The role of sweeteners in weight control and diabetes

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- Background
- Epidemiology and association studies of sweeteners and obesity and diabetes
- Intervention studies
- Conclusions
Conflict of interest statement

- **Paid Consultancy**
  - Pharmaceutical companies involved in developing anti-obesity and diabetes treatment including Abbott Laboratories, Merck, Glaxo Smith Kline, Johnson and Johnson and Roche
  - Surgical manufacturers Ethicon and Covidian
  - Nutrasweet Co. And Ajinomoto

- **Obesity Organisations**
  - Chair of the English Severe and Complex Obesity Group
  - Board member of Counterweight
  - Co-chair of the International Association for the Study of Obesity Education and Management Task Force
Relationship Between BMI and Risk of Type 2 Diabetes

Increase in USA obesity and diabetes prevalence

Data from Center for Disease Control
Elevated blood glucose levels in type 2 diabetes result from:

**Insulin resistance**: impaired insulin-mediated uptake into muscle and failure to suppress glucose output from the liver often secondary to obesity

**β cell failure**: declining insulin production

**Incretin failure**: impaired and delayed insulin secretion in response to high glycaemic foods (sugars and rapidly absorbed carbohydrates)

Diabetes and Weight Loss

- Caloric restriction per se improves glycemic control and insulin sensitivity during weight loss in obese NIDDM patients.¹
- Weight loss improves insulin sensitivity and glycemic control.²
- Moderate, intentional weight loss is associated with reduced mortality.³
- Among persons with diabetes, weight loss improves
  - lipid profiles by decreasing triglycerides and low-density lipoprotein (LDL) cholesterol levels
  - blood pressure
  - mental health, and quality of life.⁴
- Each 1 kg weight loss in first year after diagnosis increases life expectancy by 3-4 months.⁵

¹Wing RR et al. Diabetes Care. 1994;17:30-36
²Pi-Sunyer FX. Diabetes Care. 2000 Oct;23(10):1451-2
⁴Wing RR et al. Diabetes Care. 1991;14:596-599
⁵Lean ME et al. Diabetic Medicine 1990; 7:228-33
Projection for proportion of men in different BMI categories through 2050

50-60% of the adult male population will be obese by 2050

The Obvious....
Energy intake

Ingested Food
- Fat = 9 kcal/gm
- Carbohydrate = 4 kcal/gm
- Alcohol = 7 kcal/gm
- Protein = 4 kcal/gm
- Fibre = 2 kcal/gm

Absorbed Food
Usually ~ 100%
Effects of increasing losses of glucose and fat on body weight

Increasing urinary glucose loss

![Graph showing mean change from baseline body weight kg over time for 'N=23 PLA + INS', 'N=24 DAPA 10 mg + INS', and 'N=24 DAPA 20 mg + INS'. The graph shows a decrease in body weight over time for all groups, with the 'N=24 DAPA 20 mg + INS' group having the largest decrease.](image)

1Dapagliflozin in Patients With Type 2

Increasing faecal fat loss

![Graph showing percentage weight loss over time for Placebo, Orlistat 30mg, 60mg, 120mg, and 240mg. The graph shows a decrease in body weight over time for all groups, with Orlistat 240mg having the largest decrease.](image)

2Orlistat – 6 month dose ranging study

1Wilding JPH et al. Diabetes Care 2009

Energy Expenditure

Energy in

Energy stored

Energy expended

- Resting Metabolic Rate: 70%
- Thermogenesis: 15%
- Activity: 15%

MJ/24hr

10.4.2010
Hypothalamic pathways and brain areas involved in control of energy balance

- Background
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Association is not Causation:

US State Prevalence of Obesity and Preference for Voting for George Bush
US Trends in per capita calories from beverages among children and adults

- Sugar-sweetened beverages are now the primary source of sugars in the American diet.

Hu FB, Malik VS, Sugar-sweetened beverages and risk of obesity and type 2 diabetes: Epidemiologic evidence, Physiol Behav (2010)
Sugars intakes in Scottish children age 3-16

- The mean intake of non milk extrinsic sugars was 17.4% of which sucrose provided 13.4% of food energy

- Non milk extrinsic sugars intake as a percentage of food energy was considerably higher than the UK recommended population average (10% of total energy or 11% of food energy) and the Scottish Dietary Target for children (<10% of total energy)

Background

Epidemiology and association studies of sweeteners and obesity and diabetes
  – Weight

Intervention studies

Conclusions
Childhood Obesity and sugar-sweetened drinks (Planet Health)

POPULATION STUDIED
- 548 ethnically diverse children age 11.7± 0.8 yr prospectively studied 19 months 1995-1997
- Baseline and change in consumption of sugar-sweetened drinks related to obesity

RESULTS
- Odds ratio of becoming obese
  • increased by 1.6 for each additional can or glass of sugar-sweetened drink/day
  • Decreased with increasing diet-drink consumption

BUT
- Indirect measures of obesity
- Small numbers limits statistical power

Ludwig, Peterson & Gortmaker,2001
American Cancer Society Study

- 78,694 women (50-69)
- 21.6% long-term users saccharin
- Recall weight from previous year
- No difference in sweetener use at any initial weight for weight losers
- Users more likely to gain weight BUT
- Recalled body weight and sweetener use, not validated
- Excluded women who had changed dietary habits over previous 10 yrs – i.e. excluded dieters
- Overweight women lost more weight if they were sweetener users

Stellman and Garfinkel, 1986
WHO MONICA (Multinational MONItoring of trends and determinants in CArdiovascular disease) Project

- Designed to monitor temporal changes in classic risk factors of cardiovascular diseases in the general population aged 35–64 y
- 21 countries from the early 1980s to the mid-1990s in independent cross-sectional samples in two or three surveys during the study period
- Annual data on per capita total energy supply, and energy supply from all sweeteners and total fat obtained from the Food Balance Sheets of the Food and Agriculture Organization of the United Nations (FAO)
- Average annual trends in BMI and obesity were derived for each 10-year age group of each population from a simple linear regression of the individual observations on the date of examinations using sex as covariate

Estimated linear change in country’s energy supply (kcal/capita/day) during MONICA periods

- In most Western European countries, the USA, Australia, New Zealand, and China energy supply increased.
- A decrease in energy supply was found in Central and Eastern European countries.
- Changes in energy from all sweeteners and total fat showed a high correlation with the change in total energy supply: sweeteners $r=0.61$, $P<0.0001$; total fat $r=0.68$, $P<0.0001$.

Correlations between 10-year trends of country’s energy supply and of obesity in MONICA populations

- Strong correlations were found between trends in per capita total energy, energy from total fat and from all sweeteners and changes in mean BMI and prevalence of overweight and obesity across populations.
- Changes in per capita energy from sweeteners added little to explain the changes in obesity once total energy per capita had been accounted for.
- Changes in the energy from total fat per capita had a slight effect on the trends in BMI.

Nurses Study

Women who increased and maintained their sugar sweetened beverage consumption gained 8kg while those who decreased their intake and maintained a low level gained only 2.8 kg.

Means adjusted for age, alcohol intake, physical activity, smoking, post-menopausal hormone use, oral contraceptive use, cereal fiber intake, and total fat intake at each time point.

Schulze et al. JAMA. 2004;292:927-934
Change in Intake of Soft Drinks and Fruit Drinks by in African American Women in Relation to Mean Weight Change, 1995 to 2001

<table>
<thead>
<tr>
<th>Intake</th>
<th>Sugar-Sweetened Soft Drinks</th>
<th>Sweetened Fruit Drinks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Participants</td>
<td>Weight Gain, Mean (SD), kg</td>
</tr>
<tr>
<td>1995</td>
<td>2001</td>
<td></td>
</tr>
<tr>
<td>≤1 Drink/wk</td>
<td>≥1 Drinks/d</td>
<td>880</td>
</tr>
<tr>
<td>≥1 Drinks/d</td>
<td>≥1 Drinks/d</td>
<td>2032</td>
</tr>
<tr>
<td>≤1 Drink/wk</td>
<td>≤1 Drink/wk</td>
<td>14246</td>
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<tr>
<td>≥1 Drinks/d</td>
<td>≤1 Drink/wk</td>
<td>1472</td>
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<tr>
<td>All others</td>
<td></td>
<td>11057</td>
</tr>
</tbody>
</table>

Weight loss maintainers: use of artificial sweeteners and fat-modified foods

- Subjects recruited by advertising
  - Weight loss maintainers (WLM) overweight or obese, lost >10% weight for >5yrs and be weight stable
  - Control normal weight (NW) group never overweight

- Weight loss maintainers reported that compared to NW they
  - Consumed less fat and more fat-modified foods
  - Had higher dietary restraint which correlated with lower fat and energy intake
  - Consumed more artificially-sweetened beverages
  - Were physically more active

Regular soft drink intake 1991 – 1999
Nurses Study and risk of developing type-2 diabetes

Hu FB et al 2010 Physiol Behav based on data from Schulze et al. JAMA. 2004;292:927-934
- Background
- Epidemiology and association studies of sweeteners and obesity and diabetes
  - Diabetes
- Intervention studies
- Conclusions
• Women who consumed 2 or more soft drinks per day had a 24% increase in diabetes incidence relative to women who drank less than 1 soft drink per month.
• For sweetened fruit drinks a 31% increase was observed for 2 or more drinks per day relative to less than 1 drink per month.
• Consumption of orange, grapefruit juice and of diet soft drinks was not associated with diabetes risk.
• Background
• Epidemiology and association studies of sweeteners and obesity and diabetes
• Intervention studies
• Conclusions
Effect of supplementing diet with sugar-rich foods and beverages vs. artificially sweetened varieties on body weight

Overweight subjects who consumed fairly large amounts of sucrose (28% of energy), mostly as beverages, had increased energy intake, body weight, fat mass, and blood pressure after 10 wk. These effects were not observed in a similar group of subjects who consumed artificial sweeteners.

Raben A, 2002
RCT of using aspartame-sweetened foods in diet

3 Weeks
4.2 ± 0.8 MJ Diet
No ASP

16 Weeks
Active Weight Loss
4.2 ± 0.8 MJ Diet
ASP or No ASP

52 Weeks
Weight Maintenance
Encouraged to continue diet either ASP or No ASP

85 Weeks
Weight Maintenance
Encouraged to continue diet either ASP or No ASP

163 Women Randomised
Age 20-60 yr

ASP
n=136

No ASP
n=11

ASP
n=125

No ASP
n=39

ASP
n=41

No ASP
n=45

Kanders, Blackburn & Lavin, 1994
Kanders and Blackburn Study - Conclusions

- Weight loss (~10%) at 19 weeks the same between aspartame users and abstainers, but those with greatest weight loss used most aspartame
- Weight regain 5.3% in aspartame users compared to 10.3% in non-users
- No difference in subjective hunger ratings between groups
  - BUT
- Artificial design of study
- High drop-out but analyses were on completers not intention to treat

Kanders, Blackburn & Lavin, 1994
### Meta-analysis of studies using aspartame for weight loss: studies of weight loss with sweetener (excluding those showing weight gain on sucrose regimen)

<table>
<thead>
<tr>
<th>Study authors</th>
<th>Significance of effect</th>
<th>Effect size (SD)</th>
<th>Confidence limits (95%) of effect</th>
<th>Study duration (weeks)</th>
<th>Mean effect and 95% CI (units are SDs)</th>
<th>Type of control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reid &amp; Hammersley, 1998</td>
<td>1.000</td>
<td>0.000</td>
<td>Lower: 0.00  Upper: 0.793</td>
<td>1</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
</tr>
<tr>
<td>Tordoff &amp; Alleva, 1990</td>
<td>0.564</td>
<td>-0.265</td>
<td>Lower: -0.793  Upper: 0.793</td>
<td>3</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Other</td>
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<tr>
<td>Tordoff &amp; Alleva, 1990</td>
<td>0.050</td>
<td>0.612</td>
<td>Lower: -0.265  Upper: 1.252</td>
<td>3</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Other</td>
</tr>
<tr>
<td>Raben et al., 2002</td>
<td>0.087</td>
<td>0.545</td>
<td>Lower: -0.109  Upper: 1.198</td>
<td>10</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Base</td>
</tr>
<tr>
<td>Gatenby et al., 1997</td>
<td>0.175</td>
<td>0.487</td>
<td>Lower: -0.260  Upper: 1.234</td>
<td>10</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
</tr>
<tr>
<td>Kandors et al., 1988</td>
<td>0.102</td>
<td>0.490</td>
<td>Lower: -0.122  Upper: 1.102</td>
<td>12</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
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<tr>
<td>Kandors et al., 1988</td>
<td>0.623</td>
<td>-0.292</td>
<td>Lower: 1.234  Upper: 1.234</td>
<td>12</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
</tr>
<tr>
<td>Blackburn et al., 1997</td>
<td>0.919</td>
<td>0.016</td>
<td>Lower: -2.094  Upper: 0.325</td>
<td>19</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
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<tr>
<td>Kandors et al., 1990</td>
<td>0.040</td>
<td>0.613</td>
<td>Lower: 0.004  Upper: 1.223</td>
<td>52</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
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<tr>
<td>Blackburn et al., 1997</td>
<td>0.143</td>
<td>0.318</td>
<td>Lower: -0.117  Upper: 0.752</td>
<td>71</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
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<tr>
<td>Blackburn et al., 1997</td>
<td>0.028</td>
<td>0.487</td>
<td>Lower: 0.043  Upper: 0.930</td>
<td>175</td>
<td>-4.00 - 2.00  0.00  2.00  4.00</td>
<td>Sucrose parallel</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed</td>
<td>Combined (11)</td>
<td>0.000</td>
<td>0.292</td>
<td>0.129</td>
</tr>
<tr>
<td>Random</td>
<td>Combined (11)</td>
<td>0.001</td>
<td>0.295</td>
<td>0.129</td>
</tr>
</tbody>
</table>

Meta-analysis of studies using aspartame for weight loss: Summary of meta-analysis of weight loss: effect size (as SD) by type of study

- Meta-analyses both of energy intake and of weight loss produced an estimated rate of weight loss of about 0.2 kg/week—a conservative figure as it excludes comparisons where the controls gained weight because of their high-sucrose diet and the long-term follow-up data in which the aspartame groups regained less weight than the control group.

- An estimated compensation rate of around one-third of energy substituted was calculated from the studies which provided sufficient information.

De la Hunty & Ashwell. Nutrition Bulletin 2006; 31; 115–128
Sugar and sweeteners

The good news is that sugar does not need to be excluded from your diet if you have diabetes. The myth that people with diabetes shouldn't eat any sugar still persists but the truth is that people with diabetes can eat sugar. Although sugar should be limited as part of a healthy balanced diet, good blood glucose control can still be achieved when sugar and sugar-containing foods are eaten.

Use of Non-Nutritive Sweeteners in Type I and II and Gestational Diabetes

- Evidence-based nutrition practice guidelines of the American Dietetic Association
  - If persons with diabetes choose to consume products containing U.S. Food and Drug Administration (FDA)-approved non-nutritive sweeteners, at levels that do not exceed the acceptable daily intakes (ADIs), the RD should advise that some of these products may contain energy and carbohydrate from other sources that needs to be accounted for. Research on non-nutritive sweeteners reports no effect on changes in glycemic response.
    - Conclusion statements were Grade III

- If women with GDM choose to consume products containing non-nutritive sweeteners, the RD should inform them that only U.S. Food and Drug Administration (FDA)-approved non-nutritive sweeteners should be consumed and that moderation is encouraged. Research in this area is extremely limited.
  - Conclusion Statement was Grade IV
● Background

● Epidemiology and association studies of sweeteners and obesity and diabetes

● Intervention studies

● Conclusions
Body weight is physiologically regulated but these appears unable to ‘protect’ against weight gain in our current environment.

Increasing body weight commonly leads to type 2 diabetes.
- Decreasing energy by pharmacologically decreasing availability of dietary fat or sugars reduces body weight
- Increasing sugars consumption is associated with increased risk of weight gain and diabetes
- Interventions to substitute low energy sweeteners for sugars can lead to modest weight loss
- Sweeteners are not necessary for people with diabetes nor are there data that suggest they improve diabetes outcomes
Given current evidence, little can be concluded with confidence beyond the fact that requiring individuals to drink large amounts of NSBs causes greater weight gain than not doing so. Randomized controlled trials (RCT) of Non-sweetened beverage consumption reduction have been applied effectiveness studies rather than rigorously controlled efficacy studies.\(^1\)

RCTs are not appropriate methods for studying complex health and behaviour interventions.\(^2\)

\(^1\)Allison DB & Mettes RB. JAMA, January 21, 2009—Vol 301, No. 3