THERAPEUTIC DILEMMA:
NONNUTRITIVE SWEETENERS (NNS)
FOR GLYCEMIC CONTROL?

MELTEM ZEYTINOGLU, MD
HISTORY OF THE PRESENT ILLNESS

63 year-old female presents, as new referral, with uncontrolled Type 2 Diabetes

Diagnosed ~age 46

No prior hospitalizations for diabetes; No known DKA or hypoglycemic events, though does not monitor home glucose

Therapeutic regimen:

Prior: Metformin – stopped 1.5 years ago during an unrelated hospitalization
Glipizide – stopped 1.5 years ago during an unrelated hospitalization
Actos – stopped by PCP when patient started on insulin

Current: Lantus 18 U (since mid-2012) – denies non-adherence

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<tr>
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<th>7</th>
<th>6</th>
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<tbody>
<tr>
<td></td>
<td>1021</td>
<td>1003</td>
<td>1003</td>
<td>0848</td>
<td>1649</td>
<td>1132</td>
</tr>
</tbody>
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**DIABETIC SCREENING**

- Glucose, Fasting: 103
- Glucose, Non-Fasting: 105
- Glycosyl.Hemoglobin: 6.6 * 5.7 *
- Hb A1C: 8.7 * 8.3 * 6.7 * 11.6 *
PAST MEDICAL HISTORY

Type 2 Diabetes Mellitus: Lantus 18 U
Dyslipidemia: atorvastatin 20 mg
Hypertension: lisinopril, hydrochlorothiazide, metoprolol
Chronic Kidney Disease, Stage III
Primary Biliary Cirrhosis: hydroxyzine, cholestyramine-aspartame
Osteopenia: Calcium + Vitamin D
Asthma: albuterol, Symbicort
Depression
SOCIAL AND FAMILY HISTORY

SOCIAL
Unemployed
Lives Alone
1 daughter – very supportive
Tobacco 1 ppd
Previously heavy etoh use
No illicit drugs

FAMILY
Diabetes – maternal aunt
Hypertension – sister
Father died in a car accident
1 Brother shot dead in 30’s
1 brother diet of etoh liver disease in 40’s
REVIEW OF SYSTEMS

**Constitutional:** Positive for fatigue and unexpected weight change. Negative for fever, chills, diaphoresis, activity change and appetite change. **Gaining weight, increased thirst.**

**HENT:** Negative for trouble swallowing, neck pain, and voice change.

**Eyes:** **Blurriness of vision intermittently.**

**Respiratory:** Negative for apnea, cough, shortness of breath and wheezing.

**Cardiovascular:** Negative for chest pain, palpitations and leg swelling.

**Gastrointestinal:** Negative for nausea, vomiting, abdominal pain, diarrhea, constipation and abdominal distention.

**Genitourinary:** Positive for **frequency.** Negative for urgency.

**Musculoskeletal:** Positive for **myalgias and arthralgias.** Negative for back pain.

**Neurological:** Positive for **numbness in bilateral lower extremities.** Negative for dizziness, tremors, weakness, light-headedness and headaches.

**Hematological:** Negative.

**Psychiatric/Behavioral:** Positive for **dysphoric mood.** Negative for sleep disturbance. The patient is nervous/anxious.
COMPREHENSIVE DIABETES EVALUATION - HISTORY

Diabetes-Related Complications:

Microvascular:

   Retinopathy: optho last seen > 1 year ago. No known retinopathy

   Neuropathy: Bilateral numbness, tingling LE. No autonomic symptoms. No history of foot wounds/infections.

   Nephropathy: Suspected

Macrovascular:

   No known CHD, CVD, or PAD

   +Hypertension, Dyslipidemia, and Overweight (BMI 28.3)

History of Diabetes Education: Remote
COMPREHENSIVE DIABETES EVALUATION - HISTORY

Nutrition and Physical Activity:

Diet:

  Breakfast: None
  Lunch: Dinner leftovers (fried chicken or baked chicken), mashed potatoes
  Dinner: Same as lunch
  Snacks/Desserts: fruit 2 x per week, cake 2 x per week, chips
  Sugary Beverages: 72 ounces of Pepsi per day = 248 g carb

Activity: None

Psychosocial: Depression which likely contributes to worsening of her diabetes.
COMPREHENSIVE DIABETES EVALUATION:
PHYSICAL EXAMINATION

BP 133/69 | Pulse 64 | Ht 170.2 cm (5’ 7”) | Wt 81.965 kg (180 lb 11.2 oz) | BMI 28.30 kg/m2

**Constitutional:** She appears well-developed and well-nourished. No distress.

**Head:** Normocephalic and atraumatic.

**Eyes:** Conjunctivae normal and EOM are normal. Pupils are equal, round, and reactive to light.

**Neck:** Normal range of motion. Neck supple. No thyromegaly present. No thyroid nodules appreciated. Acanthosis nigricans and skin tags are absent.

**Cardiovascular:** Normal rate, regular rhythm and normal heart sounds.

**Pulmonary/Chest:** Effort normal and breath sounds normal. She has no wheezes or rales.

**Abdominal:** Soft. She exhibits no distension. There is no tenderness.

**Musculoskeletal:** Normal range of motion. She exhibits no edema and no tenderness.

**Foot examination:** no visible wounds/ulcers. 2+ dorsalis pedis/posterior tibial pulses. Patellar and Achilles reflexes normal. Normal monofilament bilaterally and vibratory sensation and proprioception are intact.

**Skin:** Skin is warm and dry. Rash noted. She is not diaphoretic. No erythema. There is a ~1 cm circumferential papular, crusted lesion on her lateral left shin which appears to be healing and is without surrounding erythema, edema, or warmth.

**Psychiatric:** Her behavior is normal. Judgment and thought content normal. Mood is depressed, tearful when discussing her blood sugars. Appears motivated to change.
## COMPREHENSIVE DIABETES EVALUATION - LABS

<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>338</td>
</tr>
<tr>
<td>Sodium</td>
<td>138</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.3</td>
</tr>
<tr>
<td>Chloride</td>
<td>102</td>
</tr>
<tr>
<td>CO2</td>
<td>26</td>
</tr>
<tr>
<td>Anion Gap</td>
<td>10</td>
</tr>
<tr>
<td>BUN</td>
<td>30</td>
</tr>
<tr>
<td>Creatinine</td>
<td>1.5</td>
</tr>
<tr>
<td>GFR</td>
<td>35</td>
</tr>
<tr>
<td>Calcium</td>
<td>9.5</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.7</td>
</tr>
<tr>
<td>Total Protein</td>
<td>7.9</td>
</tr>
<tr>
<td>T bili</td>
<td>0.1</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>287</td>
</tr>
<tr>
<td>AST</td>
<td>26</td>
</tr>
<tr>
<td>ALT</td>
<td>20</td>
</tr>
<tr>
<td>WBC</td>
<td>10.9</td>
</tr>
<tr>
<td>HGB</td>
<td>12.4</td>
</tr>
<tr>
<td>HCT</td>
<td>38.0</td>
</tr>
<tr>
<td>PLT</td>
<td>324</td>
</tr>
<tr>
<td>TSH</td>
<td>1.06</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>11.6</td>
</tr>
<tr>
<td>Urine Albumin/Creatinine</td>
<td>632.0</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>193</td>
</tr>
<tr>
<td>LDL</td>
<td>124</td>
</tr>
<tr>
<td>HDL</td>
<td>45</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>120</td>
</tr>
</tbody>
</table>
WHAT THERAPEUTIC RECOMMENDATIONS DO YOU HAVE?
IMPROVING GLYCEMIC CONTROL IN OUR PATIENT
Prevalence (%, SE) of nonnutritive sweetened beverage intake among U.S. children and adults as determined by one 24-hour recall (National Health and Nutrition Examination Survey 2007–2008) according to age group. The sample size of participation by age group for females was ages 1 to 3 (n = 575), 4 to 8 (n = 435), 9 to 13 (n = 418), 14 to 18 (n = 353), 19 to 30 (n = 513), 31 to 50 (n = 950), 51 to 70 (n = 873), and >70 (n = 484). The sample size of participation by age group for males was ages 1 to 3 (n = 617), 4 to 8 (n = 502), 9 to 13 (n = 412), 14 to 18 (n = 380), 19 to 30 (n = 518), 31 to 50 (n = 889), 51 to 70 (n = 869), and >70 (n = 466).
59,614 women (mean age 62.8) from Women’s Health Initiative Observational Cohort:
  No preexisting CVD
  Only women with diet drink intake data were included

Primary outcome:
  Composite of incident CHD, CHF, MI, PCI, ischemic CVA, PAD, CVD death

Results:
  After adjustment for CVD risk factors (demographics, BMI, smoking, hormone therapy, physical activity, energy intake, salt intake diabetes, hypertension, high cholesterol, and sugar sweetened beverage intake), women who consumed \( \geq 2 \) diet drinks per day had higher risk of CVD events (HR 1.3, 95% CI 1.1-1.5) and overall mortality (HR 1.3, 95% CI 1.04-1.5) compared to women who consumed \( \leq 3 \) diet drinks per month.


CHALLENGES OF STUDYING NNS EFFECTS

Epidemiologic studies may be limited by methodological dilemmas...

Observational studies

- Allow for long-term assessment of changes in health outcomes
- Can only identify associations and not causality
- Confounding due to many dietary and health variables correlating with NNS intake
- Poor dietary recall
- Changes in beverage habits overtime
- Reverse causality - overweight/obese individuals more likely to consume diet drinks

Intervention studies/Randomized control trials tend to be short-term

Metabolic effects seen in vitro and in animal models have often not translated to humans. Yet emerging data shows that NNS are not as metabolically inert as previously believed.
17 obese patients (BMI 42.3 +/- 1.6 kg/m2) who were insulin-sensitive and did not use NNS prior to the study.

After a 12 hour overnight fast, patients had the following plasma measurements at 20, 15, 10, 6, and 2 minutes before and at 10, 20, 30, 40, 60, 90, 120, 150, 180, 240, and 300 minutes after 75 g glucose load:
- plasma glucose, insulin, C-peptide, glucagon, glucose-dependent insulinotropic polypeptide (GIP), and active GLP-1

Subjects drank 48 mg sucralose or equivalent volume of water before glucose ingestion.


“These data suggest that sucralose ingestion is not physiologically inert but affects the glycemic response to an oral glucose load and potentiates glucose-stimulated insulin secretion in obese people.”

Figure 1—Mean plasma glucose (A), insulin (B), C-peptide (C), and glucagon (D) concentrations in obese subjects after drinking either sucralose or water 10 min before ingestion of a 75-g glucose load (given at time = 0 min). *Value significantly different from corresponding water condition value, P < 0.004.
RELATIVE SWEETNESS OF NNS TO SUCROSE – POTENT STIMULATORS OF SWEET TASTE RECEPTORS

http://www.sugar.org/other-sweeteners/artificial-sweeteners/
“Could non-nutritive sweeteners be accentuating postprandial glycemia via effects on sweet taste receptors, thereby contributing to the progression of glucose intolerance.”

FIG. 1. Putative relationships between intestinal STRs, SGLT1 and GLUT2, glucose absorption, and incretin hormones GLP-1, GIP, and PYY.


SWEET TASTE RECEPTORS, HYPERINSULINISM, AND WEIGHT GAIN?


Sweet taste receptor ligands stimulate adipogenesis and suppress lipolysis; however, these effects do not require T1R2 and T1R3 (G-protein coupled sweet taste receptors found in taste buds, gut, and pancreas), despite their expression in adipose tissue.

Some artificial sweeteners regulate adipocyte differentiation and metabolism through a sweet taste receptor-independent mechanism.
Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass

Becky R. Simon¹, Brian S. Learman², Sebastian D. Parlee², Erica L. Scheller², Hiroyuki Mori², William P. Caithorn²,⁴, Xiaomin Ning², Venkatesh Krishnan⁴, Yanfei L. Ma⁴, Björn Tyrberg⁵,⁶, Ormond A. MacDougald¹,²,³*

¹ Program in Cellular and Molecular Biology, University of Michigan, Ann Arbor, Michigan, United States of America, ² Molecular & Integrative Physiology, University of Michigan, Ann Arbor, Michigan, United States of America, ³ Department of Internal Medicine, University of Michigan, Ann Arbor, Michigan, United States of America, ⁴ Musculoskeletal Research, Lilly Research Laboratories, Indianapolis, Indiana, United States of America, ⁵ Cardiovascular and Metabolic Disease, MedImmune LLC, Gaithersburg, Maryland, United States of America, ⁶ Diabetes and Obesity Research Center, Sanford-Burnham Medical Research Institute, Orlando, Florida, United States of America

Abstract

Functional expression of sweet taste receptors (T1R2 and T1R3) has been reported in numerous metabolic tissues, including the gut, pancreas, and, more recently, in adipose tissue. It has been suggested that sweet taste receptors in these non-gustatory tissues may play a role in systemic energy balance and metabolism. Smaller adipose depots have been reported in T1R3 knockout mice on a high carbohydrate diet, and sweet taste receptors have been reported to regulate adipogenesis in vitro. To assess the potential contribution of sweet taste receptors to adipose tissue biology, we investigated the adipose tissue phenotypes of T1R2 and T1R3 knockout mice. Here we provide data to demonstrate that when fed an obesogenic diet, both T1R2 and T1R3 knockout mice have reduced adiposity and smaller adipocytes. Although a mild glucose intolerance was observed with T1R3 deficiency, other metabolic variables analyzed were similar between genotypes. In addition, food intake, respiratory quotient, oxygen consumption, and physical activity were unchanged in T1R2 knockout mice. Although T1R2 deficiency did not affect adipocyte number in peripheral adipose depots, the number of bone marrow adipocytes is significantly reduced in these knockout animals. Finally, we present data demonstrating that T1R2 and T1R3 knockout mice have increased cortical bone mass and trabecular remodeling. This report identifies novel functions for sweet taste receptors in the regulation of adipose and bone biology, and suggests that in these contexts, T1R2 and T1R3 are either dependent on each other for activity or have common independent effects in vivo.

Citation: Simon BR, Learman BS, Parlee SD, Scheller EL, Mori H, et al. (2014) Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass. PLoS ONE 9(1): e86454. doi:10.1371/journal.pone.0086454
At this time, there are insufficient data to determine conclusively whether the use of NNS to displace caloric sweeteners in beverages and foods reduces added sugars or carbohydrate intakes, or benefits appetite, energy balance, body weight, or cardiometabolic risk factors.

Paucity of data from well-designed human trials exploring the potential role of NNS in achieving and maintaining a healthy body weight and minimizing cardiometabolic risk factors.

There are some data to suggest that NNS may be used in a structured diet to replace sources of added sugars and that this substitution may result in modest energy intake reductions and weight loss.

The evidence reviewed suggests that when used judiciously, NNS could facilitate reductions in added sugars intake, thereby resulting in decreased total energy and weight loss/weight control, and promoting beneficial effects on related metabolic parameters. However, these potential benefits will not be fully realized if there is a compensatory increase in energy intake from other sources.
CONCLUSIONS

Non-nutritive sweetened beverages continue to be recommended as alternatives to sugar-sweetened beverages, which have unequivocally been linked to obesity and metabolic syndrome.

Although there is conflicting and insufficient data on the precise metabolic effects of non-nutritive sweeteners, a growing body of recent evidence supports that they are not physiologically inert, and that they may have deleterious metabolic effects.

These recommendations should make clear that although they may be used as a substitute, non-nutritive beverages should be consumed modestly and infrequently, and that unprocessed, unsweetened natural beverages such as water, milk, decaffeinated unsweetened tea, etc. should be consumed first.
Sweet Taste Receptor Deficient Mice Have Decreased Adiposity and Increased Bone Mass

Becky R. Simon, Brian S. Learman, Sebastian D. Perlee, Eric L. Scheller, Hiroaki Mori, William F. Cawthorne, Xiaolin Ning, Venkatesh Krishnan, Yanfei L. Ma, Bojan Tyberg, and Ronald A. MacDougall

Abstract

Functional expression of sweet taste receptor (T1R2 and T1R3) has been reported in numerous metabolic tissues, including the gut, fat, and liver. Recent studies have suggested that sweet taste receptor (T1R2 and T1R3) expression may play a role in energy balance and metabolism. In this study, we investigated the potential contribution of T1R2-deficient mice to adipose tissue energy balance and metabolism. T1R2-deficient mice were generated and compared to wild-type controls. Mice were fed a high-fat diet, and fat mass and energy expenditure were measured. T1R2-deficient mice had significantly lower body weight and decreased fat mass compared to wild-type controls. Furthermore, T1R2-deficient mice had increased energy expenditure compared to wild-type controls. These findings suggest that T1R2-deficient mice have decreased adiposity and increased energy expenditure, which may contribute to the regulation of energy balance and metabolism.

When fed an obeseogenic diet, T1R2 and 3 knockout mice reduced adiposity and increased energy expenditure. They also had increased peripheral bone mass and trabecular remodeling.
# POTENTIAL MECHANISMS OF EFFECTS OF NNS ON COMPENSATORY APPETITE AND FOOD INTAKE

<table>
<thead>
<tr>
<th>Potential mechanisms</th>
<th>Description</th>
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<tbody>
<tr>
<td>Cephalic phase stimulation</td>
<td>Refers to a phase of early gastric secretions when food is in the mouth but has not yet reached the stomach; NNS might affect hunger and appetite at this phase.</td>
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<tr>
<td>Nutritive and osmotic effects</td>
<td>Refers to the possibility that the lower energy density and lower osmotic load of NNS versus caloric sweeteners could alter the rate of gastric emptying or other factors of digestion and absorption that might affect sensations of satiety.</td>
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<tr>
<td>Gut peptide response</td>
<td>Refers to the effect dietary macronutrients have on gut peptides that signal satiety; if NNS were to diminish the release of these peptides relative to caloric sweeteners, it could theoretically result in lower satiety and increased energy intake.</td>
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<tr>
<td>Palatability</td>
<td>NNS are typically added to increase palatability, and palatability is assumed to stimulate hunger and/or reduce satiation/satiety, thus increasing intake.</td>
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<tr>
<td>Informed use leading to overcompensation</td>
<td>Expected energy savings attributed to the substitution of an NNS-containing product could lead to subsequent indulgence rationalized by the previous energy savings and then overcompensation.</td>
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<tr>
<td>Loss of signal fidelity</td>
<td>Sensory properties signal information about the metabolic response required by consumption of the product. If the sensory cue of sweetness leads to inaccurate or inconsistent predictive power, energy regulation may be disrupted and could lead to positive energy balance from overconsumption triggered by this signaling.</td>
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<tr>
<td>Activation of reward systems</td>
<td>Refers to the possibility that the enhanced palatability conferred by NNS could play a role in reward-motivated feeding, thus added caloric intake when a nonfood reward could be provided.</td>
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<tr>
<td>Training the palate/learning to like the familiar</td>
<td>Refers to the possibility that repeated exposure to NNS may perpetuate a preference for sweet items in the diet, including items sweetened with caloric sweeteners.</td>
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A review by Mattes and Popkin (3) concluded that the available evidence either refuted or was insufficient to refute or support each of these potential mechanisms or hypotheses for NNS increasing appetite, hunger, or energy intake. NNS indicates nonnutritive sweeteners.
FIG. 4. Insulin secretion. A: Effect of 18-h exposure to 100 μmol/L fatty acid (FA) on insulin secretion from isolated rat islets (73). B: Concentration dependence of MOG-stimulated insulin secretion from dissociated rat islets at basal 3 mmol/L glucose (73). C: Effect of artificial sweeteners on insulin secretion in dissociated rat islets (74). Effect of iron exposure in INS-1 (832/13) cells (Deeney et al., unpublished data). Data shown are means ± SEM for at least three experiments.