Effect of Fructose on Glycemic Control in Diabetes

A systematic review and meta-analysis of controlled feeding trials

Adrian I. Cozma, hbsc[1,2]
John L. Sievenpiper, md, phd[1,3]
Russell J. de Souza, scd, rd[1,2,4]
Laura Chiavaroli, msc[1,2]
Vanessa Ha, hbsc[1,2]
D. David Wang, hbsc[1,2]
Arash Mirrahimi, msc[1,2]
Matt E. Yu, hbsc[1,2]

Amanda J. Carleton, msc[1,5]
Marco Di Buono, phd[6]
Alexandra L. Jenkins, phd, rd[1]
Lawrence A. Leiter, md[1,2,7,8]
Thomas M.S. Wolever, md, phd[1,2,7,8]
Joseph Beyene, phd[9,10,11]
Cyril W.C. Kendall, phd[1,2,12]
David J.A. Jenkins, md, phd[1,2,7,8]

OBJECTIVE—The effect of fructose on cardiometabolic risk in humans is controversial. We conducted a systematic review and meta-analysis of controlled feeding trials to clarify the effect of fructose on glycemic control in individuals with diabetes.

RESEARCH DESIGN AND METHODS—We searched MEDLINE, EMBASE, and the Cochrane Library (through 22 March 2012) for relevant trials lasting ≥7 days. Data were aggregated by the generic inverse variance method (random-effects models) and expressed as mean difference (MD) for fasting glucose and insulin and standardized MD (SMD) with 95% CI for glycated hemoglobin (HbA$_{1c}$) and glycated albumin. Heterogeneity was assessed by the Cochran Q statistic and quantified by the I^2 statistic. Trial quality was assessed by the Heyland methodological quality score (MQS).

RESULTS—Eighteen trials ($n = 209$) met the eligibility criteria. Isocaloric exchange of fructose for carbohydrate reduced glycated blood proteins (SMD −0.25 [95% CI −0.46 to −0.04]; $P = 0.02$) with significant intertrial heterogeneity ($I^2 = 63\%$; $P = 0.001$). This reduction is equivalent to a ~0.53% reduction in HbA$_{1c}$. Fructose consumption did not significantly affect fasting glucose or insulin. A priori subgroup analyses showed no evidence of effect modification on any end point.

CONCLUSIONS—Isocaloric exchange of fructose for other carbohydrate improves long-term glycemic control, as assessed by glycated blood proteins, without affecting insulin in people with diabetes. Generalizability may be limited because most of the trials were <12 weeks and had relatively low MQS (<8). To confirm these findings, larger and longer fructose feeding trials assessing both possible glycemic benefit and adverse metabolic effects are required.

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The number of people with type 2 diabetes is likely to double during the next 20 years (1), leading to an increased burden of cardiovascular disease (2), renal failure (2), blindness (2), and risk of colon, breast, and other cancers (3). Diabetes profoundly alters macronutrient metabolism; the roles of diet and especially carbohydrate type and quality are therefore of considerable interest. Since 1970, the total availability of sugars has increased by ~20% (4), and high-fructose corn syrup now represents nearly 50% of caloric sweetener use in the United States (4,5). Increased total fructose consumption (from both sucrose and high-fructose corn syrup) has been implicated in the development of the obesity epidemic in the United States (6) and has been singled out in diabetes guidelines because of concerns about its effects on lipids.

Diabetes associations (2,7,8) have taken a harm-reduction approach to fructose recommendations, setting an upper threshold for intake that is based on putative adverse effects on serum lipids. The American Diabetes Association guidelines, however, acknowledge that fructose produces a lower glycemic response in people with diabetes when it replaces sucrose and starch in the diet (7). Fructose has also been shown to improve glycemia without adversely affecting lipids when exchanged for other carbohydrate in controlled feeding trials in people with type 2 diabetes (9–15). In the absence of clear guidance on the role of fructose in glycemic control, we conducted a systematic review and meta-analysis of controlled feeding trials to assess the effects of isocaloric, oral fructose exchange for carbohydrates on fasting glucose, fasting insulin, and glycated blood proteins (glycated hemoglobin [HbA$_{1c}$], glycated albumin, and fructosamine) in individuals with diabetes.

RESEARCH DESIGN AND METHODS—We followed the *Cochrane Handbook for Systematic Reviews of Interventions* for the planning and

conduct of this meta-analysis (16). The reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (17).

Study selection

We searched MEDLINE, EMBASE, and Cochrane databases through 22 March 2012 with the following search terms: fructose AND (glucose OR glycemic OR glycemic OR glycaemia OR glycemia OR insulin OR OGTT OR HOMA-IR OR HbA$_{1c}$ OR fructosamine). Manual searches supplemented the electronic search strategy. We included controlled feeding trials that investigated the effect of oral fructose in isocaloric exchange for other sources of carbohydrate on markers of glycemic control in individuals with diabetes. Trials that had <7 days of follow-up, administered fructose intravenously, lacked an adequate carbohydrate comparator, or did not provide suitable end point data were excluded. No restriction was placed on language.

Data extraction

Reports that met the inclusion criteria were each independently reviewed and extracted by at least two investigators with a standardized form. Relevant information about study design, randomization, blinding, level of feeding control, sample size, subject characteristics, fructose format, dose, reference carbohydrate, duration of follow-up, and macronutrient profile of the background diet were obtained. We extracted mean ± SD posttreatment values for fasting glucose, fasting insulin, and percentage glycated blood proteins (HbA$_{1c}$, glycated albumin, and fructosamine, with HbA$_{1c}$ preferred). Trials that did not report SDs had these values imputed from SD, 95% CI, P values, t or F statistics according to standard formulas (16). When these statistics were unavailable, an imputed pooled SD from the other trials included in the meta-analysis was applied (16). Imputations were necessary for 11 of 13 glycated blood protein trials, 8 of 16 fasting glucose trials, and 5 of 7 fasting insulin trials. The quality of each study was assessed with the Heyland methodological quality score (MQS) (18). Trials were considered to be of high quality if they obtained an MQS ≥8. Heyland score disagreements were reconciled by consensus. Authors were contacted to request additional information, where necessary.

Statistical analyses

Data were analyzed with Review Manager (RevMan) software version 5.0.25 (Nordic Cochrane Centre, Copenhagen, Denmark). Stratified aggregate analyses were conducted for undifferentiated diabetes, type 1 diabetes, and type 2 diabetes with the generic inverse variance method with random-effects models. Change from baseline differences between fructose and carbohydrate comparator for fasting glucose, fasting insulin, and percentage glycated protein were extracted as the primary end points. When these data were unavailable, end-of-treatment differences were used. Paired analyses were applied to all crossover trials (19). A weighted average was applied within studies to combine multiple comparator arms. When two separate control phases were present within the same crossover study, both phases were averaged and compared with the fructose intervention. Data were expressed as mean difference (MD) for fasting glucose and insulin, and standardized MD (SMD) for glycated blood proteins, all with 95% CI. Although baseline subject characteristics were reported in terms of HbA$_{1c}$, certain studies reported end values in terms of glycated albumin, necessitating the use of SMDs in our analysis. Between-trial heterogeneity was tested by the Cochran Q statistic with a significance level set at $P < 0.10$. Heterogeneity was quantified by the I^2 statistic, where $I^2 \geq 50\%$ was considered evidence of substantial heterogeneity (16). Sources of heterogeneity were investigated by a priori subgroup analyses assessing the effects of carbohydrate comparator, fructose form, dose, baseline values, trial quality, trial design, length of follow-up, and randomization. Sensitivity analyses were performed to determine if any single study exerted an undue influence on the overall result. To address this point, we systematically removed each individual study from the meta-analysis and


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4401 Reports Identified
 338  Cochrane Library (to March 22, 2012)
3688  EMBASE (1980 to March 22, 2012)
 371  MEDLINE (1948 to March 22, 2012)
  4   Manual Searches
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4347 Reports Excluded on Basis of Title and/or Abstract
 193 Animal or in-vitro reports
 173 Acute or short-term reports
  42 Case study reports
   2 Co-interventions
 681 Duplicate reports
  80 Letters / editorials / commentaries
 107 No suitable endpoints
  43 Observational reports
1808 Reports with no isocaloric oral fructose intake
  96 Reports with intravenous administration
1122 Review reports and meta-analyses
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54 Reports Reviewed in Full
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38 Reports Excluded
  1 Acute or short-term report
  2 Co-interventions
  2 Reports with no oral fructose intake
  3 No suitable endpoints
  5 Irretrievable reports
 25 Reports in people without diabetes
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16 Reports (18 trials) were included in the Meta-Analysis
  3 Trials in DM 1 (3 comparison arms, n=28)
 14 Trials in DM 2 (15 comparison arms, n=161)
  1 Trial in DM 1/2 (2 comparison arms, n=20)
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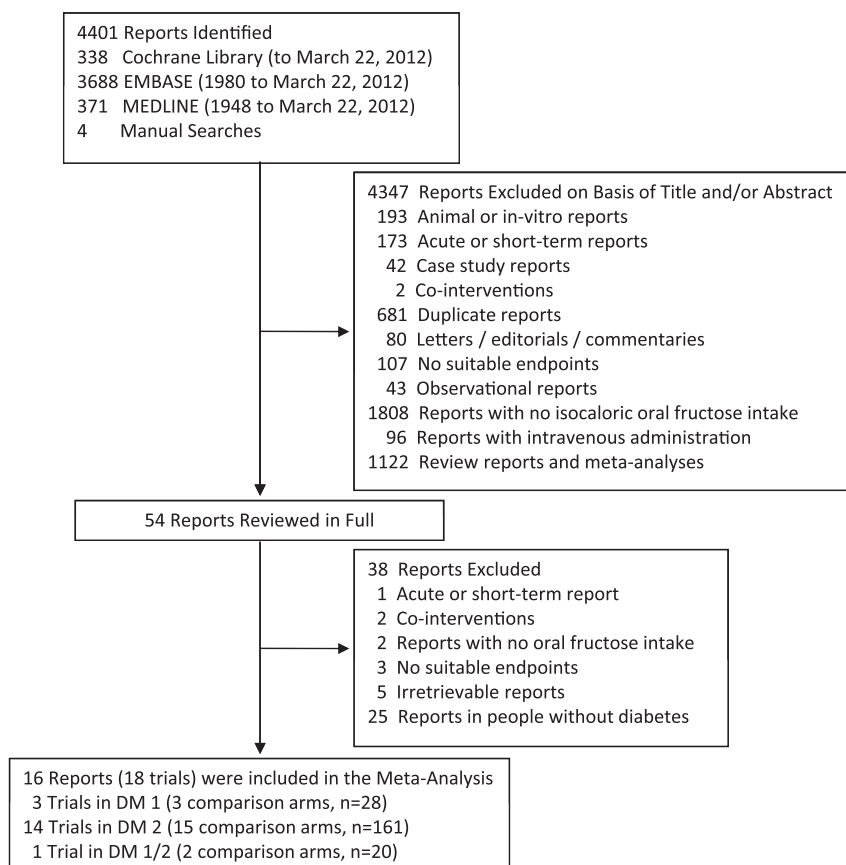**Figure 1**—*Flowchart of literature search for the effect of fructose on glycemic end points (fasting glucose, fasting insulin, and glycated blood proteins [HbA$_{1c}$ and glycated albumin]). Electronic searches of Cochrane Library, EMBASE and MEDLINE databases were supplemented by manual searches of the references of included trials. DM 1, type 1 diabetes; DM 2, type 2 diabetes; DM 1/2, both type 1 and type 2 diabetes.*

Table 1—*Characteristics of experimental trials included in the meta-analysis*

Study	Subjects	Age	Disease duration	Glucose	HbA$_{1c}$ (%)	Diabetes treatment	Design	Feeding control	Randomized	Fructose dose	Fructose form*	Comparator	Diet†	Follow-up	MQS	Funding sources
DM1																
Pelkonen et al. 1972 (24)	10 DM1 (5:5)	25.5 (19–70)	12.4 (3–22)	9.3	—	100% I	C	Metabolic	N	75 (15% E)	Mixed	Starch	40:40:20	10 days	7‡	Agency
Bantle et al. 1986(15)§	12 DM1 (6:6)	23 (15–32)	11 (2–20)	—	9.93 ± 1.84	100% I	C	Metabolic	Y	~137 (21% E)	Mixed	Starch	55:30:15	8 days	8‡	Agency, industry
Bantle et al. 1992(20)§	6 DM1 (3:3)	23 (18–34)	11 (1–26)	8.24 ± 4.21	8.07 ± 0.27	100% I	C	Metabolic	Y	~120 (20% E)	Mixed	Starch	55:30:15	4 weeks	8‡	Agency, industry
DM2																
Anderson et al. 1989 (12)	14 DM2 (14:0)	60 ± 4 (54–71)	8.8 ± 6.8 (1–23)	11.16 ± 1.11	10.6 ± 1.87	28% D, 36% D + M, 36% D + I	C	Partially metabolic	N	~55 (12% E)	Mixed	Starch	53:27:20	23 weeks	8	Agency, industry
Bantle et al. 1986(15)§	12 DM2 (5:7)	62 (36–80)	7 (0.5–29)	—	8.52 ± 2.36	42% D, 58% M	C	Metabolic	Y	~137 (21% E)	Mixed	Starch	55:30:15	8 days	8‡	Industry
Bantle et al. 1992(20)§	12 DM2 (4:8)	62 (40–72)	7 (0.25–33)	8.33 ± 2.35	7.24 ± 2.05	42% D, 42% D + I, 16% M	C	Metabolic	Y	~120 (20% E)	Mixed	Starch	55:30:15	4 weeks	8‡	Agency, industry
Crapo et al. 1986 (26)	7 DM2 (3:4)	50.9 ± 8.4		10.3 ± 3.61	—	100% D	C	Metabolic	N	~98 (13.2% E)	Mixed	Sucrose	55:30:15	2 weeks	7‡	Agency, industry
Grigoresco et al. 1988 (21)	8 DM2 (5:3)	40 ± 6.9	5.6 ± 8.9 (0.5–25)	8.0 ± 1.4	6.8 ± 1.6	50% D, 50% M	C	Nonmetabolic	Y	30 (8% E)	Mixed	Starch	50:30:20	8 weeks	8	Agency, industry
Koivisto et al. 1993 (13)	10 DM2 (4:6)	61 ± 9.5	8 ± 6.3	—	—	30% D, 70% M	C	Metabolic	Y	~55 (10% E)	Fluid	Starch	50:30:20	4 weeks	9‡	Agency, industry
Malerbi et al. 1996 (9)	16 DM2 (7:9)	54.2 ± 9.2	2.7 ± 4 (0.2–15)	7.2 ± 1.6	7.5 ± 1.2	38% D, 62% D + M	C	Nonmetabolic	N	63.2 (20% E)	Fluid	Starch, sucrose	55:30:15	4 weeks	7	Agency, industry
McAteer et al. 1987 (27)	10 DM2	64.6	5.6	—	—	—	C	Nonmetabolic	N	55 (11.6% E)	Fluid	Starch	42:38:20	4 weeks	7	Industry
Osei et al. 1987 (11)	18 DM2 (3:15)	57 ± 3.0	10.6 ± 2.1	12.65 ± 10.8	11.51 ± 2.48	22% M, 78% I	P	Nonmetabolic	Y	60 (10% E)	Mixed	Starch	50:35:15	12 weeks	8	Agency, industry
Osei et al. 1989 (10)	13 DM2 (5:8)	54 ± 10.8	10.6 ± 4.3	11.8 ± 1.12	11	31% I, 23% M, 8% D, 38% M + I	C	Nonmetabolic	Y	60 (7.5% E)	Mixed	Starch	50:35:15	26 weeks	8‡	Agency, industry
Thorburn et al. 1989 (28)	8 DM2 (4:4)	55 ± 11.2	13 ± 6.7	12.17	—	100% D	P	Metabolic	N	~100 (13% E)	Mixed	Sucrose	55:30:15	12 weeks	6‡	Agency, industry
Thorburn et al. 1990 (22)	6 DM2 (4:2)	53.7 ± 10.2	13.3 ± 7.3 (1–21)	11.5 ± 3.13	10.0 ± 4.7	100% D	C	Metabolic	N	~100 (13% E)	Mixed	Sucrose	55:30:15	100 days	4‡	Agency, industry
Vaisman et al. 2006 (23)	25 DM2	62.6 ± 10.2	—	11.47 ± 3.57	8.47 ± 0.83	92% M, 8% I	P	Nonmetabolic	Y	22.5 g/d (4.5% E)	Fluid	Starch	—	12 weeks	5	—

Table 1—Continued

Study	Subjects	Age	Disease duration	HbA$_{1c}$ (%)	Glucose	Diabetes treatment	Design	Feeding control	Randomized	Fructose dose	Fructose form*	Comparator	Diet†	Follow-up	MQS	Funding sources
Turner et al. 1979 (25)	2 DM2 (2:0)	41 ± 1.4	—	—	5.86 ± 0.20	100% D	C	Metabolic	N	~40 (6% E)	Fluid	Starch	45:40:15	2 weeks	7‡	Agency, industry
DM1/2																
Blayo et al. 1990 (14)	14 DM1, 6 DM2	46.9 ± 13.1	11.4 ± 6.4	8.35	—	—	P	Nonmetabolic	Y	~25 (5% E)	Mixed	Starch, sucrose	55:30:15	52 weeks	7	Agency, industry

Data are expressed as n, male:female ratio, median (IQR), mean ± SD, or percentage of total patients, except as marked. Age and disease duration are expressed in years; glucose is given as mean fasting glucose value obtained at study onset expressed in millimoles per liter; HbA$_{1c}$ is given as baseline HbA$_{1c}$ values obtained at study onset expressed as a percentage; fructose dose is given both in grams per day and as a percentage of total energy (E). DM1, type 1 diabetes; I, insulin therapy; C, crossover study design; DM2, type 2 diabetes; D, dietary therapy; M, medication; P, parallel study design; DM1/2, undifferentiated diabetes. *Fructose was provided in a liquid form, where all or most of the fructose was provided as a beverage; or in a crystalline form to be added to a beverage; in a mixed form, where all or most of the fructose was provided as beverages, solid foods, or crystalline fructose to be added to beverages or foods; or in a solid form, where all or most of the fructose was provided in a natural food or baked product. †Values are for the ratio of carbohydrate:fat:protein. ‡Studies with metabolic feeding control. §For Bantle et al. 1986 (15) and Bantle et al. 1992 (20), baseline HbA$_{1c}$ was measured but glycosylated blood proteins were reported as end values.

recalculated the pooled effect size from the remaining studies. Meta-regression was performed to assess the significance of subgroup effects with Stata software version 11.2 (StataCorp, College Station, TX). Publication bias was investigated by inspection of funnel plots and quantitatively assessed with Begg and Egger tests.

RESULTS

Search results

A total of 4,401 eligible reports were identified with the search; of these, 4,347 were determined to be irrelevant on review of the titles and abstracts. The remaining 54 reports were retrieved and reviewed in full, and a further 38 were excluded. A total of 16 reports (18 trials) were selected for pooled analyses (Fig. 1). The characteristics of the 18 included trials are shown in Table 1.

Glycated blood proteins

A total of 13 glycated blood protein comparisons were made among 172 subjects with type 1 diabetes (2 trials, $n = 18$) (15,20), type 2 diabetes (10 trials, $n = 134$) (9–13,15,20–23), or undifferentiated diabetes (1 trial, $n = 20$) (14). Patients had a median age of 54.2 years (interquartile range [IQR] 46.9–61 years) and a diabetes duration of 9.7 years (7–11 years). Their median baseline HbA$_{1c}$ values were 8.5% (IQR 7.9–10.1%). Ten trials were randomized (77%). Ten trials used crossover designs (77%), and three used parallel designs (23%). Starch (77%) and sucrose (7.7%) were used as carbohydrate comparators, and notably Malerbi et al. (9) and Blayo et al. (14) used both starch and sucrose comparisons (15.3%). Fructose was administered in mixed (77%) and fluid (23%) formats at a median dose of 60.0 g/day (IQR 55–120 g/day), with 6 trials (46%) exceeding the Canadian Diabetes Association (CDA) threshold of 60 g/day (2) and 10 trials (77%) exceeding the European Association for the Study of Diabetes (EASD) threshold of 30 g/day (8). Six trials (46.2%) were metabolically controlled, providing all foods consumed, six trials (46.2%) were not metabolically controlled, and one trial (7.6%) was partially metabolically controlled, providing some of all foods consumed. Background diets were 50–55% carbohydrate, 20–35% fat, and 15–30% protein. The median follow-up was 8 weeks (IQR 4–14.3 weeks). Nine trials were of high quality (MQS $\geq$ 8), with a median MQS of 8 (IQR 7–8). No eligible study measured fructosamine.

No hypercaloric feeding trials met the inclusion criteria.

Figure 2A shows the effect of isocaloric fructose exchange for other carbohydrates on glycated blood proteins. There was a significant reduction in the percentage of glycated blood proteins (SMD −0.27 [95% CI −0.49 to −0.04]; $P = 0.02$), with significant evidence of interstudy heterogeneity ($I^2 = 66\%$ [95% CI 40–81]; $P < 0.001$) in people with type 1 and type 2 diabetes combined. A significant reducing effect on glycated blood proteins was also seen in subjects with type 1 diabetes (SMD −0.78 [95% CI −1.11 to −0.44]; $P < 0.001$), with no evidence of interstudy heterogeneity ($I^2 = 0\%$, [95% CI not estimable]; $P = 0.96$). No effect was seen in the type 2 diabetes stratum, (SMD −0.13 [95% CI −0.34 to 0.09]; $P = 0.24$), with evidence of significant interstudy heterogeneity ($I^2 = 56\%$ [95% CI 10–78%]; $P = 0.02$). Systematic removal of individual studies did not alter the results. Meta-regression revealed no statistically significant subgroup effects (Supplementary Fig. 1).

Fasting glucose

A total of 16 fasting glucose comparisons were made among 176 subjects with type 1 diabetes (3 trials, $n = 28$) (15,20,24), type 2 diabetes (13 trials, $n = 128$) (9–13,15,20–22,25–27), and undifferentiated diabetes (1 trial, $n = 20$) (14). Patients had a median age of 53.9 years (IQR 40.8–60.3 years) and a diabetes duration of 9.7 years (7–11 years). Their median baseline fasting glucose values were 9.3 mmol/L (IQR 8.1–11.3 mmol/L). Nine trials were randomized (56%). Fourteen trials used crossover designs (88%), and two used parallel designs (12%). Starch (75%) and sucrose (13%) were used as carbohydrate comparators, and notably Malerbi et al. (9) and Blayo et al. (14) used both starch and sucrose comparisons (12%). Fructose was administered in mixed (75%) and fluid (25%) formats at a median dose of 61.6 g/day (IQR 55–105 g/day), with 8 trials (50%) exceeding the CDA threshold of 60 g/day (2) and 14 trials (88%) exceeding the EASD threshold of 30 g/day (8). Nine trials (56%) were metabolically controlled, six trials (38%) were nonmetabolically controlled, and one trial (6%) was partially metabolically controlled. Background diets were 40–55% carbohydrate, 20–40% fat, and 15–30% protein. The median follow-up was 4 weeks (IQR 2–12.6 weeks). Nine trials were of high quality, with a median MQS of 8 (IQR 7–8). No hypercaloric feeding trials met the inclusion criteria.
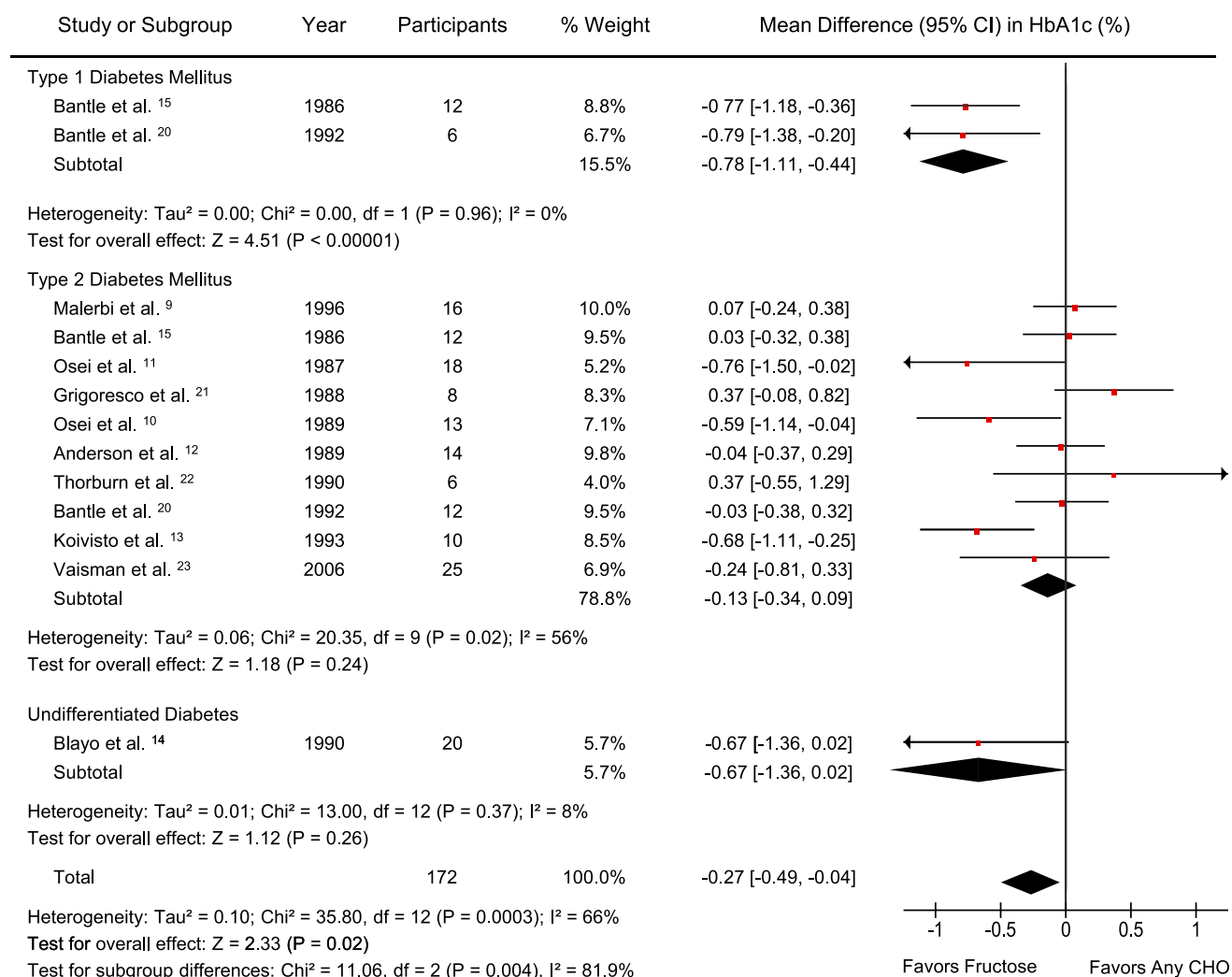
A Glycated Blood Proteins

Study or Subgroup	Year	Participants	% Weight	Mean Difference (95% CI) in HbA1c (%)
Type 1 Diabetes Mellitus				
Bantle et al. [15]	1986	12	8.8%	-0 77 [-1.18, -0.36]
Bantle et al. [20]	1992	6	6.7%	-0.79 [-1.38, -0.20]
Subtotal			15.5%	-0.78 [-1.11, -0.44]

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%
Test for overall effect: Z = 4.51 (P < 0.00001)

Type 2 Diabetes Mellitus				
Malerbi et al. [9]	1996	16	10.0%	0.07 [-0.24, 0.38]
Bantle et al. [15]	1986	12	9.5%	0.03 [-0.32, 0.38]
Osei et al. [11]	1987	18	5.2%	-0.76 [-1.50, -0.02]
Grigoresco et al. [21]	1988	8	8.3%	0.37 [-0.08, 0.82]
Osei et al. [10]	1989	13	7.1%	-0.59 [-1.14, -0.04]
Anderson et al. [12]	1989	14	9.8%	-0.04 [-0.37, 0.29]
Thorburn et al. [22]	1990	6	4.0%	0.37 [-0.55, 1.29]
Bantle et al. [20]	1992	12	9.5%	-0.03 [-0.38, 0.32]
Koivisto et al. [13]	1993	10	8.5%	-0.68 [-1.11, -0.25]
Vaisman et al. [23]	2006	25	6.9%	-0.24 [-0.81, 0.33]
Subtotal			78.8%	-0.13 [-0.34, 0.09]

Heterogeneity: Tau² = 0.06; Chi² = 20.35, df = 9 (P = 0.02); I² = 56%
Test for overall effect: Z = 1.18 (P = 0.24)

Undifferentiated Diabetes				
Blayo et al. [14]	1990	20	5.7%	-0.67 [-1.36, 0.02]
Subtotal			5.7%	-0.67 [-1.36, 0.02]

Heterogeneity: Tau² = 0.01; Chi² = 13.00, df = 12 (P = 0.37); I² = 8%
Test for overall effect: Z = 1.12 (P = 0.26)

Total		172	100.0%	-0.27 [-0.49, -0.04]

Heterogeneity: Tau² = 0.10; Chi² = 35.80, df = 12 (P = 0.0003); I² = 66%
Test for overall effect: Z = 2.33 (P = 0.02)
Test for subgroup differences: Chi² = 11.06, df = 2 (P = 0.004), I² = 81.9%

Favors Fructose   Favors Any CHO

Figure 2—*Forest plot of controlled feeding trials investigating the effect of isocaloric exchange of fructose for other carbohydrate on* (A) *glycated blood proteins (HbA$_{1c}$ and glycated albumin),* (B) *fasting glucose, and* (C) *fasting insulin. Data are SMD for glycated blood proteins and MD for fasting glucose and insulin with 95% CI (16). P values are for generic inverse variance random effects models. Interstudy heterogeneity was tested by the Cochran Q statistic (χ^2) at a significance level of P < 0.1 and quantified by I^2 (2,16). There were no studies investigating type 1 or undifferentiated diabetes for fasting insulin. CHO, carbohydrate. (A high-quality color representation of this figure is available in the online issue.)*

Fig. 2B shows the effect of isocaloric fructose exchange for other carbohydrates on fasting glucose. There was a borderline reducing effect on fasting glucose (MD −0.40 mmol/L [95% CI −0.83 to 0.03]; P = 0.07) in the overall analysis, with evidence of substantial and significant interstudy heterogeneity (I^2 = 63% [95% CI 38–79%]; P < 0.001). There was a trend favoring a reduction in fasting glucose in people with type 2 diabetes (MD −0.46 mmol/L [95% CI −0.92 to 0.01]; P = 0.06) but not type 1 diabetes (MD −0.46 mmol/L [95% CI −2.83 to 1.91]; P = 0.7), although both strata had evidence of substantial and significant interstudy

heterogeneity (I^2 = 69% [95% CI 43–83%]; P < 0.001; and I^2=65% [95% CI 0–90%]; P = 0.06, respectively). A significant fasting glucose lowering effect was seen in the overall analysis after the systematic removal of either Bantle et al. (15) (MD −0.50 mmol/L [95% CI −0.94 to −0.05]; P = 0.03) or Turner et al. (25) (MD −0.51 mmol/L [95% CI −0.96 to −0.06]; P = 0.03) during our sensitivity analysis. Similarly, the removal of either study achieved significance in the type 2 diabetes subset, with an MD of −0.57 mmol/L (95% CI −1.05 to −0.10; P = 0.02) after removal of Bantle et al. (15) and an MD of −0.59 mmol/L (95% CI

−1.09 to −0.09; P = 0.02) after removal of Turner et al. (25). There was no change in the interstudy heterogeneity during sensitivity analyses. Meta-regression revealed no statistically significant subgroup effects (Supplementary Fig. 2).

Fasting insulin
A total of 7 comparisons were made in 57 subjects with type 2 diabetes (7 trials, n = 57) (9,13,21,22,25,26,28). Patients had a median age of 53.7 years (IQR 46.0–54.6 years) and a diabetes duration of 8 years (5.6–13 years). Four trials (57%) used diet-only interventions, and three trials (43%) used a combination of diet and
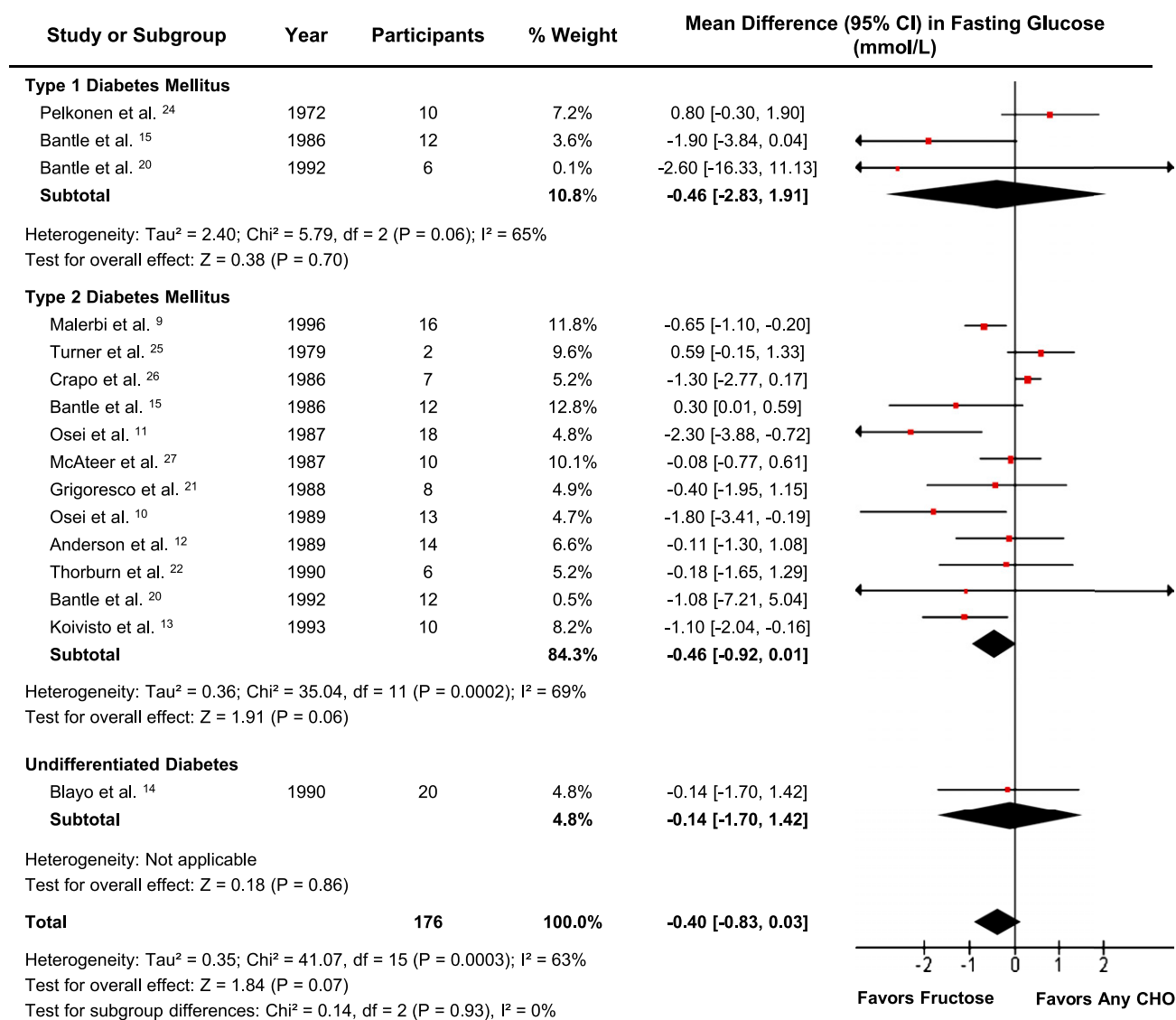
B   Fasting Glucose

Study or Subgroup	Year	Participants	% Weight	Mean Difference (95% CI) in Fasting Glucose (mmol/L)
Type 1 Diabetes Mellitus				
Pelkonen et al. [24]	1972	10	7.2%	0.80 [-0.30, 1.90]
Bantle et al. [15]	1986	12	3.6%	-1.90 [-3.84, 0.04]
Bantle et al. [20]	1992	6	0.1%	-2.60 [-16.33, 11.13]
Subtotal			10.8%	**-0.46 [-2.83, 1.91]**

Heterogeneity: Tau² = 2.40; Chi² = 5.79, df = 2 (P = 0.06); I² = 65%
Test for overall effect: Z = 0.38 (P = 0.70)

Study or Subgroup	Year	Participants	% Weight	Mean Difference (95% CI)
Type 2 Diabetes Mellitus				
Malerbi et al. [9]	1996	16	11.8%	-0.65 [-1.10, -0.20]
Turner et al. [25]	1979	2	9.6%	0.59 [-0.15, 1.33]
Crapo et al. [26]	1986	7	5.2%	-1.30 [-2.77, 0.17]
Bantle et al. [15]	1986	12	12.8%	0.30 [0.01, 0.59]
Osei et al. [11]	1987	18	4.8%	-2.30 [-3.88, -0.72]
McAteer et al. [27]	1987	10	10.1%	-0.08 [-0.77, 0.61]
Grigoresco et al. [21]	1988	8	4.9%	-0.40 [-1.95, 1.15]
Osei et al. [10]	1989	13	4.7%	-1.80 [-3.41, -0.19]
Anderson et al. [12]	1989	14	6.6%	-0.11 [-1.30, 1.08]
Thorburn et al. [22]	1990	6	5.2%	-0.18 [-1.65, 1.29]
Bantle et al. [20]	1992	12	0.5%	-1.08 [-7.21, 5.04]
Koivisto et al. [13]	1993	10	8.2%	-1.10 [-2.04, -0.16]
Subtotal			84.3%	**-0.46 [-0.92, 0.01]**

Heterogeneity: Tau² = 0.36; Chi² = 35.04, df = 11 (P = 0.0002); I² = 69%
Test for overall effect: Z = 1.91 (P = 0.06)

Study or Subgroup	Year	Participants	% Weight	Mean Difference (95% CI)
Undifferentiated Diabetes				
Blayo et al. [14]	1990	20	4.8%	-0.14 [-1.70, 1.42]
Subtotal			4.8%	**-0.14 [-1.70, 1.42]**

Heterogeneity: Not applicable
Test for overall effect: Z = 0.18 (P = 0.86)

Total		176	100.0%	**-0.40 [-0.83, 0.03]**

Heterogeneity: Tau² = 0.35; Chi² = 41.07, df = 15 (P = 0.0003); I² = 63%
Test for overall effect: Z = 1.84 (P = 0.07)
Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² = 0%

Favors Fructose   Favors Any CHO

Figure 2—*Continued*

medications for their insulin treatment before study onset. Two trials were randomized (29%). Six trials used crossover designs (86%), and one used a parallel design (14%). Starch (43%) and sucrose (43%) were used as carbohydrate comparators, and notably Malerbi et al. (9) used both starch and sucrose comparisons (14%). Fructose was administered in mixed (57%) and fluid (43%) formats at a median dose of 63.2 g/day (IQR 47.5–99 g/day), with four trials (57%) exceeding the CDA threshold of 60 g/day (2) and six trials (86%) exceeding the EASD threshold of 30 g/day (8). Five trials (71%) were metabolically controlled, and two were nonmetabolically controlled (29%).

Background diets were 45–55% carbohydrate, 20–40% fat, and 15–30% protein. The median follow-up was 4 weeks (IQR 3–10 weeks). Two trials were of high quality, with a median MQS of 7 (IQR 5.5–7.5). No hypercaloric feeding trial met the inclusion criteria.

Fig. 2C shows the effect of isocaloric fructose exchange for other carbohydrates on fasting insulin. There was no effect on fasting insulin (MD −3.92 pmol/L [95% CI −22.23 to 14.39 pmol/L]), with no evidence of interstudy heterogeneity (I^2 = 13% [95% CI 0–75]; P = 0.33) in the type 2 diabetes stratum. Sensitivity analyses did not alter the effect estimate or degree of heterogeneity for fasting insulin, and

meta-regression revealed no statistically significant subgroup effects (Supplementary Fig. 3). None of the subjects were treated with insulin.

Publication bias
Supplementary Figs. 4 and 5 show the funnel plots and Egger regression plots, respectively, for investigating publication bias. There was evidence of funnel plot asymmetry for fasting glucose (P < 0.05 by Egger test; P = 0.12 by Begg test), consistent with small-study effects. There was no evidence of publication bias for fasting insulin (P = 0.91 by Egger test; P = 1.00 by Begg test) or glycated blood protein analyses (P = 0.20 by Egger test; P = 0.43 by Begg test).

C   Fasting Insulin
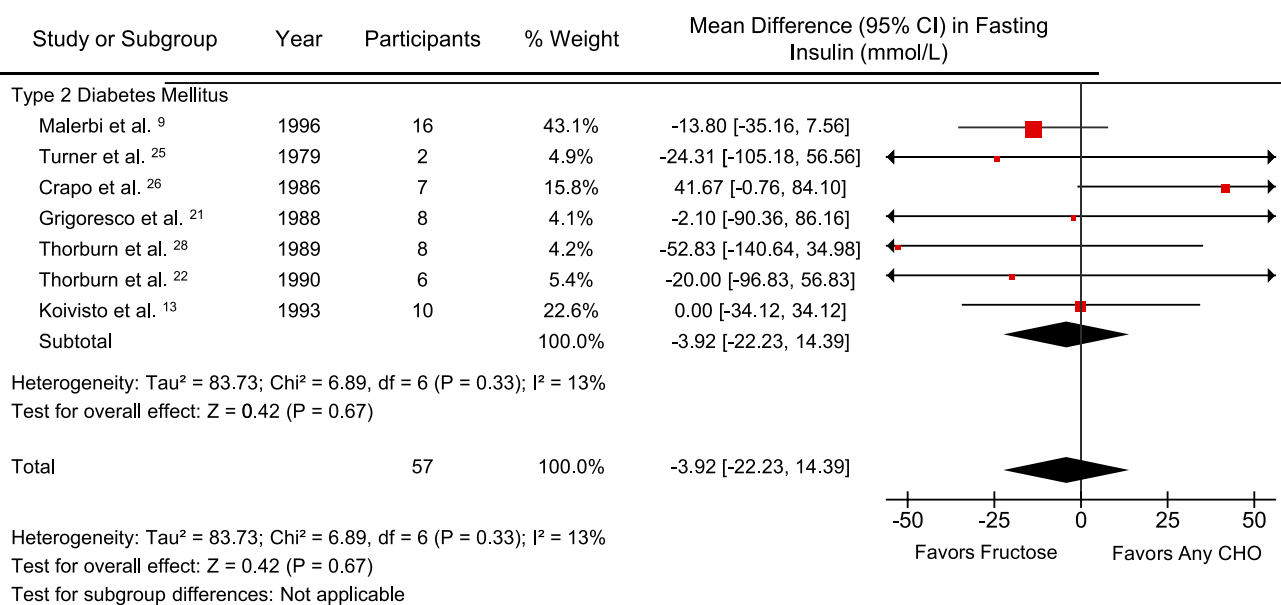

Study or Subgroup	Year	Participants	% Weight	Mean Difference (95% CI) in Fasting Insulin (mmol/L)
Type 2 Diabetes Mellitus				
Malerbi et al. [9]	1996	16	43.1%	-13.80 [-35.16, 7.56]
Turner et al. [25]	1979	2	4.9%	-24.31 [-105.18, 56.56]
Crapo et al. [26]	1986	7	15.8%	41.67 [-0.76, 84.10]
Grigoresco et al. [21]	1988	8	4.1%	-2.10 [-90.36, 86.16]
Thorburn et al. [28]	1989	8	4.2%	-52.83 [-140.64, 34.98]
Thorburn et al. [22]	1990	6	5.4%	-20.00 [-96.83, 56.83]
Koivisto et al. [13]	1993	10	22.6%	0.00 [-34.12, 34.12]
Subtotal			100.0%	-3.92 [-22.23, 14.39]

Heterogeneity: Tau² = 83.73; Chi² = 6.89, df = 6 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.42 (P = 0.67)

Total		57	100.0%	-3.92 [-22.23, 14.39]

Heterogeneity: Tau² = 83.73; Chi² = 6.89, df = 6 (P = 0.33); I² = 13%
Test for overall effect: Z = 0.42 (P = 0.67)
Test for subgroup differences: Not applicable

Figure 2—*Continued*

CONCLUSIONS—In the current aggregate analyses of 18 controlled feeding trials with 209 subjects with type 1 and 2 diabetes, isocaloric fructose exchange for other carbohydrate decreased glycated blood proteins (aggregated glycated albumin and HbA$_{1c}$) but not fasting glucose or insulin. The observed SMD reduction in glycated blood proteins may be considered clinically significant, because it was equivalent to an absolute reduction of ~0.53%. This reduction exceeds the clinically meaningful threshold of ≥0.3% proposed by the U.S. Food and Drug Administration for the development of new drugs for diabetes (29) and lies at the lower limit of efficacy expected for oral hypoglycemic agents (30). The lack of change in fasting glucose and insulin suggests that fructose consumption does not promote hepatic and systemic insulin resistance. Future meta-analyses of direct measures of insulin sensitivity would be of value.

Our observed reduction in glycated blood proteins was consistent with the findings of an earlier meta-analysis by Livesey and Taylor (31), who found an improvement in HbA$_{1c}$ (31). It is important to note, however, that their analysis, in contrast to the current meta-analysis, did not focus exclusively on diabetes. Unlike Livesey and Taylor (31), we found the reduction in glycated blood proteins to be significant only in people with type 1 diabetes in stratified analyses. This discrepancy

is likely due in part to the use of glycated albumin exclusively in the type 1 diabetes studies (15,20). The null finding in individuals with type 2 diabetes might be explained by the choice of glycated protein, because those trials used both HbA$_{1c}$ (9–13,21–23) and glycated albumin (15,20). Because the half-life of glycated albumin (~20 days) (32) is shorter than that of HbA$_{1c}$ (~35 days) (38), it is possible that the shorter type 2 diabetes studies may not have been of sufficient duration to detect true HbA$_{1c}$ changes, with the effect size too small. An improvement in glycemic control in individuals with type 2 diabetes is supported by an improvement in fasting glucose after removal of either Bantle et al. (15) or Turner et al. (25) during sensitivity analyses. It is noteworthy that the small, unusually precise study of Turner et al. (25) was a seemingly disproportionate contributor to the pooled effect, including only two participants and carrying a weight of 9%. Individual patient data revealed that one patient showed a dramatic increase in fasting glucose after fructose consumption, whereas the second patient's fasting glucose remained constant.

Subgroup analyses revealed no significant effect modification for glycated blood proteins, fasting glucose, or insulin. Although Livesey and Taylor (31) in their earlier meta-analysis found that the improvement in HbA$_{1c}$ was dependent on the degree of dysglycemia, fructose dose, and

follow-up, we did not find that these conditions altered any of the outcomes, nor in a separate analysis did we see any effect of fructose dose, follow-up, or comparator on triglycerides in type 2 diabetes with the same subgroup criteria (33). There was, however, evidence of significant interstudy heterogeneity across most subgroup categories. These may be related to real biological differences between study populations or to methodological differences between trials that were not assessed in our a priori subgroup analyses.

A number of potential mechanisms have been proposed to explain the improvements in glycemia seen with the consumption of fructose. One possibility is that the addition of fructose to the diet may help control postprandial glycemic excursions. Replacement of a high–glycemic index (GI) carbohydrate such as starch (for example, white bread, GI = 100) with a low-GI carbohydrate source such as fructose (GI = 16) (34) may decrease the GI of the diet sufficiently to result in improvement in glycemic control (35). Alternatively, an emerging body of evidence has shown that low doses of fructose (≤10 g/meal) may improve glycemic control through upregulation of the glucokinase enzyme (36), exerting a "catalytic" effect. The resulting fructose-1-P is able to displace fructose-6-P from its binding site on the glucokinase regulatory protein, allowing increased translocation of

glucokinase from the nucleus to the cytosol, where it is active. Single catalytic doses of fructose infused have shown a ~30% reduction in postprandial hepatic glucose output under hyperglycemic conditions in people with type 2 diabetes (36) and a roughly threefold increase in glycogen synthesis under euglycemic hyperinsulinemic conditions in people without diabetes (37). Both these mechanisms may be operating.

Although it appears that isocaloric fructose feeding benefits glycemia, a dose threshold for harm must also be considered because fructose, more than other sources of carbohydrate, may increase serum triglycerides. We previously showed in a meta-analysis of controlled feeding trials that fructose at doses >60 g/day (in excess of CDA recommendations) or >10% energy in isocaloric exchange for other carbohydrate increases serum triglyceride levels in type 2 diabetes (33). Livesey and Taylor (31) in their meta-analysis also showed a consistent triglyceride-raising effect of fructose at high doses (>100 g/day) across different subject types. We therefore must consider the possible adverse effects of substituting fructose for other carbohydrates at high doses. There are currently no meta-analyses investigating the effect of fructose on LDL.

A number of limitations complicate the interpretation of these aggregate analyses. First, most of these trials were relatively short, with only four trials ≥12 weeks. It is therefore possible that these shorter trials may have underestimated the HbA$_{1c}$ reduction, given the evidence that HbA$_{1c}$ reduces at ~0.1%/day at a steady state, with a half-life of 5 weeks (38). Second, several studies included participants who were receiving insulin or oral hypoglycemic agents, treatments that in themselves would be expected to influence glycemia. Third, given the small number of trials included in each stratum, meta-regression may have been underpowered to detect true differences. Fourth, a significant amount of unexplainable heterogeneity was detected in both primary and subgroup analyses, although our random-effects model did account for this heterogeneity. Fifth, study quality was poor (MQS <8) in 50% of the included trials. These deficiencies were especially of concern in the context of the small sample sizes, with most of the trials having 15 or fewer participants. There was, however, no effect of MQS (<8 vs. ≥8) in subgroup analyses. Finally, because only published trials were included, publication bias remains a possibility for all outcomes, although we noted statistical evidence of publication bias only for fasting glucose.

In conclusion, aggregate analyses of short-term controlled feeding trials showed that isocaloric fructose replacement of other carbohydrates resulted in clinically significant improvements in glycemic control, equivalent to a ~0.53% reduction in HbA$_{1c}$, without significantly affecting insulin in diabetic individuals. This benefit was seen across a full dose range (20–160 g/day), including at doses below the CDA threshold of 60 g/day, a level of exposure that is unlikely to have an adverse effect on other aspects of metabolic control. The harm-reduction approach to fructose taken by diabetes associations (2,7,8), which is based on possible adverse serum lipid effects, may need to be reconciled with a possible glycemic benefit. These conclusions, however, are limited by the short follow-up, small sample size, and poor quality of most trials included in our meta-analysis, as well as the large degree of unexplained significant heterogeneity. Larger, longer, and higher-quality trials of controlled fructose feeding that also weigh any possible glycemic benefit against adverse metabolic effects are required for definitive confirmation of these findings.

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A.I.C. was responsible for acquisition of data, analysis and interpretation of data, drafting of the manuscript, critical revision of the manuscript for important intellectual content, and statistical analysis. J.L.S. was responsible for conception and design, analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtaining funding, and supervision. J.L.S. had full access to all the data in the study and had final responsibility for the decision to submit for publication. R.J.d.S. was responsible for the analysis and interpretation of data, critical revision of manuscript for important intellectual content, statistical analysis, supervision, and obtaining funding. L.C. was responsible for the acquisition of data, critical revision of the manuscript for important intellectual content, and administrative support. V.H., D.D.W., and M.E.Y. were responsible for acquisition of the data and critical revision of the manuscript for important intellectual content. A.M. and A.J.C. were responsible for acquisition of data, critical revision of the manuscript for important intellectual content, and obtaining funding. M.D., A.L.J., L.A.L., T.M.S.W., and C.W.C.K. were responsible for critical revision of the manuscript for important intellectual content and obtaining funding. J.B. was responsible for critical revision of the manuscript for important intellectual content, statistical analysis, and obtaining funding. D.J.A.J. was responsible for analysis and interpretation of data, critical revision of the manuscript for important intellectual content, obtaining funding, and supervision.

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