Personalized Nutrition by Prediction of Glycemic Responses

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Changes in our nutrition greatly contributed to the recent metabolic syndrome epidemic.
General recommendations in nutrition

Source: USDA
Consumption of artificial sweeteners
Increase in artificial sweetener consumption is a major recent change in our nutrition.

- 86% of Americans use ‘diet’ products
- Consumers spend $21B per year on diet drinks

Sylvetsky et al., Am J Clinical Nutrition 2012
Artificial sweeteners are recommended for weight loss and for assisting in blood glucose control.

AHA & ADA joint statement
From Gardner et al., published July 2012 in Circulation and in Diabetes care:

“REPLACING SUGARY FOODS AND DRINKS WITH SUGAR-FREE OPTIONS CONTAINING NON-NUTRITIVE SWEETENERS IS ONE WAY TO LIMIT CALORIES AND ACHIEVE OR MAINTAIN A HEALTHY WEIGHT.”

“WHEN USED TO REPLACE FOODS AND DRINKS WITH ADDED SUGARS, IT CAN HELP PEOPLE WITH DIABETES MANAGE BLOOD GLUCOSE LEVELS”
Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez, Tal Korem, David Zeevi, Gili Zilberman-Schapira, Christoph A. Thaiss, Ori Maza, David Israeli, Niv Zmora, Shlomit Gilad, Adina Weinberger, Yael Kuperman, Alon Harmelin, Ilana Kolodkin-Gal, Hagit Shapiro, Zamir Halpern, Eran Segal & Eran Elinav

Suez et al., Nature 2014
What is the effect of artificial sweeteners on mice?

Suez et al., *Nature* 2014
Artificial sweeteners induce glucose intolerance in mice

- Lean mice
- Obese mice
- Different formulations
- Different doses
- Different mouse strains
Do artificial sweeteners interact with the microbiome?
What is the effect of artificial sweeteners on mice?

Suez et al., Nature 2014
Antibiotics reverse the effect of artificial sweeteners

A, Ciprofloxacin & Metronidazole (targets Gram-)
B, Vancomycin (targets Gram+)

Suez et al., Nature 2014
Transferring the microbiota of mice that consume artificial sweeteners transfers the glucose intolerance

Suez et al., Nature 2014
Transferring the microbiota grown in the presence of artificial sweeteners transfers the glucose intolerance

Suez et al., Nature 2014
Artificial sweeteners drive glucose intolerance in mice by altering the gut microbiota

... but what about people?
What happens to humans after just five days of consuming artificial sweeteners?

Suez et al., Nature 2014
Artificial sweeteners induce glucose intolerance in most but not all individuals

Responders

Non-responders

Suez et al., *Nature* 2014

The Personalized Nutrition Project
Transferring the microbiota of responders to artificial sweeteners transfers the glucose intolerance phenotype

Suez et al., *Nature* 2014
Validation studies (2015)

Diet Soda Intake Is Associated with Long-Term Increases in Waist Circumference in a Biethnic Cohort of Older Adults: The San Antonio Longitudinal Study of Aging
Sharon P.G. Fowler, MPH,* Ken Williams, MS, *† and Helen P. Hazuda, PhD *

Positive association between artificially sweetened beverage consumption and incidence of diabetes
Allison C. Sylvetsky Meni1,2 & Susan E. Swithers3 & Kristina I. Rother 1

Diet Drink Consumption and the Risk of Cardiovascular Events: A Report from the Women’s Health Initiative
Ankur Vyas, MD1, Linda Rubenstein, PhD2, Jennifer Robinson, MD, MPH1,2, Rebecca A. Seguin, PhD, CSCS3, Mara Z. Vitolins, DrPH, MPH, RD4, Rasa Kazlauskaite, MD, MSc, FACE5,6, James M. Shikany, DrPH7, Karen C. Johnson, MD, MPH8, Linda Snetselaar, RD, PhD9, and Robert Wallace, MD, MSc2,9
If nutritional changes drove the metabolic syndrome epidemic, can it be treated by restoring healthy nutrition?
What is healthy nutrition?
How can we take a science-based approach to nutrition?

David Zeevi
What should a marker of healthy nutrition satisfy?

- Relevant for weight management
- Relevant for metabolic disease
- Easily measurable quantitatively
Postprandial (post-meal) glucose response as a measure of healthy nutrition

- Directly affects fat storage, weight gain and hunger
- Strongly associated with disease: Diabetes, Obesity, Cardiovascular disease, Chronic metabolic disorders
- Easily measurable

Bonora et al., Diabetologia 2001; Cavalot et al., Diabetes Care 2011; Wang et al., Diabetes Care 2004; Temelkova-Kurktschiev et al., Diabetes Care 2000; O'Keefe et al., Am J Cardiol 2007
Maintaining normal blood glucose levels is key to fighting the rise in disease.
People have widely different glucose responses to the same food

Adapted from Vega-López et al., Diabetes Care 2007
Diets that maintain normal blood glucose levels must be personally tailored.
What could affect our response to food?

- Genetics
- Nutrition
- Microbes
- Lifestyle
The microbiome affects our response to food

Koeth et al., Nature Medicine 2013
Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome

Vrieze et al, *Gastroenterology* 2012
What could affect our response to food?

- Genetics
- Nutrition
- Microbes
- Lifestyle
The Personalized Nutrition Project: Clinical and microbiome data collected

- Gut microbiome
  - 16S rRNA Metagenomics
- Blood tests
- Questionnaires
  - Food frequency
  - Lifestyle
  - Medical
- Anthropometrics

**Diary** (food, sleep, physical activity)
Using smartphone-adjusted website
5,435 days, 46,898 meals, 9.8M Calories, 2,532 exercises

**Continuous glucose monitoring**
Using a subcutaneous sensor (iPro2)
130K hours, 1.56M glucose measurements

Profiling 800 people
Continuous glucose monitoring

Zeevi et al., Cell 2015
The Personalized Nutrition Project: Cohort statistics

- 25-70 years of age
- 55% overweight
- 22% obese
- 21% pre-diabetic

Zeevi et al., Cell 2015
Cohort bacterial composition comparable to other international cohorts
What is the variability across people in the response to the same food?
Testing the cohort response to standardized meals

Zeevi et al., Cell 2015
The same person has a highly similar post-meal response to the same standardized meal across different days

Zeevi et al., Cell 2015
Different people have widely different post-meal responses to the same standardized meal

Population Responses to Standardized Meals

Four Individual Responses to Bread

Zeevi et al., Cell 2015
Different people have opposite responses to different standardized meals

Zeevi et al., Cell 2015
Different people have widely different post-meal responses to the same real-life meals.
General recommendations in nutrition

Source: USDA
What explains the variability in people’s response to the same food?
Variability in post-meal glucose response across people associates with microbiota composition and function

Zeevi et al., Cell 2015
Variability in post-meal glucose response across people associates with microbiota composition and function

- Positive association with PPGR to glucose + bread
- High levels associate with a high-fat low-fiber diet (Wu et al., 2011)
Positive association between ABC transporters and post-meal glucose response to all standardized meals

- Positive association with **TIIDM** (Karlsson et al., 2013)
- Positive association with **western high-fat/high-sugar diet** (Turnbaugh et al., 2009)
Can we predict the personal post-prandial glucose response to any complex meal?
Meal Carbohydrates: State of the art in predicting post-meal glucose responses

State of the art

Carbohydrate-only prediction

R=0.38

Measured PPGR (iAUC; mg/dl*h)

Meal carbohydrates (g)

Zeevi et al., Cell 2015
Prediction scheme

Zeevi et al., Cell 2015
Model features

- 800 People
- 46,898 Meals
- 5,417 Days
- 800 People

- MetaPhlAn abundances
- 200 Nutrients (including fatty acids, vitamins, and minerals)
- Multiple recorded features (meal times, sleep, exercise, stress, hunger, medication)
- 30 Blood parameters

- KEGG abundances
- 16S OTUs
- Growth dynamics
- 100 Questions
- 100 FFQ features

Zeevi et al., Cell 2015
Accurate predictions of personalized glucose responses

**State of the art**

- Measured PPGR (iAUC; mg/dl*h)

**Our prediction**

- 800 participants
- Predicted PPGR (iAUC; mg/dl*h) $R=0.68$

**Prediction validation**

- 100 participants
- Predicted PPGR (iAUC; mg/dl*h)

Zeevi et al., Cell 2015
Features contributing to prediction

Meal carbohydrates (2)

Partial dependence (a.u.)

Weight (g)

Zeevi et al., Cell 2015
Features contributing to prediction
Features contributing to prediction

Zeevi et al., Cell 2015
Features contributing to prediction

Zeevi et al., Cell 2015
Can personally tailored dietary interventions improve post-prandial glucose responses?
Constructing personally tailored diets that achieve normal post-prandial glucose responses

Zeevi et al., Cell 2015
Can you distinguish between the good and bad menus?

Breakfast
- Muesli

Lunch
- Sushi
- Marzipan
- Corn and nuts

Snack
- Edamame
- Hummus and pita

Dinner
- Vegetable noodles with tofu
- Ice cream

Night snack
- Egg with bread and coffee

“Bad” Diet

“Good” Diet

Zeevi et al., Cell 2015
Can you distinguish between the good and bad menus?

**Bad Diet**
- Breakfast: Muesli
- Lunch: Sushi
- Snack: Marzipan
- Dinner: Corn and nuts
- Night snack: Toblerone and coffee

**Good Diet**
- Breakfast: Egg with bread and coffee
- Lunch: Hummus and pita
- Snack: Edamame
- Dinner: Vegetable noodles with tofu
- Night snack: Ice cream

Zeevi *et al.*, Cell 2015
A ‘good’ meal for one person can be a ‘bad’ meal for another

Participants

Pizza | Hummus | Potatoes | Chicken liver | Schnitzel

Food consumed during ‘good’ diet week

Food consumed during ‘bad’ diet week

Zeevi et al., Cell 2015
Personally tailored diets reduce the post-prandial glucose response

Zeevi et al., Cell 2015
Personally tailored diets improve post-meal responses

Zeevi et al., Cell 2015
Dietary interventions targeting post-meal glucose responses induce consistent changes in microbiota

Zeevi et al., Cell 2015
Dietary interventions targeting post-prandial glucose responses induce consistent changes in microbiota

- Bifidobacterium adolescentis decreases during ‘good’ week.
- Low levels associated with greater weight loss (Santacruz et al., 2009)
Dietary interventions targeting post-meal glucose responses induce consistent changes in microbiota

- Roseburia inulinivorans increases following the ‘good’ diet week
- Low levels associate with TIIDM (Qin et al., 2012)

Zeevi et al., Cell 2015
Summary

• Artificial sweeteners induce glucose intolerance driven by gut microbial changes
• High interpersonal variability in post-meal glucose observed in an 800-person cohort
• Using personal and microbiome features enables accurate glucose response prediction
• Short-term personalized dietary interventions successfully lower post-meal glucose
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