Relationship between gut microbiota and metabolic syndrome

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The normal gut microbiota

**Metabolic**
- Fermentation of non-digestible dietary polysaccharides and endogenous mucus
- Production of vitamin K
- Xenobiotic metabolism

**Protective**
- Protection against pathogens

**Trophic**
- Control of epithelial cell proliferation and differentiation
- Angiogenesis in the small intestine
- Development and homoeostasis of the immune system

- 1,000 bacterial species
- 150-fold more genes than the human genome
- $10^{13}$ bacterial cells in the gut (>10x total ensemble of human cells)

Gut microbiota and metabolic syndrome

WHO criteria
Presence of diabetes mellitus, impaired glucose tolerance, impaired fasting glucose or insulin resistance.

PLUS two of the following:
• Central obesity or body mass index > 30 kg/m²
• High blood pressure
• Dyslipidemia
• Microalbuminuria
Gut microbiota and metabolic disease

• What is the normal gut microbiota? Global differences?
• Is the gut microbiota altered in metabolic diseases?
• Does the gut microbiota cause disease or serve as a marker?
Gut microbiota and metabolic disease

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Altered gut microbiota in obese humans

Ley et al., Nature 2006
Reduced diversity of the gut microbiota in obese individuals

Turnbaugh et al., Nature 2009
<table>
<thead>
<tr>
<th>Author</th>
<th>Participants</th>
<th>Method (sample type)</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ley et al. [2]</td>
<td>12 obese participants on one of two diets, carbohydrate or fat-reduced, for 1 year; two lean controls</td>
<td>16S rRNA surveys by Sanger sequencing (faces)</td>
<td>Proportion of Bacteroidetes sequences increased over time, on average, and correlated with weight loss. No difference between diets</td>
</tr>
<tr>
<td>Turnbaugh et al. [5**]</td>
<td>154 participants, MZ and DZ twins and mothers, obese or lean</td>
<td>16S by Sanger and 454 pyrosequencing, metagenomics (faces)</td>
<td>Reduced levels of diversity, and reduced levels of Bacteroidetes in obese participants; metagenomes of obese participants enriched in energy-harvesting genes</td>
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<td>Schwertz et al. [6]</td>
<td>30 lean, 35 overweight, 33 obese participants</td>
<td>qPCR for Bacteroidetes, Actinobacteria, Archaea (faces)</td>
<td>More Bacteroidetes in overweight and obese vs. lean participants, and more Methanobrevibacter in lean participants</td>
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<tr>
<td>Collado et al. [7]</td>
<td>Women before and during pregnancy, 18 overweight participants and 36 controls</td>
<td>RSH/flow cytometry and qPCR (faces)</td>
<td>Higher levels of Bacteroidetes and S. aureus in overweight, positive correlation between Bacteroides levels and weight gain over pregnancy</td>
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<tr>
<td>Sotos et al. [8]</td>
<td>8 obese and overweight adolescents during weight loss</td>
<td>RSH (faces)</td>
<td>Enterobacteriaceae and sulfate-reducing bacteria reduced in group with greatest weight loss. Reduced levels of Roseburia–Eubacterium in those with less weight loss</td>
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<td>Duncan et al. [9]</td>
<td>Participants on weight loss diets over 8 weeks vs. weight maintenance</td>
<td>RSH counts (faces)</td>
<td>No difference in Bacteroidetes levels between groups; reduced levels of Roseburia and Eubacterium, and increased levels of Clostridium spp., correlate with reduced carbohydrate intake</td>
</tr>
<tr>
<td>Kalliomaki et al. [10**]</td>
<td>Obese and overweight children (n = 25) and normal weight children (n = 24); prospective study</td>
<td>qRT-PCR and FISH/flow cytometry (faces)</td>
<td>Children remaining lean at age 7 had higher levels of Bifidobacteria and lower levels of S. aureus, as infants</td>
</tr>
<tr>
<td>Santacruz et al. [11*]</td>
<td>36 adolescents on diet and physical activity, 10 weeks</td>
<td>qPCR (faces)</td>
<td>Bacteroides fragilis abundance correlated with carbohydrate intake. Levels of Bacteroides and Lactobacillus increased with weight loss</td>
</tr>
<tr>
<td>Nadal et al. [12]</td>
<td>39 adolescents on diet and physical activity, 10 weeks</td>
<td>qPCR (faces)</td>
<td>Clostridium histolyticum and E. rectale–C. coccoides reduced with weight gain; increase in Bacteroides–Prevotella in high weight loss group</td>
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<tr>
<td>Sabate et al. [13]</td>
<td>137 obese patients, 40 healthy controls</td>
<td>Glucose-hydrogen breath test (for H₂) and liver biopsy (breath, liver)</td>
<td>Bacterial overgrowth in small intestine more common in obese vs. lean participants</td>
</tr>
<tr>
<td>Zhang et al. [14*]</td>
<td>3 lean, three obese, and three postgastric bypass participants</td>
<td>Sanger and 454 sequencing of 16S rDNAs, qPCR (faces)</td>
<td>Firmicutes more abundant in lean participants, lowest after gastric bypass. Gamma-Proteobacteria and Verrucomicrobia enriched after gastric bypass; higher Archaea in obese participants; overall communities of gastric bypass and obese participants more similar to each other than to lean participants</td>
</tr>
</tbody>
</table>

DZ, dizygotic; FISH, fluorescent in-situ hybridization; MZ, monozygotic.
Gut Microbiota in Human Adults with Type 2 Diabetes Differs from Non-Diabetic Adults

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Abstract

**Background:** Recent evidence suggests that there is a link between metabolic diseases and bacterial populations in the gut. The aim of this study was to assess the differences between the composition of the intestinal microbiota in humans with type 2 diabetes and non-diabetic persons as control.

**Methods and Findings:** The study included 36 male adults with a broad range of age and body-mass indices (BMIs), among which 18 subjects were diagnosed with diabetes type 2. The fecal bacterial composition was investigated by real-time quantitative PCR (qPCR) and in a subgroup of subjects (\(N = 20\)) by tag-encoded amplicon pyrosequencing of the V4 region of the 16S rRNA gene. The proportions of phylum *Firmicutes* and class *Clostridia* were significantly reduced in the diabetic group compared to the control group (\(P = 0.03\)). Furthermore, the ratios of *Bacteroidetes* to *Firmicutes* as well as the ratios of *Bacteroides-Prevotella* group to *C. coccoides-E. rectale* group correlated positively and significantly with plasma glucose concentration (\(P = 0.04\)) but not with BMIs. Similarly, class *Betaproteobacteria* was highly enriched in diabetic compared to non-diabetic persons (\(P = 0.02\)) and positively correlated with plasma glucose (\(P = 0.04\)).

**Conclusions:** The results of this study indicate that type 2 diabetes in humans is associated with compositional changes in intestinal microbiota. The level of glucose tolerance should be considered when linking microbiota with metabolic diseases such as obesity and developing strategies to control metabolic diseases by modifying the gut microbiota.
Gut microbiota and metabolic disease

• What is the normal gut microbiota? Global differences?
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Germ-free mice are protected against diet induced obesity

Bäckhed et al., PNAS 2007
Transcriptional responses by the gut microbiota and the innate immune system

Conventionally raised (CONV-R)
- C57Bl/6
- Myd88-/-
- n = 5
- n = 5

Germ-free (GF)
- C57Bl/6
- Myd88-/-
- n = 4
- n = 6

- 12 w old males
- Duodenum, jejunum, ileum, colon
- Liver
- Subcutaneous and epididymal adipose tissue
- In total 140 microarrays
Metabolic Syndrome and Altered Gut Microbiota in Mice Lacking Toll-Like Receptor 5

Matam Vijay-Kumar,¹ Jesse D. Aitken,¹ Frederic A. Carvalho,¹ Tyler C. Cullender,² Simon Mwangi,³ Shanthi Srinivasan,³ Shanthi V. Sitaraman,³ Rob Knight,⁴ Ruth E. Ley,² Andrew T. Gewirtz¹*
**Tlr5-deficient** mice are obese and have several hallmarks of the metabolic syndrome
Transplants indicate that altered gut microbiota mediates the metabolic effects

Vijay-Kumar et al., Science 2010
Bacterial modulation of host metabolism

Reinhardt et al., JPGN 2009
Increased plasma LPS levels in high-fat fed mice

Cani et al., Diabetes 2007
A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation\textsuperscript{1–3}

*Clett Erridge, Teresa Attina, Corinne M Spickett, and David J Webb*

**TABLE 1**
Plasma endotoxin concentrations before and after the test meals\textsuperscript{1}

<table>
<thead>
<tr>
<th></th>
<th>Plasma endotoxin pg/mL</th>
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<tr>
<td><strong>Before meal</strong></td>
<td>8.2 (3.4–13.5)</td>
</tr>
<tr>
<td><strong>After no meal</strong></td>
<td>8.2 (3.3–20.7)</td>
</tr>
<tr>
<td><strong>After high-fat meal</strong></td>
<td>12.3 (4.7–26.3)\textsuperscript{2}</td>
</tr>
<tr>
<td>After cigarettes</td>
<td>10.3 (3.4–26.4)</td>
</tr>
<tr>
<td>After high-fat meal and cigarettes</td>
<td>12.6 (5.7–24.5)\textsuperscript{2}</td>
</tr>
</tbody>
</table>
Subcutaneous LPS administration increases adipose mass and inflammation

Cani et al., Diabetes 2007
Enteroendocrine cells produce peptides that regulate energy homeostasis

Cummings and Overduin JCI 2007
Bacterial modulation of host metabolism

Reinhardt et al., JPGN 2009
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