The Gut Balance Revolution

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Integrative Healthcare Symposium 2016
February 26, 2016
Learning Objectives

• Know the role of the gut microbiota in human health and disease
• Become familiar with the pathophysiology of obesity and how alterations in the gut microflora lead to obesity
• To understand how prebiotics and probiotics can promote a lean metabolism by fostering a healthy gut microbiome
79 yo gentleman presents with abdominal pain, gas, bloating, mixed bowel habits for months.

- **Pertinent positives:** diabesity, GERD, CVD, MI/stents/angioplasty, HTN, poor sleep, fatigue, melancholy.
- **Lactulose breath test:** SIBO
- **Elimination phase** - herbal protocol x 30 days and Low FODMAP diet 8 weeks
Case History

- SIBO improved, lost 27 pounds, felt like a new person - GI symptoms improved, better energy/mood
- Probiotic-rich diet - lost 10 more pounds.
- Started putting his friends on “His” weight loss diet
PPIs and SIBO

Figure 2. Meta-analysis of SIBO risk with PPI use.

Proton Pump Inhibitor Use and the Risk of Small Intestinal Bacterial Overgrowth: A Meta-analysis
Clinical Gastroenterology and Hepatology, Volume 11, Issue 5, 2013, 483–490
PPIs Delay Small Intestine Transit

Am J Physiol Gastrointest Liver Physiol. 2015 May 1;308(9):G785-93
The differences between PPI users and non-users observed in this study are consistently associated with changes towards a less healthy gut microbiome. These differences are in line with known changes that predispose to C. difficile infections and can potentially explain the increased risk of enteric infections in PPI users. On a population level, the effects of PPI are more prominent than the effects of antibiotics or other commonly used drugs.
Introduction to the Gut Microbiome
Introduction to the gut microbiome

- We are composite of species: a ‘supra-organism’
- Our microbial census exceeds the total number of our own human cells by ~10 fold
- Our largest collection of microbes resides in the intestine (~10-100 trillion organisms)
- The aggregate genomes of these gut species (microbiome) may contain >100 fold more genes than our ‘own’ genome
- The microbiome is an integral part of our genetic landscape (‘human metagenome’) and of our genetic evolution
Techniques used to characterize the gut microbiome
Ecosystems and Biodiversity

- Increased species diversity increases the efficiency and productivity of an ecosystem
- More diverse communities are functionally less susceptible to external stressors
- In relative terms, increasing stress has a stronger negative effect on low-diverse communities

Global Ecosystem Changes → Natural Processes → Biodiversity → Ecosystem Functioning → Ecosystem Services → Human Wellbeing


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**Microbiota establishment**

**At birth**
- Mother gestational age
- Sanitary conditions
- Exposure to antibiotics
- Mode of delivery
  - Vaginal birth
  - C-section

**Diversity and Stability**

**Neonate**
- Diet
  - Breast milk
  - Formula
    - > Actinobacteria and Proteobacteria
    - > Actinobacteria and Firmicutes

**6 months**
- Introduction of solid foods and complete colonization

**2,5 years**
- Similar adult microbiota

**Adult**
- Greater inter-individual variation

**Elderly**
- Age
- Diet
- Health status
- Geographical location
- Exposure to antibiotics, probiotics, prebiotics
- Stress

**> Firmicutes and Bacteroidetes**
Exposures in early life, infant gut microbiota, & future health

- Early-life exposures
  - Mode of delivery (maternal microbes)
  - Infant diet (selective substrates)
  - Antibiotics (selective killing)
  - Probiotics (selective enrichment)
  - Physical environment (environmental microbes)

- Symbiosis
  - Immune tolerance
  - Intestinal homeostasis
  - Healthy metabolism

- Dysbiosis
  - Immune disease (e.g., atopy, asthma, multiple sclerosis)
  - Intestinal disease (e.g., inflammatory bowel disease, necrotizing enterocolitis, colon cancer)
  - Metabolic disease (e.g., diabetes, obesity)

Multiple intrinsic and extrinsic factors can affect the microbiota.
The Good The Bad and the Ugly

Balanced gut microbiota
- Gut permeability;
- Toxemia/Sepsis;
- Proinflammation;
- Insulin sensitivity;
- Gut/metabolic/cardiovascular health

Harmful/Opportunistic
- High-fat/high-sugar diets, over-nutrition, sedentary lifestyle, antibiotic abuse

Prudent diet & lifestyle, probiotics/prebiotics, Anti-inflammatory/immune-potentiating therapeutics, nutraceuticals

Gut microbial dysbiosis
- Gut permeability;
- Endotoxemia/septicemia;
- Systemic inflammation;
- Insulin resistance;
- Adiposity, diabetes, MetS, CVD, NAFLD, NASH, IBD, IBS etc.
Disorders Associated with an Altered Gut Microbiome

Gastrointestinal
Gallstones, Colorectal Cancer,
Hepatic Encephalopathy, *IBS, IBD, FMF, Gastric cancer and lymphoma, *Recurrent *Clostridium difficile* infection

Non-GI
Anxiety, Arthritis, Asthma, Autism, Autoimmune disorders, *Cardiovascular*, Chronic fatigue, Chronic kidney disease, Depression, Diabetes, Eczema, *Fatty Liver, Fibromyalgia, Hypercholesterolemia, ITP, Metabolic Syndrome, Mood disorders, Multiple Sclerosis, Myoclonus dystonia, *Obesity, Oxalic kidney Stones, Parkinson’s Disease, Senile Dementia, etc.

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Non-alcoholic Steatohepatitis: a Microbiome-Driven Disease
Proposed causes of dysbiosis of the gut microbiota.
Introduction to the gut microbiome and obesity

- Two phyla of (mainly anaerobic) bacteria linked to obesity:
  - Firmicutes (positively)
  - Bacteroidetes (negatively)
- Impact on metabolism results from an *imbalance* of these phyla.
- *Cause or consequence?*
Obese mice have altered gut flora transfer of gut flora induces weight gain

Ley, et al. PNAS 102(31):11070, 2005
Microbial community transplant experiments

Measure total body fat content before and after 14-day colonization

Ley, et al. PNAS 102(31):11070, 2005
Comparison of energy extraction between obese and lean mice

Functional interactions between the gut microbiota and host metabolism

Nature 489, 242–249 (13 September 2012)
Microbiota-transplantation studies
transfer of microbes to germ free mice

(ob/ob)

Diet-induced obesity

Humanized Mice
Diet-induced obesity

Nature 2006

Cell Host Microbe
2008

Nature Sci Transl 2009

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Host remodeling of the gut microbiome and metabolic changes in pregnancy

Cell, 150: 470-480, 2012
The effects of intestinal microbiota and host physiology

SCFAs
- AMPs
  - ↑ Bacteroidetes
    - B. fragilis (PSA)
  - Gm-PG
    - Gm-LPS
- Immunocompetence
  - Tolerance
    - Immune cell activation
      - DC tolerization
      - Lymphoid organogenesis
        - Mucosal immunity
- Lipid metabolism
  - Lipoprotein metabolism
    - LIp activation
  - NFκB inactivation
      - Lactobacillus spp.
      - E. coli
      - B. thetaotaomicron
- Peristalsis
  - Glycosylation
  - GIT surface maturation
    - GIT functional maturation
- Angiogenesis
  - B. infantis
  - O. formigenes

Conjugation of linoleic acid

Nutrition

Xenobiotics metabolism

Drug disposition

Behavior

Normalization of HPA stress response

Oxalate excretion

Physiol Rev 2010;90:859–904

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Probiotics Improve Outcomes After Roux-en-Y Gastric Bypass Surgery: A Prospective Randomized Trial

Table 1 Study Demographics

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Probiotics</th>
<th>p value</th>
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<tbody>
<tr>
<td>Number</td>
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<td>19</td>
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</tr>
<tr>
<td>Age (years)</td>
<td>41.2</td>
<td>48.6</td>
<td>0.026</td>
</tr>
<tr>
<td>% Female</td>
<td>90.9</td>
<td>84.2</td>
<td>0.649</td>
</tr>
<tr>
<td>% White</td>
<td>68.2</td>
<td>63.2</td>
<td>0.859</td>
</tr>
<tr>
<td>% DM</td>
<td>18.2</td>
<td>52.6</td>
<td>0.026</td>
</tr>
<tr>
<td>% HTN</td>
<td>59.1</td>
<td>57.9</td>
<td>0.939</td>
</tr>
<tr>
<td>% PPI use</td>
<td>13.6</td>
<td>21.1</td>
<td>0.534</td>
</tr>
<tr>
<td>H. pylori+ (%)</td>
<td>37.5</td>
<td>21.4</td>
<td>0.350</td>
</tr>
<tr>
<td>Preoperative BMI (kg/m²)</td>
<td>49.6</td>
<td>45.7</td>
<td>0.0946</td>
</tr>
<tr>
<td>Preoperative weight (lb)</td>
<td>306.4</td>
<td>276.6</td>
<td>0.0512</td>
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<tr>
<td>Height (in.)</td>
<td>66.0</td>
<td>65.4</td>
<td>0.5654</td>
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<tr>
<td>Ideal body weight (lb)</td>
<td>160.2</td>
<td>157.8</td>
<td>0.5450</td>
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<tr>
<td>Excess body weight (lb)</td>
<td>146.3</td>
<td>118.8</td>
<td>0.0524</td>
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Patients in the control group (n=22) and the probiotic group (n=19) had no statistically significant difference for 38 of 40 variables. The only significant differences were the probiotic group was significantly older and had a higher rate of preoperative diabetes mellitus with a p < 0.05 significance using a two-sample t test with equal variances.
Metabolic Improvement after Bariatric surgery

Dietary Change

Enteric hormones

Gut microbiota

Systemic Inflammation
Dietary Effect on the Gut Microbiota

Green = Bacteroidetes

Red = Firmicutes

DeFilippo C et al. PNAS. 2010;107(33):14691-14696.
### Obesity Related Changes in the Microbiome

<table>
<thead>
<tr>
<th>Group by phyla</th>
<th>Study (year)</th>
<th>Subgroup within study</th>
<th>Sample size</th>
<th>SDM and 95% CI</th>
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<tr>
<td></td>
<td></td>
<td>Ow/obese</td>
<td>Control</td>
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<tr>
<td><strong>Bacteroidetes relative count (% of total sequences)</strong></td>
<td></td>
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<tr>
<td></td>
<td>Ley et al. (2006)</td>
<td>16S clonal sequencing</td>
<td>12</td>
<td>2</td>
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<tr>
<td></td>
<td>Turnbaugh et al. (2009)</td>
<td>V2 pyrosequencing, African ancestry</td>
<td>62</td>
<td>8</td>
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<tr>
<td></td>
<td>Turnbaugh et al. (2009)</td>
<td>V2 pyrosequencing, European ancestry</td>
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<td>Zhang et al. (2009)</td>
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<td></td>
<td>Collado et al. (2008)</td>
<td>FCM-FISH</td>
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<td></td>
<td>Armougom et al. (2009)</td>
<td>qPCR</td>
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<td>20</td>
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<td>Schwierz et al. (2010)</td>
<td>qPCR</td>
<td>33</td>
<td>30</td>
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<tr>
<td></td>
<td>Million et al. (2011)</td>
<td>qPCR</td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td><strong>Bacteroidetes absolute count (log cells or copies of DNA)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ley et al. (2006)</td>
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<td>V2 pyrosequencing, European ancestry</td>
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<td>26</td>
</tr>
<tr>
<td><strong>Firmicutes relative count (% of total sequences)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Armougom et al. (2009)</td>
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<td>53</td>
<td>39</td>
</tr>
<tr>
<td><strong>Firmicutes absolute count (log copies DNA)</strong></td>
<td></td>
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</tbody>
</table>

Figure 1 | Benefits of genetic richness. By comparing the complement of microbial genes in the guts of obese and non-obese individuals, Le Chatelier et al.\(^1\) show that people with relatively less-complex microbiomes have higher overall body adiposity and more inflammation-associated characteristics, indicating that they are at higher risk of metabolic diseases than people with a greater gut-bacterial richness. Cotillard et al.\(^2\) demonstrate that microbial richness increases, and inflammation decreases, in obese and overweight people with low microbial richness who commence an energy-restricted diet, but that such dietary interventions have little effect in individuals with already high microbial richness.
How sweet it is!

Artificial sweeteners induce glucose intolerance by altering the gut microbiota

Jotham Suez¹, Tal Korem²*, David Zeevi²*, Gili Zilberman–Schapira¹*, Christoph A. Thais³, Ori Maza¹, David Israeli³, Niv Zmora⁴,⁵,⁶, Shlomit Gilad⁷, Adina Weinberger⁷, Yael Kuperman⁸, Alon Harmelin⁸, Ilana Kolodkin–Gal⁹, Hagit Shapiro¹, Zamir Halpern⁵,⁶, Eran Segal² and Eran Elinav¹

“We identify NAS-altered microbial metabolic pathways that are linked to host susceptibility to metabolic disease, and demonstrate similar NAS-induced dysbiosis and glucose intolerance in healthy human subjects. Collectively, our results link NAS consumption, dysbiosis and metabolic abnormalities, thereby calling for a reassessment of massive NAS usage”..."
Use of Antibiotics in Agriculture

- >50 years of antibiotic use for growth promotion
- Economic benefits
- Low-level exposure (subtherapeutic) is sufficient for effect

Effect of STAT in Swine

(Adapted from Zimmerman, J Animal Sci, 1986)
# Antibiotic-Associated Changes in Immunity

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Effects on the microbiota</th>
<th>Effects on immunity</th>
<th>Refs</th>
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</thead>
<tbody>
<tr>
<td>Vancomycin, neomycin and metronidazole</td>
<td>• Reduced total bacteria</td>
<td>• Reduced expression of REG3γ (recovered with LPS treatment)</td>
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</tr>
<tr>
<td>Streptomycin</td>
<td>• Reduced total bacteria</td>
<td>• Reduced expression of REG3β (recovered with a TLR2 agonist)</td>
<td>37</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>• Change in the microbial composition</td>
<td>• Reduced antimicrobial defence</td>
<td>63</td>
</tr>
<tr>
<td>• Depletion of lactobacilli</td>
<td>• Increased mast cell numbers</td>
<td>• Reduced expression of MHC molecules</td>
<td></td>
</tr>
<tr>
<td>Polymyxin B</td>
<td>• Unknown</td>
<td>• Increased mast cell numbers</td>
<td>65</td>
</tr>
<tr>
<td>Vancomycin or ampicillin</td>
<td>• Depleted Gram-positive bacteria</td>
<td>• Depletion of T helper 17 cells</td>
<td>4.6</td>
</tr>
<tr>
<td>Ampicillin, gentamicin, metronidazole, neomycin and vancomycin</td>
<td>• Reduced total bacteria</td>
<td>• Reduced expression of IFNγ and IL-17A by CD4+ T cells</td>
<td>69</td>
</tr>
<tr>
<td>• Depleted SFB</td>
<td>• Reduced production of RELMβ</td>
<td>• Reduced expression of TLR2 and TLR4 in peritoneal macrophages</td>
<td></td>
</tr>
<tr>
<td>Streptomycin and cefotaxime</td>
<td>• Reduced total bacteria</td>
<td>• Macrophages less able to respond to LPS induction</td>
<td>70</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>• Changes in the composition</td>
<td>• Disrupted mucus layer</td>
<td>75</td>
</tr>
<tr>
<td>• More <em>Bifidobacterium</em> spp.</td>
<td>• Increased colonization of intestinal crypts</td>
<td>• Increased colonization of intestinal crypts</td>
<td></td>
</tr>
<tr>
<td>Ampicillin, vancomycin, neomycin and metronidazole</td>
<td>• Reduced bacterial ligand CpG DNA</td>
<td>• Suppressed immune response to oral vaccination and infection</td>
<td>84</td>
</tr>
<tr>
<td>Amoxicillin and clavulanic acid</td>
<td>• Undetermined change in the microbiota</td>
<td>• Reduced systemic IgG</td>
<td>85</td>
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<tr>
<td>Ampicillin, neomycin sulphate, metronidazole and vancomycin</td>
<td>• Reduced total bacteria</td>
<td>• Reduced bactericidal activity of bone marrow-derived neutrophils</td>
<td>3</td>
</tr>
</tbody>
</table>

IFNγ, interferon-γ; IgG, immunoglobulin G; IL-17A, interleukin-17A; LPS, lipopolysaccharide; MHC, major histocompatibility complex; RELMβ, resistin-like molecule-β; SFB, segmented filamentous bacteria; TLR, Toll-like receptor.
Antibiotics= Gut Microbiome Killer (Napalm)

Effect on Bacteria diversity from Antibiotic treatment

[caption]

Treatment with Clindamycin

Jernberg C et al. Microbiology 2010;156:3216-3223
Proposed mechanisms for STAT-induced obesity

Modulation of the gut microbiome using sub-therapeutic antibiotics leads to increased adiposity through increased production and uptake of short chain fatty acids.
Repeated exposure to broad-spectrum antibiotics at ages 0-23 months is associated with early childhood obesity. Because common childhood infections were the most frequent diagnoses co-occurring with broad-spectrum antibiotic prescription, narrowing antibiotic selection is potentially a modifiable risk factor for childhood obesity.
Low bifidobacterium in the gut microbiota of obese individuals

<table>
<thead>
<tr>
<th>Group by genus</th>
<th>Study (year)</th>
<th>Sample size</th>
<th>SDM and 95% CI</th>
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</thead>
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<tr>
<td></td>
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<td>Obese</td>
<td>Control</td>
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<td>Collado et al. (2008)</td>
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<td>Kalliomäki et al. (2008)</td>
<td>25</td>
<td>24</td>
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<td>Schwiertz et al. (2009)</td>
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<td>Balamurugan et al. (2010)</td>
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<td></td>
<td>Santacruz et al. (2010)</td>
<td>16</td>
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<tr>
<td></td>
<td>Zuo et al. (2011)</td>
<td>52</td>
<td>52</td>
</tr>
<tr>
<td>Bifidobacterium (log copies DNA/ml)</td>
<td>Armougom et al. (2009)</td>
<td>20</td>
<td>20</td>
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<tr>
<td></td>
<td>Zuo et al. (2011)</td>
<td>52</td>
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<tr>
<td></td>
<td>Million et al. (2011)</td>
<td>53</td>
<td>39</td>
</tr>
<tr>
<td>Lactobacillus (log copies DNA/ml)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Francois et al. BMC Gastroenterology 2011 11:37

Change in BMI as a percent

Time (months) in relation to baseline
Comparison of *H. pylori*+ persons at baseline, and then after eradication of *H. pylori*

Gut microbiota dysbiosis and the role of inflammation in the metabolic impairments of obesity

Gravitz, NATURE 485:S12, 2012
Diet-independent and -dependent Microbial Effects on Host Metabolism.

Nature 489, 242–249 (13 September 2012)
Dysbiosis and CVD
Features of the gut microbiota that promote obesity and insulin resistance

Nature 489, 242–249 (13 September 2012)
Mechanisms linking the gut microbiota to obesity

- Metabolism (SCFA, lipids)
- Endocrine (GLP-1, GLP-2, PYY, L-cell, Grp41r)
- Host Genetics (TLR-4, TLR-5)
- Inflammation (cytokines, inflammasome)
- Intestinal Permeability (zonulin)
- Antibiotics (meat, C-section, overuse)
- Diet (Western)
- Environment (BPA, GMOs)
- Immunity (age)
## Table 2. Illustration of the myriad ways in which glyphosate can be linked to celiac disease or its associated pathologies.

### (a) Disruption of gut bacteria

<table>
<thead>
<tr>
<th>Glyphosate Effect</th>
<th>Dysfunction</th>
<th>Consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>reduced Bifidobacteria</td>
<td>impaired gluten breakdown</td>
<td>transglutaminase antibodies</td>
</tr>
<tr>
<td>reduced Lactobacillus</td>
<td>impaired phytase breakdown reduced selenoproteins</td>
<td>metal chelation</td>
</tr>
<tr>
<td>anaerobic E. coli</td>
<td>indole toxicity</td>
<td>autoimmune thyroid disease</td>
</tr>
<tr>
<td>C. diff overgrowth</td>
<td>p-Cresol toxicity</td>
<td>kidney failure</td>
</tr>
<tr>
<td>Desulfovibrio overgrowth</td>
<td>hydrogen sulfide gas</td>
<td>inflammation</td>
</tr>
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</table>

### (b) Transition metal chelation

<table>
<thead>
<tr>
<th>Glyphosate Effect</th>
<th>Dysfunction</th>
<th>Consequences</th>
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<tbody>
<tr>
<td>cobalt deficiency</td>
<td>cobalamin deficiency reduced methionine</td>
<td>neurodegenerative diseases</td>
</tr>
<tr>
<td></td>
<td>elevated homocysteine</td>
<td>impaired protein synthesis</td>
</tr>
<tr>
<td>molybdenum deficiency</td>
<td>inhibited sulfite oxidase inhibited xanthine oxidase</td>
<td>impaired sulfate supply DNA damage/cancer</td>
</tr>
<tr>
<td>iron deficiency</td>
<td></td>
<td>teratogenesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>megaloblastic anemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>anemia</td>
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</table>

### (c) CYP enzyme inhibition

<table>
<thead>
<tr>
<th>Glyphosate Impairment</th>
<th>Dysfunction</th>
<th>Consequences</th>
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</thead>
<tbody>
<tr>
<td>vitamin D3 inactivation</td>
<td>impaired calcium metabolism</td>
<td>osteoporosis; cancer risk</td>
</tr>
<tr>
<td>retinoic acid catabolism</td>
<td>suppressed transglutaminase</td>
<td>teratogenesis</td>
</tr>
<tr>
<td>bile acid synthesis</td>
<td>impaired fat metabolism</td>
<td>gall bladder disease</td>
</tr>
<tr>
<td></td>
<td>impaired sulfate supply</td>
<td>pancreatitis</td>
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<td>xenobiotic detoxification</td>
<td>increased toxin sensitivity impaired indole breakdown</td>
<td>liver disease</td>
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<td>macrocytic anemia</td>
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<td>kidney failure</td>
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<td>venous thrombosis</td>
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<tr>
<td>nitrate reductase</td>
<td>venous constriction</td>
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</table>
Altering the Intestinal Milieu

Diet/Fermented Foods
Soluble fiber
Prebiotics
Probiotics

Standard antibiotics
Botanical Antimicrobials

Normal
Potentially pathogenic Bacteria
Excess
Strategies to modulate the microbiota

(“no substitute for life-style”)

• Antibiotics
• Prebiotics
• Probiotics
• Synbiotics
• Genetically modified bacteria
• Bacterial components, products
• Microbiota transplantation
**PROBIOTICS**

**PREBIOTICS**

- **Host**
  - Genetic background
  - Sex
  - Age
  - Immune system
  - Gut motility

- **Diet**
  - Nondigestible carbohydrates
  - Fat
  - Prebiotics or probiotics

- **Treatment**
  - Antibiotics
  - Gastric bypass

**Gut microbiota**

- Changes in microbial metabolism
  - Saccharolytic activity
  - Production of bile acids
  - Changes in composition (phylogenic)
  - Phyla: Bacteroidetes and Firmicutes
  - Class: Mollicutes
  - Species or genera:
    - Bifidobacteria
    - Faecalibacterium prausnitzii
    - Lactobacilli

**Low grade inflammation, Insulin resistance, Type 2 diabetes**

**Metabolic endotoxemia**

**Gut barrier alterations**

**Dysbiosis**

**Nutritional and genetic obesity**

**ZO-1/Occludin**
Weed, Seed, Feed
Diet-induced dysbiosis and diseases.

Chan Y et al. Clinical Consequences of Diet-Induced Dysbiosis
## Diet Can Influence Microbial Populations


<table>
<thead>
<tr>
<th>Diet</th>
<th>Bacteria Altered</th>
<th>Effect on Bacteria</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbohydrate-reduced</td>
<td>Bacteroidetes</td>
<td>Increased</td>
<td>Walker et al. BMC Microbiol. 2011;11:7. ]</td>
</tr>
<tr>
<td>Complex carbohydrates</td>
<td>Mycobacterium avium subspecies paratuberculosis and Enterobacteriaceae</td>
<td>Decreased</td>
<td>Walker et al. BMC Microbiol. 2011;11:7. ]</td>
</tr>
<tr>
<td>High <em>n</em>-6 PUFA from safflower oil</td>
<td>Bacteroidetes</td>
<td>Decreased</td>
<td>De la Serre et al. Am. J. Physiol. 2010;299:</td>
</tr>
<tr>
<td>High-fat and high-sugar</td>
<td><em>Clostridium innocuum</em>, <em>Catenibacterium mitsuokai</em> and <em>Enterococcus</em> spp.</td>
<td>Increased</td>
<td>Turnbaugh et al. Sci. Transl. Med. 2009;1</td>
</tr>
</tbody>
</table>
Restore: fertilize and seed
Prebiotic Rich Foods

- Jerusalem artichokes
- Onions
- Chicory
- Garlic
- Leeks
- Bananas
- Fruit
- Soybeans
- Burdock root
- Asparagus
- Sugar maple
- Chinese chives
- Peas
- Legumes
- Eggplant
- Honey
- Green Tea
- Yogurt, cottage cheese, kefir
Anti-obesity Effects of Probiotic Supplementation: Human Studies

Table 3 Studies conducted on humans showing effects of probiotics on metabolic disorders

<table>
<thead>
<tr>
<th>Studied subjects</th>
<th>Probiotics</th>
<th>Duration of treatment</th>
<th>Effects</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight humans</td>
<td><em>Lactobacillus gasseri</em></td>
<td>12 wk</td>
<td>↓body weight, visceral and subcutaneous fat area, BMI, waist and hip circumference, ↑serum adiponectin</td>
<td>[116]</td>
</tr>
<tr>
<td></td>
<td>SBT2055</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with increased abdominal adiposity</td>
<td><em>Lactobacillus gasseri</em></td>
<td>12 wk</td>
<td>↓body weight, visceral fat area, BMI, waist and hip circumference, body fat mass</td>
<td>[117]</td>
</tr>
<tr>
<td></td>
<td>SBT2055</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women affected by postmenopausal metabolic syndrome</td>
<td><em>Lactobacillus plantarum</em></td>
<td>90 d</td>
<td>↓serum glucose and homocysteine levels</td>
<td>[118]</td>
</tr>
</tbody>
</table>

World J Gastroenterol 2014;21;20 (43): 16079-16094
Are Probiotics a Solution for All?
Probiotics: Questions???

- Dosages \(\rightarrow\) vary from 3.6 trillion organisms, 450 billion, 20 billion, and 1 billion
- Take once a day vs. two or more times/day?
- Mixtures or not? Which strains?
- Human strains vs. synthetic strains?
- With or without FOS? i.e. Synbiotics
- Refrigerate or not?
- Live or dead?
- Casein-free?
- Bacteria or yeast?
- Oral or injectable?
- Fecal bacteriotherapy!
Long Term Successful Weight Loss with a Combination Biphasic Ketogenic Mediterranean Diet and Mediterranean Diet Maintenance Protocol

Long Term Successful Weight Loss with a Combination Biphasic Ketogenic Mediterranean Diet and Mediterranean Diet Maintenance Protocol

**Figure. 2.** Changes in body weight (A) and fat percentage (B) from baseline to month 12. Error bars indicate standard error of the mean.

**Table 2.** Changes in body weight and body fat percentage during one year diet protocol. Values are expressed as mean and standard deviation. Significance was reported in Results section.

<table>
<thead>
<tr>
<th>Anthropometric Data</th>
<th>t0</th>
<th>t1</th>
<th>t2</th>
<th>t3</th>
<th>t4</th>
<th>t5</th>
<th>t6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight</td>
<td>100.7 ± 16.54</td>
<td>93.34 ± 15.04</td>
<td>90.33 ± 13.57</td>
<td>91.81 ± 12.58</td>
<td>86.64 ± 10.56</td>
<td>84.2 ± 10.04</td>
<td>84.59 ± 9.71</td>
</tr>
<tr>
<td>% Body fat</td>
<td>43.44 ± 6.34</td>
<td>36.93 ± 6.49</td>
<td>36.26 ± 6.46</td>
<td>37.15 ± 6.82</td>
<td>34.46 ± 6.34</td>
<td>33.50 ± 6.18</td>
<td>33.63 ± 7.6</td>
</tr>
</tbody>
</table>
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- Antibiotics
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THE NEWEST MEMBER OF THE TRANSPLANT TEAM FOUND THAT THE OTHERS TREATED HIM LIKE CRAP.
The Ultimate Probiotic: Fecal Microbial Transplantation
Modulation of the microbiome influences development of obesity and metabolic syndrome.
Practice Applications

- The gut microbiome has profound influence over metabolic functions.
- The biodiversity of the gut microbiome is a major determinant of health outcomes.
- Perturbations in the gut microbiome can lead to diabetes, obesity and non-alcoholic fatty liver disease.
Questions?