Today’s Agenda

• Describe the microbiota
• Dysbiosis and diabetes
• Diet-microbiota interactions
• Application to practice

No Guts No Glory: Microbiota and Diabetes

Meghan Jardine, MS, MBA, RDN, LD, CDE
Associate Director of Diabetes Nutrition Education
Physicians Committee for Responsible Medicine
Washington, DC
Clinical Dietitian
Parkland Health & Hospital System
Dallas, TX

National Microbiome Initiative

1. Support Research
2. Develop technologies
3. Expand workforce

The Microbiota

• Microbial population living in a specific environment
• Symbiotic relationship with the host
• The human microbiome has evolved

Disclosure to Participants

Meghan Jardine has not disclosures to report
The Microbiota (cont.)

- At least 1,000 different known species
- Weight = 2 to 3 kg
- 1/3 is common to most humans
- 2/3 is unique to each individual

Microbiota/Microbiome

- Are we really human?
  - (10 percent human)
- What about the functionality of our genes?
  - (1% human)
- We share 99.9% of our genes with other people
- But we only share 10% of our microbiome

Microbiome

- Microbiome – combined genetic make-up
- Metagenomics - study of the microbiome

Projects that Study Association Between Microbiome and Health

- 16S rRNA sequencing
- 3.3 million genes catalogued
- Human Microbiome Project
- MetaHit Consortium:
  - Lower gene counts are associated with obesity
  - Human Food Project

The Symbiotic Relationship

- Digest and absorb nutrients
- Synthesize of vitamins and amino acids
- Prevent pathogenic colonization
- Regulate immune function
- Modulate of GI hormone release
- Regulate mood and behavior
- The metabolites released depends on nutrition

Microbiome

- Stomach:
  - pH 1.5-3
  - Helicobacter Pylori, Streptococcus, Prevotella
- Duodenum
- Jejunum
- Large Intestines:
  - pH 6.3
  - Highest population density
  - Fermentation of substrates
  - Bacteroides, Eubacterium, Clostridium, Ruminococcus, Bifidobacterium
- From Stomach to large intestines:
  - pH increases
  - Population density increases
  - Composition Changes
  - Functions/Metabolism depends on species and environment

References:
- Gut Microbiota Worldwatch: http://www.gutmicrobiotawatch.org/gut-microbiota-info
What shapes our Microbiota?

- Vaginal delivery
- Breast milk
- Species stabilized by age of three and is influenced by many environmental factors
- Microbial communities change throughout the lifecycle


Cesarean Delivery

- C-Sections in United States:
  - 1996: 1 in 5 births
  - 2011: 1 in 3 births
- Changes strains that inoculate baby’s gut
- Higher in Staphylococcus, Corynebacterium, and Propionibacterium
- Lower in species of Lactobacillus, Prevotella, Bifidobacterium, and the phyla Bacteroidetes
- Use of prophylactic antibiotics is standard practice


Hygiene

- Our microbiota trains the immune system
- Healthy tissues might be attacked:
  - Nerves (MS)
  - Intestines (Crohn’s disease, Celiac)
  - Pancreas (T1D)
  - Systemic (Rheumatoid arthritis, Lupus)

Infectious Diseases have Evolved

Historical Diseases:
  - Cholera
  - Pneumonia
  - Scarlet fever
  - Diphtheria
  - Whooping cough
  - Tuberculosis
  - Smallpox

Modern Day Diseases:
  - Obesity
  - Diarrhea
  - Diabetes
  - Atherosclerosis
  - Nonalcoholic fatty liver disease
  - Colitis/Crohn’s Disease
  - Autism
  - Asthma
  - Eczema
  - Multiple sclerosis
  - Alzheimer’s disease

Kingdom Bacteria

<table>
<thead>
<tr>
<th>Kingdom</th>
<th>Phylum</th>
<th>Class</th>
<th>Order</th>
<th>Family</th>
<th>Genus</th>
<th>Species</th>
<th>Strain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes</td>
<td>Clostridium</td>
<td>Clostridiales</td>
<td>Ruminococcaceae</td>
<td>Faecalibacterium</td>
<td>F. prausnitzii</td>
<td>KLE1255</td>
<td></td>
</tr>
</tbody>
</table>
Major Divisions/Phyla

- **Firmicutes** (60%) – gram positive: largest comprising 200 genera
- **Bacteroidetes** (15%) – gram negative: 20 genera
- **Actinobacteria** (15%) – gram positive
- **Proteobacteria** (1%) – gram negative


Endotoxemia and Insulin Resistance

- LPS – is a component of Gram negative cell walls
- LPS triggers an inflammatory response:
  - Inflammatory factors:
    - Damage beta-cells
    - Inactivate insulin receptors
  - High fat diet is associated with elevated blood LPS levels


Insulin Resistance/Obesity Profiles

- Reduced diversity (Low gene count)
- Higher ratio of Firmicutes to Bacteroidetes
- ↓ *Bifidobacterium*
- ↓ Butyrate producing bacteria
- ↑ Bacteria that enhance inflammation


Proposed Mechanisms for Insulin Resistance and Obesity

- **DYSBIOSIS**
  - Monosaccharides and SCFA
  - Lipogenesis
  - ↑ LPS and insulin resistance
  - ↓ FA oxidation


Gut Barrier Dysfunction

Hypothesis:

- High-fat diet leads to ↑ gut barrier permeability
- Allows Bacteria and lipopolysaccharide (LPS) to enter the host


Plant-Polysaccharides

- Indigestible oligosaccharides (soluble dietary fiber) are fermented by bacterial in colon.
- End products are short chained fatty acids (SCFA):
  - Butyrate
  - Propionate
  - Acetate

SCFA – a Bidirectional Role

- ↑ Energy harvest
- Stimulates release of gut hormones
- Improve gut barrier integrity
- Enhances mitochondrial activity


Other Nutrient Induced Changes

- **Protein:**
  - BCFA, nitrosamines, phenols, and volatile sulfur compounds
  - Increases abundance of bile-tolerant species
- **Fat:**
  - Increases gut permeability
  - Decreases SCFA production


Intestinal Microbiota and CVD

- Carnitine and choline (red meat, eggs) is metabolized by microbiota
- Increases plasma trimethyl-amine-N-oxide (TMAO)
- Increases CVD


Impact of Diet on Microbiota

De Filippo et al.

- BF diet: cereals (millet, sorghum), legumes (black-eyed peas) and vegetables.
- EU diet: animal protein, sugar, starch, fat, and low in fiber.

Carlotta De Filippo et al. PNAS 2010;107:14691-14696

16S rRNA gene surveys reveal a clear separation of two children populations investigated.
**Dietary Switch**
O'Keefe et al

- Colon Cancer Risk:
  - Rural Africans: <5:100,000
  - African Americans >65:100,000
- Rural African fiber intake >50 g/day

O'Keefe et al. Nat Commun. 2015;6:342

**14 Day In-house Dietary Switch**

- 24 healthy volunteers
- African Americans consumed rural African diet: 41 g fat/day and 55 g fiber/day
- Rural Africans consumed the Western diet: 145 g fat/day and 7 g fiber/day

**Results: Biomarkers of Colon CA risk changed in 2 weeks**

<table>
<thead>
<tr>
<th>Rural Africans</th>
<th>African Americans</th>
</tr>
</thead>
<tbody>
<tr>
<td>400% ↑ in 2° bile acids</td>
<td>70% decrease 2° bile acids</td>
</tr>
<tr>
<td>↑ Biophila wadsworthia</td>
<td>↓ B. wadsworthia</td>
</tr>
<tr>
<td>↑ Biomarkers of colon CA risk</td>
<td>↓ biomarkers of risk</td>
</tr>
<tr>
<td>↓ SCFA production</td>
<td>↑ SCFA</td>
</tr>
</tbody>
</table>

Authors propose recommended fiber intake >55g/day

**Eating Patterns and Microbiota**
De Filippis et al.

- 51 omnivores, 51 vegetarians, 51 vegans all following a Mediterranean Diet
- Adherence was based on consumption of plant-based foods

De Filippis, et al. GUT. 2015;0:1-10.

↑ Bile acids
Deconjugation by bacteria
↑ Secondary bile acids
Inflammatory Carcinogenic
Results:
- Vegan group most adherent to MD
  - Highest fecal SCFA content (p<0.001)
  - \(\uparrow\) species associated with SCFA production and reduced inflammation
- Urinary TMAO levels lowest for both veg groups (p<0.0001)
- Omnivore subjects had higher levels of phenolic and indole derivatives

What is a Prebiotic?

**Dietary fiber:**
1. Not digested or absorbed in small intestine
2. Fermented by the microbiota
3. Stimulate growth of health-promoting species of:
   - *Lactobacillus*
   - *Bifidobacterium*


Prebiotics

- Breast milk
- Jerusalem artichoke
- Chicory root
- Raw dandelion greens
- Leeks
- Onions
- Garlic
- Asparagus
- Whole grains
- Beans
- Bananas
- Wheat
- Oats
- Soybeans
- Psyllium husk (Metamucil®)

Probiotic Definition:

- **Pro** = “for”
- **Bios** = “life”
- Live micro-organisms
- Colonize
- Provide health benefits
Probiotic Benefits

- **Kills pathogens**
- **SCFA**
- **Immune function**
- **Reduces pH**
- **Improves gut barrier function**
- **↑ Diet Quality**

Probiotics – Typical Strains

<table>
<thead>
<tr>
<th>Genus</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lactobacillus</strong></td>
<td>L. acidophilus 0 DDS-1</td>
</tr>
<tr>
<td></td>
<td>L. casei</td>
</tr>
<tr>
<td></td>
<td>L. lactis</td>
</tr>
<tr>
<td></td>
<td>L. rhamnosus</td>
</tr>
<tr>
<td></td>
<td>L. salivarius</td>
</tr>
<tr>
<td><strong>Bifidobacterium</strong></td>
<td>B. longum</td>
</tr>
<tr>
<td></td>
<td>B. infantis</td>
</tr>
<tr>
<td></td>
<td>B. bifidum</td>
</tr>
<tr>
<td><strong>Sacharomyces (yeast)</strong></td>
<td>S. Boulardii (Brewer's yeast)</td>
</tr>
<tr>
<td></td>
<td>S. Cervisiae (Baker's yeast)</td>
</tr>
</tbody>
</table>

Probiotic Supplements

- Often not tested
- Generally are considered safe
- Look for USP, GMP certifications
- Take probiotic supplements with food
- 2 hours before or after antibiotics
- Changes may be transient

Food Sources of Probiotics

- **Plant-Based Sources:**
  - Sauerkraut
  - Kimchi
  - Tempeh
  - Soy sauce
  - Miso
  - Water kefir
  - Sour dough bread
- **Daily-based Sources:**
  - Yogurt

Probiotics are Effective Treatment

- Diarrhea
- IBD
- IBS
- Allergies
- Liver disease

Kechagia, et al. ISRN Nutr. 2013
**Probiotics for Diabetes**

- **Samah, et al.** systematic review of 6 RCT:
  - Significant reductions in FBG (p<0.00001)
  - A1C changes inconsistent
  - Anti-inflammatory effects are inconsistent
- **Future directions:**
  - Individualize therapies
  - Symbiotics – combination of prebiotics and probiotics

**Fecal Microbiota Transplants (FMT)**

- *Clostridium difficile*
  - Kills 40,000 people per year
  - Fecal transplants successfully treats 95% (30% with antibiotics)
- FMT Lean donors → obese/metabolic syndrome:
  - Significant ↑ in insulin sensitivity
  - ↑ gene diversity
  - ↑ butyrate producers

**Dietary Fiber Guide to Enhancing Gut Health**

<table>
<thead>
<tr>
<th>Servings</th>
<th>Fiber (grams)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3 whole-grains</td>
<td>1 oz. 1/3 c. Brown rice, millet, barley, bulgur, buckwheat Probiotic: whole wheat, oats</td>
</tr>
<tr>
<td>1 to 2 legumes</td>
<td>1/2 c. At least 3/week Beans, peas, lentils, soy beans Probiotic: tempeh</td>
</tr>
<tr>
<td>1 to 2 vegetables</td>
<td>1 c. raw 1/2 c. green leafy 1/2 c. cooked 1/2 c. starchy Prebiotic: beans, asparagus, Jerusalem artichoke, garlic, onions, dandelion greens Probiotic: sauerkraut, kimchi</td>
</tr>
<tr>
<td>1 to 4 fruit</td>
<td>1 medium 1/2 c. chopped 1/2 c. berries 1/2 T. dried Prebiotic: apples, grapes, blueberries, bananas (green)</td>
</tr>
<tr>
<td>1 nuts/seeds</td>
<td>1 oz. At least 3/week Walnuts, peanuts, cashews, almonds, chia seeds Probiotic: peanuts, almonds</td>
</tr>
</tbody>
</table>

Total: 33 to 57 grams

**Conclusions**

- Diet shapes the composition and activity of the microbiota
- Focus on high-fiber plant foods:
  - Average American consumes 15 grams fiber/day
  - Increase 14 grams fiber/day reduces energy intake by 10%
  - Ensure servings of probiotics sources
- Other considerations: smoking, stress, exercise, sleep, nature, and animals

**Thank you! Q & A**

mjardine@pcrm.org

AADE16