Therapeutic dietary alterations: how a diverse gut microbiota can reduce the risk of chronic illness

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Abstract

The importance of food consumption is in relation to preventing chronic illness and maintaining the health of the gut microbiota is a critically overlooked topic of healthcare. Through recent studies and gained increased, it has been demonstrated that a person's diet plays a significant role in the make up of their gut microbiota. The microbiota is defined as the microorganisms that colonize the body of a healthy individual and the microbiome is defined as the collective genomes of the microorganisms that make up the microbiota (Hooper, 2015, Part 1). Studies concerning the intestinal microbiome in relation to chronic illness has shown strong correlations. With increased awareness of how sensitive and important the gut microbiome is in relation to overall health, personalized dietary changes could one day be a therapeutic method for preventing and treating chronic illness.

Introduction

Most bacteria that the human body comes into contact with are bacteria that have a positive impact on the body. The human body has bacteria colonies all over it's surface including nasal passages, the mouth, the skin, and most importantly the intestines. Nasal passages can have around 100 million bacteria cells compared to the 100 trillion bacteria cells that make up the intestinal tract (Hooper, 2015, Part 1). The density of these bacteria cells inside the intestines telling of the importance they have in relation to overall health. The human microbiota is so diverse that it contains species from each major life domain which are bacteria, archaebacteria, and eukaryotes which are typically in the form of fungi (Hooper, 2015, Part 1). The composition of the gut microbiota of a person is determined by lifestyle habitats, exercise, diet, disease, and antibiotic use (Nicholson et al. 2012). An unhealthy diet alone can have a tremendous negative effect on the gut microbiota in just a short time span. An imbalance of intestinal bacteria has increased within the past sixty years within western populations due to diseases such as obesity and diabetes (Nicholson et al. 2012). The hygiene hypothesis proposes the idea that the rise of immune-related diseases is due to the increased use of antibiotics and changes in diet that are experienced in the western culture that affect gut microbiota balance (Rajpal and Brown 2013). Implementation of more extensive research concerning the gut microbiota is crucial due to its ability to help shape the body's immune system, how changes in the microbial composition of the gut microbiota can cause disease, and how restoring the gut microbiota has the ability to prevent and cure diseases.

Bacteria Amounts and Types

One of the main types of bacteria that is found within the human intestines is *Bacteroides thetaiotaomicron,* also known as B-theta. Another bacteria phyla that is extremely common within the human intestines is the *Firmicutes* (gram positive) (Singh K., et al. 2017). Other species of bacteria that are commonly found within the intestinal microbiota of humans but in lower numbers are *Escherichia coli* and *Methanobrevibacter smithii* which is a type of Archaebacteria (Hooper, 2015, Part 1). Although most of the bacteria within the gut microbiota are beneficial, certain microorganism species still invade this area and can potentially cause disease or illness. Examples of bad bacteria are *Salmonella typhi,* which is a food borne pathogen, and *Bacillus anthracis,* which can cause an upper respiratory tract infection (Hooper, 2015, Part 1). Figure 1 displays different bacterial species commonly found within the gut microbiota along with specific features of each. In correlation to the importance of the gut microbiota and chronic illness, associated disease states are included within the figure.

Symbiotic Human-bacteria Relationship

The symbiotic human-bacteria relationship is most important because it allows the body to be able to adapt to sudden dietary changes as well as maximize the amount of energy obtained from a person's diet. The gut microbiota's input in immune system development and maintenance is another reason this symbiotic relationship is so crucial to human health. These trillions of bacteria cells are prevented from invading other parts of the body by a single layer of epithelial cells (Hooper, November 2015, Part 2). The symbiotic relationship between humans and bacteria is due to an antibacterial lectin secreted by the epithelial surface which is known as *RegIIIy* (Vaishnava et al. 2011). *RegIIIy* maintains this relationship by separating the gut microbiota from the surface of the epithelial tissue of the intestines by roughly 50 micrometers (Vaishnava et al. 2011). Little is known concerning the immune mechanism that promotes the spatial relationship that is established between the microbiota and the intestinal epithelial surface (Vaishnava et al. 2011). Other animals that have positive symbiotic relationships with bacteria are termites, the Gypsy moth, and the squid. The symbiotic relationship between these animal species and their microbiota makeup demonstrate important purposes. Bacteria in the termite's gut help digest cellulose in wood, which makes up their entire diet. Squids use their symbiotic relationship with bacteria in order to obtain an anti-predator response using bioluminescence. This symbiotic relationship has evolved throughout history to provide benefits for microorganisms and their hosts.

Gut Microbiota Functions

The gut microbiota has a vast variety of functions in relation to the human body as a whole. Not only is it a major implication of digesting food, but it also plays a significant role in the development of the immune system and communicating with the brain. The reason the human body is able to adjust to dietary changes on a daily basis is due to bacterial species within the intestines. Bacteria within the gut microbiota are responsible for making a great amount of polysaccharide degrading enzymes (Hooper, 2015, Part 1). These polysaccharide degrading enzymes are responsible for helping digest the plant polysaccharides that make up the cell walls of plants. When eating any type of vegetable, these polysaccharide degrading enzymes are extremely important. The end result of breaking down these polysaccharide chains from the plant walls is obtaining energy for the body to use. Another important job of the gut microbiota are metabolic functions. Figure 2 displays a summarization of the many different metabolic functions and their specific bacterial species. Normal development of the gut microbiota is crucial to supporting the metabolic activities of the brain during the first years of development (Goyal et al. 2015). Many neural metabolic properties such as serotonin and dopamine are produced by microorganisms (Rajpal and Brown 2013). The microbiota also guides how immune cells develop, and an example of this is the stimulation of naive T cells into T reg cells which suppresses inflammation (Hooper, 2015, Part 1).

Germ-free Mice Research

An important experimental tool that has been used to progress research concerning the field of the gut microbiota is germ-free mice. These mice are raised in special conditions in a specific germ-free home that was developed for the purpose of this research by Dr. Lora Hooper's laboratory as well as other labs dedicated to gut microbiota research. The result of these mice being raised in these germ-free conditions is that they do not develop a gut microbiota. Dr. Lora Hooper is a Howard Hughes Medical Institute Investigator that has obtained outstanding research concerning the gut microbiota and it's importance. Her lab is one of the few laboratories that are executing research using germ-free mice. Studying germ-free mice has provided tremendous insight into the importance of the gut microbiota in relation to human health. Animals that are raised within a germ-free environment require an increased energy intake in order to be able to survive. Germ-free mice that were compared to regular mice had to eat 20% more calories in order to maintain the same weight as normal mice (Hooper, 2015, Part 1). This research demonstrates how the gut microbiota maximizes the amount of energy obtained through food consumption. Studies with germ-free animals has also demonstrated that bacteria is essential for immune cell recruitment (Singh K., et al. 2017). Lactic acid bacteria and *Bifidobacteria* have been shown to upregulate anti-inflammatory T regulatory cell expression in mice (Singh K., et al. 2017). The research obtained using germ-free mice has been beneficial in representing the importance of the gut microbiota in many different aspects.

How the Gut Microbiota Guides Immune Cell Development

Recent research studies have indicated that the gut microbiota has the ability to develop immunity to pathogens. One research study was executed on conventionally raised mice, antibiotic-treated mice, Schaedler mice which have a simplified microbiota, and germ-free mice to test the ability of the gut microbiota to inhibit colonization of intestinal pathogens. This study produced results that indicated much lower levels of *Salmonella* colonization in the conventionally raised mice compared to all others (Hooper, 2015, Part 1). This study indicates that the gut microbiota helps to inhibit pathogen colonization, which is an extreme immune response. *Toxoplasma gondii* is an intestinal parasite that can cause very severe disease that starts in the gut, and it can move across the entire body (Hooper, 2015, Part 1). A research study concerning this intestinal parasite resulted in data indicating that germ-free mice have a greatly reduced ability to form an immune response to *Toxoplasma gondii,* and this is due to their inability to form dendritic cells that are created from intestinal bacteria (Hooper, 2015, Part 1). These dendritic cells provide protection against intestinal parasites. These studies demonstrate the strong correlation between the immune system and the gut microbiota. Although antibiotics are used to help the immune system treat infections, there are also destroying the bacteria responsible for immune system development and assistance. Microbiota diversity and density is greatly reduced when a person is being treated with antibiotics. The research should encourage healthcare providers to help their patients reestablish gut microbiota balance after antibiotic consumption.

Fecal Microbiota Transplantation

Consumptions of antibiotics such as Vancomycin can potentially cause an overgrowth of *Clostridium difficile,* which leads to extreme inflammation in the intestines (Hooper, 2015, Part 1). Recurrent *Clostridium difficile* infection causes roughly 14,000 fatalities in the United States every year (Spector and Knight 2015). The overgrowth of this bacteria can lead to permanent damage of the intestines overtime; therefore, treatment for this problem has been developed using organisms that make up the microbiota. In order to treat this disease, a donor fecal sample is obtained by a person that is a close relative of the person being treated in order to mix the fecal sample with a saline solution and administer into the ill patient endoscopically (Hooper, 2015, Part 1). In many cases, this treatment leads to the restoration of the person's microbiota, which in turn relieves the symptoms of the disease. In a scientific trial of 516 patients, fecal microbial transplantation produced an 85% success rate compared to the 20% success rate of antibiotic treatment (Spector and Knight 2015). Another recent trial testing this new treatment had an even greater success rate of 90% (Spector and Knight 2015). The success rate of this treatment that uses the gut microbiota is promising data that should elucidate the opportunities for treatment of other illnesses and chronic diseases.

Food Types in Relation to Bacteria Composition in the Gut Microbiota

Non-digestible carbohydrates such as fiber are considered to be "microbiota accessible carbohydrates (MACs), which allow microbes to supply their host with energy (Singh K., et al. 2017). They are also known as prebiotics, which benefit one's health through stimulation and growth of specific microorganisms that make up the gut microbiota. Soybeans, barley, and raw oats are prebiotic foods, and have shown to increase bacterial variety and density (Singh K., et al. 2017). The benefits of prebiotics on immunity and metabolic function are due to increased production of SCFAs (Singh K., et al. 2017). Short chain fatty acids (SCFA) byproducts such as propionate and acetate have shown to strengthen the mucosal barrier of the intestines due to them being an energy source for epithelial cells (Singh K., et al. 2017). Fermented foods, which contain lactic acid bacteria, such as tempeh (fermented soybeans), have also shown to benefit intestinal health and are also known as probiotics. Consuming probiotic foods have been observed to increase composition of beneficial gut bacteria such as *Bifidobacteria* and *Lactobacilli* (Singh K., et al. 2017). A research study that was executed on 60 overweight adults were provided probiotic supplementation, and it resulted in an increased number in beneficial bacteria such as Bifidobacteria (Singh K., et al. 2017) Participants of this study also showed to have reduced total cholesterol as well as improved insulin sensitivity after this probiotic supplementation (Singh K., et al. 2017). Dietary polyphenols are food in common food sources such as vegetables, tea, cocoa products, and fruit that possess antioxidant properties. Studies have shown that these foods increase composition of bacteria such as *Bifidobacteria* which have shown to have positive health benefits such as cancer prevention and inflammatory bowel disease (IBD) management (Singh K., et al. 2017). Pathogenic *Clostridium* bacteria species have been observed to reduce in numbers after consumption of fruit, wine, and seed polyphenols (Singh K., et al. 2017).

Effects of Specific Diets on the Gut Microbiota

A major dietary change, such as one that is strictly plant-based, can change the composition of the gut microbiome within 24 hours (Singh K., et al. 2017). The “Western diet,” which is high in animal fat/protein and low in fiber, as well as a “gluten-free” diet have both been shown to reduce the amount of beneficial bacteria in the gut microbiota (Singh K., et al. 2017). Consuming red meat promotes a certain composition within the gut microbiota that is associated with increased levels of trimethylamine-N-oxide (TMAO), which is a compound that increases the risk of cardiovascular disease (Singh K., et al. 2017). Figure 3 illustrates the effects of consuming protein from different sources. An experiment was executed on the gut microbiota of 14 healthy children that were considered to have a traditional rural diet and 15 healthy children that were considered to have a traditional western style diet (De Filippo et al. 2010). The purpose of this experiment was to test the composition of the gut microbiota of the children to determine how their diet affects bacterial diversity (De Filippo et al. 2010). The food types that made up the diet of the children who were considered to have a rural diet were legumes such as black-eye peas and vegetables. The food types of the children with the western style eating habits were high in animal protein and sugar, and they were also considerably low in fiber (De Filippo et al. 2010). The results of the study concluded that the children with the western diet to have twice as many *Firmicutes* than *Bacteroidetes,* and this ratio is known to be a precursor of obesity (De Filippo et al. 2010). More studies need to be executed in order to gain more information concerning the effects of a vegan or vegetarian diet on the gut microbiota (Singh K., et al. 2017).

Chronic illnesses in Relation to Gut Microbiota

There are many research studies that have recently shown a correlation between the composition of the gut microbiota and different diseases such as type 2 diabetes, obesity, atherosclerosis, inflammatory bowel disease, atopic dermatitis, and autoimmune arthritis (Singh K., et al. 2017). Individuals with diseases such as diabetes and obesity have extreme intestinal bacterial imbalances when compared to the intestines of healthy individuals (Singh K., et al. 2017). Patients that suffer from type 2 diabetes will have markers in their gut microbiota that indicate the presence of the disease. The gut microbiota of patients who are obese tend to have a higher concentration of *Firmicutes* bacteria within their intestines (Singh K., et al. 2017). Being obese increases the risk of other diseases such type 2 diabetes, polycystic ovarian syndrome, hypertension, obstructive sleep apnea, cardiovascular disease, liver nonalcoholic steatohepatitis, and varying forms of cancer (Rajpal and Brown 2013). Estimates reported from the World Health Organization (WHO) in 2008 stated that roughly 200 million men and 300 million women were considered to be obese (Rajpal and Brown 2013). In 2010, the WHO reported that roughly 40 million children 5 years of age or less were considered to be overweight (Rajpal and Brown 2013). Mood disorders have also been demonstrated as a result of poor gut microbiota health. Studies have also shown major changes in a person's gut microbiota from extreme stress or inflammation to the body, such as a severe burn injury (Singh K., et al. 2017). Patients with inflammatory bowel disease typically have a reduced composition of *Bacteroides* and *Firmicutes* as well as an overall lower diversity of the gut microbiota as a whole (Singh K., et al. 2017). A distressed spatial relationship between the intestinal epithelial surface and gut microbiota correlates with IBD (Vaishnava et al. 2011). *Bifidobacteria* composition levels within the gut microbiota of people that are 60 years of age an older tend to be lower, which is also around the time of significant immune system decline (Nicholson et al. 2012). Recent studies also indicate that the gut microbiota has developmental effects on liver function and potentially other organs within the body (Heijtz et al. 2011). The use of antibiotics of demonstrated in studies to be associated with an increased risk of Crohn's disease and ulcerative colitis (Rajpal and Brown 2013). Colon cancer patients experience tremendous changes in their microbiota composition (Rajpal and Brown 2013).

Therapeutic Dietary Alterations to Increase Beneficial Bacteria Composition

The US National Institutes of Health (NIH) Human Microbiome Project was established in 2007 as well as the EU MetaHIT Consortium, which was initiated in 2008, were developed to collect data concerning the microbiota of thousands of people from different backgrounds and different ages (Rajpal and Brown 2013). It is important that more research is implemented concerning the gut microbiota in order to use the data gained from these projects to institute better preventative health care. This research also allows for the increase in personalized healthcare, which could also lead to the decrease in antibiotic resistance. There needs to be more focus on restoration of the gut microbiota after consummation of antibiotics. One possible therapeutic treatment that correlates with gut microbiota research is developing antibiotics that only target a specific bacteria phylum (Rajpal and Brown 2013). Developments for antibiotics with specific bacterial targets will cause less distress on the gut microbiota balance. Another example of a gut microbiota related therapeutic method of treatment is *Lactobacilli* and *Bifidobacteria* being successfully used as a preventative treatment of traveller's diarrhea (Singh K., et al. 2017).

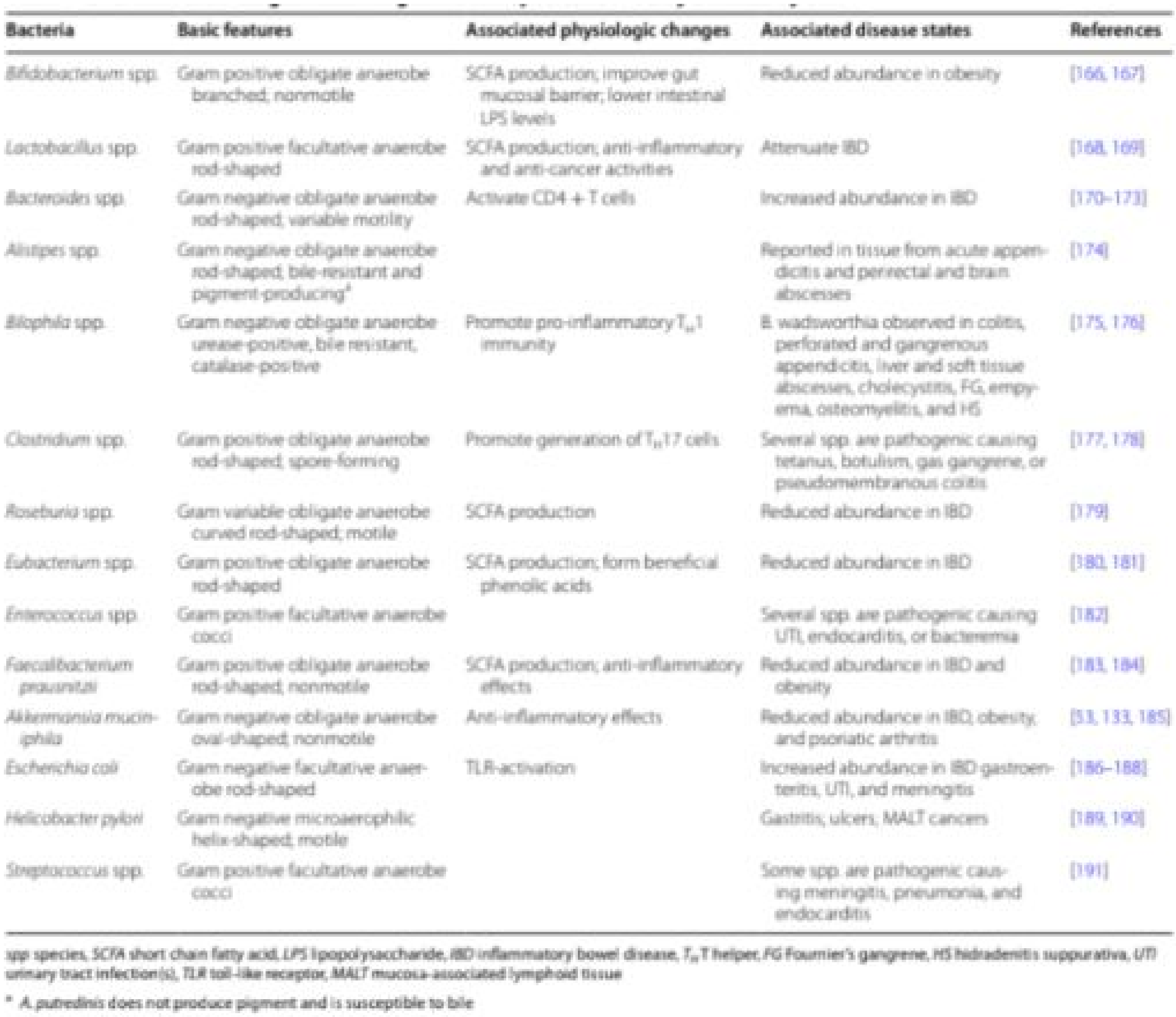
Discussion

Better understanding of the symbiotic relationship between humans and bacteria can provide more disease prevention strategies; therefore, it is important that research increase in this new fairly new field of study. Further research needs to investigate relationships such as how early antibiotic use can influence the developmental and resilience of the gut microbiota during childhood (Nicholson et al. 2012). Personalized health care can be improved by understanding the relationship between gut microbiota variations among individuals and how it affects drug metabolism and toxicity (Nicholson et al. 2012). The makeup of a person's gut microbiota can vary greatly due to lifestyle and diet; therefore, it should be high-priority to make healthy decisions in order to prevent chronic disease.

Conclusions

Recent research is demonstrating that healthy dietary changes are crucial in preventing chronic diseases and illnesses. A balanced gut microbiota is associated with an overall increased state of health. This is why it is important that healthcare providers implement more plans based on maintaining this crucial balance of bacterial species within the intestines. The strong correlation between a dysbiosis of the gut microbiota and chronic illness is another reason why the gut microbiota needs to be considered more in every aspect when attempting to prevent or treat any chronic disease. Research has been promising so far concerning the gut microbiota and curing disease. Treating a potentially fatal overgrowth of *Clostridium difficile* due to antibiotic use as well as treatment of traveller's diarrhea with gut microbiome therapeutic methods could be the beginning of many more disease treatments developed as a result of knowledge of the gut microbiota. Although the treatment of chronic diseases aspect of this research is promising, the preventative potentials through gut microbiota knowledge could contribute to healthier generations of humans to come. The composition of a person's diet has far too long been overlooked as a preventative measure of chronic disease.

Figure 1: Common gut microbiota species that are affected by diet



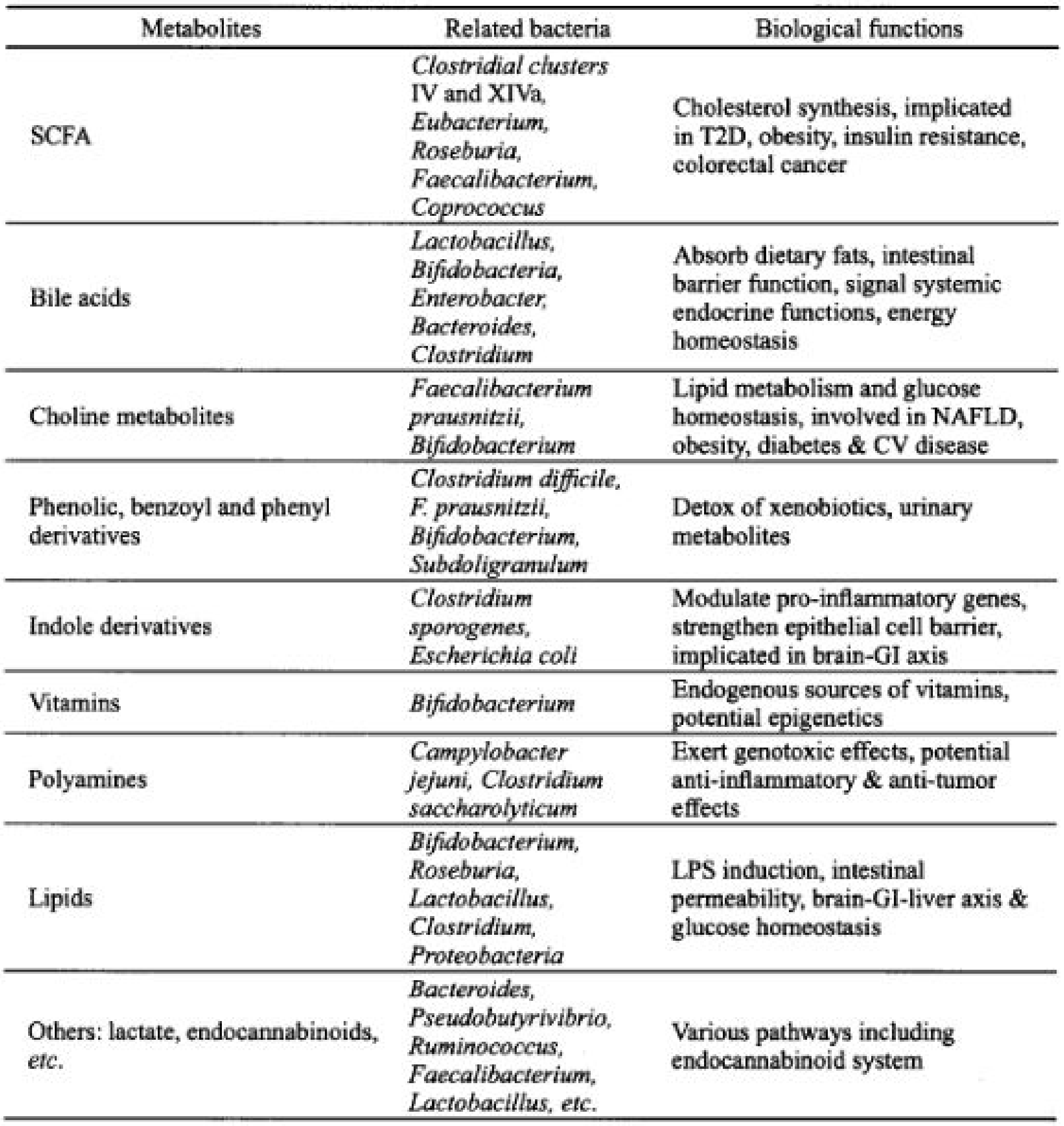
Bacteria	Basic features	Associated physiologic changes	Associated disease states	References
Bifidobacterium spp.	Gram positive obligate anaerobe branched; nonmotile	SCFA production; improve gut mucosal barrier; lower intestinal LPS levels	Reduced abundance in obesity	[166, 167]
Lactobacillus spp.	Gram positive facultative anaerobe rod-shaped	SCFA production; anti-inflammatory and anti-cancer activities	Attenuate IBD	[168, 169]
Bacteroides spp.	Gram negative obligate anaerobe rod-shaped; variable motility	Activate CD4 + T cells	Increased abundance in IBD	[170–173]
Alistipes spp.	Gram negative obligate anaerobe rod-shaped; bile-resistant and pigment-producing[a]		Reported in tissue from acute appendicitis and perirectal and brain abscesses	[174]
Bilophila spp.	Gram negative obligate anaerobe urease-positive, bile resistant, catalase-positive	Promote pro-inflammatory T_H1 immunity	B. wadsworthia observed in colitis, perforated and gangrenous appendicitis, liver and soft tissue abscesses, cholecystitis, FG, empyema, osteomyelitis, and HS	[175, 176]
Clostridium spp.	Gram positive obligate anaerobe rod-shaped; spore-forming	Promote generation of T_H17 cells	Several spp. are pathogenic causing tetanus, botulism, gas gangrene, or pseudomembranous colitis	[177, 178]
Roseburia spp.	Gram variable obligate anaerobe curved rod-shaped; motile	SCFA production	Reduced abundance in IBD	[179]
Eubacterium spp.	Gram positive obligate anaerobe rod-shaped	SCFA production; form beneficial phenolic acids	Reduced abundance in IBD	[180, 181]
Enterococcus spp.	Gram positive facultative anaerobe cocci		Several spp. are pathogenic causing UTI, endocarditis, or bacteremia	[182]
Faecalibacterium prausnitzii	Gram positive obligate anaerobe rod-shaped; nonmotile	SCFA production; anti-inflammatory effects	Reduced abundance in IBD and obesity	[183, 184]
Akkermansia muciniphila	Gram negative obligate anaerobe oval-shaped; nonmotile	Anti-inflammatory effects	Reduced abundance in IBD, obesity, and psoriatic arthritis	[53, 133, 185]
Escherichia coli	Gram negative facultative anaerobe rod-shaped	TLR-activation	Increased abundance in IBD gastroenteritis, UTI, and meningitis	[186–188]
Helicobacter pylori	Gram negative microaerophilic helix-shaped; motile		Gastritis; ulcers, MALT cancers	[189, 190]
Streptococcus spp.	Gram positive facultative anaerobe cocci		Some spp. are pathogenic causing meningitis, pneumonia, and endocarditis	[191]

spp species, *SCFA* short chain fatty acid, *LPS* lipopolysaccharide, *IBD* inflammatory bowel disease, T_H T helper, *FG* Fournier's gangrene, *HS* hidradenitis suppurativa, *UTI* urinary tract infection(s), *TLR* toll-like receptor, *MALT* mucosa-associated lymphoid tissue

[a] *A. putredinis* does not produce pigment and is susceptible to bile

This image demonstrates fourteen different bacterial species that compose the gut microbiota of the human intestines. The basic features of each bacterial species is identified along with the associated physiological changes in the body caused by the species. Associated disease research is also included within the chart. (Singh K., et al. 2017)

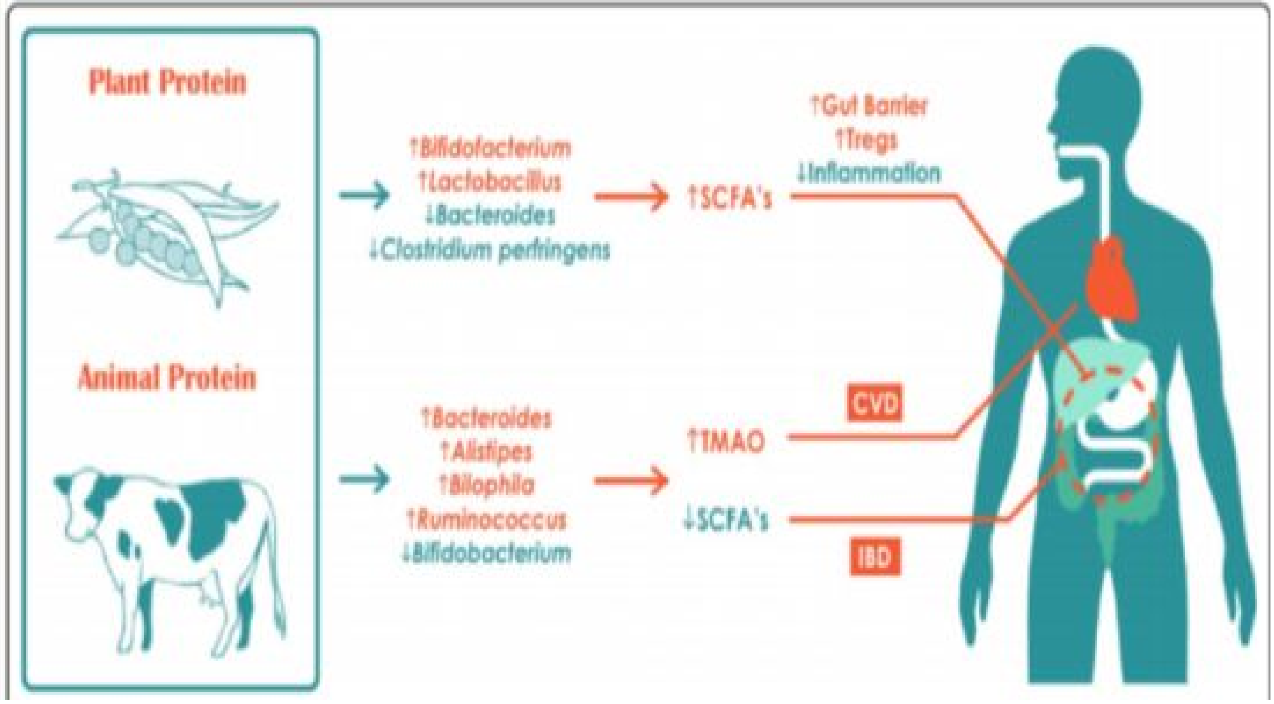
Figure 2: Metabolic functions of the gut microbiota



Metabolites	Related bacteria	Biological functions
SCFA	*Clostridial clusters* IV and XIVa, *Eubacterium, Roseburia, Faecalibacterium, Coprococcus*	Cholesterol synthesis, implicated in T2D, obesity, insulin resistance, colorectal cancer
Bile acids	*Lactobacillus, Bifidobacteria, Enterobacter, Bacteroides, Clostridium*	Absorb dietary fats, intestinal barrier function, signal systemic endocrine functions, energy homeostasis
Choline metabolites	*Faecalibacterium prausnitzii, Bifidobacterium*	Lipid metabolism and glucose homeostasis, involved in NAFLD, obesity, diabetes & CV disease
Phenolic, benzoyl and phenyl derivatives	*Clostridium difficile, F. prausnitzii, Bifidobacterium, Subdoligranulum*	Detox of xenobiotics, urinary metabolites
Indole derivatives	*Clostridium sporogenes, Escherichia coli*	Modulate pro-inflammatory genes, strengthen epithelial cell barrier, implicated in brain-GI axis
Vitamins	*Bifidobacterium*	Endogenous sources of vitamins, potential epigenetics
Polyamines	*Campylobacter jejuni, Clostridium saccharolyticum*	Exert genotoxic effects, potential anti-inflammatory & anti-tumor effects
Lipids	*Bifidobacterium, Roseburia, Lactobacillus, Clostridium, Proteobacteria*	LPS induction, intestinal permeability, brain-GI-liver axis & glucose homeostasis
Others: lactate, endocannabinoids, *etc.*	*Bacteroides, Pseudobutyrivibrio, Ruminococcus, Faecalibacterium, Lactobacillus, etc.*	Various pathways including endocannabinoid system

The gut microbiota is involved in a vast amount of metabolic processes such as the development of SCFA (short chain fatty acids). The functions for these metabolites are displayed within the figure in order to better explain the effects this metabolites have on the human body. Bacterial species that are related to these metabolic processes are also included. (Rajpal and Brown 2013)

Figure 3: Specific protein type in relation to bacterial ratio within the intestines



This diagram illustrations the different effects experienced on the gut microbiota due to specific protein consumption. As seen in the diagram, plant protein increases levels of bacterial species such as *Bifidofacterium* and *Lactobacillus*, which increases SCFA production, and this in turn reduces inflammation. Red meat consumption has demonstrated an increase in bacterial species such as *Bilophila* and *Ruminococcus,* which increase the production of TMAOs. TMAOs have shown to increase the risk of cardiovascular disease. (Singh K., et al. 2017)

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