Matrix	Time Course	Result	Reference
21 (Moderate)	8 healthy OW subjects (2M, 6F) Avg BMI: 28.1 or 28.2 kg/m^2 depending on sugar Age: 46–71 yrs 12 M NIDD Avg BMI: 30.4 to 30.9 kg/m^2 depending on sugar Age: 36–74 yrs	30 g suc 30 g fru 30 g sor 30 g mal	300 ml water (oral bolus study)	To 120 min	GLU, INS: suc > fru = mal = sor (both subject groups) Fasting C-peptide: suc = fru = mal = sor (both subject groups)	Vessby et al. (1990)
21 (Moderate)	8 healthy NW subjects (4M, 4F) Avg BMI: 24.2 kg/m^2 or 23.9 kg/m^2(mal group only) Age: 46–71 yrs 16 NIDD diabetics (13 M, 3F) Avg BMI: 30.5 kg/m^2 or 30.4 kg/m^2 (suc group only) Age: 36–74 yrs	30 g suc 30 g fru 30 g sor 30 g mal	Sweetener added as a part of jam or in juice or coffee with a breakfast meal (dietary study)	To 120 min	GLU: suc = fru = mal = sor (NW); suc > fru = mal = sor (NIDD) INS: suc = fru = mal > sor (NW); suc = fru > sor = mal (NIDD) Fasting C-peptide: suc = fru = mal = sor (both subject groups)	Vessby et al. (1990)

All subjects fasted overnight and met criteria of overweight or obese (BMI = 25.0–29.9 or ≥ 30 kg/m^2, respectively) as defined by WHO (2006) unless indicated otherwise. Studies were conducted in a crossover manner unless stated otherwise.

avg = average (mean); BL = baseline; BW = body weight; CHO = carbohydrate; EB = energy balance; EE = energy expenditure: F = female; FFA = free fatty acids; fru = fructose; gla = galactose; GLU = plasma glucose; glu= glucose; hr = hours; INS = plasma insulin; M = male; mal = maltose; min = minutes; ND = nondiabetics; NE = norepinephrine; NEG = negative energy; NEFA = non-esterified fatty acid; NIDD = non insulin-dependent diabetes; NW = normal weight; RQ = respiratory quotient; sor = sorbitol; suc = sucrose; yrs = years.

[a]criterion not defined; [b]volume not mentioned

*Evaluation system score (quality) for intervention studies as described in section entitled "Study Grading Criteria": low (<20), moderate (20–29) or high (≥ 30).

Moderate quality (scores = 20, 20, 26, and 23), short-term studies in which 75–100 g fructose or glucose was administered as a bolus dose to overweight or obese subjects indicate that, in general, energy expenditure and carbohydrate oxidation are increased and lipid oxidation is decreased after fructose ingestion (compared to glucose) (Simonson et al., 1988; Schwarz et al., 1989; Van Gaal et al., 1999; Tittelbach et al., 2000). However, in a negative energy balance situation, fat or carbohydrate oxidation are not affected differentially by fructose or glucose (Tittelbach et al., 2000). The results of these studies suggest that in obese subjects, the effect of fructose and glucose on fat or carbohydrate oxidation is variable depending on whether the subjects are in energy balance or negative energy balance. The study by Schwarz et al. (1989) showed that regardless of whether glucose or fructose was administered, there was a negative correlation between body fat and thermogenesis (i.e. women with more body fat tended to have lower thermogenic responses). Altogether, the results of these studies indicate that the individual metabolic responses of overweight or obese subjects to various monosaccharides are highly dependent on study design.

In the moderate quality study (score = 21) performed by Vessby et al. (1990), diarrhea was noted in 1/20 of the subjects within four hours of ingesting 30 g fructose in a liquid, indicating that a dose of 30 g fructose, when administered in a liquid has the potential to be malabsorbed. Diarrhea was not noted in any of the 24 subjects who ingested 30 g fructose as part of a breakfast meal. In a previously evaluated short-term (90 minute) study involving normal weight and overweight subjects, Reiser et al. (1987) noted that nine subjects ingesting 105 g fructose in drinks complained of gastric discomfort. These investigators hypothesized that the insulin responses could therefore be affected by hormones released in response to stress (such as corticoids or catecholamines).

In conclusion, the results of the majority of short-term studies suggest that ingestion of high amounts of dietary fructose induces abnormalities in carbohydrate metabolism that promote lipogenesis. Responses observed in these generally low to moderate quality studies may have been confounded by fructose malabsorption (particularly studies that were conducted with bolus, liquid doses) or alterations in normal energy intake. Because metabolic responses to fructose could be affected by hormones (such as corticoids or catecholamines) released in response to stress, the results of the short-term studies that were conducted with large, bolus doses of fructose may not accurately predict responses that may occur with ingestion of the same amount of fructose distributed over the day (either with or without meals). Therefore, the results of these studies are generally considered to be of little value for an assessment of biologically relevant effects of dietary fructose in overweight or obese individuals.

OBSERVATIONAL STUDIES

Three observational studies were located in which data for overweight or obese subjects could be analyzed (Wu et al., 2004; Aeberli et al., 2007; Bingham et al., 2007) (Table 9). As noted previously, these studies are not considered to be as substantive as intervention studies. Based on a total possible point score of 20, each observational study was given a low (<10) or moderate (10–20) quality grade. All three of the studies were considered to be of moderate quality.

Two of the observation studies analyzed the relationship between fructose intake and body weight in groups of male and female subjects that were either of normal weight or overweight/obese (Aeberli et al., 2007; Bingham et al., 2007). Another study examined this relationship in females that were "generally overweight" (Wu et al., 2004). The studies by Aeberli et al. (2007) and Bingham et al. (2007) indicated that there was no difference between daily fructose consumption in obese subjects compared to normal weight subjects. However, the study by Aeberli et al. (2007) demonstrated that overweight Swiss children ($n = 43$) had a higher percentage of fructose intake from sweets and drinks (combined) compared to normal weight children (40.0 ± 31.7% vs. 23.4 ± 26.0%, P <0.05) and a lower percentage of fructose intake from fruit and vegetables compared to normal weight children (41.9 ± 31.4% vs 58.1 ± 31.4%, P <0.05). Intake from sweets or drinks as separate entities was not determined. Total fructose intake was a significant predictor of LDL particle size (which was generally lower in overweight children), but not other lipid parameters such as HDL-C, LDL-C, total cholesterol, or TG (which was generally higher in overweight children). It should be noted that the intake of fructose reported in this study was relatively low (approximate average and range of 2 g/day and 0–12 g/day, respectively), compared to the average fructose intake of American children (approximately 50 g/day) reported by Marriott et al. (2009). Although it is possible that fructose intake is lower in Swiss than American children, it is likely that fructose intake was underreported in this study. Furthermore, the effect of decreased fiber and increased protein intake in obese children was not factored into the statistical analyses. Therefore, this study is not considered to be particularly reliable for an assessment of the relationship of fructose intake to the development of obesity.

The moderate quality study (score = 16) by Bingham et al. (2007) was a cross-sectional study involving 404 obese and 471 normal weight subjects. Urinary concentrations of fructose, glucose, and sucrose were measured to confirm reported intakes and data were analyzed according to quintiles of intake. In this study, the average fructose intake was 25 g/day in normal weight individuals (BMI <25 kg/m^2) and 26 g/day in obese individuals (BMI >30 kg/m^2). People with the lowest intake of fructose had the highest odds ratio for being obese. The odds ratio for obesity by quintile of reported sugar intake was significant for urinary sucrose ($P = 0.037$ for trend) and urinary sucrose/fructose ($P < 0.001$ for trend). Urinary sucrose/fructose ratio and urinary glucose concentrations were also significantly higher in obese compared to normal weight individuals ($P =$ 0.008 and 0.007, respectively), suggesting that the intake of glucose (rather than fructose) may be related to development of obesity.

Table 9 Observational studies on fructose intake of overweight or obese subjects*

Evaluation System Score (Quality)**	Subjects	Assessment Method	Result	Reference
18 (Moderate)	74 subjects (31 NW and 43 OW)[a] Swiss children (not presented by gender) Age: 6–14 yrs	Two 24-hr dietary recalls, and one-day dietary record	NW: Fru intake of 1.99 g/day (range 0.12–12.3 g/day) OW: Fru intake of 1.62 g/day (range 0.15–11.38 g/day) No associations between dietary fru intake and obesity	Aeberli et al. (2007)
16 (Moderate)	471 NW (203 M, 298 F); BMI: 22.9–23.2 kg/m^2 404 obese (191 M, 255 F); BMI: 33.5–34.1 kg/m^2 Age: 45-75 yrs	Food frequency questionnaire and confirmation of intake with urinalysis	NW: fru intake = 25 g/day (range 24–26 g/day) Obese: fru intake = 26 g/day (range 25–27 g/day) No associations between dietary fru intake or urinary fru and obesity	Bingham et al. (2007)
15 (Moderate)	1999 generally OW F Age: 25–69 yrs	Two food frequency questionnaires over a 4 year period	Group 1: 8.5% of energy from fru (38.8 g/day); BMI: 25.4 ± 0.2 kg/m^2 Group 2: 4.9% of energy from fru (22.1 g/day); BMI: 25.2 ± 0.2 kg/m^2 Group 3: 2.7% of energy from fru (11.8 g/day); BMI: 26.2 ± 0.2 kg/m^2 BMI inversely associated with fru intake	Wu et al. (2004)

*Subjects met criteria of overweight or obese (BMI = 25.0–29.9 or ≥ 30 kg/m^2, respectively) as defined by WHO (2006) unless indicated otherwise; **Evaluation system score (quality) for observational studies as described in section entitled "Study Grading Criteria": low (<10) or moderate (10–20).
apo B = apoprotein B; BMI = body mass index; CHO = carbohydrate; F = females; fru = fructose; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; M = males; NW = normal weight; OW = overweight; TG = triglycerides; yrs = years.
[a] The avg. BMI's reported in the study for NW and OW children were 15.9 ± 1.9 kg/m^2 and 23.4 ± 3.2 kg/m^2 (respectively). Children were classified as NW or OW using age and sex-specific data from the Centers for Disease Control and Prevention (CDC) (Ogden et al., (2002), as referenced in Aeberli et al. (2007)) and > 85th percentile values as being OW.

Wu et al. (2004) performed a moderate quality (score = 15), cohort study of 1999 healthy women (aged 25–69) from two nurses' health studies in which the relationships of several characteristics to fructose intake were assessed. Women in the highest quintile of energy from fructose (free or including fructose from sucrose) had higher energy and carbohydrate intakes, physical activity, and glycemic load, and lower BMI, cholesterol, fat and protein intakes, alcohol intake, and smoking incidence than those in the lowest quintile of fructose intake. Because this study was confounded by many factors that can affect BMI, one cannot conclude that there was a causal relationship between the ingestion of fructose and lower body weight. However, it can be concluded that, in general, women with higher fructose intakes exhibited behaviors that were associated with a healthier lifestyle than those with lower fructose intakes.

In conclusion, the results of the observational studies that have examined the relationship between fructose intake and obesity indicate that ingestion of moderate amounts of fructose is not associated with obesity. Because reported intakes of fructose were relatively low compared to current estimates of fructose consumption, it is likely that these studies are confounded by underreporting of fructose intake. Furthermore, because the observational studies did not control for many factors that can affect BMI, such studies are not considered to be particularly reliable for an assessment of the relationship of fructose intake to body weight. Nonetheless, they indicate that obese subjects do not ingest greater amounts of fructose than normal weight subjects.

CONCLUSIONS FROM THE OVERALL BODY OF EVIDENCE

The purpose of this review was to use a systematic, evidence-based approach to determine if a causal relationship exists between ingestion of fructose in a normal, dietary manner and the development of alterations in lipid and/or carbohydrate metabolism and increases in body weight in overweight or obese humans. Studies investigating the effect of fructose on blood lipids, glucose, insulin, obesity, or body weight of overweight or obese humans were identified by literature searches, obtained and reviewed. All studies that used levels of fructose consumption greater than the estimated 95th percentile (± SE) intake levels were excluded from the analysis. The remaining studies were graded according to a scale developed by the authors, based on guidance provided by FDA for evaluation of health claims. Although the majority of the studies were considered to be of moderate quality, the database is considered to be sufficient for the assessment.

The results of the majority of the short-term studies involving overweight or obese subjects show that in the short-term (i.e. up to approximately three hours after consumption), ingestion

of 30–100 g/day fructose is associated with either no change or a slight increase in serum TG and decreases in plasma insulin and glucose compared similar amounts of glucose or sucrose. In overweight or obese subjects that also have non-insulin dependent diabetes, the effects of fructose on blood glucose are considered to be beneficial. There is no evidence which suggests that fasting plasma TG are increased in overweight or obese subjects after long term ingestion of up to 60 g/day fructose. Long-term studies that utilized subjects who were either normal weight or overweight indicate that there is no effect of up to 100 g/day fructose on fasting plasma TG. An additional, long-term (four week) study performed in nine overweight subjects with impaired glucose tolerance and high TG levels (compared to normal weight subjects) shows that fasting TG are similar after consumption of either 122 g/day fructose or glucose. Because only two long-term studies with relatively few subjects have investigated the effect of ingestion of normal amounts of fructose on TG levels of overweight or obese subjects, it is clear that the long-term effects of ingestion of normal amounts of fructose on TG has not been adequately studied in this subpopulation, and may warrant further investigation. Whereas the ten studies that were performed with abnormal levels of fructose intake (>95th percentile levels) suggest that fructose increases TG in overweight or obese subjects, there is no evidence that ingestion of fructose ≤95th percentile levels of intake is also associated with this phenomenon.

There also is no evidence that ingestion of normal amounts of fructose is associated with an increase in food intake or body weight in overweight or obese individuals (compared to other carbohydrates), when it is not consumed in caloric excess. In general, overweight or obese subjects administered 40–75 g fructose or glucose two to four hours before being offered a meal consume similar amounts of food. Administration of 50 or 60 g/day fructose for 13 weeks to healthy overweight subjects or overweight or obese patients with Type II diabetes had no effect on body weight, compared to baseline. Studies using subject populations that included normal weight, overweight, and obese subjects indicate that ingestion of a diet containing up to 85 g fructose for five weeks has no effect on body weight compared to diets containing similar quantities of other carbohydrates. One study reported that consumption of 122 g/day fructose for four weeks had no effect on body weight of overweight subjects with impaired glucose tolerance; however, data supporting this finding were not presented. Therefore, no reliable studies have been conducted that have examined the effect of consumption of fructose at levels approximating 95th percentile estimates of intake on body weight of overweight or obese subjects. Although intakes of fructose in studies that have examined satiety, food intake, or body weight are lower than the 95th percentile intake calculated for the highest groups of consumers (136 g/day in 19–30 year old females and 146 g/day in 19–22 year old males), they support the conclusion that fructose does not cause biologically relevant changes in food intake or body weight in obese or overweight individuals when consumed at average levels (approximately 50 g/day).

In conclusion, the present review shows that intake of normal amounts of fructose has the same effect on TG or body weight in overweight or obese individuals as similar amounts of other carbohydrates such as glucose or sucrose. There is no evidence to suggest that ingestion of fructose at levels approaching 95th percentile levels of intake has adverse effects on body weight or serum TG in overweight or obese subjects. Studies that have shown adverse effects of fructose on these variables have been performed with abnormal levels of intake (>95th percentile).

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