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Low Calorie Sweetener (LCS) use and energy balance

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Abstract

For thirty years there has been a debate about whether low calorie sweeteners (LCS) provide a benefit for body weight management. Early studies showed that, when consumed alone in a beverage, appetite and food intake were increased. Some observational longitudinal cohort studies reported an association between LCS usage and increasing BMI, suggesting that LCS may actually promote weight gain. In the ensuing decades numerous additional observational and experimental trials have been conducted with the experimental trials nearly uniformly showing a benefit for LCS, either in weight loss or weight gain prevention. The observational trials have been more inconsistent with two recent meta-analyses indicating either a small positive association between LCS usage and BMI (weighted group mean correlation, p=0.03) or an inverse association with body weight change (−1.35 kg, p=.004). Numerous potential mechanisms have been explored, mostly in animal models, in an attempt to explain this association but none have yet been proven in humans. It is also possible that the association between LCS and BMI increase in the observational studies may be due to reverse causality or residual confounding. Randomized controlled trials are consistent in showing a benefit of LCS which suggests that simple behavioral engagement by individuals attempting to control their weight is a sufficiently strong signal to overcome any potential mechanism that might act to promote energy intake and weight gain. Based on existing evidence, LCS can be a useful tool for people actively engaged in managing their body weight for weight loss and maintenance.

Keywords

Low calorie sweeteners; Body weight; Diet beverages; Randomized trials; Observational trials

Low calorie sweeteners (LCS) have been used extensively in foods and beverages for decades, yet there continues to be controversy about their net effects on energy balance. Do they help or hinder weight management? There has been renewed interest in this discussion in recent years in the wake of a number of prospective cohort studies in which it was observed that the risk of weight gain was increased in a dose responsive manner among participants consuming diet beverages compared to those who did not consume them [1,2]. Furthermore, some studies in animals over the past decade have shown that it is possible for LCS to impair normal regulation of energy intake by disrupting the associative learning that normally occurs when sweet taste is reliably paired with metabolizable energy [3]. When animals are conditioned to receive the sweet taste signal in the form of an LCS, which is not

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accompanied by any energy, they lose their ability to appropriately regulate energy intake in the presence of caloric sweeteners, and they demonstrate hyperphagia and excessive weight gain [3]. It has been suggested that these findings provide a plausible biological mechanism by which LCS could promote weight gain in humans [3]. Identifying a plausible mechanism is an important element when making the argument that the weight gain associated with LCS consumption in the observational trials may be causal. Having a hypothetical mechanism also provides a basis for designing randomized trials that would allow direct determination of cause and effect.

Randomized controlled trials (RCTs) of LCS paint a different picture than the observational studies and suggest that LCS provide a net benefit by either preventing weight gain or inducing some weight loss. While it would seem that RCTs would hold the upper hand in determining cause and effect, it is not possible to design any one study to encompass all possible usage scenarios and conditions. Conversely, observational studies, by themselves, will always suffer from the inability to support cause and effect conclusions. It is generally not feasible or practical to adjust for every possible variable in such studies, therefore, the possibility of residual confounding remains and the potential for reverse causality is always present.

Why are the results from observational studies and RCTs leading investigators to reach different conclusions about the effects of LCS on body weight? This brief review will summarize key evidence on both sides of this discussion and will suggest possible explanations for the seemingly contradictory results.

1. Evidence from prospective cohort studies

Stellman and Garfinkel were the first to publish the observation of increased weight gain in association with consumption of LCS [4]. These authors examined a sample of 78,694 women aged 50–69 from the American Cancer Society study of mortality. They looked at LCS usage assessed one year prior to enrollment in the large observational trial and correlated usage with body weight at the start of the one year observation period as well as weight change over the ensuing year. They found that LCS usage was associated with increased body weight and decreased age at baseline and LCS users were significantly more likely to gain weight over the year than non-users. Examination of food frequency questionnaires did not reveal any differences in dietary patterns that would explain the association of LCS and weight gain. The authors concluded that the study does not provide evidence that LCS either supports weight loss or prevents weight gain.

Since that initial observation a number of other prospective cohort studies have reported similar observations [5–8] of an association between LCS consumption and surrogate measures of energy balance such as body weight, body mass index (BMI) and waist circumference. Studies by Fowler and colleagues [1] have renewed the question of whether LCS may actually be promoting weight gain and thereby having the counter-intuitive effect of fueling the obesity epidemic as opposed to helping reverse it. In the largest of these studies, the San Antonio Heart Study from 1979 to 1988, approximately 5,000 participants were examined and follow up evaluations were performed on 3,682 participants who

returned 7–8 years later [1]. BMI increased over the follow up period in a dose responsive fashion and participants in the highest LCS intake quartile (>21 diet beverages per week) had a nearly doubled odds ratio (OR 1.93, 95% CI: 1.20, 3.11, p=0.007) for becoming overweight or obese [1]. The BMIs of LCS users were significantly greater in quartiles 2–4 compared with non-users, and the overall adjusted change in BMI was 47% greater among LCS users compared to non-users.

These findings are provocative and raise the question as to what mechanism might be responsible for the association between LCS use and change in BMI. Is it possible that LCS consumption is a marker for other behaviors and beliefs associated with risk of weight gain that are not captured in the variables measured?

While it is tempting to suggest that reverse causality may be the explanation [9], the fact that the authors adjusted for starting BMI and dieting behavior makes this explanation less likely. However, it is not clear how dieting behavior was defined in the study; therefore, there is no way of knowing which behavioral practices the participants engaged in. For example, might people report that they are dieting simply on the basis that they are using diet beverages? How many of the “dieters” were actually restricting calories below their daily energy expenditure on a regular basis? One curious finding in the San Antonio Heart study was that there was no significant association between sugar-sweetened beverage intake and BMI. This seems to be inconsistent with a large body of literature from other prospective cohort studies that shows a fairly consistent association between sugar-sweetened beverages and measures of body weight and BMI [10]. The largest of these studies, which include the two Nurses Health Studies and the Health Professionals Follow up Study, reported both a significant positive association between sugar-sweetened beverages and weight and a significant negative association between LCS use and weight [11]. How does one reconcile these findings? Finally, in the Fowler study [1], the LCS users reported consuming an average of 223 fewer calories per day than did non-users despite their higher BMI at baseline and subsequent weight gain. This does not make sense without considering systematic underreporting bias and, if that is the explanation, it raises questions about potential bias affecting the other instruments used to assess variables used in the adjustment of the data.

Two recent meta-analyses of existing published prospective cohort studies concluded that associations between LCS use and BMI are inconsistent. In the comprehensive review by Rogers and colleagues [12] a meta-analysis of 12 human trials found no significant change in BMI (−0.002 kg/m2/year, 95% CI −0.009 to 0.005) with LCS use compared to non-use. In the meta-analysis reported by Miller and Perez [13] a small but significant positive association between LCS usage and BMI (weighted group mean correlation = 0.03 kg/m2; 95% CI: 0.01 to 0.06) was found but there was no significant association with body weight or fat mass. Based on the existing literature describing prospective cohort studies, the association between LCS use and measures of body weight is variable and relatively weak.

Despite this weak association, prospective cohort studies should not be dismissed without thorough examination and investigation of potential plausible mechanisms by which they could affect body weight. Observational studies have many strengths including their size,

length of observation, diversity of participants, naturalistic setting and low intensity of interaction with participants (which may alter behavior) and diversity of product usage conditions (e.g., consumed mostly alone, consumed with meals, added to diet, substituted for another beverage, etc.). The limitations include their observational nature, the inability to measure and account for all possible variables, the limited number of repeated measures of exposure (especially considering the length of study) and the absence of psychometric measures relevant to dieting behaviors and product usage.

At the same time, such studies suffer from the potential for reverse causality and residual confounding. Confounding seems especially problematic for studies examining eating behavior given the difficulty in measuring it objectively and the prevalent cognitive biases reported pertaining to eating behavior measurement [14,15]. Furthermore, few observational studies collect detailed information about how participants are using the products of interest, their cognitive intentions, their level of cognitive engagement and other psychometric factors as well as their beliefs about the products pertinent to the outcomes being studied. These factors are likely to have a significant impact on weight outcomes.

2. Possible mechanisms by which LCS could promote weight gain

As mentioned previously the use of observational studies to support cause and effect conclusions is considerably strengthened by direct evidence of plausible biological mechanism(s) substantiating the potential for a given exposure to affect weight, weight gain or BMI. Mattes and Popkin [16] published a comprehensive review of the potential mechanisms by which LCS might affect appetite and food intake as well as other elements of energy balance and hence body weight. From their review of existing literature they concluded that there was no evidence for LCS affecting body weight by a mechanism aside from affecting energy and macronutrient intakes which would mediate other outcome variables.

Dozens of studies have investigated the effects of LCS on appetite and food intake [for reviews see [16,17]. Although early studies found clear evidence for an appetite stimulating effect of LCS [18], in subsequent studies this did not translate into increased food intake [16,19, 20]. Collectively, the literature supports the concept that, when consumed in liquid form in the absence ofother food, LCS can stimulate appetite; however, when consumed with food no such effect is observed [16,20]. Since approximately 75% of LCS consumption occurs with meals [21] the potential to affect food intake would be minimized by usage condition. When LCS are substituted for regular calorie products short term studies have shown that caloric compensation is only about one third of the calories substituted, thus providing the benefit of a net calorie reduction [20].

A number of other mechanisms have been considered, including the potential for LCS to stimulate sweet receptors in the gut, which in animal models can affect gut hormone release and intestinal glucose uptake [22,23]. One of the most compelling mechanisms proposed is disruption of associative learning [3]; however, such a mechanism has not yet been demonstrated in humans [24]. Mattes and Popkin [16] concluded in their review that existing

evidence in humans does not support the various mechanisms that have been proposed for how LCS might affect energy balance.

3. Evidence from Randomized Controlled Trials

In principle, the strongest data for addressing the question of whether LCS help or hinder weight management come from randomized controlled trials (RCTs). The longest such trial to date was a study among 163 obese women that had three phases, a 16 week weight loss phase, a one year maintenance phase and a 2 year follow up phase [25]. Overweight and obese women were randomly assigned to receive either food and beverage products containing aspartame (asp) in substitution for their full calorie counterparts or were asked to abstain from use of asp-containing products for the duration of the entire study. Both groups received a multidisciplinary weight loss program including diet and exercise instruction. Women in both groups lost an average of 10% body weight during the 16 week weight loss phase. During maintenance and follow up the asp group regained less weight than the non-asp group (asp: 2.6%, 4.6% at weeks 71 and 175 vs. non-asp: 5.4% and 9.4%). The asp group lost more weight overall (p=.028) and regained less during follow up (p=.046). Hunger and desire for sweets was not different between treatments as compared to baseline. The authors concluded that use of asp in a multidisciplinary weight loss program may facilitate long term weight loss maintenance.

In a more recent trial [26] Tate and colleagues addressed the question of whether simple substitution of non-caloric beverages (either water or diet beverages) for caloric beverages would promote weight loss compared to an attention control (AC) group that received no specific dietary instructions. Three hundred eighteen overweight and obese adults were randomly assigned to the AC, water and diet beverage groups. The two beverage groups were provided with a supply of water or diet beverage throughout the 6 month trial. After 6 months participants in the diet beverage group had a greater probability of achieving a 5% weight loss compared to the AC group (OR 2.29, 95% CI 1.05, 5.01; p=.04). The OR for the water group was not significantly different than the AC group. (OR 1.87, 95% CI .84, 4.14; p=.13). In a secondary analysis of dietary patterns of the study participants [27] it was found that both beverage study groups (diet beverage, water) reported reducing intake of total energy, carbohydrates, total sugar, added sugar and other calorie containing nutrients. The diet beverage group reported a greater reduction in dessert consumption compared to water drinkers at 6 months. These results are not consistent with the hypothesis that diet beverages stimulate cravings for sweets offsetting weight loss and stimulating weight gain.

Rogers and colleagues [12] comprehensively reviewed both the animal and human randomized trial literature on the effects of LCS consumption on energy intake and body weight. In animals two-thirds of studies reported that consumption of LCS either had no effect or reduced body weight. Of the studies that showed an increase in body weight with LCS exposure, two thirds used a learning paradigm testing the hypothesis that dissociating sweet taste from metabolizable energy by using LCS when compared to glucose disrupted normal regulation of caloric intake leading to overconsumption of the base diet and excess weight gain. The dietary paradigm used in these studies is quite different from the human dietary context in which sweetness is distributed throughout the diet derived from both LCS

and sweeteners providing energy. Such learning effects have not yet been explored in humans but are worthy of examination. Meta-analyses of both short term and longer term human studies found LCS use led to reduced energy intake. Body weight in the longer studies was also reduced when compared to sugar consumption (−1.35 kg, 95% CI −2.28 to −0.42) or water (−1.24 kg, 95% CI −2.22 to 0.26). Another recent meta-analysis [13] reviewed results of RCTs published prior to September of 2013. Results showed significant benefits for body weight (−0.80 kg; 95% CI: −1.17, 0.43), BMI (−0.24; 95% CI: −.41, −0.07), fat mass (−1.10 kg; 95% CI: −1.77, −0.44) and waist circumference (−0.83 cm; 95% CI: −1.29, −0.37). The authors concluded that substituting LCS for the regular calorie versions of foods and beverages results in modest weight loss and LCS can be a useful tool to improve compliance during weight loss and maintenance. In fact, of all the intervention trials reported to date only one small study among males [28] reported a positive effect of LCS on body weight (weight gain).

Despite the consistent results from existing RCTs, recent dietary guidelines scientific advisory committees have expressed uncertainty about the role of LCS in managing body weight and have called for additional studies examining the effects of LCS on weight loss and maintenance [29,30]. Therefore, we conducted a one year RCT among overweight and obese participants comparing LCS to water during 12 weeks of weight loss and 40 weeks of weight maintenance using an equivalence trial design [31,32]. The hypothesis tested was that the two treatment groups would lose an equivalent amount of weight (equivalence being set at ± 1.7 kg at 12 weeks and ±2.2 kg at one year). Most RCTs of LCS effects on body weight have used regular sugared beverages as the comparison group. Few trials have compared LCS beverages to water which is the recommended beverage for optimal health [33].

Three hundred eight participants (BMI 27–40 kg/m^2) were recruited across two sites (University of Colorado, Denver and Temple University, Philadelphia). Participants had to be regular LCS beverage drinkers (at least three, 12 ounce servings per week) and had to be willing to drink either two 12 ounce LCS beverages a day or two 12 ounce servings of bottled water per day (while abstaining from LCS beverages) for one year. During the 12 week weight loss phase participants attended weekly classes at which they received instruction on diet and physical activity behaviors to promote weight loss. Daily calorie targets were set at the level of individual resting metabolic rate rounded up to the nearest 100 kcal. During the 40 week maintenance phase participants attended monthly meetings that reinforced dietary and physical activity behaviors necessary to maintain a weight loss. Classroom curriculum for both groups was the same except for instruction about test beverage consumption.

At the end of the 12 week weight loss phase, weight loss between the water and LCS groups was not equivalent with the LCS group losing significantly more weight than the water group (5.95 vs. 4.09 kg, p<.0001) [31]. Furthermore, significantly more participants in the LCS group lost at least 5% of their body weight compared to the water group (64% vs. 43%, p=.0002). At the one year time point the treatment groups were also not equivalent [32] with the LCS group having maintained about twice as much weight loss as the water group (6.21 vs. 2.45 kg. p<.001). In addition, a greater proportion of participants in the LCS group had

achieved at least a 5% weight loss compared to the water group (44.5% vs. 25.5%, p<.001). Cardio-metabolic blood markers (total cholesterol, LDL, triglycerides) were improved, commensurate with the amount of weight lost. Fasting blood glucose was not different between treatment groups after 12 weeks or one year and there was no indication that LCS had an adverse effect on glucose homeostasis [31,32]. Self-reported measures of hunger were different between the groups with LCS participants reporting feeling less hungry at the end of 12 weeks (p=.013) and 52 weeks (p=.022) compared to the water group [31,32]. There were no differences between groups in class attendance, beverage compliance, caffeine intake or objectively measured physical activity (assessed with arm band accelerometers) over the course of the year-long study [31,32].

It was somewhat surprising that the LCS group performed better than the water group in this trial given that both beverages contribute zero calories to the diet. It is not possible from the data collected to determine the reason for greater weight loss in the LCS group, although the reduced hunger ratings reported by the LCS group may be part of the explanation. Feeling less hungry may have allowed the LCS group to better adhere to the weight management dietary regimen compared to the water group. Because participants in the water group were habitual consumers of LCS beverages prior to the study they were required to make two behavior changes during the trial; stopping consumption of LCS beverages and starting regular consumption of water. This may have been a more challenging behavioral task than that assigned to the LCS group who had to make one behavior change by adjusting their consumption of diet drinks to a minimum of two 12 ounce servings per day. Other possible explanations for the difference in weight loss (and dietary compliance) may include sensory specific satiety or monotony [34–36] in the LCS group through repeated exposure to sweet taste which may have reduced the pleasantness (and intake) of other caloric sweet products in the diet. It is, however, unclear whether sensory specific satiety or monotony are transferable such that exposure to sweet taste in one food would reduce pleasantness of a different sweet food consumed at a different time. Another possibility is the suggestion by Bellisle and colleagues [37] that there may be an optimal “reward homeostasis” that people seek and removing some of the reward stimulus from the diet of the water group (in this case sweetness) may have driven participants to seek sweetness elsewhere in the diet. If such a phenomenon were operating in our study it could have contributed to increased energy intake and reduced weight loss in the water group. Results of this study provide further substantiation that LCS do not impair weight loss in individuals intentionally trying to lose weight as part of a purposeful program. Furthermore, the greater weight loss in the LCS group clearly demonstrates that under the conditions studied LCS do not enhance appetite and food intake compared to water. Other studies have shown that dietary quality actually tends to be higher among LCS users compared to non-users [27,38] providing further evidence that LCS do not drive overconsumption of sweets or other high calorie foods. Finally, these findings are consistent with other studies showing that LCS can be a useful tool to help people successfully manage body weight over the course of many years [39,40].

4. Expectations for LCS effects on body weight

When examining studies of LCS and body weight or other related measures it is useful to account for the context in which those studies are done and what would be the expectations

for effects on body weight considering the larger body of literature on body weight regulation. Under what conditions would LCS be expected to impact body weight? Clearly, in order for weight loss to occur, an individual must be in a state of negative energy balance in which energy expenditure is greater than energy intake. Thus, it might be expected that experimental conditions in which LCS products are substituted for their full calorie counterparts (e.g., swapping regular soda for diet soda) might be expected to create a net caloric deficit and negative energy balance for some period of time (until the body adapts and a new steady state of energy balance is reached). Conditions in which LCS are added to the diet without removing some other calorie source would not be expected to create negative energy balance and hence, weight loss would not occur (e.g., a person who wasn't drinking a sugar-sweetened beverage adopts diet beverages thinking they get "free" sweetness without the consequences). Recent trends in LCS usage suggest they are mostly added to the diet vs. substituted for caloric sweeteners [41]. Finally, the intentions, level of effort, beliefs and expectations of an individual may affect the outcome, as significant weight loss rarely happens in the absence of intention and cognitive effort. If someone believes that merely adopting diet beverage consumption will stimulate weight loss or if they believe the calorie savings are greater than they actually are, this may drive other counter-productive behaviors that would mitigate weight loss such as giving themselves permission to eat a highly caloric dessert because they drank a diet beverage.

Given these considerations it might be expected that LCS would have the greatest potential benefit under two scenarios. First, LCS could have utility as a tool for primary weight gain prevention when substituted for full calorie beverages. This is because the body has weak defenses against primary weight gain such that passive overconsumption of energy can fuel the 1–2 pound average yearly weight gain seen in the population [42,43]. In other words, unlike the case when the body is in negative energy balance and is fighting to preserve existing energy stores, it does not resist energy reductions that prevent net new weight gain. The second scenario when LCS might be expected to provide a benefit would be during cognitively active weight management (weight loss and maintenance) when the individual is motivated to lose weight, has high intentionality and is actively engaged in a regimen of energy restriction (and possibly exercise). In this case LCS can be a tool to reduce dietary energy intake while preserving sweet taste which adds pleasure to the eating experience. A diet including LCS may thereby improve compliance to a calorie restricted regimen. Simply substituting LCS for regular sugar in the diet may produce some weight loss but, in the absence of other persistent energy restriction or increased energy expenditure, this weight loss would be expected to be small as the body counteracts negative energy balance [44].

5. Perspective and future direction

After decades of research there remain a number of unanswered questions about the effects of LCS on energy balance. The reasons for the different results between observational trials and RCTs are not entirely clear although one could argue that simple reverse causality and residual confounding in the observational studies provides the explanation. Although this seems somewhat unsatisfactory, there is currently insufficient evidence from human studies to support alternative mechanisms explaining how LCS might promote weight gain [16].

Existing evidence from randomized trials does not support adverse effects on weight loss and weight maintenance and, collectively, results show a positive net benefit.

The biggest criticism of RCTs seems to be the use of LCS in conjunction with weight management programs that provide structure and education on diet and exercise [3]. The fact that LCS promote weight loss and maintenance in that context shows that whatever mechanism is believed to explain the association of LCS and weight gain from observational studies must be relatively weak and can easily be overcome by cognitive intent and engagement during a weight loss program. A critical question in this discussion is why would anyone expect to lose weight simply by drinking diet soda or using other LCS products without paying attention to the total diet and exercise? This is tantamount to saying "I bought a weight loss book and read it but didn't lose any weight". Weight management in the modern environment for most people requires constant cognitive engagement. One reason that prospective cohort studies have not shown a benefit of LCS may be that participants are not cognitively engaged in weight loss but are "passively" dieting or are using ineffective strategies for controlling their total energy intake. It is important for future prospective observational studies to include more comprehensive psychometric measures of dieting behaviors, behavioral intentions and degree of cognitive engagement with dieting. In addition, repeated measures of product exposure and dieting behavior over time are needed to account for changes in consumer habits in this age of constantly changing dietary advice. Perhaps one way to bridge the gap between the observational science and the RCTs is for the epidemiologists and interventionists to get together to design studies combining the strengths of both approaches. At the same time, more work is needed to explore putative mechanisms by which LCS might affect energy balance in humans so that these may be investigated in randomized trials.

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HIGHLIGHTS

- Some observational studies link low calorie sweeteners (LCS) and weight gain
- Randomized clinical trials show LCS help with weight management
- Reverse causality, engagement, intention and beliefs may explain different results
- Current evidence supports LCS as a useful tool to help manage body weight