Very High Fructose Intake Increases Serum LDL-Cholesterol and Total Cholesterol: A Meta-Analysis of Controlled Feeding Trials

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Abstract

Fructose is widely used as a sweetener in the production of many foods, yet the relation between fructose intake and cholesterol remains uncertain. In this study, we performed a systematic review and meta-analysis of human, controlled, feeding trials involving isocaloric fructose exchange for other carbohydrates to quantify the effects of fructose on serum total cholesterol (TC), LDL cholesterol (LDL-C), and HDL cholesterol (HDL-C) in adult humans. Weighted mean differences were calculated to determine changes from baseline cholesterol concentrations by means of generic, inverse variance, random-effect models. The Heyland Methodological Quality was used to assess the quality of the study. Subgroup analyses and meta-regression were conducted to explore the possible influences of study characteristics. Twenty-four trials (with a total of 474 participants) were included in the meta-analysis. In an overall pooled estimate, it was shown that fructose exerted no effect on HDL-C. Meta-regression analysis indicated that fructose dose was positively correlated with the effect sizes of TC and LDL-C. Subgroup analyses showed that isocaloric fructose exchange for carbohydrates increased TC by 13.0 mg/dL (95% CI: 4.7, 21.3; P = 0.002) and LDL-C by 11.6 mg/dL (95% CI: 4.4, 18.9; P = 0.002) at >100 g fructose/d. However, no effect was shown on TC or LDL-C when the fructose intake was ≤100 g/d. In conclusion, it was shown that very high fructose intake (>100 g/d) increases serum LDL-C and TC concentrations. Larger, longer, and higher-quality human, controlled, feeding trials are needed to confirm these results.

Introduction

Hyperlipidemia is a common risk factor for coronary heart disease, with 44.4% of adults in the United States having abnormal total cholesterol (TC) values and 32% having elevated LDL cholesterol (LDL-C) concentrations (1). Compared with individuals with normal blood lipid, those with hyperlipidemia have a 3-fold risk of heart attack (2). Lifestyle modification must be initiated in conjunction with both primary and secondary prevention of coronary heart disease. More suggestions should be given about what constitutes healthy eating.

Fructose is the most common, naturally occurring monosaccharide and has become a major constituent of our modern diet. Fruits, vegetables, and other natural sources account for nearly one-third of our dietary fructose, with the other two-thirds provided by beverages and other foods (e.g., candies, jams, syrups, etc.) (3). Fructose is preferred by many people, especially those with diabetes mellitus, due to its low glycemic index (23 vs. 100% in glucose) (4). After intestinal uptake, fructose is mainly removed from the blood stream via the liver in an insulin-independent manner and is used for the intrahepatic production of glucose, fatty acids, and lactate. Cross-sectional studies in humans have suggested that excessive fructose consumption may lead to adverse metabolic effects, such as dyslipidemia or increased visceral adiposity (5–7). The Dietary Guidelines for Americans (2010) point out that there is a lack of sufficient evidence to set a tolerable upper intake of carbohydrates for adults (8). Although The Canadian Diabetes Association suggests consumption of no more than 60 g of added fructose per day by people with diabetes for its TG-raising effect (9), the threshold dose of fructose that creates an adverse influence on cholesterol remains controversial.

To determine the effect of fructose on cholesterol, a substantial number of clinical trials have been performed on adult humans with differences in health status. These trials used a range of intake levels of fructose and various protocols, thus making it difficult to reach a consistent conclusion by reviewing the results of these studies. Therefore, in this study, a systematic review of the scientific literature and meta-analysis of controlled feeding trials was performed to evaluate the effects of isocaloric...
oral fructose exchange of carbohydrates on cholesterol and to clarify the active factors of fructose.

Materials and Methods

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (10).

Search strategy. Data from up to and including December 2012 stored in PubMed, Embase, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wangfang database were searched (in English and Chinese) for studies examining the effects of fructose on cholesterol. The following search strategy was used: fructose and (lipemia or lipaemia or lipids or cholesterol or “total cholesterol” or “LDL cholesterol” or “HDL cholesterol”). The search was restricted to trials on humans.

Study selection. All clinical trials using fructose and indexed within the above databases were collected. Two independent reviewers (T.A. and R.C.Z.) screened the abstracts and titles for initial inclusion. If this was not sufficient, full text articles were obtained and reviewed by at least 2 independent reviewers (T.A., R.C.Z., Q.Z., or Y.H.). Any disagreements were resolved through discussion. Controlled feeding trials investigating the chronic effects of fructose on blood cholesterol were included from both randomized and nonrandomized studies, provided that they met the following criteria: studies in which participants were administered fructose for at least 2 wk; studies on the effects of oral free (unbound, monosaccharide) fructose when compared with an isocaloric control diet in which another carbohydrate was used in place of fructose; studies that were performed on human adults with either a parallel or crossover design; and studies in which participants in both the experimental and control groups were instructed to consume the same energy and composition of the diet (percentage of carbohydrates, fat, and protein). If the studies reported any comparisons, all such comparisons were included in the meta-analysis.

Data extraction and quality assessment. Two reviewers (T.A. and R.C.Z.) independently extracted relevant data from eligible studies. Disagreements were then resolved by 1 of the 2 authors (Y.H.Z. or J.Z.). These data included information regarding study features (author, year of publication, study design, randomization, blinding, sample size, comparator, fructose form, dose, follow-up, and macronutrient profile of the background diet); participant characteristics (gender, age, and health status); and baseline and final concentrations or net changes of TC, LDL-C, and HDL cholesterol (HDL-C). Data initially extracted were converted to system international units (e.g., TC: 1 mmol/L converted to 38.6 mg/dL). For multi-arm studies, only intervention groups that met the inclusion criteria were used in the analysis. If the blood lipid concentrations were measured several times at different stages of the trials, only the final records of lipid concentrations at the end of the trials were extracted for use in the meta-analysis. The quality of each study was assessed using the Heyland Methodological Quality Score (MQS) (11) and generalized as follows: randomization, analysis, blinding, patient selection, comparability of groups at baseline, extent of follow-up, treatment protocol, co-intervention, and outcomes. Higher scores represent higher quality (MQS ≥8).

Data synthesis. Statistical analyses were performed using Stata software (version 11.0; StataCorporation) and REVMAN software (version 5.2; Cochrane Collaboration). Separate pooled analyses were conducted by using the generic, inverse variance, random-effects models. The different changes from baseline between fructose and carbohydrate comparators for TC, LDL-C, and HDL-C were used to estimate the principle effect. Paired analyses were applied to all crossover trials according to the methods of Elbourne et al. (12). Weighted mean differences of fructose consumption on cholesterol concentrations, as well as corresponding 95% CIs, were calculated. A 2-sided P value < 0.05 was set as the level of significance for an effect. The variances for net changes in serum cholesterol were used to estimate the principle effect. For studies without net changes directly reported, net changes were calculated by using the means ± SDs of cholesterol concentrations at baseline and the end of the intervention period (13). SDs were calculated from SEs when they were not directly given. If these data were unavailable, the missing SDs were extrapolated in the meta-analysis by borrowing SDs derived from other trials (14). In addition, a conservative degree of correlation of 0.5 was assumed to impute the change-from-baseline SDs, with sensitivity analyses performed across a range of possible correlation coefficients (0.25 and 0.75) (13). For crossover trials in which only final measurements were included, the differences in mean final measurements were assumed on average to be the same as the differences in mean change scores (13). Inter-study heterogeneity was tested by using the Cochrane’s Q-test (P < 0.1) and was quantified by the $I^2$ statistic, where $I^2$ ≥ 50% was evidence of substantial heterogeneity. To explore the potential effects of factors on the primary outcomes and investigate the possible sources of heterogeneity, meta-regressions and predefined subgroup analyses stratified by comparator, study duration, randomization, health status, study design, and study quality were performed. As for studies that used a range of fructose doses, the average doses were calculated based on the average reported energy intake and body weight of participants. Sensitivity analyses were also performed according to the Cochrane Handbook for Systematic Reviews. Funnel plots and Egger’s linear regression tests were conducted to detect publication bias.

Results

Based on the search criteria, a total of 1602 eligible studies were identified (no Chinese language studies were found), among which 1565 studies were excluded after review of the titles and abstracts. The remaining 37 studies were retrieved and fully reviewed. Another 15 of these did not meet the inclusion criteria and were thus excluded from the final analysis. Therefore, a total of 22 studies (providing data for 24 trials) involving 474 participants (15–36) were included in the meta-analysis (Fig. 1; Table 1).

The reports of Koh et al. (22) and Reiser et al. (23) included 2 trials (bringing the total number of trials to 24). Eleven trials were randomized (17,18,20,21,25,27–29,31,34,36); 9 used crossover (15–19,21–32); and 5 used parallel designs (20,33–36). As for the 19 crossover trials, 10 trials reported the washout period (16,18,22,25,27–31) and 9 trials did not (15,17,19,21,23,24,26,32). The trials varied in size from 8 to 131 participants. The mean age of the trial participants ranged from 26.7 to 64.4 y. A total of 17 trials (15,17–23,25,27,28,30,31,34,36) was performed in outpatient settings, 3 trials (26,29,32) in inpatient settings, and 4 trials in both outpatient and inpatient settings (16,24,33,35). Nine trials were conducted on diabetic individuals (19–21,24–27,29,30), 8 on healthy participants (17,18,22,23,28,31,34,35), 3 on overweight/obese individuals (32,33,36), 2 on hyperinsulinemic participants (16,23), 1 on impaired glucose-tolerant participants (22), and 1 individual with type IV hyperlipoproteinemia (15). The background diets were 42–55% carbohydrate, 25–38% fat, and 13–20% protein. The carbohydrate comparators chose starch in 13 trials (15,16,21,23–25,27–30,32,36), glucose in 6 (22,31,33–35), sucrose in 3 (17,18,26), and mixed carbohydrates in 2 (19,20). Four trials used fructose in crystalline form (16,18,20,21), 5 in liquid form (19,32–35), and 15 in mixed form (15,17,22–31). The reported mean baseline serum TC ranged from 170 to 231 mg/dL, LDL-C from 90.7 to 157 mg/dL,
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**TC.** A total of 22 trials (16–34,36) reported the value of TC and the pooled estimate was 2.5 mg/dL ([95% CI: −3.0, 8.0]; \(P = 0.38\)) without statistical heterogeneity \(I^2 = 25\%\); \(P = 0.14\)) (Fig. 2). Univariate meta-regression showed that the fructose dose was positively related to TC, even after being adjusted for study duration and health status \(\text{regression coefficient} = 0.18 \ (95\% \text{ CI: } 0.06, 0.31); \ P = 0.008\) (Table 2). This indicated that there was a dose-response relationship between fructose consumption and TC. Subsequently, we tested the heterogeneity by dose and defined the fructose doses of \(\leq 60, >60–100, \text{ and } >100 \text{ g/d as moderate, high, and very high, respectively,} \) according to the Canadian Diabetes Association and reference ranges for fructose (9,37,38). It was shown that fructose increased TC by 13.0 mg/dL ([95% CI: 4.7, 21.3]; \(P = 0.002\)) when fructose intakes were \(>100 \text{ g/d, but no effect was shown on TC if the fructose was} \leq 100 \text{ g/d. Predefined subgroup analyses were conducted} \) using other study characteristics (Supplemental Table 2). Sensitivity analyses according to possible correlation coefficients \(0.25 \text{ and } 0.75\), removal of crossover trials without a washout period or with a 2-wk fructose intake, and systematical removal of each individual trial did not alter the overall analysis or analyses stratified by dose.

**HDL-C.** The result of HDL-C was calculated based on 24 trials (15,16,18,20,22,23,25–35) and the mean difference was \(2.1, 0.9\); \(P = 0.46\) without heterogeneity \(I^2 = 0\%\) (Fig. 3). Univariate meta-regression showed that the fructose dose was positively related to HDL-C even after being adjusted for comparators, study duration, and health status \(\text{regression coefficient} = 0.15 \ (95\% \text{ CI: } 0.03, 0.28); \ P = 0.02\) (Table 2). This indicated that there was a dose-response relationship between fructose consumption and HDL-C. Subsequently, we tested the heterogeneity by dose and stratified fructose doses according to the Canadian Diabetes Association and reference ranges for fructose (9,37,38). Fructose intake \(>100 \text{ g/d} \) significantly increased LDL-C by 11.6 mg/dL ([95% CI: 4.4, 18.9]; \(P = 0.002\)). Predefined subgroup analyses were conducted using other study characteristics (Supplemental Table 2). Sensitivity analyses according to possible correlation coefficients \(0.25 \text{ and } 0.75\), removal of crossover trials without a washout period or with a 2-wk fructose intake did not alter the overall analysis or analyses stratified by dose. The removal of the study by Cybulska et al. (15) resulted in an LDL-C-raising effect in the overall analysis \(P = 0.03\).

**Discussion**

In this meta-analysis of 24 controlled feeding trials involving 477 participants, isocaloric exchange of fructose for other carbohydrates had no effect on the serum HDL-C concentration. Meta-regression revealed that fructose dose was positively correlated with the effect sizes of TC and HDL-C. A very high
fructose intake could significantly increase serum TC and LDL-C concentrations.

The overall analysis showed that fructose intake in isocaloric exchange for other carbohydrates exerted no effects on cholesterol at a median experimental dose of 79.3 g/d, which is higher than the 90th percentile (mean, 78 g/d) and lower than 95th percentile (mean, 87 g/d) in the United States, as reported by the NHANESIII (39). As for participants with diabetic mellitus, Sievenpiper et al. (40) did not report in their meta-analysis any threshold effects on TC and LDL-C can only help to better inform nutritional guidance and avoid inappropriate marketing of carbohydrates. Larger and more well-controlled feeding trials are required to confirm whether fructose intakes of <100 g/d contribute to high cholesterol.

The dose-dependent effect on TG was also reported in a recent meta-analysis that concluded the same dose threshold of 100 g/d for a TG-increasing effect of fructose on the fasting TG concentration in adult humans (38). For healthy participants who consumed 150 g/d fructose, endogenous cholesterol synthesis and the fat content of the viscera and liver have been shown to increase (42). All evidence has proven that fructose has adverse effects at very high or excessive doses. The mechanism of cholesterol increase by fructose may be due to increased amounts of advanced glycation end products, which cause damage to the concept that fructose does not increase cholesterol in individuals with generalized levels of exposure.

The results of the subgroup analyses showed that the effects of fructose intake on TC and LDL-C were significant when the fructose dose was >60 g/d (median, 97.5 g/d). The results of our study seem to support the concept that fructose does not increase cholesterol in both males and females aged 19–22 y, which is the group with the highest level of exposure in the United States (39). Due to the inconsistency in characteristics among included trials, it is difficult to provide suitable advice for most patients. The dose threshold effects on TC and LDL-C can only help to better inform nutritional guidance and avoid inappropriate marketing of carbohydrates. Larger and more well-controlled feeding trials are required to confirm whether fructose intakes of <100 g/d contribute to high cholesterol.
studies have shown that elevated uric acid may contribute to LDL-C increases, an effect that may be reduced by allopurinol (44). Based on the NHANES 1999-2004 estimates (39), the increase of fructose consumption (>100 g/d) sometimes was accompanied by an increase in total energy intake or certain micronutrient deficiency (45). In the first scenario, the high energy content may cause overweight or obesity.

The meta-analysis of this study did not show any significant effect of fructose on HDL-C. However, Perez-Pozo et al. (44) reported a significant HDL-C-lowering effect in 74 adult men given 200 g/d fructose in a randomized, 2-wk crossover trial, suggesting that excessive fructose dose intake may also affect HDL-C. Further trials are required to determine the threshold of fructose on HDL-C.

Compared with a previous meta-analysis on this topic (40), our study included more information concerning the effect of fructose on cholesterol. First, Sievenpiper et al. (40) included only trials that had >7 d of follow-up. Our study required that trials must include participants who received fructose for at least 2 wk, which could more effectively reflect the effects of fructose on cholesterol. Second, there was only one trial in the Sievenpiper et al. (40) study with an average dose of fructose >100 g/d. We included 7 trials in our study, which is enough to assess the effect of fructose at a very high dose relevant to population exposures. Third, Sievenpiper et al. (40) investigated the effect of fructose on lipids on individuals with type 2 diabetes. We included all participants regardless of health status, provided that the selection criteria were met. It is our thought that this study will provide a more complete understanding of the impact of fructose consumption on cholesterol.

There are several limitations to this study. First, many trials had a relatively small sample size and most were funded by industries, which may affect the quality of the studies. Second, the change of fructose in the background diet may affect the practical utility of the outcomes of the meta-analyses. Most of the trials only reported a background diet with <3% of total energy derived from fructose, while other trials did not report the proportion of fructose in the background. Thus, it was difficult to ensure the dose of background fructose and introduce it to the meta-regression. Third, the data provided by Reiser et al. (23) must be interpreted with caution. Although this study met all of the inclusion criteria, the authors chose a low dose of fructose in their study, which may limit the generalizability of the results.

### TABLE 2 Meta-regression models investigating the effects of dietary fructose dose on serum TC and LDL-C concentrations

<table>
<thead>
<tr>
<th>TC</th>
<th>LDL-C</th>
</tr>
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<tbody>
<tr>
<td>Fructose (g/d)</td>
<td>Regression coefficient (95% CI)</td>
</tr>
<tr>
<td>Model 1</td>
<td></td>
</tr>
<tr>
<td>Fructose (g/d)</td>
<td>0.16 (0.05, 0.27)</td>
</tr>
<tr>
<td>Model 2</td>
<td></td>
</tr>
<tr>
<td>Fructose (g/d)</td>
<td>0.18 (0.06, 0.31)</td>
</tr>
</tbody>
</table>

1 LDL-C, LDL cholesterol; TC, total cholesterol.
2 Single covariate random effect regression.
3 Multivariate regression: dose of fructose adjusted for study duration and health status (diabetic, prediabetic, and healthy). For health status, health was defined as the reference category and the 2 other categories had their own dummy variables. Each category’s dummy variable had a value of 1 for its category and 0 for all others.
4 Duration of the fructose diet.
polysaturated:saturated rate of the fatty acid as the background diet, which may alter the metabolism of the fructose, because diets high in SFAs may enhance intestinal fructose absorption (46). Fourth, some of the included trials lacked test statistics, baseline values, or SDs. These problems were overcome according to the methods proposed by the Cochrane Handbook for Systematic Reviews of Interventions (13). Fifth, small numbers of studies were shown in many subgroups (e.g., parallel design and nonstarch as comparators) according to the predefined subgroup analyses. Therefore, we could not obtain the actual effects of these modifiers on the final results. Sixth, average fructose doses were used in our subgroup analysis and meta-regressions. This could not accurately reflect the effect of individual experimental doses and resulted in ecological bias. Therefore, the threshold dose mentioned in our meta-analysis needs to be carefully considered and should be confirmed by further studies. Finally, it is difficult to differentiate the effects of other modifiers, such as exercise and age, from those included in the trials. These factors may also influence the final results. Fructose may indeed be metabolized during exercise and the rate of metabolism differs between active and sedentary lifestyles. Most of the participants were requested to follow a designed

**FIGURE 3** Forest plot for the effect of dietary fructose on serum LDL-C concentration during the isocaloric exchange of fructose with other carbohydrates. Weighted mean differences (95% CI) are reported. The subgroups were stratified by fructose dose (≤60, >60–100, and >100 g/d). The weight of each study is represented by the size of the box; variance is represented by the length of the horizontal line. LDL-C, LDL cholesterol.

**FIGURE 4** Forest plot for the effect of dietary fructose on serum HDL-C concentration during the isocaloric exchange of fructose with other carbohydrates. Weighted mean differences (95% CI) are reported. The weight of each study is represented by the size of the box; variance is represented by the length of the horizontal line. HDL-C, HDL cholesterol.
regimen at home, but it is not easy to maintain such active intensity. In addition, the age of the participants in our meta-analysis ranged from 18 to 72 y. Evidence from animal experiments shows that fructose absorption may be affected by age, as older rats have decreased fructose absorption (47). However, no human trials have been performed to assess the difference in fructose effects among different age groups. Therefore, further studies are required to limit or isolate the degree of heterogeneity present in the study population in order to more effectively assess the effect of age.

In conclusion, the meta-analysis of this study shows that fructose in isocaloric exchange for other carbohydrates has significant increasing effects on TC and LDL-C in individuals with very high fructose intake (>100 g/d). It appears that this effect is not dose dependent when fructose is consumed in moderate or high doses (<100 g/d). Further studies should concentrate on larger, longer, and higher-quality human, controlled, feeding trials, the results of which will provide a more efficient assessment of the effects of fructose on cholesterol.

Acknowledgments
T.A., R.C.Z., and J.Z. designed the study; T.A., R.C.Z., Q.Z., Y.H., and Y.H.Z. preformed the research; T.A. and R.C.Z. performed the statistical analysis; R.C.Z. wrote the manuscript; and J.Z. had primary responsibility for the final content. All authors read and approved the final manuscript.

Literature Cited

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