A science-based approach to nutrition:

Personalized Nutrition by Prediction of Glycemic Responses

Eran Segal
Weizmann Institute of Science
The metabolic disease epidemic

- 1 in 10 diabetic
- 70% overweight
- 4 in 10 obese
Changes in our nutrition greatly contributed to the recent metabolic syndrome epidemic
Changes in our nutrition greatly contributed to the recent metabolic syndrome epidemic

- Reduced fat consumption and increased carbohydrates consumption
- Increased consumption of added sugar
- Increased consumption of food additives and artificial sweeteners
- Changed meal times and introduced shift working
If nutritional changes drove the metabolic syndrome epidemic, can it be treated by restoring healthy nutrition?
Studying the link between nutrition, lifestyle, genetics, and microbiome
How can we take a science-based approach to nutrition?

Tal Korem

Dudi Zeevi
Science based approach to nutrition: 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 obesity, diabetes, CVD
- Easily measurable quantitatively
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.
THE PERSONALIZED NUTRITION PROJECT

1,000 PARTICIPANTS

50,000 MEALS

2,000,000 GLUCOSE MEASUREMENTS
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
What is the variability across people in the response to the same food?
Testing the cohort response to standardized meals

800 x

Continuous glucose monitoring
Using a subcutaneous sensor (iPro2)

130K hours, 1.56M glucose measurements

Standardized meals (50g available carbohydrates)

Day 1 Day 2 Day 3 Day 4 Day 5 Day 6 Day 7

Bread Bread Bread & butter Bread & butter Glucose Glucose Fructose

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

**Graphs:**
- **Bread & Butter:**
  - Glucose: $R = 0.77$
  - Bread: $R = 0.70$

**Glucose:**
- $R = 0.74$

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

**Population Responses to Standardized Meals**

- Glucose
- Bread
- Bread & butter
- Fructose

**Four Individual Responses to Bread**

- Participant 67, iAUC = 139
- Participant 663, iAUC = 81
- Participant 637, iAUC = 44
- Participant 358, iAUC = 15

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

Zeevi et al., Cell 2015
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
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)

Zeevi *et al.*, Cell 2015
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

Calorie prediction

Measured PPGR (iAUC, mg/dl*h)

Main cohort prediction

Validation

Zeevi et al., Cell 2015
Prediction scheme

Zeevi et al., Cell 2015
Model features

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

- 200 Nutrients
  - Including fatty acids, vitamins and minerals

- Multiple recorded features
  - Meal times, sleep, exercise, stress, hunger, medication

- 30 Blood parameters
- 100 Questions
- 100 FFQ features
- MetaPhlAn abundances
- KEGG abundances
- 16S OTUs
- Growth dynamics

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

State of the art

Meal carbohydrates (g)

Measured PPGR
(iAUC, mg/dl*h)

Predicted PPGR
(iAUC, mg/dl*h)

Our prediction
800 participants

R = 0.38

R = 0.68

Prediction validation
100 participants

Zeevi et al., Cell 2015
Meal and lifestyle factors affect the post-meal glucose response

Zeevi et al., Cell 2015
Microbiome features affect the post-meal glucose response

Zeevi et al., Cell 2015
Can personally tailored dietary interventions improve post-prandial glucose responses?

Daphna Rothschild  Orly Ben-Yaacov  Michal Rein
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?

<table>
<thead>
<tr>
<th>Meal</th>
<th>Bad Diet</th>
<th>Good Diet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breakfast</td>
<td>Muesli</td>
<td>Sushi</td>
</tr>
<tr>
<td>Lunch</td>
<td>Marzipan</td>
<td>Corn and nuts</td>
</tr>
<tr>
<td>Snack</td>
<td>Marzipan</td>
<td>Hummus and pita</td>
</tr>
<tr>
<td>Dinner</td>
<td>Toblerone and coffee</td>
<td>Vegetable noodles with tofu</td>
</tr>
<tr>
<td>Night snack</td>
<td>Egg with bread and coffee</td>
<td>Edamame</td>
</tr>
</tbody>
</table>

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

**Bad Diet**
- Muesli
- Sushi
- Marzipan
- Corn and nuts
- Toblerone and coffee

**Good Diet**
- Egg with bread and coffee
- Hummus and pita
- Edamame
- Vegetable noodles with tofu
- Ice cream

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

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

**Breakfast**
- Orange juice
- Bread with butter
- Grapes

**Lunch**
- Schnitzel
- Peach
- Bread with butter
- Grapes

**Snack**

**Dinner**
- Croissant
- Goulash with rice
- Halva
- Hummus
- Red wine

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

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- Breakfast: Orange juice
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*Zeevi et al., Cell 2015*
Personally tailored diets reduce the post-prandial glucose response

Zeevi et al., Cell 2015
Foods that appear in the ‘good’ diet of one person may appear in the ‘bad’ diet of another

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-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
High interpersonal variability in post-meal glucose response to identical meals

Personal and microbiome features enables accurate glucose response prediction

Short term personalized dietary interventions successfully lower post-meal glucose
Why can’t we maintain our weight after dieting?

Christoph Thaiss  |  Shmulik Motola  |  Daphna Rothschild
People tend to regain their weight after a successful diet.
A mouse model of recurring obesity
Is there a “memory” of previous obesity?
Is there a memory of previous obesity?
Some differences in 16S microbiome composition are retained after weight loss.
Does the microbiome have a causal role in enhanced weight regain?
Antibiotic treatment abolishes effect of previous obesity
Microbiome transfer to germ free mice transmits enhanced weight regain phenotype
Can we predict weight regain using only microbiome composition?
A microbiome-based predictor accurately predicts the degree of future weight gain
Multiple microbiome factors contribute to predictions

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**Figure 4**

Controls

"Ex-obese mice"

True postiive rate

0.0

0.0 0.5 1.0

ROC score 0.960.5

1.0

Prediction of weight gain

Predicted

16S-based prediction of weight gain

Weeksellaceae (F)

Lactobacillus (G)

Mollicutes (C)

Actinobacteria (P)

Tenericutes (P)

Bacteroides uniformis (S)

Bacteroides acidificiens (S)

Tissierellaceae (F)

Bacteroides (G)

Gammaproteobacteria (C)
Can we treat relapsing obesity by targeting the microbiome?
Fecal Microbiome Transplantation (FMT) abolishes microbiome-driven metabolic memory

Figure 5: Weight gain over time in different groups. NC: normal control; primHFD: primed high-fat diet; cycHFD: cycled high-fat diet; cycHFD + NC FMT: cycled high-fat diet followed by normal control fecal transplantation; cycHFD + cycHFD FMT: cycled high-fat diet followed by cycled high-fat diet fecal transplantation; HFD: high-fat diet.
‘Post-biotic’ therapy abolishes microbiome-driven metabolic memory
‘Post-biotic’ therapy abolishes microbiome-driven metabolic memory

![Graph showing weight gain over time for different groups on a high-fat diet (HFD). The graph includes lines for PrimHFD, CycHFD + Vehicle, CycHFD + XN1/XN2, and HFD. The x-axis represents time in weeks, ranging from 0 to 15, and the y-axis represents weight in grams, ranging from 20 to 45. The legend indicates the different groups. There is a significant difference indicated by an asterisk (*) between groups.](image-url)