Effects of Diet on Gut Microbiota Profile and the Implications for Health and Disease

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Gut microbes are present in large concentrations on the human intestinal mucosal surface and play important roles in health and disease of the host. Numerous groups of gut microbes are associated with immunological and metabolic diseases and in maintaining health status of the host. Among these health- and disease-associated gut microbes, Bacteroides, Clostridium and Bifidobacterium appear regularly in the list. Scientific and clinical evidence available to date indicates that diet is a major driving factor for the establishment of the gut microbiome. Slow digestible carbohydrates (human milk glycan, inulin and fructooligosaccharide), insoluble complex carbohydrates and protein diets favor the growth of Bacteroides, Clostridium and Bifidobacterium. Fat on the other hand suppresses the number of Bacteroides, Clostridium and Bifidobacterium; whereas polyphenols in general suppress Bacteroides and Clodtridium but enhance the Bifodobacterium. The implication is that dietary habits could be a major determinant of health and disease susceptibility. Dietary strategies could be an effective means of potentially inducing changes in intestinal microbiota and are certainly achievable, thus facilitating correction of intestinal microbiome aberrations or imbalances to improve our health. Most of the physiological and functional interactions between individual dietary components and the concoction of foods in a meal and gut microbiota have not yet been well studied. A concerted effort is required to acquire better understanding of their interaction in order to rationally maintain our intestinal microbiome homeostasis and general health through dietary intervention.

Key words: gut microbes, microbiome, microbiota profile, diet

GUT MICROBES AND HEALTH

Gut microbes play important roles in health and disease of the host for the obvious reasons that they are present in large concentrations, closely associated with the host mucosal surface and interact with the host.

It has been widely demonstrated in animal and clinical studies that gut microbiota are involved in maturation and regulation of host immunity and gut functions. Capsular antigen of the human commensal Bacteroides fragilis triggers T cell-dependent immune responses that can affect both the development and homeostasis of the host immune system [1–3]. Colonization of the intestinal tract by Lactobacillus and Bifidobacterium exerts a barrier effect and protects the host against pathogens [4–6]. Escherichia coli, Klebsiella pneumonia and Streptococcus viridans on the other hand significantly increase intestinal permeability. An increase in permeability can lead to inappropriate immune responses, resulting in diseases like Crohn’s disease [7], Celiac disease and associated type 1 diabetes mellitus [8].

It has been reported that disruption of the microbiome balance can result in overgrowth of Gram-negative enteric bacteria such as Pseudomonas and Staphylococcus aureus and a lower level of Bifidobacterium, Eubacterium rectale/Clostridium coccoides group and Bacteroides-like MIB, resulting in a higher incidence of systemic infection [9] and metabolic disorder [10].

Certain intestinal bacteria such as Bacteroides, Enterobacteriaceae and Clostridium are able to produce mutagens in the presence of dietary precursors, through the actions of β-glucuronidase and nitroreductase [11]. Free radical-producing Enterococcus faecalis, has a positive correlation with human adenomas [12].

Additionally, certain lactic acid bacteria, such as Lactobacillus rhamnosus and Lactobacillus acidophilus, produce bactericidal substances such as bacteriocins, lactic acid and acetic acid [13]. Lower intestinal pH also increases inhibitory activities of other organic acids. Bacterial metabolites such as hydrogen peroxide can also be cytotoxic to other bacteria [5, 14]. Bifidobacterium produces antimicrobial agents that inhibit Gram-positive and Gram-negative organisms [15].

Bacterial fermentation of dietary fiber and slowly
digestible carbohydrates forms a range of bacterial metabolites, including short-chain fatty acids (SCFAs), typically acetate, propionate and butyrate. These represent additional energy sources for the host, which would otherwise not available. Acetate is mainly metabolized in the peripheral tissues and is lipogenic, whereas propionate is transported to the liver and is gluconeogenic. Butyrate is the preferred energy source for the colonocytes and has a role in regulating host gene expression [16, 17].

Methanogens comprise up to 10% of all anaerobes in the colons of healthy adults [18–20]. The most common methanogenic archaeon found in the gut is Methanobrevibacter smithii, which can reduce CO₂ with H₂ to methane, allowing an increase in transformation of nutrients into calories [21]. The colonization of Methanobrevibacter in anorexia nervosa patients has been suggested to be an adaptive attempt towards optimization of food transformation in very low calorie diet intake by these patients. The hosts, however, do pay a price in harboring Methanobrevibacter, as it is related to constipation and diverticulosis [22, 23].

The two most abundant bacteria phyla found in healthy individuals are the Bacteroidetes and Firmicutes [24, 25]. The relative abundance of the two phyla in healthy adults appears to be relatively constant, although they do not always comprise the same species. This suggests multiple representatives of the functional groups [26]. The existence of dominant groups of bacteria presumably acts to conserve the metabolic functions essential to gut health, and indeed, a functional gene core has been identified in the gut metagenome [27]. Overall, a balanced gut microbiota composition confers benefits to the host, while microbial imbalances are associated with metabolic and immune-mediated disorders (as summarized in Table 1). It is interesting to note that Bacteroides among the Bacteroidetes, and lactic acid bacteria (Bifidobacterium) and Clostridium among the Firmicutes consistently appear in diseases involving intestinal microbiome aberrations (in Table 1), and their aberrations could be either higher or lower in abundance. These again support the notion that microbiome homeostasis contributes to gut health and disease.

There is increasing clinical evidence demonstrating that these gut microbiota-linked diseases could be prevented and reverted through microbial (probiotic) intervention. Probiotics are live microorganisms that when administered in adequate amounts confer a health benefit in the host [55]. In clinical studies providing a selected Bifidobacterium or Lactobacillus to mothers with a family history of atopic diseases 2-4 weeks before delivery and to the newborn for 6 months, the incidences of atopic diseases was successfully reduced by half in the infants, and the beneficial effect was still evident after seven years [56, 57]. Lactobacillus, Bifidobacterium, Streptococcus and Escherichia coli showed a protective effect against inflammatory bowel disease in human studies [58, 59]. Lactobacillus and Bifidobacterium improve the clinical conditions in patients with irritable bowel syndrome [60]. In a study on mutagenicity of beef consumption, Lactobacillus casei intake was shown to reduce mutagenicity in urine. This was attributed to reduction in the population of pro-mutagen-forming intestinal bacteria [61]. In patients who underwent surgical treatment for superficial bladder cancer, intake of Lactobacillus prolonged the recurrence-free period [62, 63]. These studies suggest that intestinal microbiota are directly involved in the causation of these diseases, and demonstrate the prospect of balancing gut microbiota for prevention and treatment of these diseases.

Consumption of Lactobacillus-fermented milk resulted in an increase in Lactobacillus and Bifidobacterium counts accompanied by a decrease in Clostridium counts [64]. Other fermented foods, such as Japanese natto and miso, also affect intestinal microbiota. Consumption of these foods resulted in increased levels of Bacillus and Bifidobacterium and decreased levels of Enterobacteriaceae and Clostridium [65].

The probiotic approach, though effective in amending the gut microbiome, is a reactive approach nonetheless, as the gut environment of a diseased individual probably favors the proliferation and establishment of aberrant disease-causing microbes. Maintaining intestinal microbiome homeostasis is arguably a desirable approach in disease prevention. To achieve intestinal microbiome homeostasis, it is necessary to understand factors that influence microbiome composition.

The composition of the gut microbiota is influenced by endogenous and external factors, such as microbes acquired at birth, diet, host physiology, drug intake and disease [66]. Of these factors, the diet is considered a major driver for changes in gut microbiota diversity, as it provides nutrition and alters the microenvironment for microbes. It could be safely assumed that the distinct differences in microbiota of the adult and infant types are the responses to the host physiological stage and to their different diets. Dietary strategies could be an effective means of potentially inducing changes in intestinal microbiota and are certainly achievable, thus facilitating correction of intestinal microbiome aberrations or imbalances to improve our health.
It was estimated that about 40% of the microbial genes present in each human individual are shared with at least half of the human individuals in the same geographical cohort [27]. This suggests the existence of a functional core (core microbiome). The functional core may contain shared metabolic functions (e.g., degradation of carbohydrates, production of vitamins) as well as sequential pathways that would, respectively, restrict or expand functional diversity. Several recent
reviews have discussed evolutionary and functional aspects of microbial diversity in the human intestine [67–69]. The aim of this paper was to extend and exploit new insights, so as to provide better understanding of the responsiveness, variability and resilience of the gut microbiome community with regard to dietary intake and host physiology.

**Carbohydrates and sugars**

Slow digestible oligosaccharides

The most studied dietary components affecting human health and the gut microbiota are the slowly digestible complex carbohydrates, such as oligosaccharides, which are termed prebiotics [70]. They are slowly digestible by human digestive enzymes but fermentable by some gut microbes, thus selectively stimulating the proliferation and/or activity of selected gut bacterial populations.

The first naturally slowly digestible oligosaccharides we encounter are the human milk glycans (HMG), which enrich the gut microbiota that are able to metabolize complex carbohydrates [71]. The ability of certain *Bifidobacterium* strains (in particular *B. infantis*) to efficiently use HMG suggests that production of milk oligosaccharides by the mother may be a strategy to ensure the presence of this group of bacteria in the infant gut [72]. The consumption of HMG by *Bacteroides* species [73] suggests that milk glycans may attract different groups of mutually benefiting microbes to the infant intestine. The colonization of *Bacteroides* in our intestinal tract is an example of the highly evolved microbe-host interactions in establishing gut microbiome homeostasis. The appearance of *Bacteroides thetaiotaomicron* in the gut human gut induces the production of fucα1,2Galβ-containing glycans, which serves as a selective carbon substrate for the bacterium [74].

Consumption of Jerusalem artichoke inulin was reported to increase the fecal *Bifidobacterium* level and to cause a small though significant increase in the level of the *Lactobacillus/Enterococcus* group [75]. Besides the *Bifidobacterium*, two groups of butyrate-producing bacteria, namely *Faecalibacterium prausnitzii* and a group of clostridial cluster XIVa bacteria, were found to increase following inulin/fructooligosaccharide (FOS) supplementation in a human intervention study, [26, 76]

During a feeding trial in which each subject consumed a GOS-containing product, the fecal microbiota composition was significantly altered and showed an increase in the abundance of *Bifidobacterium* [77]. The enrichment of *Bifidobacterium* was generally at the expense of *Bacteroides*.

Simple sugars

Digestible carbohydrates are eventually broken down into constituent simple sugars. Adhesion of microbes to the gastrointestinal surface is considered a prerequisite for their colonization and modulation of local and systemic physiological (immunological, hormonal) activities of the host and for competitive exclusion of pathogens [78]. The sterospecific adhesion-receptor interaction involves sugar moieties on the intestinal surface and sugar-binding adhesins on the microbial cell surface [79–81]. Sugars in food may interfere with the adhesion of intestinal microbes, both probiotics and pathogens, to the intestinal surface [82, 83], leading to an altered intestinal microbiota profile.

The *Prevotella* human enterotype is associated with a high intake of carbohydrates and simple sugars, indicating an association with a carbohydrate-based diet typical of agrarian societies [84]. Changes in microbiome composition were detectable within 24 hours of initiating controlled feeding [84]. Self-reported vegans were also found to be in the *Prevotella* enterotype.

Insoluble complex carbohydrates

Plant products are high in slowly digestible and nondigestible carbohydrates. Consumption of 2 apples a day among Japanese resulted in a significant increase in fecal bifidobacteria and clostridia (including the pectinase-positive *C. perfringens*) after a week [85]. The effect was attributed to apple pectin. Similarly, fecal bifidobacteria and lactobacilli were found to increase significantly during the consumption of kiwifruit (2 a day), and the effect was obvious within a day [86]. The effects were, however, temporary, and the microbiota profile returned to that of the baseline upon cessation of consumption [85, 86].

The energy sources that support the microbial community of the large intestine are dietary components that resist degradation in the upper intestinal tract, together with endogenous products such as mucin. Anaerobic metabolism by the microbiome community in the colon produces short-chain fatty acids together with CO2, H2 and CH4 [87]. These fermentation products have significant effects on the gut environment and on the host, as energy sources, regulators of gene expression and cell differentiation and anti-inflammatory agents. Butyrate, for example, is considered to play a particularly important role as an energy source for colonocytes and in the maintenance of gut health [88, 89].

In an animal study and an *in vitro* gastrointestinal tract model, cereal cellulose and insoluble non-starch polysaccharides (NSP) were found to increase *Ruminococcus flavefaciens*-like and *Clostridium*
xylanolyticum-like phylotypes. The cereal amylose content increased the abundance of Clostridium butyricum-like phylotypes, whereas the amylpectin and starch contents increased the abundance of Clostridium ramosum-like phylotypes, members of Clostridium cluster XIVa and Bacteroides-like bacteria [90–93].

In a human study, the abundance of Ruminococcus bromii and Eubacterium rectale/Roseburia groups showed significant responses to nondigestible carbohydrates [25]. In a separate study, decreasing nondigestible carbohydrate intake significantly decreased both the detectable numbers of the E. rectale/Roseburia group and butyrate production [94]. This strong positive correlation between numbers of the E. rectale/Roseburia group, butyrate detection and nondigestible carbohydrate intake is supported by other human studies [95] and in vitro studies [96].

It was reported that a Japanese diet containing a high level of dietary fiber led to lower counts of anaerobic bacteria such as Clostridium, Bacteroides and Bacillus subtilis, and higher counts in Bifidobacterium and Fusobacterium [97, 98]. A slightly different observation was reported by Finegold et al. [99] in a study comparing the Japanese diet (containing soybean, radishes, cabbage, fish, seaweed and green tea) and Western diet (high in meat); they concluded that the Japanese diet resulted in an intestinal microflora with lower counts of anaerobic bacteria such as Eubacterium rectal-C. coccoides and Eubacterium; and some Ruminococcus species.

The African diet consists mainly of cereal (millet, grain, sorghum), legumes (black-eyed peas) and vegetables and is generally high in starch, fiber and non-animal protein. African children showed a significant enrichment in Bacteroidetes and depletion in Firmicutes, with a unique abundance of bacteria from the genus Prevotella and Xylanibacter [100]. The latter is known to contain a set of bacterial genes for cellulose and xylan hydrolysis that is not found in EU children.

Bacteroides plays an essential role within the distal gut in the degradation of the fiber consumed by the adult host. Bacteroides use a series of membrane protein complexes, termed Sus-like systems, to catabolize plant cell wall glycans in our diets [101]. It is hypothesized that by providing HMG, the mother ensures the presence of this group of bacteria in the infant intestine, allowing the smooth transition from milk to solid vegetable foods in the postweaning diet. Plants were the main source of foods for humans during the first 40 over million years of human history, that is, before they became omnivorous.

The major nondigestible carbohydrate in wheat is arabinoxylan (represents 50% of the dietary fiber); it is selectively degraded in the colon by xylanases and arabinofuranosidases, producing Bifidobacteria (B. animalis spp lactis), Roseburia and Bacteroides-Prevotella [102].

A consequence of the fermentation of nondigestible carbohydrates in the proximal colon is the production of organic acids and lowering of luminal pH [103]. Assuming that the increased dietary intake in general of an obese individual resulted in a reduced colonic pH, this pH change could be an important factor in the observed community shift, as different microbes have varying optimal pHs for growth and activities. In a 4-week short-term weight loss program, short-term decreases in Roseburia and Bifidobacterium were observed in response to reduced carbohydrate intake, but no change was observed in Bacteroides [94]. The proportion of Bacteroides only increased gradually during a 52-week weight loss period. This may imply the involvement of some longer-term physiological mechanism (pH change) rather than a short-term response to diet in the abundance of gut Bacteroides.

Fat and fatty acids

Obesity is a major health concern in developed countries. A high-fat (HF) diet in an animal model was found to modulate the dominant intestinal bacterial population; Bacteroides-like bacteria were significantly reduce, and so were the E. rectal-C. coccoides group and Bifidobacterium [10, 104]. The polyunsaturated fatty acid component of fat appears to be a determinant factor for the adherence of intestinal bacteria to the mucosal surface and their growth [105]. In animal models, an HF diet induced pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α, favoring hyperinsulinemia and excessive hepatic and adipose tissue lipid storage, leading to metabolic disorder (type 2 diabetes and insulin resistance) [106–110]. The relationship between HF feeding and the development of a low-grade inflammatory tone and metabolic disease have been attributed to reduced numbers of Bifidobacterium and a higher plasma endotoxin (Gram-negative bacteria-derived lipopolysacchaide) concentration.

Protein

The quantity and quality of protein constituents in food are clearly different in Western and Eastern diets. In an early study based on culturally dependent methods, consumption of meat among human subjects increased the counts of fecal Bacteroides, Bifidobacterium,
Peptococcus and anaerobic Lactobacillus species [111]. A recent study by Kaberdoss et al [112] using molecular techniques for comparison of the fecal microbiota of lacto-vegetarian and omnivorous young women showed that Clostridium cluster XIa bacteria (also referred to as the Clostridium coccoides group) and butyrate-producing bacteria, specifically Roseburia–E. rectale, were significantly more abundant in the fecal microbiota of omnivores [112]. Functional attributes that have been identified for Clostridium cluster XIa species include acetogenesis [113], utilization of aromatic compounds from the diet [114], metabolism of linoleic acid [115] and degradation of mucin [116].

Bacteroides enterotype has been proposed to be associated with a diet high in animal protein, a variety of amino acids and saturated fats [84, 100], which suggests that meat consumption as in a Western diet characterized this enterotype. The high protein and fat enterotype appears to be stable; a 10-day dietary intervention (low-fat, high-fiber diet) did not result in alteration of enterotypes [84]. This, however, casts uncertainty on the direct association of Bacteroides and a high animal protein and saturated fat diet. Residual proteins that enter the large intestine are fermented by Bacteroides and Clostridium [117] into a range of products depending on the amino acid composition. For example, branched-chain amino acids yield branched chain fatty acids, including isobutyrate and isovalerate. In the presence of typical colonic concentrations of SCFAs, growth of human colonic Bacteroides was found to be strongly inhibited at a pH of 5.5 (acidic), whereas many Firmicutes, including the most abundant butyrate producers, were less affected. The effect of diet on Bacteroides could be pH dependent.

Nonnutritive dietary components

Antibacterial foods such as Capsicum annuum (red pepper) and Allium sativum (garlic) have been shown to inhibit Bacillus cereus, B. subtilis, and C. tetani, and Helicobacter pylori [119].

Our dietary intake of polyphenols ranges between 0.15 and 1 g/day [120]. The predominant polyphenols in foods and beverages are flavonoids, consisting mainly of catechins, proanthocyanidins, anthocyanidins, flavonols and flavones. A significant portion of dietary polyphenols is not absorbed, and those absorbed into the body are metabolized in the liver, excreted through the bile as glucuronides and accumulated in the ileal and colorectal lumen [121]. Phenolic compounds from olives [122], tea [123], wine [124] and berries [125–128] have demonstrated antimicrobial properties. Tea polyphenols have been shown to inhibit the growth of Bacteroides, Clostridium (C. perfringens and C. difficile), E. coli and Salmonella typhimurium [123]. Wild blueberries (Vaccinium angustifolium) have been reported to increase the proportion of Bifidobacterium and Lactobacillus acidophilus population after 6 weeks of consumption, but showed no effect on Bacteroides, Prevotella, Enterococcus and C. coccoides [125, 128].

The effects of polyphenols are related to the chemical structure of the compounds and bacterial species. Caffeic acid generally exerted a more significant inhibitory effect on microbial growth than epicatechin, catechin, 3-O-methylgallic acid and gallic acid [123]. Another in vitro study showed that (+)-catechin increased the counts of the C. coccoides–E. rectale group and E. coli, but inhibited those of C. histolyticum [129]. The effects of (−)-epicatechin were less pronounced in increasing the growth of the C. coccoides–E. rectale group.

Interestingly, the growth of beneficial bacteria (Bifidobacterium and Lactobacillus) was relatively unaffected or favored by dietary polyphenols [122, 129]. Resveratrol, a potent antioxidant found in wine, favored the growth of Bifidobacterium and Lactobacillus [124] and abolished the expression of virulence factors of Proteus mirabilis for invasion of human urothelial cells [130]. Anthocyanins from berries have also been proven to inhibit the growth of pathogenic Staphylococcus, Salmonella, H. pylori and B. cereus [126, 127]. Phenolics, and flavonoids may also reduce the ability of L. rhamnosus to adhere to intestinal epithelial cells [131].

Polyphenols are widely found in plant products (fruits, vegetable, tea leaves). Humans were largely herbivorous for the first 4 million years or so of history. Polyphenol-tolerant and degrading gut microbes must have evolved to be commensal; polyphenols thus serve the function as a gate stopper for microbes (pathogens) that enter the gut occasionally.

STARVATION

Undernourishment in general leads to an abundance of enteric pathogens, such as Campylobacteraceae (35-fold more compared with healthy control subjects), Helicobacteraceae (12-fold) and Bacteroidaceae (4-fold) [132]. On the other hand, Enterobacteriaceae, Shewanellaceae, Thermotogaceae, Eubacteriaceae, Streptococcaceae, Methanosarcinaceae and Thermoprotei were reduced by half.
GENERAL CONCLUSION

Diet is clearly a major determining factor of the gut microbiome. The response of the gut microbiota to dietary impact is often rapid; alteration was observed within 24 hours. The enterotype is, however, determined by long-term dietary habits in terms of the proportion and type of carbohydrates, protein and fat. Few nonnutritive dietary components have been studied; polyphenols show potential as moderators of gut microbiome homeostasis. Nonnutritive dietary components should be the focus in future study of the dietary effects on the gut microbiome.

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