Atherosclerosis 232 (2014) 125–133

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review

Effect of fructose on postprandial triglycerides: A systematic review and meta-analysis of controlled feeding trials

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ARTICLE INFO

Article history:
Received 23 May 2013
Received in revised form
9 October 2013
Accepted 22 October 2013
Available online 2 November 2013

Keywords:
Sugar
Nutrition
Lipids and lipoprotein metabolism
Clinical trial
Systematic review
Meta-analysis

ABSTRACT

Background: In the absence of consistent clinical evidence, concerns have been raised that fructose raises postprandial triglycerides.
Purpose: A systematic review and meta-analysis was conducted to assess the effect of fructose on postprandial triglycerides.
Data sources: Relevant studies were identified from MEDLINE, EMBASE, and Cochrane databases (through September 3, 2013).
Data selection: Relevant clinical trials of ≥7-days were included in the analysis.
Data extraction: Two independent reviewers extracted relevant data with disagreements reconciled by consensus. The Heyland Methodological Quality Score (MQS) assessed study quality. Data were pooled by the generic inverse variance method using random effects models and expressed as standardized mean differences (SMD) with 95% confidence intervals (CI). Heterogeneity was assessed (Cochran Q statistic) and quantified (I^2 statistic).
Data synthesis: Eligibility criteria were met by 14 isocaloric trials ($n = 290$), in which fructose was exchanged isocalorically for other carbohydrate in the diet, and two hypercaloric trials ($n = 33$), in which fructose supplemented the background diet with excess energy from high-dose fructose compared with the background diet alone (without the excess energy). There was no significant effect in the isocaloric trials (SMD: 0.14 [95% CI: −0.02, 0.30]) with evidence of considerable heterogeneity explained by a single trial. Hypercaloric trials, however, showed a significant postprandial triglyceride raising-effect of fructose (SMD: 0.65 [95% CI: 0.30, 1.01]).
Limitations: Most of the available trials were small, short, and of poor quality. Interpretation of the isocaloric trials is complicated by the large influence of a single trial.

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0021-9150
http://dx.doi.org/10.1016/j.atherosclerosis.2013.10.019

Conclusions: Pooled analyses show that fructose in isocaloric exchange for other carbohydrate does not increase postprandial triglycerides, although an effect cannot be excluded under all conditions. Fructose providing excess energy does increase postprandial triglycerides. Larger, longer, and higher-quality trials are needed.
Protocol registration: ClinicalTrials.gov identifier, NCT01363791.

Contents

1. Introduction

Postprandial lipids were first associated with atherogenesis in 1979 by Zilversmit [1]. Several studies have demonstrated that non-fasting trigycerides, in particular peak postprandial triglycerides, are better predictors of cardiovascular risk than fasting triglycerides. The Copenhagen City Heart Study demonstrated an association between increased nonfasting triglycerides and myocardial infarction and death with postprandial triglycerides 4 h after the last meal (within the peak range) the strongest predictors of cardiovascular events [2]. In the Women's Health Study, non-fasting triglyceride levels were more strongly correlated with cardiovascular disease incidence than fasting triglycerides, which lost significance after adjustment for total and HDL cholesterol [3]. Based on these data, the American Heart Association has proposed an initial lipid screen for non-fasting triglycerides with a cut point of 200 mg/dL (2.26 mM) [4].

Dietary factors which contribute to raised postprandial triglycerides have become a focus of concern. Particular attention has been focussed on the role of fructose. Highly reproducible animal models of fructose overfeeding have shown raised triglycerides secondary to increases in triglyceride secretion [5], impaired VLDL clearance, and enhanced fatty acid esterification [6]. Whether these findings hold true in humans under "real-world" intake patterns is unclear. Earlier systematic reviews and meta-analyses of controlled feeding trials have suggested a dose threshold for triglyceride-raising effects of fructose with increases in fasting triglyceride seen only at doses >60-g/day in type 2 diabetes [7] and ≥100-g/day across different metabolic phenotypes [8]. The threshold appears to be even lower for postprandial triglycerides with increases seen only at ≥50-g/d [8], a threshold roughly equivalent to the average fructose intake in the US [9]. This effect of fructose on postprandial triglycerides, however, is derived largely from acute, single-bolus studies [8]. The effect of fructose on postprandial triglycerides under chronic feeding conditions needs further investigation.

To assess the effects of longer-term fructose intake on postprandial triglycerides, we conducted a systematic review and meta-analysis of controlled feeding trials.

2. Methods

We followed the Cochrane Handbook for Systematic Reviews of Interventions for the planning and conduct of this meta-analysis [10]. The reporting followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines [11]. The review protocol is available at ClinicalTrials.gov (registration number: NCT01363791).

2.1. Study selection

We searched Ovid MEDLINE (1946 through September 3, 2013), Embase (1980 through September 3, 2013) and The Cochrane

Library (1991 through September 3, 2013), using the search terms: "fructose AND (triglyceride OR triacylglycerol OR triacylglyceride OR VLDL OR LDL OR chylomicron OR lipemia OR lipaemia OR lipid OR apoB100 OR apoB48 OR cholesterol)". No restrictions were placed on language or study type during the search. We included clinical interventions that investigated the chronic effect of exchanging isocaloric or hypercaloric oral fructose for a reference carbohydrate on postprandial triglycerides in humans. Comparisons were considered "isocaloric" if oral fructose in the fructose arm was exchanged for the reference carbohydrate in the control arm in an iso-energetic and iso-glucidic manner and "hypercaloric" if the oral fructose in the fructose arm was provided as a supplement to the background diet providing excess energy (E) relative to the background diet alone in the control arm. Trials with <7 days follow-up, which lacked an adequate carbohydrate control, or administered IV-fructose were excluded.

2.2. Data extraction

Two reviewers (DW and AC) independently extracted the following study characteristics: design (parallel or crossover), randomization, blinding, sample size, subject characteristics (age, sex, BMI, and diabetes status), fructose form (solid, liquid or mixed), dose, control reference carbohydrates (sucrose, starch, glucose, high-fructose corn syrup), follow-up, and macronutrient profile of the background diet. The quality of each study was assessed by each reviewer using the Heyland Methodological Quality Score (MQS) which assigns a score from 0 to 1 or 0–2 over 9 categories of quality related to study design, sampling procedures, and interventions for a total of 13 points [12]. Trials receiving scores of 8 or more were considered to be of higher quality. Disagreements were reconciled by consensus through discussion with another investigator (JLS). Mean ± SD postprandial triglyceride endpoints (peak or mean postprandial triglycerides, 24 h post-meal area under the curve for triglycerides, and 2-h triglyceride difference post-meal) were extracted. For trials reporting post-meal area under the curve, peak postprandial triglycerides values were extracted from the graph. Trials reporting both start and end values had change from baseline values calculated. End differences were calculated for all other trials. Missing SD values were calculated from SEM, P-values, or t statistics using standard formulas [13]. Where these statistics were not reported, SD values were imputed using a correlation coefficient, derived from a trial reporting complete data, for between treatment SD [13]. If SD coefficients could not be imputed, then missing SDs were derived from the pooled-SD imputed for the other trials [14].

2.3. Statistical analyses

Data were analyzed using Review Manager (RevMan) version 5.1.6 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for primary analyses and Stata (version 12, College Station, USA) for subgroup and dose response analyses. Pooled analyses for isocaloric fructose feeding trials were conducted using the Generic Inverse Variance method using random effects models. Analyses were stratified by diabetes and non-diabetes. The main outcome was postprandial triglycerides reported as peak, mean, or 2-h change from baseline. Where more than one of these endpoints was reported, the order of preference was peak > mean > 2-h change from baseline postprandial triglycerides. Owing to the pooling of different postprandial

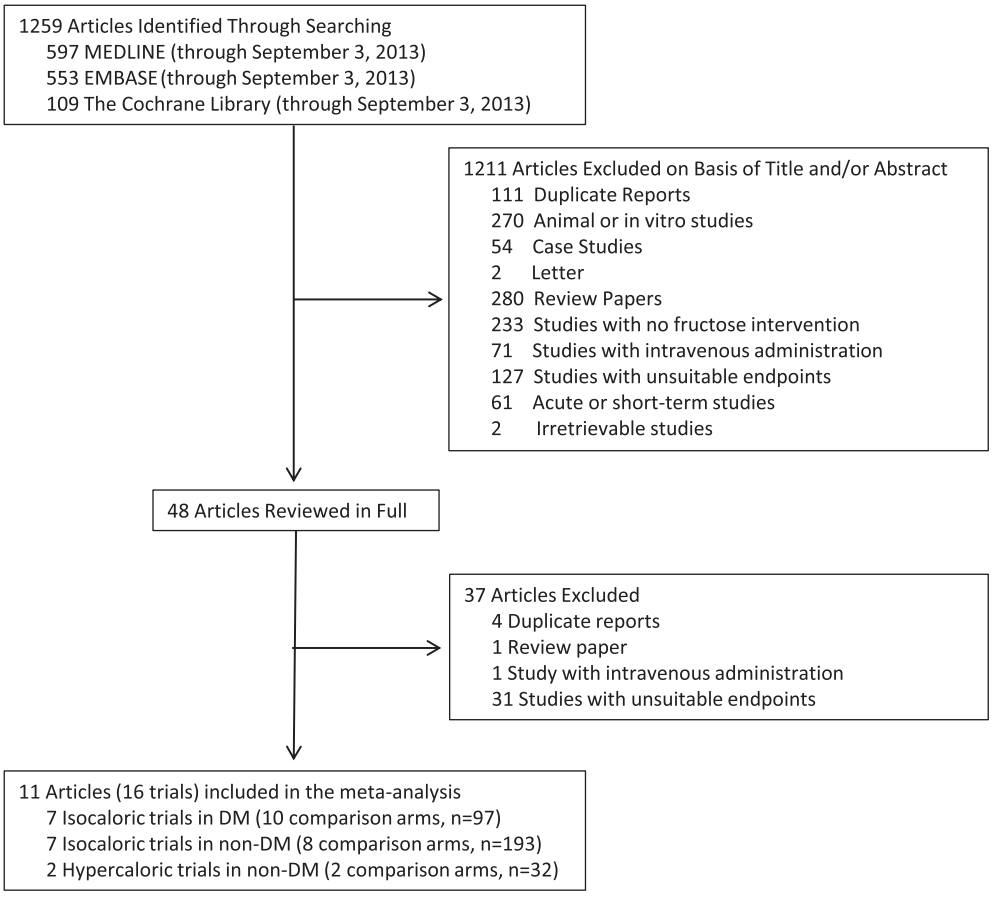

Fig. 1. Flow of the literature search. "unsuitable endpoints" indicates the absence of postprandial triglycerides endpoints.

Table 1
Characteristics of controlled feeding trials investigating the effect of fructose on postprandial triglycerides.[a]

Study	Subjects	Mean age ± SD or range	Baseline postprandial triglycerides[b]	Setting	Design[c]	Feeding control[d]	Randomization
Isocaloric trials							
Diabetes							
Bantle et al., 1986 [23]	12 DM1 (6-M: 6-F)	23-y (15–32-y)	1.54 ± 0.78-mM	O P, USA	C	M	Yes
Bantle et al., 1986 [23]	12 DM2 (5-M: 7-F)	62-y (36–80-y)	3.27 ± 0.79-mM	OP, USA	C	M	Yes
Anderson et al., 1989 [26]	14 DM2 (14-M:0-F)	60 ± 15-y	2.69 ± 0.40-mM	IP/OP, USA	C	S	No
Bantle et al., 1992 [17]	6 DM1 (3-M: 3-F)	23-y (18–34-y)	1.05 ± 0.61-mM	OP, USA	C	M	Yes
Bantle et al., 1992 [17]	12 DM2 (4-M: 8-F)	62-y (40–72-y)	2.34 ± 0.87-mM	OP, USA	C	M	Yes
Malerbi et al., 1996 [18]	16 DM2 (7-M:9-F)	54-y (34–66-y)	2.25 ± 0.40-mM	OP, Brazil	C	S	No
Vaisman et al., 2006 [22]	25 DM2	62 ± 10-y	Starch: 0.40 ± 0.34-mM Fructose: 0.16 ± 0.53-mM	O P, Isreal	P	S	Yes
Overweight/obesity							
Swarbrick et al., 2008 [21]	7 OW/OB (0-M:7-F)	61-y (50–72-y)	1.07 ± 0.92-mM	IP, USA	C	M	No
Stanhope et al., 2009 [25] [k]	32 OW/OB (16-M:16-F)	54 ± 8.1-y	Glucose: 2.57 ± 0.90-mM Fructose: 3.19 ± 0.96-mM	IP/OP, USA	P	M/S	No
Otherwise healthy							
Huttenen et al., 1976 [24]	68 N	28 ± 7.0-y	Sucrose: 1.57 ± 0.92-mM Fructose: 1.46 ± 0.65-mM	OP, Finland	P	S	No
Swanson et al., 1992 [20]	14 N (7-M:7-F)	34-y (19–60-y)	1.28 ± 0.60-mM	OP, Denmark	C	M	Yes
Bantle et al., 2000 [16]	12 N (12-M)	42 ± 12-y	1.33 ± 0.79-mM	OP, USA	C	M	Yes
Bantle et al., 2000 [16]	12 N (12-F)	40 ± 11-y	1.88 ± 0.79-mM	OP, USA	C	M	Yes
Stanhope et al., 2011 [19] [k]	48 N (27-M:21-F)	28 ± 7.1-y	Glucose: 1.5 ± 0.8-mM HFCS: 1.8 ± 0.8-mM	IP/OP, USA	P	M/S	No
Hypercaloric trials							
Overweight/obesity							
Stanhope et al., 2009 [25] [k]	17 OW/OB (9-M:8-F)	52 ± 9.3-y	2.39 ± 1.32-mM	IP/OP, USA	C	M/S	No
Otherwise healthy							
Stanhope et al., 2011 [19] [k]	16 N (9-M:7-F)	28 ± 6.8-y	1.20 ± 0.40-mM	IP/OP, USA	C	M/S	No

[a] DM1 denotes type 1 diabetes mellitus; M, male(s); F, female(s); DM2, type 2 diabetes mellitus; OW, overweight; OB, obese; N, normal, y, year; P, parallel; C, crossover; IP, inpatient; OP, outpatient; M, metabolic; S, supplement; E, energy; wk, week(s); d, days; h, hours; PPTG, postprandial triglycerides.
[b] Baseline postprandial triglycerides represents baseline postprandial triglycerides or the postprandial triglycerides on the control treatment (comparator) in the crossover trials. It represents the baseline postprandial triglycerides on each treatment arm in the parallel trials.
[c] Designs were either crossover (C) or parallel (P).
[d] Metabolic (M) feeding control represents the provision of all meals, snacks, and study supplements (test sugars and foods) consumed during the study under controlled conditions. Supplement (S) feeding control represents the provision of study supplements.
[e] Doses were administered on a g/d, % energy, or g/kg body weight basis. Doses preceded by "~" represent average doses calculated based on the average reported energy intake or weight of participants. If these data were not available, then the average dose was based on a 2000-kcal intake or 70-kg weight.
[f] Fructose was provided in one of three forms: (1) liquid form, where all or most of the fructose was provided as beverages or crystalline fructose to be added to beverages; or (2) mixed form, where all or most of the fructose was provided as a mix of beverages, solid foods (not fruit), and/or crystalline fructose.
[g] Comparator refers to the reference carbohydrate (starch, glucose, sucrose, or HFCS) in the isocaloric trials and diet alone (weight-maintaining, background diet) in the hypercaloric trials. Fructose was exchanged for the reference carbohydrate providing an energy matched comparison in the "isocaloric" trials, whereas it was added to the diet alone (+fructose) providing excess energy relative to the diet alone in the hypercaloric trials.
[h] Values are for energy from carbohydrate:fat:protein. "–" indicates that the information was not available.
[i] Study quality was assessed by the Heyland Methodological Quality Score (MQS) (12). Trials scored ≥8 were considered to be of higher quality.
[j] Agency funding represents funding from government, university, or not-for-profit, health agency sources. None of the trialists declared any conflicts of interest.
[k] Two reports (19,25) contained both isocaloric and hypercaloric trials. In the isocaloric trials, there was over-feeding (positive energy balance) on both the fructose and comparator arms, such that the comparisons were energy matched. The fructose and comparator (glucose) arms in the two isocaloric, parallel trials also featured an outpatient ad libitum, over-feeding period (8-weeks and 10-days, respectively) followed by a shorter inpatient energy-balanced, weight-maintaining period (2-weeks and 3.5-days, respectively). The same fructose arm was compared with the diet alone given over a shorter inpatient energy-balanced, weight-maintaining period (2-weeks and 3.5-days, respectively) in the hypercaloric, crossover trials. The MQS was higher for the isocaloric, parallel trials than the hypercaloric, crossover trials of Stanhope et al. (25), as the hypercaloric trials were not blinded and randomized, respectively.

triglyceride endpoints, data were expressed as standardized mean differences (SMD) with 95% CI, where SMD is interpreted as follows: <0.4 is small effect size, 0.4–0.7 is a moderate effect size, and >0.7 is a large effect size. Change from baseline differences were preferred to end differences. Paired analyses were applied to all crossover trials according to Elbourne et al. [14]. To prevent a unit-of-analysis error induced by including trials with multiple intervention arms, we combined arms to create single pair-wise comparisons. Inter-study heterogeneity was tested by Cochran's Q (χ^2) with the significance level set at $P < 0.10$ and quantified by the I^2 statistic, where $I^2 \geq 50\%$ is evidence of substantial heterogeneity and ≥75%, considerable heterogeneity [10]. Potential sources of methodological heterogeneity were investigated by sensitivity analyses and a priori subgroup analyses, investigating the effect of comparator (starch, sucrose, glucose or HFCS), fructose format (fluid or mixed), dose (Canadian Diabetes Association (CDA) thresholds [15], ≤60-g/day or >60-g/day) follow-up (≤4-weeks or >4-weeks), randomization, study design (parallel or crossover), study quality (MQS < 8 or ≥8), and energy balance (neutral, positive). A continuous dose response relationship was assessed by random effects meta-regression.

2.4. Role of the funding source

This work was funded by a Canadian Institutes of Health Research (CIHR) Knowledge Synthesis grant (funding reference number, 102078) and a grant from the Calorie Control Council. R.J.D. was funded by a CIHR Postdoctoral Fellowship Award, A.M. was funded by a CIHR Canada Graduate Scholarship Master's award and DJAJ was funded by the Government of Canada through the Canada Research Chair Endowment. None of the sponsors had a role in any aspect of the present study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Fructose dose[e]	Fructose form[f]	Comparator[g]	Diet[h]	Energy balance	Follow-up	MQS[i]	Endpoint	Funding type[j]
								-
~136-g/d (21% E)	Mixed	Starch, Sucrose	55:30:15	Neutral	8-d	8	Peak-PPTG	Agency-Industry
~136-g/d (21% E)	Mixed	Starch, Sucrose	55:30:15	Neutral	8-d	8	Peak-PPTG	Agency-Industry
~55-g/d (12% E)	Mixed	Starch	55:25:20	Neutral	23-wk	8	Mean-PPTG	Agency-Industry
~120-g/d (20% E)	Mixed	Starch	55:30:15	Neutral	4-wk	8	Peak-PPTG	Agency-Industry
~120-g/d (20% E)	Mixed	Starch	55:30:15	Neutral	4-wk	8	Peak-PPTG	Agency-Industry
63.2-g/d (20% E)	Liquid	Starch, Sucrose	55:30:15	Neutral	4-wk	7	Mean-PPTG	Agency-Industry
22.5-g/d (4.5% E)	Mixed	Starch	–	Neutral	12-wk	5	2 h-PPTG	–
~125-g/d (25% E)	Liquid	Starch	55:30:15	Neutral	10-wk	7	Peak-PPTG	Agency
~182-g/d (+25% E)	Liquid	Glucose	55:30:15	Positive	2-wk	6	Peak-PPTG	Agency
69 g/d (14% E)	Mixed	Sucrose	–	Neutral	95-wk	5	Peak-PPTG	–
~120-g/d (20% E)	Mixed	Starch	55:15:30	Neutral	4-wk	8	Peak-PPTG	Agency-Industry
85-g/d (17% E)	Mixed	Glucose	55:30:15	Neutral	6-wk	9	Peak-PPTG	Agency
85-g/d (17% E)	Mixed	Glucose	55:30:15	Neutral	6-wk	9	Peak-PPTG	Agency
~168-g/d(+25% E)	Liquid	Glucose, HFCS	55:30:15	Positive	2-wk	6	Peak-PPTG	Agency
~+182-g/d (+25% E)	Liquid	Diet alone	55:30:15	Positive	8-wk	5	Peak-PPTG	Agency
~+168-g/d(+25% E)	Liquid	Diet alone	55:30:15	Positive	2-wk	6	Peak-PPTG	Agency

3. Results

3.1. Search results

Fig. 1 shows the systematic search and selection of the literature. A total of 1259 reports were identified as eligible on the initial search, of which 1211 reports were excluded based on the title or abstract. The remaining 48 reports were retrieved and reviewed, where a further 37 were excluded. A total of 11 reports met the eligibility criteria and were included in this meta-analysis [16–26]. These 11 reports contained 14 isocaloric trials and 2 hypercaloric trials.

3.2. Trial characteristics

Trial characteristics are shown in Table 1. There were 14 isocaloric trials in 290 otherwise healthy (5 trials), overweight/obese (2 trials), and diabetic participants and 2 hypercaloric trials involving 33 participants without diabetes. Participants in isocaloric trials tended to be older (median age, 54 years [range, 23–62 years]) and male (51%), whereas those in hypercaloric trials were middle-aged (median age, 40 years [range, 28–52 years]) and similarly, male (55%). Median baseline postprandial triglycerides was 1.61 mmol/L ([IQR: 1.28–2.34 mmol/L]) in isocaloric trials and 1.80 mmol/L (range, 1.20–2.39 mmol/L) in the two hypercaloric trials.

Isocaloric and hypercaloric trials tended to be small (median number of participants, 14 [range, 6–68] and 16.5 [range, 16–17], respectively). Most (71%) isocaloric trials were conducted in outpatient settings (71%) with the majority of trial centers located in the United States (71%). Both hypercaloric trials were conducted in outpatient/inpatient settings in the United States. Follow-up was short with a median follow-up of 4 weeks (range, 2- to 95 weeks) in the isocaloric trials and 5 weeks (range, 2–8 weeks) in the two hypercaloric trials.

Most isocaloric trials (57%) and neither of the hypercaloric trials were randomized. Most isocaloric (71%) trials and both hypercaloric trials also used crossover designs. Comparators in isocaloric trials were starch (8 trials), sucrose (3 trials), glucose (4 trials) and HFCS (1 trial); the background diet alone was the comparator in both hypercaloric trials. Fructose was administered in mixed (71%) form in the isocaloric trials and in fluid form in both hypercaloric trials. Median fructose doses were 120-g/d (range, 22.5–182 g/d) or 20% *E* (range, 4.5–25% *E*) in the isocaloric trials and +175-g/d (range, +168–182 g/d) or +25% *E* in the two hypercaloric trials.

The diets provided a range of energy and macronutrient profiles. Most isocaloric trials (86%) provided energy under weight-maintaining conditions (neutral energy balance), but 2 trials (15%) provided excess energy in both trial groups (positive energy balance) [19,25]. Macronutrients were similar across the isocaloric and hypercaloric trials: 55% carbohydrate energy, 15–30% and 30% fat energy, and 15–30% and 15% protein energy, respectively. Metabolic feeding control was used by the majority of isocaloric trials (46%), while a combination of metabolic and supplement feeding control was used by both hypercaloric trials.

The Heyland MQS (maximum possible score, 13) ranged from 6 to 8 in isocaloric trials and from 5 to 6 in the two hypercaloric trials; 8 isocaloric trials (57%) and neither of the hypercaloric trials were considered high quality (Heyland MQS $\geq$ 8). Research funding was reported from agency (44%), a combination of agency and industry (44%), or undeclared (12%) sources.

3.3. Isocaloric feeding trials

There was no significant effect of isocaloric exchange of fructose for other carbohydrate in the overall analysis (SMD : 0.14 [95% CI: −0.02, 0.30]) (Fig. 2). There was, however, a significant triglyceride raising effect in overweight/obese participants (SMD: 0.69 [95% CI: 0.20, 1.19]) and a tendency for a postprandialtriglyceride raising effect in otherwise healthy participants (SMD = 0.30 [95% CI: −0.00, 0.60], $P = 0.05$). The effect in participants with diabetes was not significant (SMD: −0.00 [95% CI: −0.15, 0.14]). There was also evidence of considerable interstudy

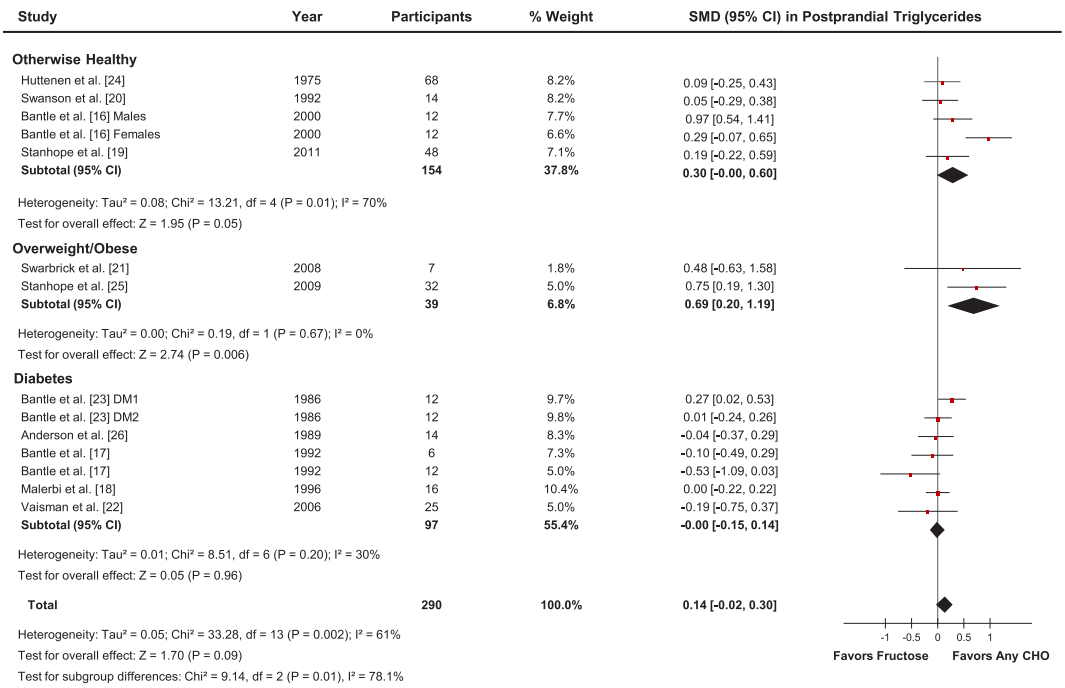

Fig. 2. Forest plots of controlled feeding trials of the effect of isocaloric exchange of fructose for other sources of carbohydrate on pooled postprandial triglyceride endpoints in diabetic and non-diabetic subjects. Three pooled effect estimates (diamonds) are shown: one each for trials in diabetes, non-diabetes, and their combination. Paired analyses were applied to all crossover trials. Data are standardized mean differences (SMD) with 95% CI. *P* values are for Generic Inverse Variance random effects models. Inter-study heterogeneity was tested by Cochran's Q at a significance level of $P < 0.10$ and quantified by I^2.

heterogeneity in the effect seen in otherwise healthy participants ($I^2 = 70\%$, $P = 0.01$) which was driven almost exclusively by the Bantle et al. [16] trial in males and weakened considerably by the removal of anyone trial. There was no evidence of heterogeneity in the overweight/obese participants ($I^2 = 0\%$, $P = 0.67$) or participants with diabetes ($I^2 = 30\%$, $P = 0.20$). The heterogeneity in the otherwise healthy participants drove significant heterogeneity in the overall analysis ($I^2 = 61\%$, $P = 0.002$) and was again explained by Bantle et al. [16]. Systematic removal of each individual trial during sensitivity analyses showed that the removal of Bantle et al. [16] eliminated the evidence for heterogeneity in the healthy participants and the overall analysis.

None of the a priori subgroup analyses were significant (Appendix Fig. 1). Fructose in isocaloric substitution for glucose, however, did increase postprandial triglycerides, although this effect was not statistically different from the lack of effect of fructose on postprandial triglycerides where starch, sucrose, or HFCS were the comparators ($P < 0.10$). This effect was again influenced considerably by Bantle et al. [16]. Significant evidence of unexplained heterogeneity remained within most of the analyses.

Meta-regression analyses did not show evidence of a significant association between fructose dose and effect size (*P* for slope = 0.981) (Appendix Fig. 2).

3.4. Hypercaloric feeding trials

Fructose supplementation significantly increased postprandial triglycerides (SMD = 0.65 [95% CI: 0.30–1.01]) in hypercaloric trials (Fig. 3), with no evidence of interstudy heterogeneity. Neither sensitivity nor subgroup analyses were performed owing to the small number of trials.

3.5. Publication bias

Funnel plots were inspected for the presence of publication bias in isocaloric trials (Appendix Fig. 3). There was a suggestion of funnel plot asymmetry where a small number of trials favoring a postprandial decreasing effect of fructose. However, neither Egger nor Begg tests provided sufficient evidence of publication bias for postprandial triglycerides (Egger test, $P = 0.514$; Begg test, $P = 0.870$). Too few trials were available for a meaningful assessment of publication bias in the hypercaloric trials.

4. Discussion

This systematic review and meta-analysis of 14 controlled feeding trials in 290 diabetic and non-diabetic participants

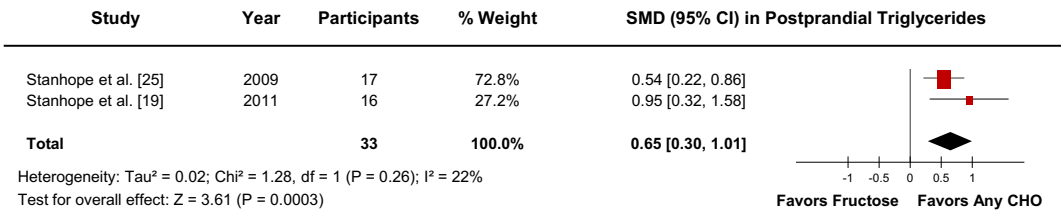

Fig. 3. Forest plots of controlled feeding trials of the effect of fructose supplementing control diets with fructose providing excess energy at high doses compared with the control diets alone on pooled postprandial triglyceride endpoints in diabetic and non-diabetic subjects. Data are standardized mean differences (SMD) with 95% CI. *P* values are for Generic Inverse Variance random effects models. Inter-study heterogeneity was tested by Cochran's Q at a significance level of $P < 0.10$ and quantified by I^2.

demonstrates that in isocaloric trials, in which fructose is provided in isocaloric substitution for other carbohydrate, fructose does not raise postprandial triglycerides. However, in hypercaloric trials, in which fructose supplements the background diet with excess energy (+25% energy) at high doses (~+175-g/day) compared with the background diet alone, fructose does show a significant postprandial triglyceride raising effect. The increase in postprandial triglycerides was 0.81 mmol/L.

The lack of an overall effect of fructose on postprandial triglycerides in the isocaloric trials was unexpected. Fructose is thought to mediate increases in triglyceride by acting as an unregulated substrate for hepatic de novo lipogenesis. It has also been shown to upregulate fatty acid synthase levels, independent of insulin, leading to increases in triglyceride secretion and impaired lipoprotein lipase activity leading to a decreased triglyceride clearance in animal models [27]. Acute, single-bolus feeding studies have supported these mechanisms, demonstrating that fructose leads to greater triglyceride and VLDL levels compared to equal amounts of glucose in healthy, normal weight [28] and obese [29] participants. The reasons for why similar effects were not seen in the present analyses of longer-term trials may relate to dose. The animal models provide fructose at 60% energy [30] and the two acute, single-bolus feeding studies which have found an effect tested intakes of fructose 30–40% energy. A third acute, single-bolus feeding study of fructose compared with glucose at a lower level of intake (25% energy) did not show a significant increase in postprandial triglycerides [31]. In the present analyses, the available isocaloric trials which failed to show an effect of fructose tested median intakes at 20% energy. A postprandial triglyceride-raising effect was seen only in the hypercaloric trials where fructose provided 25% excess energy relative to the background diet alone. These same trials, however, used excess energy diets (positive energy balance) in both the fructose arm and another comparator arm with glucose, so permitting the effect of fructose to be isolated from that of energy under matched yet excess energy feeding conditions [25,29]. Neither of these trials alone or when pooled showed an effect of fructose on postprandial triglycerides in these comparisons. In the absence of an effect in isocaloric comparisons, energy appears to be the dominant driver of the effect of fructose on postprandial triglycerides in the hypercaloric comparisons.

We performed categorical subgroup analyses and continuous meta-regression analyses to assess the robustness of the relationship between fructose and postprandial triglycerides. Previous meta-analyses identified a dose-threshold for a triglyceride-raising effect of fructose: ≥50-g/d for postprandial and ≥100-g/d for fasting triglycerides across different participant groups [8] and >60-g/d for fasting triglycerides in type 2 diabetes [7]. We could not reproduce these thresholds. No dose response was seen in either our categorical or our continuous analyses over the dose range studied (22.5–182-g/day or 4.5–25% energy). Subgroup effects have also been shown for other related endpoints in our earlier systematic reviews and meta-analyses. We showed that comparator (starch) and follow-up (≤4-weeks) modified the effect of fructose on triglycerides in type 2 diabetes [7], while metabolic status (overweight/obesity) and fructose form (fruit) modified the effect of fructose on body weight. On the other hand, we did not report any significant subgroup effects for blood pressure [32], uric acid [33] or glycemic control [34]. In the present set of analyses, none of these subgroup analyses were significant, although effect modification could not be ruled out in all cases. Participants who were overweight/obese showed a postprandial triglyceride raising-effect and those who were otherwise healthy showed a tendency for a postprandial triglyceride raising effect. A postprandial triglyceride raising-effect was also observed where fructose was provided in isocaloric substitution for glucose. These subgroup effects, however, should be interpreted with caution. The effect in overweight/obese participants would not have been expected to differ from the non-significant effect in people with diabetes, most of whom shared an overweight/obese phenotype. The data in otherwise healthy participants or where glucose was the comparator were influenced considerably by a single trial [16]. Finally, formal tests of interaction showed that the effect of fructose where glucose was the comparator did not differ from the lack of effect of fructose on postprandial triglycerides where starch, sucrose, or HFCS were the comparator.

Several limitations exist within the analyses. First are the inconsistent results between similarly designed trials. A group from the University of Minnesota [16,17,23] and another group from the University of Californian at Davis [19,21] each conducted three trials. These trials had many similar procedures and reporting. However, they did not have consistent postprandial triglyceride effects. The widely varying results contribute to the considerable heterogeneity in the overall and subgroup analysis. Sensitivity analyses demonstrated the heterogeneity in the data can be attributed to 1 of the trials from the University of Minnesota in males [16]. This calls for further trials with longer follow up and more varied fructo`se form and intake levels. Second, much of the data presented are end-difference values. The majority of trials only reported end values so a comprehensive review of change from baseline effect could not be reported. This results in the inability to determine the effects of baseline triglyceride differences between treatment groups caused by randomization variation. However, in subgroup analyses of randomized and non-randomized trials, no differences were observed. Third, there were only 1 trial with follow up >10 weeks. Longer term trials would be effective in providing evidence of persistent effects of fructose intake. However, subgroup analyses of trials with follow up >4-wks show no significant overall effects. Fourth, peak postprandial triglycerides for three trials were extracted from day-long metabolic profiles [16,21]. However, the peak postprandial triglyceride values from these profiles were found between 4 and 6 h post meal, which is consistent with previous reports. Finally, only two trials administered fructose below the CDA recommended limit of 60 g/day [15]. The average dose, 101.1 g/day, exceeds the 95th percentile (87 g/d) of fructose intake in the U.S. [9]. Subgroup analysis of trials with doses >60 g/d did not show overall differences between although this demonstrates a need of further trials at more physiological fructose doses.

In conclusion, our systematic review and meta-analysis demonstrates that fructose in isocaloric exchange for other carbohydrate does not raise postprandial triglycerides. A small effect, however, cannot be ruled out under all isocaloric conditions. As there may be a postprandial triglyceride raising effect of fructose in overweight/obese participants and the direction of the pooled effect estimate favors a triglyceride-raising effect of fructose with the lower bound of the 95% CI lying very close to unity in otherwise healthy participants, it is possible that the overall meta-analysis may become significant with the addition of new trials conducted in these groups. Interpretation of these data, however, remains complicated by several factors including the large influence of a single trial [16]. In contrast, there is a consistent and substantial postprandial triglyceride-raising effect of fructose seen in hypercaloric trials, in which fructose supplements background diets with excess energy at extreme doses. In the absence of a clear effect in the isocaloric trials, this postprandial triglyceride-raising effect seems more attributable to excess energy than fructose. The small number and size of the available trials, as well as the methodological limitations and heterogeneity driven by a single trial calls for further, larger longer, and higher quality fructose feeding trials at real world doses to assess the effects of fructose on postprandial triglycerides.

Funding

This work was funded by a Canadian Institutes of Health Research (CIHR) Knowledge Synthesis grant (funding reference number, 102078) and a research grant from the Calorie Control Council. R.J.D. was funded by a CIHR Postdoctoral Fellowship Award and A.M. was funded by a CIHR Canada Graduate Scholarship Master's award. VH and AIC were supported by Ontario Graduate Scholarships. AC was also funded by Canadian Institutes of Health Research (CIHR)-Fredrick Banting and Charles Best Canada Graduate Scholarship and Banting and Best Diabetes Centre (BBDC)-Novo Nordisk Studentship. DJAJ was funded by the Government of Canada through the Canada Research Chair Endowment. None of the sponsors had a role in any aspect of the present study, including design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

Contributions

Conception and design

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Analysis and interpretation of the data

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Drafting of the article

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Competing interests

J.L.S. has received research support from the Canadian Institutes of health Research (CIHR), Calorie Control Council, The Coca-Cola Company (investigator initiated, unrestricted grant), Pulse Canada, and International Tree Nut Council Nutrition Research & Education Foundation. He has received travel funding, speaker fees, and/or honoraria from the American Heart Association (AHA), American College of Physicians (ACP), American Society for Nutrition (ASN), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH), Canadian Diabetes Association (CDA), Canadian Nutrition Society (CNS), University of South Carolina, Calorie Control Council, Diabetes and Nutrition Study Group (DNSG) of the European Association for the Study of Diabetes (EASD), International Life Sciences Institute (ILSI) North America, International Life Sciences Institute (ILSI) Brazil, Abbott Laboratories, Pulse Canada, Canadian Sugar Institute, Dr. Pepper Snapple Group, and The Coca-Cola Company. He is on the Clinical Practice Guidelines Expert Committee for Nutrition Therapy of both the Canadian Diabetes Association (CDA) and European Association for the study of Diabetes (EASD), as well as being on the American Society for Nutrition (ASN) writing panel for a scientific statement on the metabolic and nutritional effects of fructose, sucrose and high fructose corn syrup. He is an unpaid scientific advisor for the International Life Science Institute (ILSI) North America, Food, Nutrition, and Safety Program (FNSP). His wife is an employee of Unilever Canada. R.J.D. and J.B. have received research support from the CIHR, Calorie Control Council, and The Coca-Cola Company (investigator initiated, unrestricted). R.J.D. has served as an external resource person to the World Health Organization's (WHO) Nutrition Guidelines Advisory Group (NUGAG), and was the lead author of a systematic review and meta-analysis commissioned by the WHO of trans fatty acids and health outcomes. The WHO paid for his travel and accommodation to attend the 5th NUGAG Meeting in Hangzhou, China (4-7 Mar, 2013). L.C. a casual Clinical Research Coordinator at GI Laboratories, Toronto, Canada. L.C., V.H., A.M., and A.J.C. have received research support from the CIHR. M.D. is the Vice President, Science & Research at the American Heart Association, Dallas, Texas. A.L.J. is a part owner, Vice-President, and Director of Research of Glycemic Index Laboratories, Toronto, Canada. She has received research support from the CDA. T.M.S.W. is a part owner and the President of Glycemic Index Laboratories, Toronto, Canada and has authored several popular diet books on the glycemic index for which he has received royalties from Phillipa Sandall Publishing Services and CABI Publishers. He has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for CIHR, CDA Dairy Farmers of Canada, McCain Foods, Temasek Polytechnic, Northwestern University, Royal Society of London, Glycemic Index Symbol program, CreaNutrition AG, McMaster University, Canadian Society for Nutritional Sciences, National Sports and Conditioning Association, Faculty of Public Health and Nutrition—Autonomous University of Nuevo Leon, Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes. C.W.C.K. has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Calorie Control Council, The Coca Cola Company (investigator initiated, unrestricted), Abbott Laboratories, Advanced Food Materials Network, Almond Board of California, American Peanut Council, American Pistachio Growers, Barilla, California Strawberry Commission, Canola Council of Canada,

Danone, General Mills, Hain Celestial, International Tree Nut Council, Kellogg, Loblaw Brands Ltd, Oldways, Orafti, Paramount Farms, Pulse Canada, Saskatchewan Pulse Growers, Solae and Unilever. D.J.A.J. has received consultant fees, honoraria, travel funding, or research support from or served on the scientific advisory board for the CIHR, Canadian Foundation for Innovation (CFI), Ontario Research Fund (ORF), and Advanced Foods and Material Network (AFMNet) Calorie Control Council, The Coca Cola Company (investigator initiated, unrestricted), Barilla, Solae, Unilever, Hain Celestial, Loblaws Supermarkets, Inc., Sanitarium Company, Herbalife International, Pacific Health Laboratories, Inc., Metagenics/MetaProteomics, Bayer Consumer Care, Oldways Preservation Trust, The International Tree Nut Council Nutrition Research & Education, The Peanut Institute, Procter and Gamble Technical Centre Limited, Griffin Hospital for the development of the NuVal System, Soy Advisory Board of Dean Foods, Alpro Soy Foundation, Nutritional Fundamentals for Health, Pacific Health Laboratories, Kellogg's, Quaker Oats, The Coca-Cola Sugar Advisory Board, Pepsi Company, Agrifoods and Agriculture Canada (AAFC), Canadian Agriculture Policy Institute (CAPI), The Almond Board of California, The California Strawberry Commission, Orafti, the Canola and Flax Councils of Canada, Pulse Canada, the Saskatchewan Pulse Growers, and Abbott Laboratories. D.D.W., A.I.C., and L.A.L. have no declared conflicts of interest related to this paper.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.atherosclerosis.2013.10.019.

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