Effect of Important Food Sources of Fructose-Containing Sweets on Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Controlled Trials

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ABSTRACT

Introduction: Fructose as a source of excess calories increases non-alcoholic fatty liver disease (NAFLD) markers1. Whether this effect is mediated by the food matrix is unknown. We conducted a systematic review and meta-analysis of controlled feeding trials in participants with and without diabetes assessing the effect of important food sources of fructose-containing sugars at different levels of energy control on NAFLD markers (NCT02716870).

Methods: MEDLINE, Embase, and Cochrane Library were searched through January 30, 2018, using controlled terminologies. Studies were included if they were randomized, controlled feeding trials (RCTs) comparing fructose-containing sweeteners with controls and assessing markers of NAFLD for at least 4 weeks. Studies were categorized into addition, subtraction, and ad libitum trials. Primary outcomes were alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. Indirect effect was considered significant if the effect size was different between addition and subtraction trials.

Results: We included 39 trials (63 trial comparisons, n=1,404) assessing the effect of 8 food sources (sugar containing beverages, juices, fruit, dried fruit, starch, added sugar substitutes, and mixed comparator) across the 4 energy levels. Total fructose-containing sugars increased IHCL in addition trials (standardized mean difference=1.49 [95% CI 1.00, 1.99]), with no effect in subtraction, and ad libitum trials. There was evidence of interaction by food source in addition trials with SSB decreasing IHCL and ALT, and mixed sources increasing AST. Effects were consistent in participants with and without diabetes. The overall certainty of evidence was high for SSB on IHCL, and ALT in addition trials and moderate to very low for all other comparisons.

Conclusion: Energy control and food source appear to mediate the effect of fructose-containing sugars on NAFLD markers in people with and without diabetes. High certainty evidence suggests that SSBs provide excess energy increase NAFLD markers, while the evidence is less certain that mixed sources show the same effect and other food sources do not. More high-quality randomized trials of different food sources are needed to improve our estimates.

INTRODUCTION

Fructose as a source of excess calories increases non-alcoholic fatty liver disease (NAFLD) markers1. Whether this effect is mediated by the food matrix is unknown. We aim to conduct a systematic review and meta-analysis of controlled feeding trials in people with and without diabetes for the effect of fructose sources of fructose-containing sugars at different energy levels on NAFLD markers.

METHODS

Protocol

- Conduct: Cochrane Handbook for Systematic Reviews of Interventions2
- Reporting: PRISMA guidelines3
- Protocol registration: ClinicalTrials.gov (NCT02716870)

Databases

Medline, Embase, and the Cochrane Library were searched through January 10, 2020. Manual searches of the reference lists of included studies supplemented the systematic search.

PICOTS Framework

<table>
<thead>
<tr>
<th>Framework</th>
<th>Description</th>
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<tbody>
<tr>
<td>PIC</td>
<td>Patient: Individuals of all ages with and without diabetes</td>
</tr>
<tr>
<td>O</td>
<td>Intervention: Food and beverage sources of fructose-containing sugars</td>
</tr>
<tr>
<td>C</td>
<td>Comparator: Diet and food free or lower in fructose-containing sugars</td>
</tr>
<tr>
<td>T</td>
<td>Outcome: Primary: Intrahepatic lipid (IHCL); Secondary: Alanine aminotransferase (ALT) and aspartate aminotransferase (AST)</td>
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<tr>
<td>S</td>
<td>Setting: Randomized and non-randomized controlled trials</td>
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</tbody>
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Primary Statistical Analyses

Generic inverse variance using random effects models (SMR for IHCL and MD for ALT and AST, 95% confidence intervals [CIs]). Interaction between food sources of fructose-containing sugars with each energy control assessed by χ² statistic.

Heterogeneity

Cochran’s Q (p≤0.10), quantified by I² (substantial when I²>50%). Sources of heterogeneity explored by sensitivity and subgroup analyses.

Risk of Bias

Cochrane Collaboration Tool.

Summary Plots and GRADE Assessments

HLC SUPERPLOT TABLE

ALT SUPERPLOT TABLE

AST SUPERPLOT TABLE

RESULTS

Study Characteristics

<table>
<thead>
<tr>
<th>Food Source</th>
<th>Subtraction trials</th>
<th>Addition trials</th>
<th>Subtraction trials</th>
<th>Addition trials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sugar sources=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSB=1</td>
<td>Healthy mean difference=-0.22 (95% CI -0.43, -0.01)</td>
<td>Healthy mean difference=-0.22 (95% CI -0.43, -0.01)</td>
<td>Healthy mean difference=-0.22 (95% CI -0.43, -0.01)</td>
<td>Healthy mean difference=-0.22 (95% CI -0.43, -0.01)</td>
</tr>
<tr>
<td>Fruit=2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit juice=1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit=3</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Dried fruit=4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baked starch=5</td>
<td></td>
<td></td>
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<tr>
<td>Added sugar substitute=6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fructose=7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucrose=8</td>
<td></td>
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</tbody>
</table>

Total fructose-containing sugars increased IHCL in addition trials, with no effect in subtraction, substitution, and ad libitum trials.

Total fructose-containing sugars showed null effects on ALT and AST in substitution, addition, substitution, and ad libitum trials.

There was evidence of interaction by food source in addition trials with SSBs increasing IHCL and ALT, and mixed sources increasing AST. All other food sources showed null effects.

The effect of fructose-containing sugars on all NAFLD outcomes were not significantly different between participants with and without diabetes.

LIMITATIONS

- Risk of bias: prominent “High” risk of bias ratings (>33% of trial comparisons)
- Indirectness interaction by food source; limited number of food sources identified; or lack of generalizability of the results to the general population
- Imprecision: all CI crossed the minimally important difference for harm or benefit

CONCLUSIONS

- Energy control and food sources appear to mediate the effect of fructose-containing sugars on NAFLD markers in people with and without diabetes
- There was evidence of interaction by food source in addition trials with SSBs increasing IHCL and ALT, and mixed sources increasing AST
- Evidence for SSBs providing excess energy is of high certainty, suggesting that the available evidence provides a good indication of its increasing effect on IHCL and ALT. We are less confident in the evidence for mixed sources and other food sources at different levels of energy control which were graded as moderate to very low
- More high-quality randomized trials of different food sources are needed to improve our estimates.

REFERENCES


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