Human Gut Microbiome and Metabolic Syndrome: A Literature Review

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Biographical Narrative

Shannon Connolly is a junior at Southern Oregon University, pursuing a Bachelor of Science degree in Biology, with an emphasis in Biomedical Science and a minor in Psychology. Shannon’s strongest research interests include studies in microbiology and neuroscience. These two fields of science feed her curiosity for understanding how the microbiome and the central nervous system work together to create health and disease in the human body. Other fields of study that intrigue Shannon are endocrinology, genetics, immunology, nutrition, and the functional medicine. Shannon intends to pursue a Ph.D. in Microbiology and Neuroscience, and is preparing for medical school as an option for further studies. Her passion is to share what she learns about how the human body heals in a format that can be understood by people from a wide variety of education backgrounds. She believes that it is a human right and responsibility to know how the body heals, and what causes illness. Shannon has strong conviction that spreading this basic knowledge will impact society by encouraging self-care and independence, rebalancing medical priority, and mending the epidemic of disease due to lifestyle choices.

Abstract

Germ theory, originally proposed in the mid-sixteenth century, caused a shift in our understanding of disease. Currently, an equally revolutionary awareness is unfolding. Scientists have learned that, to a great extent, individual lifestyle choices influence the population of microorganisms living on and within the human body. These invisible organisms, which outnumber human cells by a ratio of 10:1, influence disease and well-being of the host. This literature review examines peer-reviewed articles from 2011-2015 which explore the relationship between metabolic syndrome and human gut microbiome. Beginning with an introduction of microbes and their function in human health, the paper further explores the connection between gut environment and the symptoms of metabolic syndrome. Finally, the review investigates what researchers have learned thus far regarding manipulation of microbial societies within an individual for the purpose of regaining and maintaining health. In summary, the literature reviewed suggests that early-life exposure to beneficial microbes, reduction in some antibiotic use, prebiotics, probiotics, and fecal transplants have potential for medicinal therapies for many disorders, including metabolic syndrome.

Key Terms: Gut Microbiota, Human Microbiome, Metabolic Syndrome
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Introduction

‘Paradigm shift’ is a phrase recently and frequently used among scientists when referring to our newfound mutualistic relationship with the microbes that inhabit the human body. Expanding computational technology and DNA sequencing have made it possible to examine microorganisms that have previously eluded us, such as those residing in the human digestive tract. Recently, researchers have discovered that microbial imbalance in the human gut is linked with several diseases, including metabolic syndrome, which affects nearly 35% of all adults living within the United States (JAMA-Journal of the American Medical Association 2015). Studies have revealed that early childhood experiences, such as birthing method, nutrition, environment, and antibiotic treatment set the framework for each unique microbiota. Though the infrastructure is set within the first three years of life, lifestyle choices and other factors continually shape the composition of microbes living in and on the host. This literature review condenses peer-reviewed research and scientific periodicals from 2011-2015 with the purpose of exploring therapeutic applications of microbial manipulation through diet, environment, and transfer of microbes to reverse symptoms of metabolic syndrome.

Research Article

Microbes are organisms too small to be seen with the naked eye. They are ubiquitous and able to survive in the most severe conditions, without light, water, oxygen, and at extreme temperatures and pH levels. Bacteria, which have been evolving for 3.5 billion years (Reid and Greene 2014) and reproduce exponentially within minutes (Norris 2014), are found on and within all animals, including humans. In fact, cell for cell, humans are ninety percent microbes, 10 percent human; genetically we are less than one percent hominid (Annalisa, et al. 2014). Scientists now refer to the collection of microorganisms living on an within us as an organ that, if gathered up and put into a flask, would weigh approximately 2.5 pounds and take up about 3 pints of space (Reid and Greene 2014). Humans are now referred to as “superorganisms” (Annalisa, et al. 2014), being made up of not one but many organisms, with more than 1,000 different species included in the human microbiota (Reid and Greene 2014). Additionally, each individual has a unique and ever changing ecosystem of microbes, within which each species has different needs, functions, and bi-products (Norris 2014).

Before scientists had the ability to sequence DNA, their study of microbes was limited to about 5,000 lab culture-able species (Reid and Greene 2014). Many microbes could not be grown in the laboratory due to their environmental needs. Now, using met-omics technology, researchers estimate that there are between 100 million and 1 billion different species of bacteria. Through computational analysis we are able to study their function and other properties that were previously unknowable. Though their morphology comes in just three phenotypes – rods, spheres, and spirals - scientists have learned that genetically they are as different from each other as a human is from a nematode (Reid and Greene 2014).

Today, scientists study microbes by comparing their DNA. The 16S rRNA gene is found in all, and only, bacteria and archaea cells. It is about 1500 nucleotides long and different for each species. To study a particular bacteria, specific regions from the 16S rRNA gene are copied using polymerase chain reaction, and then sequenced and mapped.

While the term microbiota refers to the different species living on and within a host, microbiome is the term used to describe the full collection of genetic material and the microbiota that carry them. This review will focus on microbiota and genetic material of the human digestive tract, henceforth referred to as the gut microbiome.

The human gut is the entire tract, from mouth to anus, through which consumed food travels. Human intestines provide residence to one of the most compressed populations of microbes known
on earth (Annalisa, et al. 2014). Microbial diversity and quantity increases from the stomach to the colon (Sommer and Backhed 2013) to reach a final density of 1010 microbial cells per gram (Annalisa, et al. 2014). Human and animal studies rely on fecal samples, rich with microbial species, to observe the effects of environmental changes on microbiota.

We now are beginning to understand that each species of bacteria not only has a specific function, such as influencing the hosts metabolism and behavior, they also have a preferred environment, which is continuously being altered by the lifestyle choices of the host (Sommer and Backhed 2013). This information has led to the paradigm shift in our relationship to microbes, from viewing bacteria and viruses as the enemy that needs to be destroyed with antibiotics and harsh cleansers, to a crucial constituent of ourselves that, if cared for properly, will care for their host in return.

**Known Functions and Species**

Microbial species differ in their function and preferred environment. The conditions in which gut microbiota reside in are continuously being altered by life events and choices of the host. This, in turn, causes the populations of microbes to be in constant flux. The greater the diversity of microbes living on and within the host, the more stable and flexible the ecosystem. Since functions of bacteria often overlap, if one population is reduced or goes extinct, a more diverse microbiota allows for other microbes with similar activity to fill in the gap.

Beneficial human gut microbiome play a key role in a number of fundamental processes crucial to the health of their host. They aid in nutrition through synthesis of many micronutrients, including many B vitamins and vitamin K (Kau, et al. 2011); modulate metabolism enzymes and energy harvest from the diet of the host (Tsai, Cheng and Pan 2013); synthesize essential fatty acids (Velasquez-Manoff 2015); and digest polysaccharides: plant material that is otherwise indigestible by human cells (Sommer and Backhed 2013). Intestinal microbiota also influence many physiological aspects in their host such as the development of bone and other tissues (Sommer and Backhed 2013) and the stimulation and production of protective antibodies (Velasquez-Manoff 2015). They provide protection against pathogenic invaders (Sommer and Backhed 2013) and aid in the metabolism of drugs (Fukuda and Ohno 2013). Some of their metabolites, such as short chain fatty acids (SCFA's), have anti-inflammatory, anti-oxidizing effects (Annalisa, et al. 2014). Most surprisingly, gut microbes influence behavior, such as dietary choices of the host, via signals sent to the brain through the vagus nerve (Norris 2014). Further experiments have linked gut microbiome dysbiosis—an imbalance in the intestinal micro-ecosystem—to depression and anxiety (Velasquez-Manoff 2015). Though the human gut microbiome is constantly changing in response to the environment (Norris 2014), there are four common dominant phyla in the adult colon, presented in Table 1 with their basic metabolic function.

<table>
<thead>
<tr>
<th>Species</th>
<th>Known function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes - Gram Positive</td>
<td>Active carbohydrate metabolism</td>
</tr>
<tr>
<td>Bacteriodetes – Gram Negative</td>
<td>Digestion of complex carbohydrates</td>
</tr>
<tr>
<td></td>
<td>Energy production and conversion</td>
</tr>
<tr>
<td></td>
<td>Amino transport and metabolism</td>
</tr>
<tr>
<td>Actinobacteria – Gram Positive</td>
<td>Active carbohydrate metabolism</td>
</tr>
<tr>
<td></td>
<td>Sugar metabolism</td>
</tr>
<tr>
<td>Proteobacteria – Gram Negative</td>
<td>Many are opportunistic pathogens</td>
</tr>
</tbody>
</table>

**Table 1.** Four dominant gut bacterial phyla and known metabolic functions (Ottman, et al. 2012)

**Microbiota Changes through Life**

Infants receive their first exposure to microbes from their mother during birth. This inoculation, along with other early childhood factors, determines the overall phylogenetic structure of the adult microbiota (Kau, et al. 2011) and contributes to the nutritional needs of the infant (Cell Press 2015). Vaginal...
microbes of a mother ready to give birth are rich in Bifidobacteria, a lactic acid producing bacteria that, in the gut, contributes to strengthening the intestinal wall, thus preventing infection from pathogens. A lack of transfer of Bifidobacteria from mother to infant may significantly affect the health of the newborn later in life (Annalisa, et al. 2014). In a study of 98 Swedish infants, babies delivered through the birth canal had microbes similar to their mother’s vaginal colonies, while infants delivered by Cesarean-section had microbes resembling those found on skin (Cell Press 2015). Another study of 24 infants revealed that delivery by C-section was correlated with lower microbiota diversity, a lower abundance of Bacteroidetes, and a higher association with allergic diseases (Jakobsson, et al. 2014). Further research showed an increased risk of babies delivered by C-section becoming overweight later in life (Cox, et al. 2014). Researchers are currently experimenting with swabbing C-section delivered babies with their mother’s vaginal microbes to improve the first inoculation of microbiota (Wallis 2014). Additionally, it has been correlated that the weight gain of the mother during pregnancy influences her own, and thus the infant’s, gut microbiome. Women who gained excessive weight were linked to a dominance of potentially pathogenic Bacteroides, while leaner mothers carried a population dominated by beneficial Bifidobacterium (Annalisa, et al. 2014). After birth, feeding influences gut microbiota.

Breastfed infants appear to have a microbial advantage over formula fed babies. Computational analysis has revealed that breast-fed infants have a gut microbiota dominated by Bifidobacteria and Lactobacillus, -both lactic acid producing, beneficial bacteria- while formula-fed and weaned babies tend to have populations dominated by Roseburia, Clostrium, and Anaerostipes (Cell Press 2015). One study correlated that breast fed, vaginally delivered babies have less risk for obesity and diabetes than formula-fed and C-section delivered babies (Wallis 2014).

In addition to birthing method and early feeding, other factors that influence an infant’s first exposure to microbes include gestational age, infant hospitalization, and antibiotic therapies (Velasquez-Manoff 2015). Researchers have found a significant correlation between early-life antibiotic use and development of childhood obesity (Cox, et al. 2014) (Velasquez-Manoff 2015). It is suspected that antibiotics eradicate key gut bacteria that help immune cells mature, leading to long-term consequences including obesity, allergies, and autoimmune disease (Cell Press 2015). Conversely, children raised around livestock, and therefore a wide variety of microbes, have half the risk of developing symptoms of irritable bowel syndrome in their later years (Velasquez-Manoff 2015). Though early life colonization stabilizes by the age of three years (Kau, et al. 2011), lifestyle influences, such as culture, diet, stress, exercise and antibiotic use continue to shift an individual's microbiome throughout their lives. Getting older seems to negatively affect the diversity of microbiota. There are, however, extraordinary differences between individuals of later years, which are linked to the dietary habits and living environment of the host (Ottman, et al. 2012).

**Metabolic syndrome**

Researchers have discovered that microbial imbalance in the human gut is closely linked with metabolic syndrome (Sommer and Backhed 2013). Currently, metabolic syndrome effects nearly 35% of all adults in the United States, and over 46% of people over the age of 60 (JAMA-Journal of the American Medical Association 2015). Metabolic syndrome is defined as co-occurrence of three of the following five conditions:

- abdominal obesity
- elevated blood pressure
- low levels of HDL cholesterol
- high blood sugar after fasting
- high levels of triglycerides
There is a notable difference between the gut microbiome of a healthy subject and that of an individual suffering from metabolic diseases (Kau, et al. 2011). Specifically, individuals displaying symptoms of metabolic syndrome have an increase in the energy harvested from the diet; a decrease in beneficial bacteria, such as Bacteroidetes (Kau, et al. 2011); and a decrease in overall diversity of gut microbiota (Kau, et al. 2011) (Fukuda and Ohno 2013). This dysbiosis effects the function of the microbiome. The loss of beneficial gut bacteria gives rise to a compromised gut barrier, increased fat storage, reduced satiety, systemic inflammation, and an increase in pathogenic bacteria (Kau, et al. 2011). Obesity, diabetes mellitus type 2, and atherosclerosis represent a few of the many diseases related to metabolic syndrome.

**Obesity**

Obesity is typically described using the body mass index system (BMI), which is calculated by an individual’s weight in kilograms divided by their height in meters squared. A normal weight adult typically has a BMI of 18.5-24.9 kg/m², while an obese individual is classified as having a BMI of 30 kg/m² or greater (Annalisa, et al. 2014). Worldwide, humans experienced an obesity peak in 2006 when 34% of the population was classified as obese. Children have not escaped the epidemic. In 2013 it was reported by the World Health Organization that, worldwide, 42 million children under the age of five were obese. The highest rates of obesity are in the richest countries of the world, and are further divided as the poverty or disadvantaged social class of those wealthy nations (Annalisa, et al. 2014). Recently, a new syndrome has been defined: normal weight obesity (NWO). People classified in the category of NWO have fat mass greater than 30%, but display normal body weight (Annalisa, et al. 2014).

Diseases related to obesity include atherosclerosis, diabetes mellitus type 2, non-alcoholic fatty liver disease, and certain types of cancer (Parekh, et al. 2014). There is a strong genetic component, with more than 41 genes directly related to obesity (Tsai, Cheng and Pan 2013). Children of obese parents have an 80% chance of developing obesity, while children on non-obese parents have a 10% chance of excessive weight gain (Tsai, Cheng and Pan 2013). This phenotype, however, is preventable through lifestyle choices and appears to be due, in part, to environment.

Environmental factors, such as an imbalance of caloric intake and calories expended, insufficient sleep, and the use of some pharmaceutical drugs can influence the genetic expression of obesity (Tsai, Cheng and Pan 2013). Recent studies suggest that microbes may play a part, as well. Gut microbes influence obesity through increased dietary energy harvest, effects on the feeling of satiety after eating, increased fat storage, and systemic inflammation (Annalisa, et al. 2014). Translational animal studies relating obesity to gut microbes demonstrated that the microbiome of obese rodents had an increased capacity to harvest energy from the diet of the host compared to that of non-obese mice on the same diet (Ottman, et al. 2012) (Hartstra, et al. 2015). Another study using microbe-induced obese mice observed that early life is a critical time frame for long-lasting metabolic changes. Early life exposure to low-dose penicillin, which reduces the diversity of gut microbiota, was correlated to adulthood adiposity in animal models. This reduction in species effects hepatic gene expression, metabolic hormone levels, and abdominal fat accumulation (Cox, et al. 2014).

Human studies have revealed that from early-on in life, obese children display different gut microbiota than lean children, and that manipulation of the gut microbiota in childhood may prevent obesity (Fukuda and Ohno 2013). As with animal subjects, human obesity is linked with a decrease in gut microbial diversity (Sommer and Backhed 2013). Reports have confirmed that a high-fat diet alters gut microbiota in such a way that leads to a compromised gut barrier (Kau, et al. 2011). Further studies suggest that gut microbiota linked with obesity induce chronic low-grade inflammation in the host gastrointestinal tract (Fukuda and Ohno 2013).
Since gut microbiota play a substantial role in metabolism, scientists have divided people into two subgroups: those with high-efficiency bioreactors and those with low-efficiency bioreactors (Annalisa, et al. 2014). A microbiota dominance of high-efficiency bioreactors is comprised of bacteria with a greater capacity to extract energy from the host’s diet (Sommer and Backhed 2013). The high-efficiency subclass is correlated with a predisposition to obesity (Annalisa, et al. 2014) (Hartstra, et al. 2015).

**Diabetes mellitus type 2**

When the pancreas does not produce enough insulin, or when the body cannot use the insulin it produces, the chronic disease of diabetes occurs. Diabetes mellitus type 1 is characterized by a lack of insulin production and is commonly referred to as juvenile diabetes. Diabetes mellitus type 2 is the body’s ineffective use of insulin, often referred to as adult onset diabetes. The latter results from excess body weight and low physical activity (World Health Organization 2014).

Patients suffering from type 2 diabetes are identifiable by their gut microbiota. In one study, scientists were able to compose a mathematical model to analyze gut microbiota from which they were able to accurately identify which of the 145 European female subjects had diabetes-like metabolism (Fukuda and Ohno 2013). A similar study in China found predicting diabetes based on gut microbe analysis equally accurate (Fukuda and Ohno 2013).

It is apparent that dysbiosis of gut microbiota correlates with type 2 diabetes. Patients with type 2 diabetes display an increase in opportunistic pathogenic bacteria, and a decrease in beneficial bacteria (Fukuda and Ohno 2013). Specifically, researchers found subjects with type 2 diabetes had an increase of Firmicutes and a decrease in the relative abundance of Bacteroidetes (Ottman, et al. 2012). As with obesity, exposure to certain antibiotics increases the risk of diabetes (Boursi, et al. 2015).

One study conducted in Israel suggested that ingestion of antibiotics had a substantial influence on gut microbiota, leading to symptoms of diabetes (Boursi, et al. 2015). In a group of over 200,000 subjects, all with incidence of diabetes, and over 800,000 matched control subjects, it was revealed that, though a single antibiotic dose in a time-window of one year had no long term effect on an increased chance of diabetes symptoms appearing, treatments of 2-5 runs did show an escalation of symptoms, and the prevalence rose proportionally with the number of antibiotic courses taken. In another antibiotic study, Vancomycin given to obese mice reduced beneficial bacteria, leaving the immune system of the host prone to overreacting, leading to systemic inflammation and allergic reaction (Velasquez-Manoff 2015). In addition to antibiotic use, ageing appears to also have an influence on the microbiota that co-exist on an individual (Yatsumenko, et al. 2012).

**Atherosclerosis**

Arteries bring blood to the heart and other parts of the body. Atherosclerosis is the buildup of plaque in the arteries, which hinders blood flow. According to the World Health Organization, cardiovascular disease was the cause of morbidity for 17.5 million people in the year 2012, and is the leading cause of death among the non-communicable diseases (World Health Organization 2015). It, too, is a disease of metabolic syndrome that has been correlated with dysbiosis of gut microbiome. The inflammatory status of patients with cardiovascular disease is associated with characteristic changes in the gut microbiome, specifically an increase in Collinsella bacteria to which the immune system reacts. The subsequent systemic inflammation may lead to the development of hardened arteries and atherosclerosis (Fukuda and Ohno 2013).

Two molecules in particular have been linked to the promotion of atherosclerosis: choline and trimethylamine N-oxide (TMAO). In the gut, choline is converted to TMA by microbes. TMA is further converted to TMAO, which is a known to cause atherosclerosis (Fukuda and Ohno 2013). Scientists who researched the connection between the microbiota and TMAO have concluded that diet choices
of the host influence both the microbiota composition and the ability of the microbes to metabolize TMA and TMAO from L-carnitine, found in meat products (Fukuda and Ohno 2013).

**Manipulation of Gut Microbiota**

Studies suggest that gut microbiome can be intentionally altered to halt and reverse the symptoms of metabolic syndrome through diet and transfer of microbes. Human studies of short-term alterations of diet have confirmed that the microbiome of the host is strongly linked to the individual’s diet. Comparing subjects with plant-based diet – grains, legumes, fruits and vegetables, to those with an animal-based diet - meat, eggs, and cheese-, significant changes were reported from a five-day experiment. The subjects on the animal-based diet showed an increase in Bilophila wadsworthia – linked with inflammatory bowel disease (Lawrence, et al. 2014). Long-term diet studies have revealed Bacteroides dominating high protein and animal fat diets, and increased Prevotella, many of which are pathogens, linked with high carbohydrate consumption (Fukuda and Ohno 2013).

Unfortunately, North American’s typically live on a diet mainly composed of high protein, fat, and sugar products, with a low representation of plant fiber (Velasquez-Manoff 2015). One study that included people from three regions of the world, the Amazons of Venezuela, rural Malawi, and US metropolitan areas, collected 531 human fecal samples studied for bacterial content, and 110 fecal samples studied for genetic material. From the data, researchers found a significant difference in the microbial composition of fecal matter between the three countries. Most startling was the difference in diversity and composition between the US subjects and the other two locations. The Western diet population represented a gut microbiome that was much less diverse. The microorganisms that seem to thrive in the gut environment created by the Western diet contribute to a compromised gut barrier (Kau, et al. 2011). Nourishment from this diet is not adequate to meet the needs of the most significantly beneficial bacteria that reside in the colon.

**Prebiotics**

Prebiotics are plant fibers obtained from unprocessed or lightly processed plant-based food. Inulins, which are a group of polysaccharides naturally derived from plants, promote the growth of Bifidobacteria, which have been shown to reduce body weight gain, improve in glucose homeostasis, and improve obesity related inflammation in animal subjects (Fukuda and Ohno 2013). Gut bacteria that are most beneficial to humans require plant fiber for their nutrition (Velasquez-Manoff 2015). Plant fiber consists of polysaccharides and peptides which humans cannot digest (Ottman, et al. 2012). It is from this plant fiber that Short Chain Fatty Acids (SCF) are formed as a result of fermentation by gut bacteria. SCFA’s halt inflammation of the intestinal barrier and benefit the mucosal lining of the intestines through antioxidant action, as shown in Figure 1. A healthy mucosal lining prevents invasion from pathogenic bacteria. Contrarily, diets high in certain fats and sugars reduce beneficial bacteria, which leads to a compromised intestinal barrier and encourages opportunistic pathogens, leading to systemic inflammation in the host, as shown in Figure 2.
Red Wine and Dark Chocolate

No report about diet and human health would be complete without a section addressing red wine and dark chocolate. Fortunately, there are studies suggesting they are both beneficial to human microbiome, in moderate doses. One controlled study performed in Spain used ten healthy men who consumed red wine each day over a four week period. Fecal DNA samples were taken, and bacteria was quantified using polymerase chain reaction. The results showed a change in the gut microbiota over the four-week period, and physiological alterations such as lowered systolic and diastolic blood pressure, lowered triglycerides, lower overall cholesterol, and lower HDL cholesterol. The conclusion reached by the researchers was that drinking red wine can significantly influence the growth of beneficial bacteria by inhibiting the growth of non-beneficial bacteria, and potentiating the growth of probiotic bacteria (Queipo-Ortuno, et al. 2012).

Cocoa studies have revealed that the polyphenols that result from microbial fermentation of cocoa result in various biological activities, some of them with anti-inflammatory action (Khan, et al. 2014). Another dietary factor contributing to the composition of the gut microbiome is the ingestion of probiotics.

Probiotics

Probiotics are preparations which contain live, beneficial bacteria that, when ingested, have positive effects on the health of the host. Research suggests that the ingestion of live bacteria can add to the microbiota normally found in the gastrointestinal tract. Foods that are fermented with lactic acid bacteria (LAB), such as fermented vegetables, dairy, and soy, unless treated, contain those bacteria and their metabolites. LAB effect intestinal flora directly (Tsai, Cheng and Pan 2013). Probiotics appear to contribute to the health of the host by modulating immunological parameters, decreasing intestinal permeability, and producing regulatory metabolites (Tsai, Cheng and Pan 2013). It is also suggested that LAB can influence the regulation of metabolism-related hormones that improve obesity (Tsai, Cheng and Pan 2013).

<table>
<thead>
<tr>
<th>Supplemented Bacteria</th>
<th>Changes - mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactobacillus plantarum PL62</td>
<td>Decreased body weight gain and glucose concentration in obese mice</td>
</tr>
<tr>
<td>Lactobacillus rhamnosus PL60</td>
<td>Reduce body weight gain and mass of white adipose tissue in mice fed high-fat diet</td>
</tr>
<tr>
<td>Lactobacillus paracasei F19</td>
<td>Decreased total body fat and reduced amount of triglycerides in mice fed high-fat diet</td>
</tr>
<tr>
<td>Lactobacillus reuteri ATCC4659</td>
<td>Reduction of body weight gain, adipose, and liver weights</td>
</tr>
<tr>
<td>L. acidophilus NCDC13</td>
<td>Increased Bifidobacteria in feces; did not reduce adiposity</td>
</tr>
<tr>
<td>Lactobacillus ingluviei</td>
<td>Increased body weight gain, liver weight, and metabolism</td>
</tr>
</tbody>
</table>

Table 2. Supplemented probiotics and their effects in mice (Fukuda and Ohno 2013).

Research is currently being conducted on both animal and human subjects in regarding the benefits of probiotics and the numbers of bacteria necessary to influence the host.

Laboratory animal studies have found probiotics decrease body weight gain and glucose concentrations (Fukuda and Ohno 2013). Table 2 displays the observations of researchers experimenting with exposure of probiotics to laboratory mice.

Human studies have shown that probiotics encourage the health of the host, as well. Probiotic dietary intervention may be beneficial to the host by improving the gut environment, modulating immune functions, preventing pathogens from infecting the host, and regulating fat storage (Fukuda and Ohno 2013). Table 3 display the probiotic influence in human research.
There have been conflicting reports regarding fermented milk products. One study found no observable changes in gut microbiome upon the ingestion of fermented dairy products, but there were other significant changes in metabolic-carbohydrate-pathways (Ottman, et al. 2012). Another study, which also reported little change in microbial communities, showed reductions in the stress response in animals after consuming dairy-based probiotics (Mayer, et al. 2014). In addition to dietary changes, gut microbiota can be influenced by a more direct method in especially challenging circumstances: fecal transplants.

### Fecal Transplants

Physicians have had remarkable success treating patients with difficult to manage infections and disease with fecal microbiota transplantation therapy. Fecal transplants can be considered a type of probiotic therapy, since they add beneficial bacteria to the host. This is not a novel idea. In fact, Ge Hong, a Chinese physician from the 4th century, prescribed Yellow Soup as a remedy for diarrhea. Yellow Soup was a broth made from dried or fermented feces collected from a healthy individual. The infected patient ingested the liquid, and the inoculation of bacteria brought the ailing subject back to health. Modern methods have expanded the potential of this ancient therapy to broader ailments and refined prescription.

Researchers have found that when gut microbes are transplanted from an obese human into germ-free mice, the rodents gain weight. The weight gain is reversible by the transplant of gut microbes from a healthy weight donor (Ley 2015). This suggests that the gut microbiome of obese individuals is contributing to their obesity, and that altering the gut flora may reverse weight gain and disease related to obesity. Additionally, diabetic subjects who received fecal transplants from healthy donors showed an increase in insulin sensitivity and increased butyrate-producing microbiota, suggesting that fecal transplant from healthy donors may be developed as a therapy for diabetes (Parekh, et al. 2014).

This unconventional method of manipulating microbiota holds great promise for aiding healing in the most difficult cases that otherwise may be untreatable. Physicians of human subjects showed a 90% of success extinguishing infections of Clostridium difficile by the transfer of healthy microbiota to the infected patient via fecal transplants (Proctor 2013). Chemotherapy and radiation patients have shown a reduced recovery time upon receiving inoculum of their own gut microbiota, that was cultured and stored prior to the patient receiving the cancer treatments (Proctor 2013).

### The Future

Continued research is necessary for a full understanding of the microbiome on human health. Still, there is excitement among scientists regarding the shift in perspective that is taking place. Neurobiologists are studying the effect of gut microbiome on the brain and have found links to both depression and anxiety (Mayer, et al. 2014). The immune and endocrine systems continue to be explored as new studies reveal links to most non-communicable, lifestyle diseases. Though variations in individual gut microbiome may require personalized treatment of patients (Schloissnig, et al. 2013), understanding variation in gut microbial populations may lead to medical therapies that encourage

<table>
<thead>
<tr>
<th>Supplemented Bacteria</th>
<th>Changes - humans (healthy-overweight)</th>
</tr>
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<tbody>
<tr>
<td>Lactobacillus gasseri SBT2055</td>
<td>Reduction of abdominal visceral and subcutaneous fat</td>
</tr>
<tr>
<td>L. rhamnosus GG (in infant formula – 6 months)</td>
<td>Better growth and higher weight gain; prevented excessive weight gain in the children</td>
</tr>
</tbody>
</table>

Table 3. Supplemented probiotics and their effects in humans (Fukuda and Ohno 2013).
health and heal disease (Schloissnig, et al. 2013). Knowledge of the interrelationship between gut microbiome, the immune system, and metabolism opens the possibilities for novel approaches to the treatment of metabolic syndrome (Chen, He and Huang 2014).

**Conclusion**

Scientists are still wrestling with the question of causality, searching for answers as to whether metabolic disease is causing, contributing, or a consequence of altered microbiota (Sommer and Backhed 2013). This review concludes that manipulation of gut microbiota, by way of early-life exposure to beneficial microbes, reduction in antibiotic use, ingestion of prebiotics and probiotics, and fecal transplants, has potential for medicinal therapies for metabolic syndrome and many other non-communicable diseases.


