Gut Microbiota

by

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Objectives:

- Overview of gut microbiota and their function
- Role of gut microbiota in various disease pathology
- Impact of diet and lifestyle on the composition of gut flora
- Impact of various medications on Gut flora
- Importance and ways to replenish or restore the gut flora
- Recent researches
- Role of dietitians and nutritionists in helping to maintain healthy gut flora
Microbiome

- “A Collection of different microbes and their functions or genes found in an environmental habitat” (1)

Microbiota

- “Entire population of microorganisms that colonizes a particular location” (2)
- Includes bacteria, viruses, fungi etc.
Normal Gut Microbiota:

Over 35,000 bacterial species (2)

“Unique for each individual” (6)

Predominant phyla - Firmicutes, Bacteroidetes, Actinobacteria and Verrucomicrobia, Proteobacteria.

Danish study of gut flora - High Gene count (HGC) and Low Gene Count (LGC)

- HGC individuals: “functionally much robust gut microbiome and low prevalence of metabolic disorders and obesity” (2)

- LGC individuals: “harbor higher proportion of pro-inflammatory bacteria” (2)
Distribution of the normal human gut flora (2):
Factors that contribute to variations in gut flora:

Age:

- “the infant gut could be colonized by organisms even in utero” (2)

- “meconium is rich in genera such as Escherichia-Shigella, Enterococcus, Leuconostoc, Lactococcus, and Streptococcus” (2)

- “first microbiota profile is largely shaped by the mode of delivery” (2):
  - Vaginal delivery - Ex. Lactobacillus and Prevotella (2)
  - C-section - maternal skin flora - Ex. Streptococcus, Corynebacterium, and Propionibacterium (2)

- Also depend on the type of feeding - breast-fed vs formula-fed
Factors that contribute to variations in gut flora:

Diet - will go over this in detail in the later part of this presentation

Geographic Locations:

- Mostly based on the type of diet consumed

- “African children had a higher abundance of *Prevotella*” (2) : Agrarian diet

- European children consumed Western diet had higher amount of *Bacteroides*.

Immune system: suppressed

Medications: antibiotics, PPI, metformin, etc
Functions of Gut Flora: *Nutrient metabolism*

- **Carbohydrates**
  - $\rightarrow$ Butyrate, propionate, acetate $\rightarrow$ energy for host

- **Lipids**
  - $\rightarrow$ enhances the activity of lipoprotein lipase in adipose tissue

- **Synthesis of vitamin K and vitamin B**

- **Synthesis of conjugated linoleic acid**
  - $\rightarrow$ antidiabetic, anti atherogenic, hypolipidemic, anti obesogenic, immunomodulator property

- **Converts primary bile acids to secondary bile acids in colon**

- **Increases the concentration of pyruvic acid, citric acid, fumaric acid, malic acid**

- **Degradation of polyphenols**
Xenobiotics:

- Gut microbiota affects the metabolism and bioavailability of drugs.

- Drugs can transform the composition of microbes \(^{(13)}\)

- The exact mechanism remains unclear.
- “Induce synthesis of antimicrobial proteins (AMP) such as cathelicidins, C-type lectins, and (pro)defensins by the host Paneth cells via a pattern recognition receptor (PRR) mediated mechanism” (2)

- “Bacteroides thetaiotaomicron and Lactobacillus innocua appear to be among the key individual species that drive this production” (2)

- “Produce lactic acid, which can augment the antimicrobial activity of host lysozyme by disrupting the outer membrane of the bacterial cell wall” (2)

- “Keep a check on the overgrowth of pathogenic strains by inducing local immunoglobulins” (2)
Gram Neg. Organisms (Eg. Bacteroides) ---> activate ---> Intestinal dendritic cells (IDC)

IDC ----> induces ----> intestinal mucosal plasma cells ----> secretory IgA

Sec. IgA -------> coats the gut microbiota that are resistant to degradation by bacterial proteases
Functions of Gut flora: *Maintain the integrity of the Gut barrier*

- “*Bacteroides thetaiotaomicron* is reported to induce expression of the small proline-rich protein 2A, which is required for maintenance of desmosomes at the epithelial villus” (2)

- “Maintains the tight junctions by TLR2 mediated signaling that is stimulated by the microbial cell wall peptidoglycan” (2)

- “The endocannabinoid system is yet another entity that regulates gut microbiota mediated maintenance of the gut barrier function. Eg. increase the levels of endocannabinoids that control gut barrier functions by decreasing metabolic endotoxemia” (2)
- “Contributes to structural development of the gut mucosa by inducing the transcription factor angiogenin-3, which has been implicated in the development of intestinal microvasculature” (2)

- “Significant reduction of villus capillary network in germ-free (GF) mice, which in turn can impair nutrient digestion and absorption” (2)

- “GF mice that have a lower intestinal surface area, thin villi (secondary to lower regeneration), increase cell cycle time and impaired peristalsis” (2)
Impact of Alteration in Normal Gut flora:

- Reduced capability to synthesize vitamin B12
- Reduced activities of microbial reductases
- Increased tendency for DNA alterations
- Elevated stress response, and immune dysfunction
Assoc. between gut microflora & different pathologies:

1. Stress
2. Diabetes
3. Obesity
4. Inflammatory bowel disease (IBD)
5. Irritable bowel syndrome (IBS)
6. Small bowel bacterial overgrowth (SIBO)
7. Non Alcoholic Fatty Liver Disease (NAFLD)
8. Colorectal cancer
GI distress:

- “Motility, visceral perception, GI secretions, intestinal permeability and intestinal microbiota” (9)

“The enteric microbiota influence the development and function of the ENS and immune system which affects CNS function” (9)

*Stress ----> Increases sys. Proinflammatory cytokines ----> Act on Pituitary → HPA axis ---> signals CNS via vagus nerve ---> mast cell activation in the GI tract . (9)
Obesity and insulin resistance:

- Decreased diversity of gut microbiota in obese and T2DM individuals (6)

- “Low gene diversity and a less diverse composition of the microbiota associated with high BMI, fat mass, lower insulin sensitivity, dyslipidemia as well as increased markers of inflammation” (6)

Mechanism by which Gut microbiota affects Obesity:

- Dietary fibers ---> fermented by gut microbes ---> SCFAs (propionate, acetate, butyrate). Acetate ameliorates vs induces obesity and insulin resistance. (6)

- may alter the physicochemical properties of endogenous metabolites. Eg. bile acid metabolism in ileum and large intestine. (6)
- Dysbiosis of gut microbiota

- Fewer bacterial species.

- “Firmicutes and Bacteroidetes are decreased in IBD, whereas Actinobacteria and Proteobacteria are considerably increased” (12)

- Colon and TI affected commonly in IBD, which is also an area that is rich in microbes (12)

- “Alterations of the Microbiota: Cause or Consequence of IBD?” (12)

- Gut microbiota alteration causes inflammation or alteration in gut physiology leads to inflammation which in turn alters the gut microbiota composition.
Irritable bowel syndrome (IBS)

- Chronic Abdominal cramping/discomfort with associated irregular bowel habits accompanied by +/- anxiety

- Types: C- IBS, D-IBS, A-IBS

- Pathophysiology of IBS not well understood.

- Changes in composition of gut microbiota leads to increased intestinal gut permeability, Increased GI transit, visceral hypersensitivity

- ? SIBO causes IBS or IBS leads to SIBO

- Low FODMAP diet decreases the symptoms of IBS by changing the composition of gut microbes (14)
SIBO:

Imbalance and alteration in normal small intestinal gut flora, in terms of both volume and quality.

Etiology:

- Disorders of protective antibacterial mechanism. Eg. Pancreatic insufficiency, achlorhydria, Immune deficiency, etc (8)

- Anatomical alterations. Eg. fistula, SBO, diverticula, surgeries like Roux en Y, ileocecal resections, etc. (8)

- Motility disorders. Eg. Irritable bowel syndrome, Delayed gastric emptying, autonomic diabetic neuropathy, scleroderma etc. (8)

- Inflammatory bowel disease
Clinical symptoms:

- Dyspepsia (bloating, burping, indigestion), flatulence, abdominal cramping/discomfort, diarrhea, steatorrhea, weight loss, malnutrition, vit B12 deficiency

Diagnosis:

- Hydrogen breath test
- Jejunal aspirate analysis for SCFAs
- Serum unconjugated bile acids analysis

Tx:

- Abx (Rifaximin, cephalexin, metronidazole, neomycin, etc.)
SIBO Diet

Elemental diet
Low FODMAP diet
Specific Carbohydrate diet
Paleo diet
Gluten free diet
NAFLD:

Possible mechanism:

- High fat diet leads to deposition of lipids in liver by “bacterial overgrowth, gut leakiness, increased endotoxemia absorption, and inflammation” (7)
Diet
- PUFA and n-3 PUFA
- Non-digestible carbohydrates
- Vitamin E
- Cinnamon
- Protein
- Prebiotics
- Probiotics

Exercise
- Voluntary activity
- Structured running

Overall effects
- Reduced blood flow to GI tract
- Improved metabolic control
- Body weight
- Improved body composition
- Blood lactate
- Endotoxemia

Liver effects
- Hepatic lipids
- Lipogenesis
- Plasma triglycerides
- Cholesterol
- Bile acid synthesis

Gastrointestinal effects
- Gut motility
- SCFA production
- Epithelial integrity
- Inflammation
- Bile acid excretion
- Fat absorption
- Altered hormone release

Altered bacterial composition and increased diversity
Ref: Gut Microbiota: the next gen frontier in preventive and therapeutic medicine, Ravinder Nagpal, Hariom Yadav, Francesco Marotta. Front med, 23 June 2014
Impact of diet on Gut microbiota:

Fibers:

- Lack of fibers → substantial loss of microbial diversity

- When fiber is reintroduced, this effect is not fully reversed and increases in severity over multiple generations (15)

- Consumption of high fiber diet is recommended

- Fecal transplantation did restore some of the gut microbiota
Sonnenburg et al. found that mice fed a low-fibre diet had a lower species diversity in their gut microbiota than mice fed a high-fibre diet. In first-generation mice, most (but not all) of this diversity was recoverable when mice on the low-fibre diet were switched to a high-fibre diet. However, the authors found that diversity loss was greater in each subsequent generation maintained on a low-fibre diet, and that the degree of recovery also decreased, implying extinction of some microbial species.

Impact of diet on Gut microbiota:

Westernized diet:

- Increased consumption of sugar, and fatty foods.
- Greater amount of microbes that are linked to obesity
- Increased intestinal permeability
- Increased risk for chronic diseases like IBD, NAFLD, etc
Table 1. Shifts in gut microbiota derived from different dietary strategies of dietary modifications.

<table>
<thead>
<tr>
<th>Dietary strategy</th>
<th>Basis/Mechanism</th>
<th>Affected species</th>
<th>Observed effects</th>
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</thead>
<tbody>
<tr>
<td>Carbohydrate ↓</td>
<td>Related with beneficial effects because of the association with SCFA production and phenolic compounds, known to have anti-inflammatory effects.</td>
<td><em>Bifidobacteria</em> ↓, <em>Clostridium</em> ↓, <em>Bacteroidetes</em> ↓</td>
<td>Decrease SCFA: Butyrate production. Decrease fiber-derived phenolic acids.</td>
</tr>
<tr>
<td>Protein ↑</td>
<td>Proteolitic fermentation produces beneficial compounds, but putrefaction is considered detrimental for the host’s health.</td>
<td><em>Bacteroidetes</em> ↑, <em>Lactobacillus</em> ↑, <em>Bifidobacterium</em> ↑</td>
<td>Amelioration of obesity, inflammation and metabolic complications.</td>
</tr>
</tbody>
</table>

SCFA: short chain fatty acids; PUFA: polyunsaturated fatty acids.
Recent Research:


**Results**

HC diet substantially increased plasma (1.6-fold) and liver cholesterol levels (21-fold), biliary cholesterol secretion (4.5-fold) and fecal neutral sterol excretion (68-fold, each \( p < 0.001 \)) but not fecal bile acid excretion. Interestingly, despite the profound changes in intestinal cholesterol homeostasis no differences in microbial composition between control and HC-fed mice were detected. In both groups the main phyla were *Bacteroidetes* (55%), *Firmicutes* (27%) and *Verrucomicrobia* (14%).

**Conclusion**

Our results demonstrate that in mice HC diet alone does not alter the microbiota composition despite inducing substantial adaptive changes in whole body cholesterol homeostasis. The impact of Western diet on intestinal microbiota thus seems to be mediated exclusively by its high fat content.
Recent Research:


Multi-species probiotics reduced depressive-like behaviour independently of diet. Metabolomics revealed metabolites that may mediate the antidepressant-like effect. Probiotics skewed leukocyte cytokine pattern towards T-cell related cytokines. Probiotics and high-fat diet oppositely affected hippocampal HPA axis regulation.

Objective: the effect of dietary supplementation with cellulose, a nonfermentable fiber, on the gut microbiota, inflammatory markers, and survival in two murine models of sepsis.

Intervention: Mice were assigned to low-fiber, normal-fiber, or high-fiber diets with or without antibiotics for 2 weeks and then subjected to sepsis by cecal ligation and puncture or endotoxin injection. Fecal samples were collected for microbiota analyses before and after dietary interventions.

RESULTS:

Mice that received a high-fiber diet demonstrated increased survival after cecal ligation and puncture relative to mice receiving low-fiber or normal-fiber diets. The survival benefit was associated with decreased serum concentration of pro-inflammatory cytokines, reduced neutrophil infiltration in the lungs, and diminished hepatic inflammation. The high-fiber diet also increased survival after endotoxin injection. Fiber supplementation yielded an increase in relative abundance of the genera Akkermansia and Lachnospiraceae, taxa commonly associated with metabolic health. Administration of antibiotics to mice on the high-fiber diet negated the enrichment of Akkermansia species and the survival benefit after cecal ligation and puncture.

CONCLUSION:
Dietary supplementation with cellulose offers a microbe-mediated survival advantage in murine models of sepsis.
Transplantation of fecal microbiota from patients with irritable bowel syndrome alters gut function and behavior in recipient mice

BY GIADA DE PALMA, MICHAEL D. J. LYNCH, JUN LU, VI T. DANG, YIKANG DENG, JENNIFER JURY, GENEVIEVE UMEH, PEDRO M. MIRANDA, et.al SCIENCE TRANSLATIONAL MEDICINE01 MAR 2017

Abstract

To evaluate a functional role for commensal gut bacteria in IBS, we colonized germ-free mice with the fecal microbiota from healthy control individuals or IBS patients with diarrhea (IBS-D), with or without anxiety, and monitored gut function and behavior in the transplanted mice. Microbiota profiles in recipient mice clustered according to the microbiota profiles of the human donors. Mice receiving the IBS-D fecal microbiota showed a taxonomically similar microbial composition to that of mice receiving the healthy control fecal microbiota. However, IBS-D mice showed different serum metabolomic profiles. Mice receiving the IBS-D fecal microbiota, but not the healthy control fecal microbiota, exhibited faster gastrointestinal transit, intestinal barrier dysfunction, innate immune activation, and anxiety-like behavior. These results indicate the potential of the gut microbiota to contribute to both intestinal and behavioral manifestations of IBS-D and suggest the potential value of microbiota-directed therapies in IBS patients.
Recent Research:


Conclusion:

The consumption of PFM with *B. lactis* CNCM I-2494 and lactic acid bacteria is associated with a modest but consistent and significant improvement of outcomes related to gastrointestinal discomfort in healthy adults.
Restoring Gut flora:

Three ‘P’s’ for gut health: probiotics, prebiotics and polyphenols (1)

Prebiotics:

- Nondigestible carbohydrates that act as food for probiotics.
- Eg. leeks, garlic, onion, fibers

Probiotics:

- Live bacteria and yeast.
- Helpful for digestion
- Most probiotics have bacterial sp. of *Lactobacillus* and *Bifidobacterium*
- Yeast: *Saccharomyces boulardi*
Probiotics: Use

- Diarrhea
- Constipation
- Bloating
- Cramping
- Restore gut flora after antibiotic use

Avoid probiotics in critically ill patients, postoperative, infants, weak immune system (4)
Different sources of probiotics:

- Foods (yogurt, sauerkraut, miso soup, Kimchi, Kombucha tea)
- Supplements - oral pills, liquids, gummies
- Skin cream
Probiotics in the market

- **Florastor**: *Saccharomyces boulardii lyo*

- **Culturelle**: *Lactobacillus rhamnosus GG*

- **Align**: B. infantis 36524

- **Nature’s Bounty**: Lactobacillus Acidophilus

- **VSL #3**: *Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei, Lactobacillus delbrueckii subsp. bulgaricus*

- **Phillips Colon Health**: Lactobacillus gasseri, Bifidobacterium bifidum,
Fecal transplant

Done by either colonoscope or oral capsule intake or by use of rectal suppository/enema

More efficient when done by colonoscope.

FDA approved procedure for recurrent Clostridium difficile infection.

May be beneficial in IBS, IBD, SIBO etc.


5. No reference.


Questions?
Thank you!