Heterogeneous effects of fructose on blood lipids in individuals with type 2 diabetes: systematic review and meta-analysis of experimental trials in humans
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CRD summary
The authors concluded that isocaloric fructose exchange for carbohydrates raised triglycerides and lowered total cholesterol in type 2 diabetes patients, only under specific conditions. This conclusion appeared to reflect the evidence, but limitations in the review, in particular analyses based on a small number of patients from heterogeneous studies, suggest that it may not be reliable.

Authors' objectives
To evaluate the effects of isocaloric fructose exchange for carbohydrates on blood lipids in people with type 1 and 2 diabetes.

Searching
EMBASE and CINAHL were searched for articles from inception to February 2008. MEDLINE and the Cochrane Library were searched for articles from inception to February 2009. Search terms were reported and no language restrictions were applied. The authors stated that manual searches were also conducted, but no details were reported.

Study selection
Clinical intervention studies that evaluated the chronic effects of exchanging oral fructose for carbohydrates, on blood lipids, in people with type 2 diabetes, were eligible for inclusion. Studies were excluded if the follow-up was less than seven days, intravenous fructose was used, control treatments were hypercaloric, not isoglucidic, or unbalanced, or only non-fasting results were reported. The review assessed triglycerides, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein (HDL) cholesterol.

The included studies evaluated crystalline, liquid, and mixed-format fructose in doses ranging from 20 to 160g per day. Control treatments included starch, sucrose, and mixed carbohydrates. Most of the studies were in patients with type 2 diabetes and the others were in patients with type 1 or undifferentiated diabetes.

The authors did not state how the papers were selected for the review.

Assessment of study quality
Two reviewers independently assessed and scored validity using the 13-point Heyland score that includes criteria for study design and sampling. Disagreements were resolved by consensus after discussion with two other reviewers. Randomisation, blinding, sample size, and metabolic control were also assessed; it was not clear if these criteria formed part of the Heyland score.

Data extraction
Where possible, the means and standard errors for lipid values after treatment were extracted into a standard form; if not reported, these statistics were estimated, using reported methods. Paired-analyses and standardised mean differences were used for crossover studies. For studies with multiple treatment arms a single pair-wise comparison was calculated.

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Methods of synthesis
Separate analyses were conducted for any diabetes, type 1 diabetes, and type 2 diabetes. Pooled standardised mean differences with 95% confidence intervals were calculated using a fixed-effect model in the absence of significant
statistical heterogeneity and a random-effects model in its presence. Heterogeneity was assessed using the Cochran Q statistic and the I² statistic.

Heterogeneity was examined using sensitivity and a priori subgroup analyses to explore the effect of reference carbohydrate, fructose format, dose, length of follow-up, Heyland quality score, randomisation, and each study in turn. Post hoc subgroup analyses examined the influence of feeding control, design, washout in crossover studies, and background diet. Inverse variance weighted piecewise polynomial regression was used to estimate the dose thresholds. Multiple regression models assessed the independent predictors of the intervention effects.

The possibility of publication bias was explored using a funnel plot.

Results of the review
Sixteen controlled studies (reported in 14 papers) were included (n=236 patients). Nine of these were randomised controlled trials (RCTs). The quality scores ranged from four to eight; nine studies were considered to be of high quality (scoring eight or more). Eight studies were metabolically controlled. Treatment groups included from six to 18 patients. The duration of follow-up ranged from one to 52 weeks and it was 12 weeks or more in only five studies.

There was no statistically significant effect of isocaloric fructose exchange for carbohydrate in patients with any, or type 1 or 2 diabetes for any outcome. Significant heterogeneity was found for triglycerides, total cholesterol, and HDL cholesterol (I² >50%). Analyses were based on between one and 16 studies with between six and 236 patients.

Isocaloric fructose exchange for carbohydrate raised triglycerides and lowered total cholesterol, without heterogeneity, in type 2 diabetes patients under specific conditions, without any significant effect on low-density or high-density lipoprotein cholesterol. Triglyceride was raised when the control was starch (five studies), fructose dose was greater than 60g per day (six studies), and follow-up was four weeks or less (six studies). Total cholesterol was lowered when studies were not randomised and were of low quality (four studies), when dietary fat provided more than 30% of energy (three studies), and when crystalline fructose was used (three studies).

The results were generally similar using multivariate regression analyses. There was limited evidence of publication bias for triglycerides and there was no evidence of publication bias for other outcomes.

Authors’ conclusions
Isocaloric fructose exchange for carbohydrates raised triglycerides and lowered total cholesterol in type 2 diabetes patients, only under specific conditions.

CRD commentary
The review question was clearly stated. The inclusion criteria were specified for the intervention and broadly defined for study design and review outcomes. The criteria for participants were confusing; the study aim was to include type 1 and 2 diabetes patients, but the inclusion criteria specified only type 2, while both type 1 and 2 patients were included. Several relevant sources were searched and no language restrictions were applied, but only limited attempts were made to minimise publication bias. The potential for publication bias was acknowledged and assessed and little evidence was found. Methods were used to minimise reviewer errors and bias in the extraction of data and assessment of validity, but it was not clear whether similar steps were taken in study selection. Study validity was assessed, but generally only the aggregate scores were reported, which makes it difficult to judge the quality of the studies and hence the reliability of the evidence. Data from small studies that differed with respect to the intervention dose and format and control carbohydrate content were pooled and this may not have been appropriate. Heterogeneity was assessed and various analyses were conducted to investigate the potential sources of heterogeneity including study quality. The authors acknowledged some limitations of their review, such as the inclusion of studies with short-term treatment, underpowered subgroup analyses, and the use of multiple regression models, based on a small number of studies.

The evidence appeared to support the authors’ conclusions, but a lack of detailed results for the validity assessment and analyses based on a small number of patients from heterogeneous studies suggest that the conclusion may not be reliable.
Implications of the review for practice and research

Practice: The authors stated that the heterogeneity in the data should be considered in the formulation of guidelines.

Research: The authors stated that there was a need for adequately powered long-term (six months or more) RCTs to evaluate the effects of the exchange of a wide range of doses of fructose for starch and sucrose in patients with type 2 diabetes. Research into hypercaloric feeding was also required.

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