Gut Reaction

Mary ET Boyle, Ph. D.
Department of Cognitive Science
UCSD
- Prenatal diet
- Exercise
- Gut microbiome

? →

- More efficient nutrient extraction?
- Storage?

- Compare microbiota of lean vs obese
Does adiposity change microbiota community?

Shifts in the balance of bacteria

Homeostatic feedback between microbiota and host energy balance?
gut bacteria

\[ \rightarrow \text{harmful} \]

\[ \rightarrow \text{helpful} \]
Obesity alters gut microbial ecology

Ruth E. Ley†, Fredrik Bäckhed†, Peter Turnbaugh†, Catherine A. Lozupone‡, Robin D. Knight§, and Jeffrey I. Gordon*‡

1Center for Genomes Sciences, Washington University School of Medicine, St. Louis, MO 63108; and Departments of 4Molecular, Cellular, and Developmental Biology and 5Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309

Contributed by Jeffrey I. Gordon, June 14, 2005

We have analyzed 5,088 bacterial 16S rRNA gene sequences from the distal intestinal (cecal) microbiota of genetically obese ob/ob mice, lean ob/+ and wild-type siblings, and their ob/+ mothers, all fed the same polysaccharide-rich diet. Although the majority of mouse gut species are unique, the mouse and human microbiota(s) are similar at the division (superkingdom) level, with Firmicutes and Bacteroidetes dominating. Microbial-community composition is inherited from mothers. However, compared with lean mice and regardless of kinship, ob/ob animals have a 50% reduction in the abundance of Bacteroidetes and a proportional increase in Firmicutes. These changes, which are division-wide, indicate that, in this model, obesity affects the diversity of the gut microbiota and suggest that intentional manipulation of community structure may be useful for regulating energy balance in obese individuals.

Ley, R. et al (2005) PNAS vol. 102 no. 31
“Bacterial diversity in the distal gut (ceca) of C57BL6 mice. (A) Phylogenetic tree of 5,088 mouse ceca-associated 16S rRNA sequences reported in this study and 11,831 human colon-associated 16S rRNA sequences from ref. 11. Data from bacteria harvested from both mammalian hosts were obtained by using the same 16S rRNA gene-directed primers and PCR cycle numbers. The bar represents 15% sequence divergence.”

Ley, R. et al (2005) PNAS vol. 102 no. 31
causation?
cause & effect studies

microbiota of obese mice

transferred

Germ free mice

outcome?

within 2 weeks
have a 14% of 60% in body fat
despite eating less
than before the xfer
Gut microbiota

06/06 mice

50% more

Fermitutes

Bacteroidetes

50% fewer Bacteroidetes

100%
Obesity Correlates with a Shift in the Abundance of Bacteroidetes and Firmicutes. Regardless of family membership, obesity was associated with a large shift in the relative abundance of the specific taxa present (P < 0.01; see Fig. 5B). The change in community structure occurred at the division level. The cecal microbiota of obese mice had a statistically significant 50% reduction in Bacteroidetes, relative to lean mice, and a significantly greater proportion of Firmicutes (P < 0.05, Fig. 2C). The changes were division-wide (there was no specific subgroup that was preferentially lost or amplified within these divisions) and occurred independently of kinship and gender.

Our study included a single runted animal with an ob/ob genotype. Its body mass (20 g) was equivalent to that of lean ob/+ and +/+ siblings, but the ratio of its epididymal fat-pad mass to total body mass was significantly greater (1.6% vs. 0.7% of total body mass; z = 6.64; P < 0.0001). This individual consumed
Prospectus: Contribution of the Population Structure of the Gut Microbiota to Obesity. Together, these results show that the development of obesity in $ob/ob$ mice affects the relative abundance of the major gut bacterial divisions derived from a maternal inoculum. The mechanisms responsible for directing these changes in microbial diversity remain to be defined, although broad division-level effects are not typical of an immune response to bacteria (22).

$ob/ob$ mice are more efficient at harvesting energy from food than are lean $+/+$ animals (23, 24). The observed alterations in community structure within the distal gut microbiota of $ob/ob$ animals may represent an unheralded contributing factor to their pattern of fuel partitioning. In domestic animals, antibiotics are commonly used to increase the efficiency of conversion of fuel in the diet to body mass (25), although the influence of these antibiotics on gut microbial ecology has not been determined with large-scale molecular phylogenetic surveys.
Two groups of beneficial bacteria are dominant in the human gut, the Bacteroidetes and the Firmicutes. Here we show that the relative proportion of Bacteroidetes is decreased in obese people by comparison with lean people, and that this proportion increases with weight loss on two types of low-calorie diet. Our findings indicate that obesity has a microbial component, which might have potential therapeutic implications.

To investigate the relation between gut microbial ecology and body fat in humans, we studied 12 obese people, who were randomly assigned to either a fat-restricted (FAT-R) or to a carbohydrate-restricted (CARB-R) low-calorie diet. The composition of their gut microbiota was monitored over the course of 1 year by sequencing 16S ribosomal RNA genes from stool samples (for details, see supplementary information).

Bacterial lineages were remarkably constant within people over time: communities from the same person were generally more similar to one another than to those from other people (Fig. 1a). Before diet therapy, obese people had fewer Bacteroidetes ($P<0.001$) and more Firmicutes ($P=0.002$) than did lean controls (Fig. 1b). Over time, the relative abundance of Bacteroidetes increased ($P<0.001$) and the abundance of Firmicutes decreased ($P=0.002$), irrespective of diet type (Fig. 1b).

Human gut microbes associated with obesity

**a**, Clustering of 16S ribosomal RNA gene sequence libraries of faecal microbiota for each person (in different colours) and time point in diet therapy (T0, baseline; T1, 12 weeks; T2, 26 weeks; T3, 52 weeks) in the two diet-treatment groups (fat restricted, FAT-R; carbohydrate restricted, CARB-R), based on UniFrac analysis of the 18,348-sequence phylogenetic tree. **b**, Relative abundance of Bacteroidetes and Firmicutes. For each time point, values from all available samples were averaged (n was 11 or 12 per time point). Lean-subject controls include four stool samples from two people taken 1 year apart, plus three other stool samples. Mean values ± s.e. are plotted. **c**, Change in relative abundance of Bacteroidetes in subjects with weight loss above a threshold of 2% weight loss for the CARB-R diet and 6% for the FAT-R diet.

Q: Can you predict by only looking at a person’s microbiome if one is lean or obese?
Germ-free mice inoculated with microbiota from obese or lean human twins take on the microbiota characteristics of the donor. Those receiving the obese microbiota (red outline) had an increase in adiposity, whereas those receiving the lean microbiota (blue outline) remained lean.

If fed an appropriate diet, mice harboring the obese microbiota, when cohoused with mice harboring the lean microbiota, are invaded by the lean microbiota and do not develop increased adiposity (blue and red outline).

By contrast, the obese microbiota does not effectively colonize mice harboring the lean microbiota, and these mice remain lean.

Weight Gain After Fecal Microbiota Transplantation

Neha Alang¹ and Colleen R. Kelly²

¹Department of Internal Medicine, Newport Hospital, and ²Division of Gastroenterology, Center for Women’s Gastrointestinal Medicine at the Women’s Medicine Collaborative, The Miriam Hospital, Warren Alpert School of Brown University, Providence, Rhode Island

Fecal microbiota transplantation (FMT) is a promising treatment for recurrent *Clostridium difficile* infection. We report a case of a woman successfully treated with FMT who developed new-onset obesity after receiving stool from a healthy but overweight donor. This case may stimulate further studies on the mechanisms of the nutritional-neural-microbiota axis and reports of outcomes in patients who have used non-ideal donors for FMT.

After extensive discussion, the patient elected to undergo fecal transplant. As per the patient’s request, her 16-year-old daughter was chosen as the stool donor. At the time of FMT, her daughter’s weight was ~140 pounds (BMI of 26.4), but it increased later to 170 pounds. Her daughter had no other health problems, and screening for human immunodeficiency virus 1 and 2, syphilis, and viral hepatitis A, B, and C, *C. difficile*, *Giardia lamblia*, and routine stool culture for enteric pathogens were negative. The patient was retreated for *H. pylori* with quadruple therapy (metronidazole, tetracycline, bismuth, and proton pump inhibitor), and the FMT was performed 2 weeks later via colonoscopy. A total of 600 cc of the suspension of donor stool in sterile water was infused through the colonoscope starting in the terminal ileum. The colon and the terminal ileum appeared normal at the time of the procedure. She improved and did not suffer a further CDI recurrence after FMT.
The patient presented again 16 months after FMT, and reported an unintentional weight gain of 34 pounds. She weighed 170 pounds and had become obese (BMI of 33). She had not lost any weight over the months she was being treated for CDI. She had been unable to lose weight despite a medically supervised liquid protein diet and exercise program. Her serum cortisol and thyroid panel were normal. She has continued to gain weight despite efforts to diet and exercise, and at 36 months post-FMT her weight was 177 pounds (BMI of 34.5). She has also developed constipation and unexplained dyspeptic symptoms.

Our patient reported unintentional rapid weight gain after FMT. There are several possible contributions to the weight gain, including the resolution of CDI (with subsequent increased appetite) and concurrent treatment of *H. pylori*. There is a known association between *H. pylori* treatment and weight gain, especially in children, thought to be due to restoration of ghrelin levels after eradication of the bacteria [1]. However, it is notable that she was never obese prior to FMT, and that the stool donor similarly experienced significant weight gain, raising the possibility that the obesity was at least in part a consequence of FMT. The hypothesis of FMT triggering or contributing to obesity is supported by animal models demonstrating that an obese microbiota can be transmitted [2]. An important limitation in our case is that the microbiome sequencing comparing the patient and the donor is not known.
setts, who worked as a postdoctoral researcher in the Gordon lab.

Furthermore, the microbiomes of obese individuals have a different effect than those of normal-weight mice. “They gain about twice as much body fat over the course of two weeks if you colonize them with a sample that comes from an obese donor,” says Turnbaugh. “And that can be from a mouse that’s obese because of a genetic mutation in leptin, or mice that are obese due to consuming a high-fat, high-sugar diet.” Researchers have even shown that germ-free mice that receive gut microbes from

But not everyone finds these data convincing. Germ-free mice given obesity-associated microbiota gain weight, but they do not actually become obese themselves, points out Eric Martens, a microbiologist at the University of

...transplantable obesity.

Moreover, diet is a major factor in obesity, and diet also shapes the microbiota. Often, changes in the levels of gut microbes produced...
Enterobacter cloacae B29

Pathogen

Environments

Not obese if fed normal diet

Obese only if fed high fat diet

(Zhao)
SHORT COMMUNICATION

An opportunistic pathogen isolated from the gut of an obese human causes obesity in germfree mice

Na Fei¹ and Liping Zhao¹,²
¹State Key Laboratory of Microbial Metabolism and School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai, China and ²Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China

Lipopolysaccharide endotoxin is the only known bacterial product which, when subcutaneously infused into mice in its purified form, can induce obesity and insulin resistance via an inflammation-mediated pathway. Here we show that one endotoxin-producing bacterium isolated from a morbidly obese human’s gut induced obesity and insulin resistance in germfree mice. The endotoxin-producing Enterobacter decreased in relative abundance from 35% of the volunteer’s gut bacteria to non-detectable, during which time the volunteer lost 51.4 kg of 174.8 kg initial weight and recovered from hyperglycemia and hypertension after 23 weeks on a diet of whole grains, traditional Chinese medicinal foods and prebiotics. A decreased abundance of endotoxin biosynthetic genes in the gut of the volunteer was correlated with a decreased circulating endotoxin load and alleviated inflammation. Mono-association of germfree C57BL/6J mice with strain Enterobacter cloacae B29 isolated from the volunteer’s gut induced fully developed obesity and insulin resistance on a high-fat diet but not on normal chow diet, whereas the germfree control mice on a high-fat diet did not exhibit the same disease phenotypes. The Enterobacter-induced obese mice showed increased serum endotoxin load and aggravated inflammatory conditions. The obesity-inducing capacity of this human-derived endotoxin producer in gnotobiotic mice suggests that it may causatively contribute to the development of obesity in its human host.

“Gnotobiotic mice mono-associated with *E. cloacae* B29 become obese and insulin resistant with increased endotoxin load and provoked systemic inflammation under HFD feeding.”

A gut microbiota-targeted dietary intervention for amelioration of chronic inflammation underlying metabolic syndrome

Shuiming Xiao¹, Na Fei¹, Xiaoyan Pang¹, Jian Shen², Linghua Wang¹, Baorang Zhang¹, Menghui Zhang¹, Xiaojun Zhang¹, Chenhong Zhang¹, Min Li¹, Lifeng Sun¹, Zhengsheng Xue¹, Jingjing Wang¹, Jie Feng¹, Feiyan Yan¹, Naisi Zhao¹, Jiaqi Liu¹, Wenmin Long¹ & Liping Zhao¹,²

¹State Key Laboratory of Microbial Metabolism, School of Life Sciences and Biotechnology, Shanghai Jiao Tong University, Shanghai, China; and
²Ministry of Education Key Laboratory of Systems Biomedicine, Shanghai Centre for Systems Biomedicine, Shanghai Jiao Tong University, Shanghai, China

Abstract

Chronic inflammation induced by endotoxin from a dysbiotic gut microbiota contributes to the development of obesity-related metabolic disorders. Modification of gut microbiota by a diet to balance its composition becomes a promising strategy to help manage obesity. A dietary scheme based on whole grains, traditional Chinese medicinal foods, and prebiotics (WTP diet) was designed to meet human nutritional needs as well as balance the gut microbiota. Ninety-three of 123 central obese volunteers (BMI ≥ 28 kg m⁻²) completed a self-controlled clinical trial consisting of 9-week intervention on WTP diet followed by a 14-week maintenance period. The average weight loss reached 5.79 ± 4.64 kg (6.62 ± 4.94%), in addition to improvement in insulin sensitivity, lipid profiles, and blood pressure. Pyrosequencing of fecal samples showed that phylotypes related to endotoxin-producing opportunistic pathogens of Enterobacteriaceae and Desulfovibrionaceae were reduced significantly, while those related to gut barrier-protecting bacteria of Bifidobacteriaceae increased. Gut permeability, measured as lactulose/mannitol ratio, was decreased compared with the baseline. Plasma endotoxin load as lipopolysaccharide-binding protein was also significantly reduced, with concomitant decrease in tumor necrosis factor-α, interleukin-6, and an increase in adiponectin. These results suggest that modulation of the gut microbiota via dietary intervention may enhance the intestinal barrier integrity, reduce circulating antigen load, and ultimately ameliorate the inflammation and metabolic phenotypes.

**Dietary intervention**

We designed three ready-to-use food formulas based on whole grains, traditional Chinese medicinal (TCM) foods, and prebiotics (WTP diet). Formula No. 1 was a pre-cooked mixture of 12 component materials from whole grains and TCM food plants that are rich in dietary fiber, including adlay (*Coix lachrymal-jobi* L.), oat, buckwheat, white bean, yellow corn, red bean, soybean, yam, big jujube, peanut, lotus seed, and wolfberry, which was prepared in the form of canned gruel (370 g wet weight per can) by a contract food manufacturer (Shanghai Meilin Meida Food Co., Ltd., Shanghai, China). Each can contained 100 g of ingredients (59 g carbohydrate, 15 g protein, 5 g fat, and 6 g fiber) and 336 kcal (70% carbohydrate, 17% protein, 13% fat). Formula No. 2 was a powder preparation for infusion (20 g per bag) containing bitter melon (*Momordica charantia*) and oligosaccharides, which included fructo-oligosaccharide and oligosomaltose, and totally accounted for 34% of the formula No. 2. Formula No. 3 contained soluble prebiotics, including guar gum, pectin, konjac flour, other fermentable dietary fiber (Fibersol 2, resistant starch, hemicellulose), and oligosaccharides, and was administered in the form of powder for infusion (50 g per bag). The two infusion formulas were designed to facilitate the modulation of gut microbiota with a mild antibacterial effect and gas-producing function (Fei & Zhao, 2013).

![Fig. 1. The schematic overview of the dietary intervention.](image-url)
Fig. 2. Dietary intervention changed intestinal microbiota. Groups of bacteria changed at the (a), (b) phylum, (c) family, and (d) genus levels. Bacteria numbers are expressed as the proportion of total intestinal microbiota, and data are mean ± SEM. *P < 0.05; **P < 0.01.

Changes in biomarkers along the causal pathway

We focused on the changes in the following biomarkers along the pathway likely connecting gut microbiota to the pathogenesis of obesity (Table 3 and Fig. 3): an intestinal permeability marker, L/M ratio, a gut-derived antigen load marker, LBP, inflammation markers including CRP, pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β), anti-inflammatory adipokine (adiponectin), and insulin sensitivity. The L/M ratio and LBP were significantly decreased by the end of Phase I accompanied by improvements in systemic inflammatory tone, characterized by the reduction in CRP and IL-6, and the increase in adiponectin. Eventually, insulin sensitivity was increased.

Table 3. Inflammatory biomarkers, LBP, and gut permeability of the obese subjects at baseline, 9, and 23 weeks after the intervention

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Baseline (−30 day)</th>
<th>Phase I (9 week)</th>
<th>Phase II (23 week)</th>
<th>Medical reference range</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive protein (mg L⁻¹, n = 67)</td>
<td>6.60 (5.10–8.20)</td>
<td>4.90** (4.20–6.20)</td>
<td>5.93* (4.69–6.85)</td>
<td>0–10</td>
</tr>
<tr>
<td>LBP (μg mL⁻¹)</td>
<td>23.21 (15.54–35.50)</td>
<td>19.98** (14.15–30.83)</td>
<td>23.08†† (11.51–36.99)</td>
<td>–</td>
</tr>
<tr>
<td>IL-1β (pg mL⁻¹)</td>
<td>0.07 (0.03–0.12)</td>
<td>0.07 (0.05–0.15)</td>
<td>0.06 (0.04–0.12)</td>
<td>–</td>
</tr>
<tr>
<td>IL-6 (pg mL⁻¹)</td>
<td>2.28 (1.79–3.12)</td>
<td>2.02* (1.62–2.62)</td>
<td>1.68***†† (1.27–2.46)</td>
<td>–</td>
</tr>
<tr>
<td>TNF-α (pg mL⁻¹)</td>
<td>1.07 (0.87–1.49)</td>
<td>1.03 (0.81–1.40)</td>
<td>1.04* (0.82–1.50)</td>
<td>–</td>
</tr>
<tr>
<td>Adiponectin (μg mL⁻¹)</td>
<td>3.57 (2.56–5.22)</td>
<td>3.82** (2.90–5.90)</td>
<td>4.23***†† (3.06–6.17)</td>
<td>–</td>
</tr>
<tr>
<td>L/M ratio (n = 76)</td>
<td>0.026 (0.020–0.031)</td>
<td>0.022** (0.019–0.026)</td>
<td>0.023* (0.019–0.026)</td>
<td>–</td>
</tr>
</tbody>
</table>

LBP, lipopolysaccharide-binding protein; IL, interleukin; TNF-α, tumor necrosis factor-α; L/M ratio, lactulose/mannitol ratio. Results were expressed as median (interquartile range).

Significantly different from baseline, *P < 0.05, **P < 0.01; Significantly different from Phase I, †P < 0.05, ††P < 0.01 (two-tailed test).
I'm full... that cheese was perfect.

I'm still hungry.
New therapeutic targets for noncognitive reductions in energy intake, absorption, or storage are crucial given the worldwide epidemic of obesity. The gut microbial community (microbiota) is essential for processing dietary polysaccharides. We found that conventionalization of adult germ-free (GF) C57BL/6 mice with a normal microbiota harvested from the distal intestine (cecum) of conventionally raised animals produces a 60% increase in body fat content and insulin resistance within 14 days despite reduced food intake. Studies of GF and conventionalized mice revealed that the microbiota promotes absorption of monosaccharides from the gut lumen, with resulting induction of de novo hepatic lipogenesis. Fasting-induced adipocyte factor (Fiaf), a member of the angiopoietin-like family of proteins, is selectively suppressed in the intestinal epithelium of normal mice by conventionalization. Analysis of GF and conventionalized, normal and Fiaf knockout mice established that Fiaf is a circulating lipoprotein lipase inhibitor and that its suppression is essential for the microbiota-induced deposition of triglycerides in adipocytes. Studies of Rag1-/- animals indicate that these host responses do not require mature lymphocytes. Our findings suggest that the gut microbiota is an important environmental factor that affects energy harvest from the diet and energy storage in the host.

Cohousing Ln and Ob mice prevents increased adiposity in Ob cage mates (Ob). (A) Adiposity change after 10 days of cohousing. *P < 0.05 versus Ob controls (Student’s t test). (B) Bacteroidales from Ln microbiota invade Ob microbiota. Columns show individual mice.

Microbial Modulation of Energy Availability in the Colon Regulates Intestinal Transit

Anita Wichmann,1,2 Ava Allahyar,1,2 Thomas U. Greiner,1,2 Hubert Plovier,1,2 Gunnel Östergren Lundén,1,2 Thomas Larsson,1,2 Daniel J. Drucker,3 Nathalie M. Delzenne,4 Patrice D. Cani,4,5 and Fredrik Bäckhed1,2,6,*

1Wallenberg Laboratory/Sahlgrenska Center for Cardiovascular and Metabolic Research, Sahlgrenska University Hospital, Gothenburg 40530, Sweden
2Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg 41345, Sweden
3Department of Medicine, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, ON M5G 1X5, Canada
4Metabolism and Nutrition Research Group, Louvain Drug Research Institute, Université Catholique de Louvain, Brussels 1200, Belgium
5WELBIO (Walloon Excellence in Life Sciences and BioTechnology), Université Catholique de Louvain, Brussels 1200, Belgium
6Section for Metabolic Receptology and Enteroendocrinology, Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health Sciences, University of Copenhagen, Copenhagen 2200, Denmark

*Correspondence: fredrik.backhed@wlab.gu.se
http://dx.doi.org/10.1016/j.chom.2013.09.012

Diabetes and obesity are two metabolic diseases characterized by insulin resistance and a low-grade inflammation. Seeking an inflammatory factor causative of the onset of insulin resistance, obesity, and diabetes, we have identified bacterial lipopolysaccharide (LPS) as a triggering factor. We found that normal endotoxemia increased or decreased during the fed or fasted state, respectively, on a nutritional basis and that a 4-week high-fat diet chronically increased plasma LPS concentration two to three times, a threshold that we have defined as metabolic endotoxemia. Importantly, a high-fat diet increased the proportion of an LPS-containing microbiota in the gut. When metabolic endotoxemia was induced for 4 weeks in mice through continuous subcutaneous infusion of LPS, fasted glycemia and insulinemia and whole-body, liver, and adipose tissue weight gain were increased to a similar extent as in high-fat–fed mice. In addition, adipose tissue F4/80-positive cells and markers of inflammation, and liver triglyceride content, were increased. Furthermore, liver, but not whole-body, insulin resistance was detected in LPS-infused mice. CD14 mutant mice resisted most of the LPS and high-fat diet–induced features of metabolic diseases. This new finding demonstrates that metabolic endotoxemia dysregulates the inflammatory tone and triggers body weight gain and diabetes. We conclude that the LPS/CD14 system sets the tone of insulin sensitivity and the onset of diabetes and obesity. Lowering plasma LPS concentration could be a potent strategy for the control of metabolic diseases.

Responses of Gut Microbiota and Glucose and Lipid Metabolism to Prebiotics in Genetic Obese and Diet-Induced Leptin-Resistant Mice


Insight into the prebiotic concept: lessons from an exploratory, double blind intervention study with inulin-type fructans in obese women

Evelyne M Dewulf,¹ Patrice D Cani,¹ Sandrine P Claus,² Susana Fuentes,³ Philippe GB Puylaert,³ Audrey M Neyrinck,¹ Laure B Bindels,¹ Willem M de Vos,³ Glenn R Gibson,² Jean-Paul Thissen,⁴ Nathalie M Delzenne³

What is already known on this subject?
- Dysbiosis is associated with obesity and related metabolic disorders.
- Dietary inulin-type fructans (ITF) selectively change the gut microbiota composition and improve host physiological functions in obese rodents.
- The beneficial effect of ITF (prebiotic effect) in non-obese humans is often linked to a promotion of bifidobacteria in the colon.

What are the new findings?
- ITF prebiotics induce a huge bifidogenic effect but also modify numerous other bacteria in obese women.
- The changes in gut microbiota induced by ITF prebiotics are correlated with bacterial-related metabolites (phosphatidylcholine, lactate, hippurate) and with serum lipopolysaccharide levels, despite a lack of significant effect on body weight.
- As inferred from the Human Intestinal Tract Chip (HITChip) analysis (phylogenetic microarray based on 16S rRNA gene sequences for the study of the human gastrointestinal microbiota) and the metabolomic signatures, the prebiotic approach selectively changes microbiota-related host functions.

How might it impact on clinical practice in the foreseeable future?
- ITF prebiotics might be used to support the dietary advice to control obesity and related metabolic disorders including diabetes, and cardiovascular or liver disease. Our results indicate bacterial types or functions that could constitute novel therapeutic targets in this major public health issue.

Trial profile. Of the 44 enrolled patients, eight patients failed to complete the study for the following reasons: pregnancy (one patient), loss of contact during follow-up (one patient), gastro-oesophageal reflux (two patients), personal reasons (two patients) and absence of weight loss (two patients). Of the 36 patients who completed the study, three patients per group were excluded from the analysis because of antibiotic treatment during the study and inadequate or missing faecal sampling.

Getting By(pass) with Help from Our Little Friends

One of the most durably effective treatments for severe obesity is gastric bypass surgery. Despite its powerful effect on weight loss and remission of diabetes, the cost and associated risk of this procedure prevents its application to a large population of obese patients, prompting a search for less invasive treatments. The population structure of the trillions of microorganisms that reside in the human gut is markedly altered after gastric bypass, but the functional importance of these changes is unknown. In a new study, Liou et al. use a mouse model of gastric bypass surgery to characterize changes in the gut microbiota, both temporally and along the length of the gastrointestinal tract. Gastric bypass induced substantial, rapid, and sustained changes to the gut microbial communities that were independent of both diet and the weight loss associated with this procedure. The observed changes in this mouse model were similar to those previously observed in human gastric bypass patients. Transfer of the surgically altered microbial community to nonoperated, germ-free mice resulted in weight loss and decreased body fat. Gastric bypass was also associated with changes in the production of short-chain fatty acids, changes that were conveyed to the previously germ-free mice that received the microbiota from these operated animals. These observations demonstrate that specific alterations in the gut microbiota contribute to the beneficial effects of bariatric surgery on energy balance and obesity. They suggest new approaches to the treatment of obesity and related metabolic diseases that harness the ability of the gut microbiota to influence host metabolic physiology.

Conserved Shifts in the Gut Microbiota Due to Gastric Bypass Reduce Host Weight and Adiposity

Alice P. Liou, Melissa Paziuk, Jesus-Mario Luevano Jr., Sriram Machieni, Peter J. Turnbaugh, Lee M. Kaplan

Roux-en-Y gastric bypass (RYGB) results in rapid weight loss, reduced adiposity, and improved glucose metabolism. These effects are not simply attributable to decreased caloric intake or absorption, but the mechanisms linking rearrangement of the gastrointestinal tract to these metabolic outcomes are largely unknown. Studies in humans and rats have shown that RYGB restructures the gut microbiota, prompting the hypothesis that some of the effects of RYGB are caused by altered host-microbial interactions. To test this hypothesis, we used a mouse model of RYGB that recapitulates many of the metabolic outcomes in humans. 16S ribosomal RNA gene sequencing of murine fecal samples collected after RYGB surgery, sham surgery, or sham surgery coupled to caloric restriction revealed that alterations to the gut microbiota after RYGB are conserved among humans, rats, and mice, resulting in a rapid and sustained increase in the relative abundance of Gammaproteobacteria (Escherichia) and Verrucomicrobia (Akkermansia). These changes were independent of weight change and caloric restriction, were detectable throughout the length of the gastrointestinal tract, and were most evident in the distal gut, downstream of the surgical manipulation site. Transfer of the gut microbiota from RYGB-treated mice to nonoperated, germ-free mice resulted in weight loss and decreased fat mass in the recipient animals relative to recipients of microbiota induced by sham surgery, potentially due to altered microbial production of short-chain fatty acids. These findings provide the first empirical support for the claim that changes in the gut microbiota contribute to reduced host weight and adiposity after RYGB surgery.

A complicated relationship status

Nothing is simple about the links between the bacteria living in our guts and obesity.

By Sarah Deweerdt