Acute glycemic and insulminemic effects of low-energy sweeteners: a systematic review and meta-analysis of randomized controlled trials

Arno Greyling, Katherine M Appleton, Anne Raben, and David J Mela

ABSTRACT

Background: It has been suggested that low-energy sweeteners (LES) may be associated with an increased risk of metabolic diseases, possibly due to stimulation of glucose-responsive mechanisms.

Objective: We conducted a systematic review and meta-analysis of human intervention studies examining the acute effect of LES intake on postprandial glucose (PPG) and postprandial insulin (PPI) responses, in order to comprehensively and objectively quantify these relations.

Methods: We systematically searched the Medline, OVID FSTA, and SCOPUS databases until January 2020. Randomized controlled trials comparing acute postprandial effects on PPG and/or PPI after exposure to LES, either alone, with a meal, or with other nutrient-containing preloads to the same intervention without LES were eligible for inclusion. PPG and PPI responses were calculated as mean incremental area under the curve divided by time. Meta-analyses were performed using random effects models with inverse variance weighing.

Results: Twenty-six papers (34 PPG trials and 29 PPI trials) were included. There were no reports of statistically significant differences in the effects of LES on PPG and PPI responses compared with control interventions. Pooled effects of LES intake on the mean change difference in PPG and PPI were \(-0.02\) mmol/L (95% CI: \(-0.09, 0.05\)) and \(-2.39\) pmol/L (95% CI: \(-11.83, 7.05\)), respectively. The results did not appreciably differ by the type or dose of LES consumed, cointervention type, or fasting glucose and insulin levels. Among patients with type 2 diabetes, the mean change difference indicated a smaller PPG response after exposure to LES compared with the control (\(-0.3\) mmol/L; 95% CI: \(-0.53, -0.07\)).

Conclusions: Ingestion of LES, administered alone or in combination with a nutrient-containing preload, has no acute effects on the mean change in postprandial glycemic or insulminemic responses compared with a control intervention. Apart from a small beneficial effect on PPG (\(-0.3\) mmol/L) in studies enrolling patients with type 2 diabetes, the effects did not differ by type or dose of LES, or fasting glucose or insulin levels. This review and meta-analysis was registered at PROSPERO as CRD42018099608.

Keywords: noncaloric sweeteners, nonnutritive sweeteners, artificial sweeteners, postprandial, glucose, insulin, diabetes

Introduction

Low-energy sweeteners (LES) are often used to replace sugars in food and beverage formulations because they can provide sweet taste with little or no energy contribution or cariogenicity. As such, a range of different LESs are common in the global food supply and are frequently used by manufacturers providing lower-calorie or -sugar alternatives to various food and beverage products. In the United States NHANES 2007–2012, about 50% of respondents reported consuming LES-containing products over a 2-d period.

Despite extensive safety evaluations of these compounds by regulatory bodies, there is an ongoing debate regarding potential detrimental health effects of LES intake, mainly based on selected animal and human observational studies, that LES consumption may increase...
Acute glycemic effects of low-energy sweeteners

TABLE 1  Trial selection criteria

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants/population Age: children 3–10 y, adolescents 10–18 y, adults ≥18 y</td>
<td>Hospitalized/critically ill patients</td>
</tr>
<tr>
<td>Healthy participants and those with impaired glucose homeostasis</td>
<td>Cointervention with insulin or drugs affecting glucose homeostasis</td>
</tr>
<tr>
<td>(prediabetes, diabetes type 1 or 2, impaired glucose tolerance, overweight or obesity)</td>
<td></td>
</tr>
<tr>
<td>Intervention Acute exposure to LES alone; in water, diet beverage, or intragastric infusion; or with meal or other nutrient-containing preloads</td>
<td></td>
</tr>
<tr>
<td>Comparators Above intervention without inclusion of LES</td>
<td>Trials measuring postprandial blood glucose or insulin responses for &lt;120 min (for quantitative meta-analysis only)</td>
</tr>
<tr>
<td>Outcomes Acute postprandial blood glucose response (defined as iAUC) after exposure to LES or control</td>
<td></td>
</tr>
<tr>
<td>Acute postprandial insulin response (defined as iAUC) after exposure to LES or control</td>
<td></td>
</tr>
</tbody>
</table>

1iAUC, incremental AUC; LES, low-energy sweeteners.

Methods

The protocol for this systematic review and meta-analysis was registered in the international prospective register of systematic reviews (PROSPERO, registration number: CRD42018099608), and conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (22).

Search strategy

To qualify for inclusion, trials had to meet the predefined inclusion criteria outlined in Table 1.

PubMed/Medline, OVID FSTA, and SCOPUS were searched (from the date of inception until January 2020) to identify potentially relevant studies conducted in human participants and published in English. Titles, abstracts, and keywords were searched for variations and combinations of the following terms: Artificial sweetener(s), nonnutritive sweetener(s), low-calorie sweetener(s), low-energy sweetener(s), sucralose, aspartame, stevia, steviol, saccharin(e), acesulfame, erythritol, diet (beverage OR drink OR soda), low-calorie (beverage OR drink OR soda), low-energy (beverage OR drink OR soda), glucose, insulin and glyc(a)emic (full PubMed search syntax in the Supplementary Methods). Bibliographies from obtained publications were also screened for additional potentially relevant studies.

Screening and selection of trials

A 2-step screening and selection process was followed. During the first step, titles, abstracts, and keywords of publications were screened separately by 2 of the authors (AG and DJM) to identify potentially eligible studies. During the second step, the full texts of these publications were examined to gauge eligibility based on the stated inclusion criteria. In cases of interreviewer disagreement, questions on study eligibility were resolved through consensus and consultation with the other coauthors (KMA and AR).

Data extraction and quantification

The following information was extracted from eligible publications by means of a predefined data extraction file: 1) publication details (author, year of publication, country); 2) study design characteristics (crossover or parallel, blinding); 3) subject characteristics (age, gender, and health status); 4) intervention and control treatment characteristics (type and dosage of LES, presence and type of meal/nutrient-containing preload, type of control); 5) postprandial glucose and insulin incremental AUC (iAUC) and associated measures of variance; 6) risk of bias indicators. If no iAUC values were reported, postprandial data per measured timepoint were extracted [either from tables and text or from figures by means of a web-based plot digitizing tool (23)].
Data were extracted by 2 independent reviewers (AG, DJM) and differences resolved by consensus.

**Data synthesis and statistical analysis**

Where postprandial data at individual timepoints were extracted, the iAUC was calculated by the trapezoidal method (24). The variances of these iAUCs were based on the SD of the respective individual timepoints and calculated by means of matrix algebra involving a covariance matrix with the assumed correlation structure being compound symmetry (25). For this purpose, the correlation between timepoints was assumed to be 0.75 for glucose and 0.5 for insulin. These assumptions were based on PPG and PPI measurements at repeated timepoints in previous studies conducted by our group (26–29).

Prior to meta-analysis, all glucose and insulin data were transformed into SI units [mmol/L for glucose (= 0.0555 × mg/dL) and pmol/L for insulin (= 6 × μU/mL)]. The outcomes were expressed as mean postprandial changes by dividing the iAUCs by the duration of the postprandial measurement period (120 min). When measures of variance were not reported, they were imputed using variance data from the other studies included in the meta-analysis (30).

For both glucose and insulin, the principal effect measure was the difference in the mean postprandial changes between LES and control interventions. Pairwise analyses were applied to all crossover trials as described by Elbourne et al. (31). The weighted effect estimates and corresponding 95% CIs were calculated using random effects models with inverse variance weighting (32) using the PROC MIXED procedure in SAS (SAS v9.4, SAS Institute). Pooled effects calculated by means of fixed effects models served as sensitivity analyses. Several trials included in the meta-analyses included ≥2 different comparisons (e.g., different doses or types of LES) in the same subjects (33–41). To ensure that these trials did not contribute a disproportionate weight to the meta-analyses due to double counting of the same subjects, the weight of each comparison was divided by the total number of included comparisons in the respective trial (42).

Influence analyses were conducted by systematically excluding 1 study at a time and reanalyzing the remaining data to determine whether a specific study was exerting excessive influence on the overall outcomes. In studies for which enough data were available, the potential effects of predefined covariates on the overall outcomes were assessed by means of subgroup (minimum of 4 comparisons per subgroup) and weighted meta-regression analyses (≥10 comparisons per covariate) (43, 44). The predefined covariates were LES type, health status (healthy; having type 2 diabetes), coexposure type (i.e., LES consumed in a fasted state; LES consumed with a meal or other nutrient-containing preload), baseline fasting glucose, and insulin and LES dose.

**Risk of bias assessment**

Assessment of the risk of bias (RoB) in the included studies was done by means of the Cochrane Collaboration’s tool for assessing RoB (45). For this purpose, 7 different domains were considered (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias). The assessments were carried out independently by 2 authors (AG and DJM), and differences were resolved by consensus.

Publication bias was evaluated by means of visual inspection of funnel plots (constructed by plotting inverse SE against the respective weighted mean difference in glucose and insulin iAUC for each trial) and Egger’s regression test (with \( P < 0.1 \) indicating asymmetry) (46).

Heterogeneity was assessed by means of the Cochran’s \( Q \) statistic (significant at \( P < 0.1 \)) and quantified by the \( I^2 \) statistic (with values of 25%, 50%, and 75% considered to be low-, moderate-, and high-level heterogeneity respectively) (47).

**Network meta-analysis**

In the absence of enough studies with head-to-head comparisons of the PPG and PPI effects of the different LES types included in the review, a post hoc network meta-analysis was conducted to study any potential differences (or informative lack thereof) in this regard. Random effects frequentist network meta-analyses were fitted for PPG and PPI using MetaInsight software, which utilizes the netmeta package on the R statistical software (48). Heterogeneity was assessed through visual assessment of the network meta-analysis comparison plots and the associated between-study SD produced by the models. Consistency between effect estimates obtained from direct and indirect information are necessary for assumptions underpinning a network meta-analysis to hold. If there is substantial inconsistency in a network, joint analysis can be misleading. The presence of inconsistency was evaluated by calculation of the difference between direct and indirect estimates in all closed loops in the network.

**Results**

**Included trial characteristics**

The systematic searches retrieved a total of 5105 potentially relevant papers after removal of duplicates (Figure 1). After exclusion of those that did not meet the predefined inclusion criteria, 26 papers remained that were included in the quantitative synthesis (meta-analysis) (33–41, 49–65). The 26 included papers reported on 34 trials (experiments) with information on PPG responses (yielding 55 comparisons) and 29 trials with information on PPI responses (yielding 50 comparisons). The characteristics of these trials are summarized in Table 2. Additionally, 18 papers (66–83) that reported glucose and/or insulin responses for time periods < 120 min postprandially were included in the qualitative synthesis and are summarized in Supplementary Table 1.

A total of 452 individual participants took part in the 55 comparisons for PPG, and 394 participants in 50 comparisons provided data for PPI. The number of participants per comparison ranged from 6 to 31. Mean age ranged from 18 to 66 years. Forty-one comparisons included healthy lean participants. The remaining 14 comparisons were comprised of patients with diabetes (\( n = 9 \) type 2 diabetes and \( n = 1 \) type 1 diabetes) and participants with obesity but no other health condition (\( n = 4 \)).
Records identified through database searching \( (n = 6597) \)

Additional records identified through other sources \( (n = 0) \)

Records after duplicates removed \( (n = 5104) \)

Records screened \( (n = 5104) \)

Records excluded \( (n = 4923) \)

Full-text papers assessed for eligibility \( (n = 181) \)

Papers with PPG/PPI measurement period ≥120 min included in quantitative synthesis (meta-analysis) \( (n = 26) \)

\( \text{PPG: } n = 25 \text{ papers} \)

\( \text{PPI: } n = 22 \text{ papers} \)

\( (34 \text{ trials, } 55 \text{ comparisons}) \)

Papers with PPG/PPI measurement period <120 min included in qualitative synthesis \( (n = 18) \)

\( \text{PPG: } n = 17 \text{ papers} \)

\( \text{PPI: } n = 10 \text{ papers} \)

\( (17 \text{ trials, } 20 \text{ comparisons}) \)

\( (10 \text{ trials, } 11 \text{ comparisons}) \)

FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the study selection procedure. iAUC, incremental AUC; LES, low-energy sweeteners; PPG, postprandial glucose response; PPI, postprandial insulin response.

In all comparisons, participants started from a fasting baseline. In 12 comparisons, LES was administered to participants in a noncaloric vehicle (capsules, water, “diet” beverage or intragastric infusion). In the remaining comparisons, LES was administered either in conjunction with a standardized carbohydrate-containing meal \( (n = 23) \) or a 75-g glucose load \( (n = 20) \). The types of LES administered were sucralose \( (13 \text{ comparisons}) \), l-arabinose \( (n = 10) \), aspartame \( (n = 9) \), saccharin \( (n = 5) \), erythritol \( (n = 3) \), stevia/steviosides \( (n = 3) \), acesulfame potassium \( (n = 4) \), and combinations of sucralose and accesulfame potassium \( (n = 6) \) and sucralose, acesulfame potassium, and aspartame \( (n = 1) \). The types of control treatments administered were water or other unsweetened beverage \( (31 \text{ comparisons}) \), isocaloric (and isocarbohydrate) meals or beverages without LES \( (n = 21) \), saline \( (n = 2) \), and corn starch placebo capsules \( (n = 1) \).

Effects of LES intake on PPG and PPI responses

In the primary meta-analyses using random effects models, there were no statistically significant effects of LES intake on the mean change differences in PPG and PPI responses \([-0.02 \text{ mmol/L mean PPG (95% CI: } -0.09, 0.05) \text{ and } -2.39 \text{ pmol/L mean PPI (95% CI: } -11.83, 7.05) \text{ respectively}] \) (Figures 2 and 3). In meta-analyses using fixed effects models, the overall estimates of PPG and PPI mean change differences remained similar \([-0.01 \text{ mmol/L mean PPG (95% CI: } -0.04, 0.02) \text{ and } -1.41 \text{ pmol/L mean PPI (95% CI: } -4.12, 1.29) \text{ respectively}] \).

Meta-regression and subgroup analyses

Meta-regression analyses found no statistically significant influence of baseline fasting glucose and insulin or dose of LES used on the mean change differences in PPG and PPI responses to LES (Table 3). However, subgroup analyses of health status (Table 4) indicated a statistically significant difference in the mean change difference in PPG response to LES when comparing healthy participants and those with type 2 diabetes. Thus, there was a small statistically significant reduction in mean PPG for LES compared with the control in the type 2 diabetes subgroup \([-0.3 \text{ mmol/L (95% CI: } -0.53, -0.07) \text{)]\) whereas no change was evident in the healthy subgroup \([-0.01 \text{ mmol/L (95% CI: } -0.07, 0.06) \text{]}. No further influences on PPG or PPI mean change differences were evident when dividing studies by LES type or coexposure type (LES consumed in a noncaloric compared with a meal or nutrient-containing preload).
<table>
<thead>
<tr>
<th>First author, year [country]</th>
<th>Study design</th>
<th>n</th>
<th>Mean age (y)</th>
<th>Health status</th>
<th>LES type</th>
<th>LES dose (mg)</th>
<th>Control</th>
<th>Meal test</th>
<th>Meal carbohydrate content (g)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ahmad, 2018 (49) [Pakistan]</td>
<td>CO, S</td>
<td>20</td>
<td>24.1</td>
<td>Healthy</td>
<td>Stevia</td>
<td>3000</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Azari, 2017 (50) [US]</td>
<td>CO, S</td>
<td>10</td>
<td>33.5</td>
<td>Healthy</td>
<td>Saccharin</td>
<td>18</td>
<td>Water</td>
<td></td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Brown, 2009 (51) [US]</td>
<td>CO, BNR</td>
<td>22</td>
<td>18.5</td>
<td>Healthy</td>
<td>Sucralose + acesulfame K</td>
<td>45.6; 25.9</td>
<td>Carbonated water</td>
<td>75 g glucose</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Brown, 2012 (52) [US]</td>
<td>CO, BNR</td>
<td>25</td>
<td>18.8</td>
<td>Healthy</td>
<td>Sucralose + acesulfame K</td>
<td>45.6; 25.9</td>
<td>Carbonated water</td>
<td>75 g glucose</td>
<td>75</td>
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<td>Burns, 1991 (33) [US]</td>
<td>CO, BNR</td>
<td>8</td>
<td>26.1</td>
<td>Healthy</td>
<td>Aspartame</td>
<td>500</td>
<td>Unsweetened beverage</td>
<td>100 g sucrose</td>
<td>0</td>
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<tr>
<td>Cooper, 1988 (53) [Australia]</td>
<td>CO, BNR</td>
<td>17</td>
<td>62.2</td>
<td>T2D</td>
<td>Saccharin</td>
<td>93¹</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>47</td>
<td></td>
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<tr>
<td>Ford, 2011 (54) [UK]</td>
<td>CO, S</td>
<td>8</td>
<td>22-27</td>
<td>Healthy</td>
<td>Sucralose</td>
<td>41.5</td>
<td>Water</td>
<td></td>
<td>0</td>
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<tr>
<td>Gregersen, 2004 (55) [Denmark]</td>
<td>CO, BNR</td>
<td>12</td>
<td>65.8</td>
<td>T2D</td>
<td>Stevioside</td>
<td>1000</td>
<td>Corn starch</td>
<td>Mixed meal</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Halchou-Jensen, 2015 (34) [Denmark]</td>
<td>CO, D</td>
<td>17</td>
<td>22.5</td>
<td>Healthy</td>
<td>l-Arabinose</td>
<td>2900</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>68</td>
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<tr>
<td>Halschow-Jensen, 2015 (34) [Denmark]</td>
<td>CO, D</td>
<td>17</td>
<td>22.5</td>
<td>Healthy</td>
<td>l-Arabinose</td>
<td>2900</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Horwitz 1988, (35) [US]</td>
<td>CO, BNR</td>
<td>12</td>
<td>28</td>
<td>Healthy</td>
<td>Aspartame</td>
<td>400</td>
<td>Unsweetened beverage</td>
<td>Fasted</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Krog-Mikkelsen, 2011 (36) [Denmark]</td>
<td>CO, D</td>
<td>15</td>
<td>25</td>
<td>Healthy</td>
<td>l-Arabinose</td>
<td>1000</td>
<td>Isocaloric beverage</td>
<td>75 g sucrose</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Ma, 2009 (37) [Australia]</td>
<td>CO, S</td>
<td>7</td>
<td>24</td>
<td>Healthy</td>
<td>Sucralose</td>
<td>800</td>
<td>Saline</td>
<td>Fasted</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nichol, 2020 (65) [US]</td>
<td>CO, BNR</td>
<td>10</td>
<td>27</td>
<td>Healthy</td>
<td>Sucralose</td>
<td>48</td>
<td>Water</td>
<td>75 g glucose</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Overduin, 2016 (56) [UK]</td>
<td>CO, S</td>
<td>10</td>
<td>29.5</td>
<td>Obese</td>
<td>Erythritol</td>
<td>3000</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Parmalavalli, 2011 (57) [India]</td>
<td>CO, BNR</td>
<td>6</td>
<td>NR</td>
<td>T2D</td>
<td>Stevia</td>
<td>2000</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>50</td>
<td></td>
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<tr>
<td>Pepino, 2013 (58) [US]</td>
<td>CO, BNR</td>
<td>17</td>
<td>35.1</td>
<td>Obese</td>
<td>Sucralose</td>
<td>18</td>
<td>Water</td>
<td>75 g glucose</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Prat-Langemard, 2000 (59) [France]</td>
<td>CO, BNR</td>
<td>24</td>
<td>23.2</td>
<td>Healthy</td>
<td>Aspartame</td>
<td>270</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>Slama, 1984 (60) [France]</td>
<td>CO, BNR</td>
<td>12</td>
<td>51–57</td>
<td>T2D</td>
<td>Saccharin</td>
<td>2000</td>
<td>Isocaloric meal</td>
<td>Mixed meal</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>Solomi, 2019 (61) [UK]</td>
<td>CO, BNR</td>
<td>10</td>
<td>27.2</td>
<td>Healthy</td>
<td>Aspartame + acesulfame K (Diet Coke)</td>
<td>55.9; 38.5</td>
<td>Water</td>
<td>25 g glucose</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Steinert, 2011 (38) [Switzerland]</td>
<td>CO, D</td>
<td>12</td>
<td>23.3</td>
<td>Healthy</td>
<td>Acesulfame K</td>
<td>220</td>
<td>Water</td>
<td>Fasted</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Influence analyses, assessment of potential biases, and heterogeneity

Influence analyses conducted by omitting any single study from the meta-analyses did not materially affect results for PPG or PPI (Supplementary Table 2). Overall, all studies had some risk of bias, most notably regarding blinding (most studies were single blind as participants could not be blinded due to the nature of the interventions), as well as unclear reporting of random sequence generation and allocation concealment (Supplementary Table 3). To evaluate potential effects (lack of) blinding, a post hoc analysis was conducted, including only the 7 trials (16 comparisons) (34, 36, 38, 63, 64) reported as being double-blind. The outcomes of both random and fixed effect meta-analyses were similar to those of the main analyses (Supplementary Table 4).

Both PPG and PPI mean change differences showed low to moderate heterogeneity ($P$ value for $Q$ statistic < 0.01; $I^2 = 44.7\%$; and $P < 0.01$, $I^2 = 48.3\%$ respectively) between studies. Egger’s linear regression test did not indicate the potential presence of publication bias ($P$ value of intercept = 0.48 and 0.83 for PPG and PPI respectively). In addition, visual inspection of the funnel plots did not confirm an obvious presence of publication bias, with the PPG and PPI changes scattered relatively uniformly around the overall estimates (Figure 4A and B).

The network meta-analyses produced similar results to the main analyses. The respective evidence network plots for PPG and PPI are shown in Supplementary Figures 1 and 2 respectively. For PPG and PPI mean change differences, there was no evidence of an effect of the different LES types compared with each other or the control intervention (Supplementary Tables 5 and 6). For each outcome, the posterior between-study SD was below 0, suggesting low heterogeneity (Supplementary Figures 3 and 4) and tests for inconsistency found no statistically significant differences between any of the direct and indirect comparisons (Supplementary Tables 7 and 8).

Discussion

This meta-analysis quantifying evidence from 34 randomized controlled intervention trials found that intake of LES had no statistically significant effects on the mean change differences in acute postprandial glucose or insulin responses compared with a control intervention. Our findings for LES in a noncaloric (e.g., water) vehicle are in accordance with the outcome of a recent meta-analysis that compared the effects of different caloric and noncaloric sweeteners on 120 min PPG responses (34, 36, 38, 63, 64). This is now confirmed based on a standard 120 min postprandial period of analysis for glucose and for insulin as well. A somewhat older network meta-analysis that compared the effects of different caloric and noncaloric sweeteners on 120 min PPG responses concluded that the data were inconclusive (85); however, many relevant trials have been published since that analysis, which included only 2 of the 34 trials here.

LESs are often consumed in conjunction with caloric nutrients i.e., protein, fat, and carbohydrates. As such, for the first time, our meta-analysis also included studies where LESs were administered along with standardized mixed meals,
**FIGURE 2** Forest plot showing mean change difference in PPG after LES intake. Horizontal lines represent 95% CIs. The diamond represents the pooled estimate determined using a random effects model [−0.02 mmol/L (95% CI: −0.09, 0.05)]; Q statistic P value < 0.01; $I^2$: 44.7%. Diff, difference; LES, low-energy sweeteners; LL, lower limit; PPG, postprandial glucose response; UL, upper limit.
Acute glycemic effects of low-energy sweeteners

Study | Mean Change Diff | LL | UL | Weight |
--- | --- | --- | --- | --- |
Azari 2017 (Saccharin) (50) | 18.62 | 33.99 | 71.22 | 2.9% |
Brown 2009 (Healthy; Sucrose + Acesulfame K) (51) | 13.04 | 46.49 | 72.57 | 2.1% |
Burns 1991 (Sucrose preload; Aspartame) (33) | 1.17 | -54.72 | 57.06 | 0.8% |
Burns 1991 (Fasted; Aspartame) (33) | -6.08 | -61.97 | 49.81 | 0.8% |
Cooper 1988 (Saccharin) (53) | -4.92 | -44.02 | 34.18 | 3.9% |
Ford 2011 (Sucrose) (54) | -6.22 | -11.44 | -0.99 | 9.3% |
Gregersen 2004 (Stevioside) (55) | 27.04 | -7.95 | 62.03 | 4.6% |
Halschou-Jensen 2015 (5900 mg L-Arabinose) (34) | 25.64 | 0.22 | 51.07 | 0.7% |
Halschou-Jensen 2015 (2900 mg L-Arabinose) (34) | 6.73 | -14.21 | 27.66 | 0.9% |
Halschou-Jensen 2015 (4900 mg L-Arabinose) (34) | 18.63 | 0.72 | 36.54 | 1.1% |
Halschou-Jensen 2015 (2500 mg L-Arabinose) (34) | 24.87 | 5.39 | 44.34 | 1% |
Halschou-Jensen 2015 (10,200 mg L-Arabinose; Liquid meal) (34) | 11.01 | -111.92 | 133.95 | 0.1% |
Halschou-Jensen 2015 (10,200 mg L-Arabinose; Semi-solid meal) (34) | -50.31 | -122.46 | 21.84 | 0.3% |
Halschou-Jensen 2015 (10,200 mg L-Arabinose; Solid meal) (34) | 72.69 | -57.67 | 203.05 | 0.1% |
Helou 2019 (Lean; Acesulfame K) (64) | 8.54 | -24.99 | 42.07 | 4.7% |
Helou 2019 (Obese; Acesulfame K) (64) | -55.62 | -141.27 | 30.02 | 1.2% |
Horwitz 1988 (Healthy; Aspartame) (35) | 9.1 | 0 | 18.2 | 4.2% |
Horwitz 1988 (Healthy; Saccharin) (35) | 3.58 | -5.34 | 12.5 | 4.2% |
Horwitz 1988 (T2D; Aspartame) (35) | 1.16 | -19.51 | 21.84 | 2.8% |
Horwitz 1988 (T2D; Saccharin) (35) | -2.98 | -24.82 | 18.87 | 2.7% |
Krog-Mikkelsen 2011 (1000 mg L-Arabinose) (36) | -15.74 | -36.51 | 5.04 | 1.5% |
Krog-Mikkelsen 2011 (2000 mg L-Arabinose) (36) | -37.97 | -58.97 | -16.96 | 1.4% |
Krog-Mikkelsen 2011 (3000 mg L-Arabinose) (36) | -39.53 | -60.77 | -18.29 | 1.4% |
Ma 2009 (800 mg Sucrose) (37) | 0 | -24.98 | 24.98 | 2.5% |
Ma 2009 (80 mg Sucrose) (37) | 0 | -24.98 | 24.98 | 2.5% |
Nichol 2020 (Lean; Sucrose) (65) | -54.74 | -171.6 | 61.92 | 0.8% |
Nichol 2020 (Obese; Sucrose) (65) | 93.17 | -89.94 | 276.28 | 0.3% |
Overduin 2016 (Lean; Erythritol) (56) | -44.86 | -74.24 | -15.49 | 5.6% |
Overduin 2016 (Obese; Erythritol) (56) | -125.84 | -210.31 | -41.37 | 1.4% |
Pepino 2013 (Sucrose) (58) | 81.19 | 13.22 | 149.16 | 1.8% |
Prat-Larqueimin 2000 (Aspartame) (59) | 22.77 | 8.18 | 37.37 | 7.9% |
Slama 1984 (Saccharin) (60) | 31.46 | -24.52 | 87.44 | 2.6% |
Steinert 2011 (Acesulfame K) (38) | -0.41 | -15 | 14.17 | 2% |
Steinert 2011 (Aspartame) (38) | -8.97 | -31.57 | 13.63 | 1.4% |
Steinert 2011 (Sucrose) (38) | -13.31 | -36.08 | 9.47 | 1.4% |
Sylvestry 2016 (88 mg Sucrose) (39) | 11.78 | -43.17 | 66.73 | 0.3% |
Sylvestry 2016 (170 mg Sucrose) (39) | -6.85 | -44.91 | 31.02 | 0.6% |
Sylvestry 2016 (250 mg Sucrose) (39) | -17.78 | -50.77 | 15.21 | 0.7% |
Sylvestry 2016 (Sucrose + Acesulfame K; Water) (39) | 104.18 | 7.03 | 201.32 | 0.1% |
Sylvestry 2016 (Sucrose + Acesulfame K; Cola) (39) | 113.55 | 16.77 | 210.33 | 0.1% |
Sylvestry 2016 (Sucrose + Acesulfame K + Aspartame) (39) | 102.88 | 13.01 | 192.75 | 0.1% |
Temizkan 2015 (Healthy; Aspartame) (40) | -75.71 | -128.19 | -23.23 | 0.9% |
Temizkan 2015 (Healthy; Sucrose) (40) | -37.28 | -93.1 | 18.54 | 0.8% |
Temizkan 2015 (T2D; Aspartame) (40) | -37.52 | -125.38 | 50.35 | 0.4% |
Temizkan 2015 (T2D; Sucrose) (40) | -85.42 | -172.54 | 1.69 | 0.4% |
Wolf-Novak 1990 (Aspartame) (62) | -19.87 | -66.13 | 26.4 | 3.8% |
Wolnerhanssen 2016 (Erythritol) (63) | 4.39 | -11.82 | 20.67 | 7.6% |
Wu 2016 (Acesulfame K) (41) | 13.72 | -49.35 | 76.79 | 0.3% |
Wu 2016 (Acesulfame K + Sucrose) (41) | -0.49 | -64.02 | 63.54 | 0.3% |
Wu 2016 (Sucrose) (41) | -5.3 | -56.2 | 45.6 | 0.4% |
Overall: P = 0.62, I² = 48.3% | -2.39 | -11.83 | 7.05 | 100% |

FIGURE 3 Forest plot showing mean change difference in PPI after LES intake. Horizontal lines represent 95% CIs. The diamond represents the pooled estimate determined using a random effects model \([-2.39\text{ pmol/L mean PPI (95\% CI: -11.83, 7.05)}\]; Q statistic \(P\) value < 0.01; \(I^2\); 48.3%. \(\text{Diff, difference; LES, low-energy sweeteners; LL, lower limit; PPI, postprandial insulin response; UL, upper limit.}\)
carbohydrate-containing beverages, or a 75-g glucose preload. In this regard, subgroup analyses found a similar absence of effect of LES on the mean change differences in PPG and PPI when consumed either with or without a carbohydrate or nutrient-containing preload. This suggests that nutrient and/or food matrix interactions probably do not play a role in determining potential effects of LES intake on acute glycemic responses.

The outcomes of the 18 studies in which glucose and/or insulin responses were measured for time periods <120 min postprandially are mostly consistent with the results of our meta-analyses. Most studies reported no effects (67, 69–78, 83) or very small changes (70, 74, 76) in PPG and PPI responses after LES ingestion.

The findings of the few included trials of immediate cephalic phase responses were inconsistent, with four of these (66, 68, 79, 82) reporting no effects on glucose or insulin, and 2 (80, 81) reporting increased cephalic phase PPI responses but no effects on PPG. This is noteworthy since, although effects of sweetness itself have been suggested (86, 87), it would seem that sweet taste stimuli alone are not sufficient to elicit meaningful acute glycemic responses. A recent systematic review of studies utilizing preingestive sweet taste stimulation designs also suggested that oral sweet taste activation from LES has limited effects on human glucose homeostasis (84).

Meta-analyses of data from some observational studies suggest an association between LES intake and an increased risk of developing metabolic diseases, particularly type 2 diabetes (8, 9). However, difficulties in the accurate assessment of LES exposure and problems with reverse causality and confounding factors raise concerns regarding the reliability and interpretation of associations from observational studies (88–90). Conversely, our meta-analysis and other reviews (15, 84) show that data from human intervention studies suggest no effects of LES intake on postprandial glucose responses.

We note, however, that among patients with type 2 diabetes, the mean change difference indicated a smaller PPG response after exposure to LES compared with the control. Similar effects were also noted in the meta-analysis of Nichol et al. (15). This might suggest a potential direct glucose-lowering benefit of LES intake for these individuals. However, effect sizes are small and were found from only 9 comparisons, all of which were judged to be of high risk of performance bias and included only 86 individuals. Moreover, it is uncertain whether the 0.3-mmol/L reduction in the PPG response is truly replicable or would be of any long-term clinical relevance in diabetes management. A number of longer-term trials of LES show no significant effects on glycemic control in this population (16). We have no obvious explanation or hypothesis for any differential response in the short term, although this could be related to the poorer glycemic control in people with diabetes.

Several limitations of this meta-analysis should be noted. Firstly, we did not have an a priori hypothesis that different types of LESs would differ in their effects on the mean change in PPG or PPI responses. We therefore assumed that it was appropriate to pool the effects of different LES types in the same meta-analysis. Concerns have, however, been raised that different LES types might differ in their physiological effects (91). If there is a hypothesis that the effects of specific LESs may differ, then a network meta-analysis could be a more appropriate statistical approach. Network meta-analyses allow for the pooling of outcomes derived from direct and indirect evidence across multiple different treatments while preserving the benefits of randomized comparisons within each trial. We did conduct a post hoc network meta-analysis to study any potential informative heterogeneity in this regard. The outcomes were in line with our main analyses, suggesting no evidence of a difference in PPG or PPI effects for the different LES types compared with each other or a control treatment. The outcome of this analysis should be interpreted with caution; however, since it was conducted after the studies, data and outcomes of the main analyses were known.

Second, most of the included studies had relatively small sample sizes, potentially obscuring possible intervention effects due to a lack of statistical power. However, small study biases are generally associated with the erroneous overestimation of effect size and statistical significance (92, 93). Third, as a result of the sweet-tasting nature of the interventions, only a small number of the included studies that had specific design considerations (i.e., administration via capsule/gastric infusion or concomitantly with glucose/sucrose) were double-blinded. It is possible that detection bias has occurred in studies in which the participants and, in some cases, the investigators were not blinded as to the treatments. However, a post hoc analysis including only the studies reported as being double-blind had outcomes similar to those of the main analyses. This finding suggests that potential performance bias was likely not an issue in this case. Regarding the subgroup and post hoc analyses, another potential limitation is that many aspects of the studies covary. For example, all of the double-blind studies were conducted in healthy subjects, whereas all of the studies in subjects with type 2 diabetes were not blinded (potentially high risk of performance bias), and all of the sucralose and l-arabinose studies were relatively recent, whereas most of the aspartame and saccharin studies were older. As such,

<table>
<thead>
<tr>
<th>Covariates</th>
<th>β</th>
<th>SE</th>
<th>P</th>
<th>β</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline fasting glucose per 1-mmol/L increase</td>
<td>−0.059</td>
<td>0.04</td>
<td>0.15</td>
<td>2.17</td>
<td>2.87</td>
<td>0.45</td>
</tr>
<tr>
<td>Baseline fasting insulin per 1-pmol/L increase</td>
<td>−0.001</td>
<td>0.001</td>
<td>0.32</td>
<td>−0.04</td>
<td>0.11</td>
<td>0.75</td>
</tr>
<tr>
<td>Sucralose dose per 10-mg increase</td>
<td>0.004</td>
<td>0.003</td>
<td>0.22</td>
<td>0.08</td>
<td>0.19</td>
<td>0.66</td>
</tr>
<tr>
<td>L-Arabinose dose per 1000-mg increase</td>
<td>0.001</td>
<td>0.024</td>
<td>0.96</td>
<td>0.96</td>
<td>3.93</td>
<td>0.81</td>
</tr>
</tbody>
</table>

1LES, low-energy sweeteners; PPG, postprandial glucose; PPI, postprandial insulin.
TABLE 4  Mean change difference in PPG and PPI after LES intake within different subgroups1

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of studies</th>
<th>Effect (mmol/L)</th>
<th>95% CI</th>
<th>P within subgroup</th>
<th>P between subgroups</th>
<th>Chi-squared</th>
<th>Df</th>
<th>P</th>
<th>Mean change difference in PPI (pmol/L)</th>
<th>95% CI</th>
<th>P between subgroups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LES type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Sucralose</td>
<td>13</td>
<td>0.05</td>
<td>−0.07, 0.18</td>
<td>0.40</td>
<td>33.45</td>
<td>7.11</td>
<td>6</td>
<td>0.31</td>
<td>−3.58</td>
<td>−21.06; 13.90</td>
<td>0.69</td>
</tr>
<tr>
<td>1-Arabinose</td>
<td>10</td>
<td>−0.03</td>
<td>−0.22, 0.16</td>
<td>0.77</td>
<td>34.91</td>
<td>10.34</td>
<td>6</td>
<td>0.16</td>
<td>−6.90</td>
<td>−32.63; 18.83</td>
<td>0.60</td>
</tr>
<tr>
<td>Aspartame</td>
<td>9</td>
<td>0.05</td>
<td>−0.09, 0.20</td>
<td>0.46</td>
<td>0</td>
<td>9.23</td>
<td>6</td>
<td>0.28</td>
<td>1.82</td>
<td>−13.27; 16.92</td>
<td>0.81</td>
</tr>
<tr>
<td>Sucralose + Ace K</td>
<td>6</td>
<td>0.12</td>
<td>−0.14, 0.38</td>
<td>0.36</td>
<td>0</td>
<td>4.22</td>
<td>4</td>
<td>0.52</td>
<td>25.32</td>
<td>−24.28; 74.92</td>
<td>0.32</td>
</tr>
<tr>
<td>Saccharin</td>
<td>5</td>
<td>−0.04</td>
<td>−0.20, 0.13</td>
<td>0.66</td>
<td>0</td>
<td>5.12</td>
<td>5</td>
<td>0.46</td>
<td>−0.29</td>
<td>−17.03; 16.44</td>
<td>0.97</td>
</tr>
<tr>
<td>Ace K</td>
<td>4</td>
<td>−0.12</td>
<td>−0.29, 0.05</td>
<td>0.16</td>
<td>0</td>
<td>2.74</td>
<td>4</td>
<td>0.27</td>
<td>2.74</td>
<td>−21.07; 26.54</td>
<td>0.82</td>
</tr>
<tr>
<td>Coexposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Without nutrient preload</td>
<td>12</td>
<td>0.02</td>
<td>−0.11, 0.15</td>
<td>0.76</td>
<td>44.8</td>
<td>1.48</td>
<td>1</td>
<td>0.48</td>
<td>0.09</td>
<td>1.00; 1.77</td>
<td>0.48</td>
</tr>
<tr>
<td>With nutrient preload</td>
<td>43</td>
<td>−0.03</td>
<td>−0.11, 0.04</td>
<td>0.40</td>
<td>41.46</td>
<td>38.12</td>
<td>38</td>
<td>0.18</td>
<td>−3.48</td>
<td>−15.38; 8.42</td>
<td>0.57</td>
</tr>
<tr>
<td>Health status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Healthy</td>
<td>41</td>
<td>−0.01</td>
<td>−0.07, 0.06</td>
<td>0.80</td>
<td>36.31</td>
<td>5.56</td>
<td>1</td>
<td>0.02</td>
<td>0.45</td>
<td>1.00; 1.77</td>
<td>0.45</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
<td>9</td>
<td>−0.30</td>
<td>−0.53, −0.07</td>
<td>0.01*</td>
<td>32.69</td>
<td>7.23</td>
<td>7</td>
<td>0.01*</td>
<td>−2.86</td>
<td>−12.01; 6.30</td>
<td>0.54</td>
</tr>
</tbody>
</table>

1Ace K, acesulfame potassium; PPG, postprandial glucose; PPI, postprandial insulin.

In conclusion, this review provides an up-to-date overview of controlled human intervention studies on the effects of LES consumption on acute postprandial glycemic and insulinemic responses. Our analyses indicate that under acute conditions, LES do not exert an independent effect on the mean change in postprandial blood glucose or insulin responses compared with a control intervention. Some small reductions in the outcomes of the subgroup analyses should be interpreted with caution. Last, most of the studies included in this meta-analysis investigated the effect of a single LES administered alone. No evidence or reasonable explanatory hypothesis as to why the intake of a combination of LESs would have different effects on glucose homeostasis than a single LES alone was found. Therefore, our conclusions in this regard cannot be extrapolated to other combinations of LESs. There is, however, currently no evidence to perform a subgroup analysis on potential combinations of LESs, and further studies are needed to address this topic.

In conclusion, this review provides an up-to-date overview of controlled human intervention studies on the effects of LES consumption on acute postprandial glycemic and insulinemic responses. Our analyses indicate that under acute conditions, LES do not exert an independent effect on the mean change in postprandial blood glucose or insulin responses compared with a control intervention. Some small reductions in the outcomes of the subgroup analyses should be interpreted with caution. Last, most of the studies included in this meta-analysis investigated the effect of a single LES administered alone. No evidence or reasonable explanatory hypothesis as to why the intake of a combination of LESs would have different effects on glucose homeostasis than a single LES alone was found. Therefore, our conclusions in this regard cannot be extrapolated to other combinations of LESs. There is, however, currently no evidence to perform a subgroup analysis on potential combinations of LESs, and further studies are needed to address this topic.
PPI, based on limited studies, were found in studies enrolling patients with type 2 diabetes, but overall the null results do not seem to differ appreciably by the type of LES consumed, dose of LES, or fasting glucose or insulin concentrations. A post hoc network meta-analysis also indicated no evidence of a difference in PPI or PPI effects for the different LES types compared with each other or a control treatment. As it has been suggested that different LES types may differ in their physiological effects, future work adopting an a priori network meta-analysis approach is recommended.

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The authors’ responsibilities were as follows—DJM and AG: conceived and designed the study, conducted the literature review, and drafted the manuscript; AG: conducted the statistical analysis; KMA and AR: amended and approved the protocol and provided critical revision and important intellectual content; all authors: made significant contributions to this manuscript; and all authors: read and approved the final manuscript.

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Acute glyceremic effects of low-energy sweeteners

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