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Tailoring the Gut Microbiome Through Diet to Target Short Chain Fatty Acids and Trimethylamine N-Oxide for Heart Failure Prevention

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Abstract

The number of people diagnosed with heart failure is on the rise—it's becoming an epidemic. There are treatment options available for heart failure, but unfortunately there is not a cure. However, most cases of heart failure can be prevented. One mechanism that provides promise for preventing heart failure is the implementation of a heart healthy diet. However, not in the context that most are familiar with. In this case, a heart healthy diet is in reference to the ability of diet to tailor the gut microbiome in order to target specific metabolites that are associated with heart failure. Diet plays a huge role in the compositional makeup of the gut microbiome and affects the metabolites produced by the gut microbiome. Heart failure is associated with a decrease in short chain fatty acids and an increase in trimethylamine N-oxide. The gut microbiome of someone with heart failure is in a state of dysbiosis. Diet can be used to manipulate the gut microbiome back to a state of symbiosis and help counter the imbalances found in patients with heart failure. A diet high in plant-based foods can increase the bacteria responsible for producing short chain fatty acids. A diet low in animal products can decrease the bacteria involved in the production of trimethylamine N-oxide. Following a diet that combines the two can potentially alter the gut microbiome and induce favorable changes to prevent the development or progression of heart failure.

Introduction

Advances in medicine have resulted in an aging population. With an older population, however, comes problems of its own. One such problem is the rising prevalence of heart failure (HF). Unfortunately, HF is a progressive disease that currently has no cure, even with the extensive advances in medicine. Fortunately, most cases can be prevented (Ponikowski et al., 2014).

Individuals are encouraged to lead healthy lives to avoid the development of HF. Following a healthy lifestyle involves getting plenty of exercise, avoiding the use of tobacco products, getting the recommended amount of sleep, addressing any health concerns, and eating healthy (Arnett et al., 2019). A heart healthy diet is recommended for those at risk of developing HF. This entails lowering salt intake, avoiding trans fats, increasing whole grain consumption, and reducing red meat consumption (Cavusoglu et al., 2015).

The health benefits of following a heart healthy diet have been well studied, but there is one aspect that has been overlooked—how a heart healthy diet affects the gut microbiome (GM). The GM has become a topic of interest because of recent evidence that suggests its role in health. The variation of the species present in the GM depends on many factors, including genetics,

medications, environment, and most notably—diet (Peng et al., 2018).

Given that diet is emphasized as a preventable measure against HF, the interaction between diet, the GM, and HF needs to be properly understood. It is known that the GM produces important metabolites depending on the diet of the host. Two of the most notable metabolites of the GM are short chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO) (Peng et al., 2018). It is also known that these metabolites play a role in health and have been linked to either improving cardiovascular function—SCFAs—or reducing cardiovascular function—TMAO (Chakaroun et al., 2022). It is also known that patients with HF have a GM that is in a state of dysbiosis with some significant changes compared to heart healthy individuals (Kamo et al., 2017).

However, the interaction between the three of these topics has not been thoroughly studied—specifically, the ability of using diet to induce favorable changes in the GM by up or down regulating the metabolites associated with HF. Therefore, this review will address the question of whether diet can be used to manipulate the GM—both in composition and in metabolite production—and induce favorable changes to potentially reduce the risk of HF.

Heart Failure

A healthy functioning heart can supply enough blood to keep up with the demands of the body. When the heart fails to do this, heart failure (HF) is diagnosed (Mudd & Kass, 2018). There are four stages of HF that have various effects on the individual. The stages are as follows: Stage A (at risk for HF), Stage B (pre-HF), Stage C (symptomatic HF), and Stage D (advanced HF) (Maio et al., 2022). In Stages A and B, there are no signs or symptoms of HF, but there are indications that HF could develop or has begun to progress.

The diagnosis of HF is an umbrella diagnosis because it is used to describe the above condition which can be due to any number of underlying reasons. There are many conditions that contribute to HF such as diabetes, hypertension, left ventricular hypertrophy, and coronary artery disease (American Heart Association). Obesity is also a contributing factor to HF as it increases the risk of the above conditions and puts strain on the heart (Massie et al., 2002). Obesity continues to rise, especially in the United States, with over 30% of the adult population classified as obese (Flegal et al., 2010). Thus, HF is expected to continue affecting numerous individuals.

The number of people living with HF is rising and is slowly becoming a global epidemic. Between 2013 and 2016, there was an estimated 6.2 million Americans (age ≥20) diagnosed with HF compared to 5.7 million between 2009 and 2012 (Virani et al., 2020). Unfortunately, the outlook and survival rate of HF is poor. An estimated 17-45% of patients emitted to the hospital with HF die within one year of admittance and the majority die within five years of admittance (Ponikowski et al., 2014). HF causes stress not only for those suffering, but also on caretakers and the health care system. Strains on the health care system from HF are expected to increase with more of the population reaching older ages and the rising prevalence of HF (Ponikowski et al., 2014).

HF is a progressive disease that has high mortality and morbidity, so it is of the utmost importance that individuals at risk of developing HF or in the process of progressive HF are attended to early on to slow or even stop the progression of the disease. One way that HF can be diagnosed and monitored is with a lab test that measures B-type natriuretic peptide (BNP) (Cleveland Clinic, 2022). BNP is a hormone that becomes elevated when the heart is not functioning properly. Elevated levels are associated

with the stages of HF and can aid in the diagnosis of HF. A study by Ammar et al. (2007) sought to classify the prevalence of HF stages and track BNP levels across the four stages. It was found that 56% of participants were categorized as being in Stage A and B and had mean BNP levels of 32 pg/mL and 53 pg/mL, respectively (Ammar et al., 2007). The participants in this study were all aged 45 or above and only 32% of them could not be classified as being in any of the four stages of HF, thus showing just how prevalent HF is. The fact that the majority (56%) of individuals could be classified in the first two stages means that early treatment and prevention is highly beneficial to most individuals with HF.

Since HF is a progressive disorder that is often irreversible, prevention is key. The general guidelines for maintaining health are applicable to those diagnosed with HF. Reducing salt intake, monitoring weight, and getting regular exercise are all usually recommended for those with HF who are physically able. However, it should be noted that there is mixed evidence as to whether these guidelines are effective in helping those suffering from HF (Cavusoglu et al., 2015). Since diabetes, hypertension, and obesity are contributing factors to developing HF, these conditions should be treated and monitored to help reduce the development and progression of HF. Often it is necessary to use more definitive treatment methods to help slow down the progression of HF, reduce hospitalizations, and improve quality of life.

Currently, most treatments for HF involve medications in addition to the lifestyle modifications mentioned. Usually life-long therapy with medication is needed and treatment typically involves adding multiple medications as the disease progresses. The most common types of medication used in patients with HF include beta-blockers (BB), spironolactone, angiotensin-converting enzyme inhibitors (ACEIs), hydralazine with long-acting nitrates, and angiotensin receptor blockers (ARBs) (Niriayo et al., 2018).

In addition to medication, there are also surgical interventions and devices that can be used to mitigate the problems associated with HF. One mechanism is the use of implantable pacemakers to help achieve cardiac resynchronization. The implantable cardioverter defibrillator (ICD) and the left ventricular assist device (LVAD) are other potential device options. Electrical stimulation can also be used to alter heart function without initiating a contraction. This treatment is known as non-excitatory cardiac contractility modulation and shows promise for helping patients with HF (Mudd & Kass, 2008).

While there are multitudes of medication options and surgical interventions that can be utilized for those suffering from HF, the symptoms can often be relieved in most patients, but modern treatments for HF do not prolong life for about 50% of patients (Ponikowski et al., 2014). Furthermore, since HF is an umbrella diagnosis, not all patients suffering from HF have the same underlying conditions. Approximately half of patients suffering from the disease have a type of HF known as HFPEF (heart failure with preserved ejection fraction) and do not respond to current available treatments. HFPEF death rates have been constant and unchanging over the years. Treatments for patients that have a rapid worsening of symptoms, like in acute HF, often only provide relief from symptoms, which leaves these patients still struggling with the underlying causes of their HF, thus usually leading to a high death risk post-hospitalization (Ponikowski et al., 2014). Even surgical interventions are not as effective as they should be. About 30% of patients that receive implantable pacemakers (which allows for cardiac resynchronization) do not respond clinically the way they should. Predicting which patients who will require surgical interventions, like ICD, is

often difficult as well, which makes treatment that much harder (Mudd & Kass, 2008).

Given that treatment options cannot cure HF and are not always effective, finding mechanisms to prevent HF is imperative. As mentioned earlier, preventative measures for HF involve lifestyle modifications—most notably, diet modification. Those at risk for HF or diagnosed with HF are often asked to follow a heart healthy diet. This diet usually entails reducing salt intake, increasing whole grain consumption, avoiding trans-fat, reducing the consumption of processed foods, and overall reducing portion sizes (Arnett et al., 2019). There has been evidence that following a plant-based diet can be very beneficial to heart health and reduce the risk of various cardiovascular diseases (CVDs)—diseases which often lead to the development of HF. One explanation for the benefit of following a plant-based diet to reduce the risk of developing HF is the link between the gut microbiome (GM) and heart health. The GM produces metabolites that play an important role in the onset and development of CVDs (Peng et al., 2018) and diet affects the production of these GM metabolites.

Gut Microbiome

The gut microbiome (GM) is a topic that has gained a lot of traction in the past few years. The GM is composed of about 40 trillion bacterial cells that are dominated by five main bacterial phyla: Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Verrucomicrobia (Chakaroun et al., 2022). Of the five phyla found in the GM, 90% of the bacterial species come from the Firmicutes, Bacteroidetes, and Proteobacteria (Attri et al., 2022, p. 2).

It is known that the GM plays a crucial role in maintaining health by preventing infectious diseases (Attri et al., 2022, p. 10). However, recently it has been discovered that the GM plays a more significant role in health than previously thought. In fact, the GM is coined "the second brain" because of its involvement in a multitude of metabolic activities and enteric nervous system which communicates with the brain via the vagus nerve (Attri et al., 2022, p. 3). The GM affects the metabolism, nutrition absorption, physiology, and immune function of the host.

The most abundant phylum in the gut is the Firmicutes (Chakaroun et al., 2022). This phylum is composed of both helpful bacterial groups—like Clostridia—and known pathogen bacterial groups—like Bacilli. The Clostridia class is home to many bacteria that are butyrate producers including *Faecalibacterium* and *Roseburia*. Having high proportions of butyrate-producing bacteria is heart healthy (Chakaroun et al., 2022). The Bacilli class is home to a variety of bacteria, some of which are associated with pathogenic organisms—like *Streptococcus*. While having plenty of butyrate producing bacterial species is beneficial, an overpopulation of Firmicutes is linked to health issues.

Bacteroidetes are the primary degraders of carbohydrates. They breakdown polysaccharides that humans cannot digest and produce acids—like acetic acid, propionic acid, and succinic acid—which are then used as an energy source and help kill pathogens. This phylum also includes species that have anti-inflammatory effects and are involved in postbiotic activities that promote health (Nkosi et al., 2022). Bacteroidetes species also support the production of vitamin B's and colonization resistance (Chakaroun et al., 2022). In general, having a high percentage of Bacteroidetes is considered beneficial to health.

The Proteobacteria phylum (currently the largest bacterial phylum) is home to many opportunistic pathogens (Chakaroun et al., 2022). This phylum has been linked to gut inflammation (Rizzatti et al., 2017). One important group within this phylum is the Enterobacteriaceae family, which is linked to endocarditis and

intravascular infections (Bennett et al., 2015). When there is a decrease in butyrate producing bacteria, there is an increase in the production of nitrate which allows Enterobacteriaceae to thrive. Having an increased number of Proteobacteria species is linked to numerous health conditions—like obesity, inflammatory bowel disease, lung disease, and atherosclerosis—and dysbiosis (Rizzatti et al., 2017).

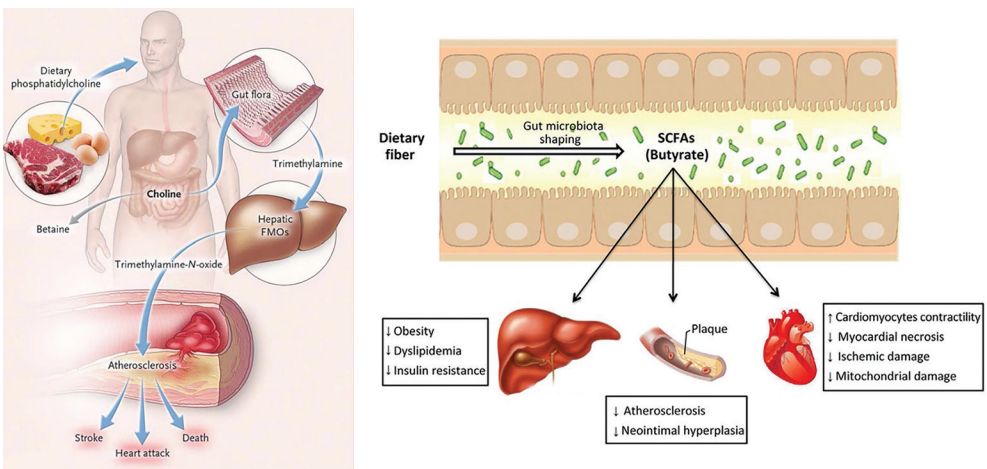
Metabolites of the Gut Microbiome

The dietary macronutrients present in food are used by the GM to produce metabolites. The two main metabolites of the GM are short chain fatty acids (SCFAs) and trimethylamine N-oxide (TMAO) (Peng et al., 2018). SCFAs are produced when the GM metabolizes dietary fiber. Dietary fiber is found in plant-based foods such as fruits, vegetables, whole grains, legumes, nuts, and seeds (Mayo Clinic). The main SCFAs are carboxylic acids such as butyrate, propionate, and acetate (Peng et al., 2018). These end products enter circulation and have been shown to be beneficial to heart health by lowering blood pressure and cholesterol (Chakaroun et al., 2022). SCFAs—like butyrate—have been shown to have a protective effect by reducing inflammation that is linked to cardiac injury (Yukino-Iwashita et al., 2022) (Figure 1).

When high levels of choline, carnitine, and phosphatidylcholine are consumed and present in the gut, they become metabolized by specific gut microorganism into the precursor molecule trimethylamine (TMA). TMA is then absorbed and enters circulation where it is converted to TMAO in the liver. High TMAO levels can contribute to the development of atherosclerosis—the buildup of plaque that leads to the narrowing of arteries (Peng et al., 2018) (Figure 1).
High levels of TMAO have been correlated with increased risk for various CVDs, such as coronary artery disease, myocardial infarction, hypertension, atrial fibrillation, myocardial fibrosis, and HF (Peng et al., 2018). TMAO levels are used as a prognostic value for cardiovascular outcomes. The precursors to TMAO—choline, carnitine, and phosphatidylcholine—come mainly from animal products such as red meat, fish, and eggs (Kałużna-Czaplińska & Gątarek, 2021).

Figure 1

Left: Schematic Showing Negative Effects of TMAO (Tang et al. 2013)
Right: Schematic Showing the Positive Effects of SCFAs (Paparo et al. 2017)



Note. TMAO contributes to the buildup of plaque (left) while SCFAs offer a protective effect (right).

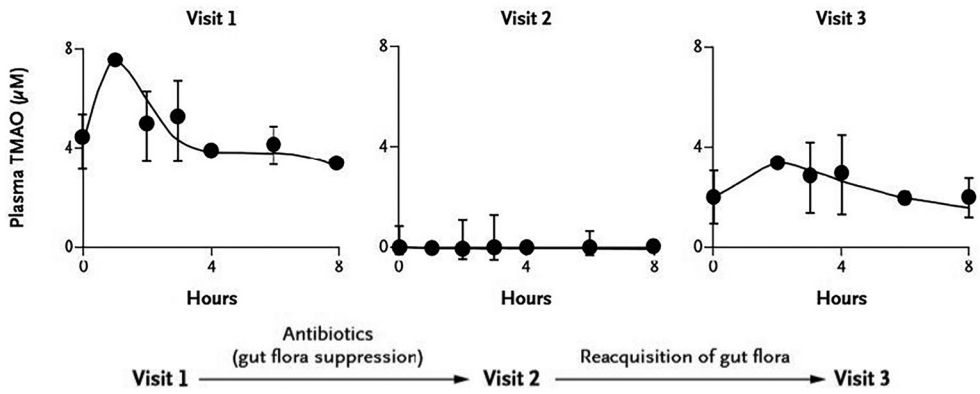
Production of TMAO from phosphatidylcholine is dependent on bacteria in the GM. Tang et al. (2013) demonstrated this dependence by giving healthy participants phosphatidylcholine (in the form of two hard boiled eggs) and measuring the plasma TMAO levels after consumption. After this initial visit, the participants were asked to take a broad spectrum antibiotic for a week to suppress the GM. Participants then consumed more phosphatidylcholine and when TMAO levels were measured, there was a significant decrease in plasma TMAO levels (Figure 2, Visit 2). A month after stopping the antibiotics, the participants repeated the study one last time and a time-dependent return of TMAO production was seen (Figure 2, Visit 3). Thus, without the bacterial species in the GM, production of TMAO from phosphatidylcholine does not occur (Tang et al., 2013).

Association Between Short Chain Fatty Acids and Heart Failure

The production of SCFAs have been shown to be beneficial to heart health (Chakaroun et al., 2022), and maintaining a healthy SCFA-producing microbiome is essential to mitigating cardiovascular problems. It should be no surprise then, that patients who are experiencing heart related issues (like hypertension—a precursor to HF) have reduced levels of SCFAs in their blood plasma (Calderon-Perez et al., 2020). Notably, butyrate levels are greatly reduced in patients that have hypertension compared to patients that are normotensive (Figure 3). Thus, diminished SCFA levels are one mechanism that can be used to identify patients at risk for developing cardiovascular diseases—like HF.

Figure 2.

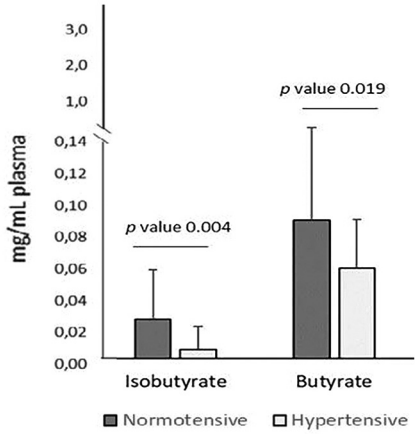
Production of TMAO from Phosphatidylcholine Depends on the GM



Note. Plasma TMAO levels after consuming phosphatidylcholine (Visit 1). Plasma TMAO levels after consuming phosphatidylcholine after taking a broad-spectrum antibiotic for a week (Visit 2). Plasma TMAO levels after consuming phosphatidylcholine one month after stopping broad-spectrum antibiotic use (Visit 3) (Modified from Tang et al. 2013).

Figure 3

Plasma Levels of Isobutyrate and Butyrate in Normotensive Patients and Hypertensive Patients. (Modified from Calderon-Perez et al. 2020)



Note. SCFAs—like butyrate—are reduced in hypertensive patients.

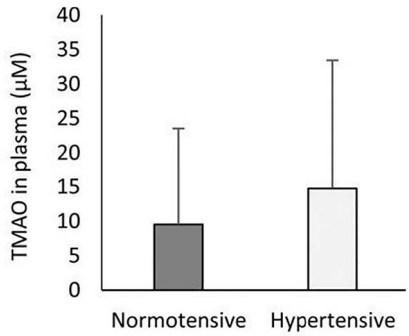
Association between Trimethylamine N-Oxide and Heart Failure

High levels of TMAO are linked to HF (Tang et al., 2013). The production of TMAO is connected to atherosclerotic burden (Chakaroun et al., 2022). Atherosclerosis is one of the precursors to the development of HF. It has been demonstrated that a microbial transplant from mice containing high TMAO producing bacterial strains to mice with a normal bacterial makeup resulted in the normal mice having an increase in atherosclerotic burden (Gregory et al., 2015). In addition, high TMAO levels have been associated with impaired systolic and diastolic function and associated with increased inflammation. TMAO levels are a better predictor of morbidity and death than Body Mass Index (BMI), type II diabetes, kidney function, and history of cardiovascular diseases (CVDs) (Chakaroun et al., 2022).

In addition to atherosclerosis, increased TMAO levels have been linked to diabetes, myocardial infraction, and hypertension (Zhang et al., 2021)—all precursors to developing HF. It has been shown that TMAO levels in blood plasma are elevated in patients with hypertension compared to normotensive patients (Figure 4). Thus, having high levels of TMAO is an indication of being at risk for developing HF or in the beginning stages of progressive HF (Calderon-Perez et al., 2020).

Figure 4

Plasma Levels of Isobutyrate and Butyrate in Normotensive Patients and Hypertensive Patients. (Modified from Calderon-Perez et al. 2020)



Note. TMAO levels are elevated in hypertensive patients.

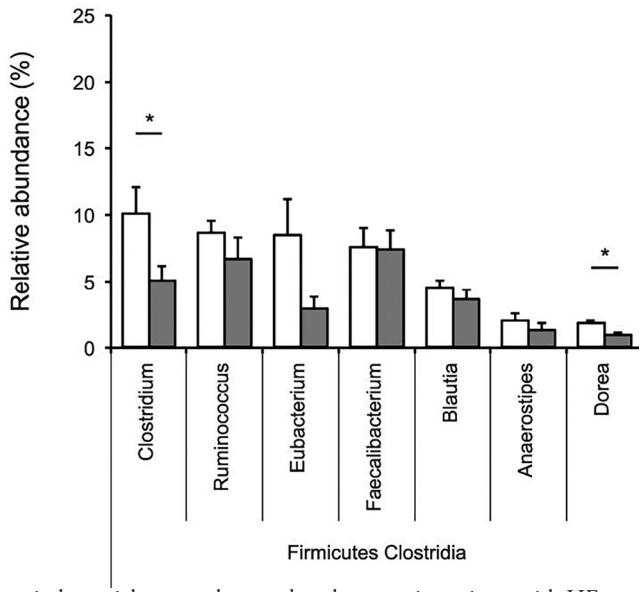
Compositional Alterations in Gut Microbiome in Patients with Heart Failure

Those suffering from HF often have a GM in a state of dysbiosis. There is an overall decrease in bacterial richness and a change in bacterial composition compared to healthy individuals. The species present in the GM of healthy individuals and individuals with HF can be classified by taking fecal samples and using 16S ribosomal RNA gene sequencing. This was done by Kamo et al. (2017) to compare the GM in healthy individuals, young HF patients (aged <60 years old), and older HF patients (aged >60 years old). It was discovered that there was an overall decrease in Firmicutes that produce butyrate (Clostridia) in young patients with HF compared to healthy individuals (Figure 5). There was an overall increase in Firmicutes associated with pathogens (Bacilli) in young patients with HF compared to healthy individuals (Figure 6). A general decrease in Bacteroidetes was also seen in young patients with HF compared to healthy individuals (Figure 7). Thus, meaning that there is an overall increase in the Firmicutes/Bacteroidetes ratio in those with HF (Kamo et al., 2017).

Individuals suffering with HF also have increased Proteobacteria in their GM compared with healthy individuals (Zhao et al., 2022; Chakaroun et al., 2022). Kamo et al. (2017) did not find a significant difference between the relative abundance of Proteobacteria in healthy individuals compared to young heart failure patients (aged <60 years old) (Figure 8). However, they did find an increase in Proteobacteria in older heart failure patients (aged >60 years old) compared to the younger patients with heart failure (Figure 8). This could be suggestive that an increased abundance of Proteobacteria leads to worsening HF (as older patients often have more progressed cases of HF). However, it could also be that the older HF patients have an increased Proteobacteria population due to age-related comorbidities or prolonged medication use (Kamo et al., 2017). Nevertheless, increased abundance of Proteobacteria is seen in patients with HF.

Figure 5

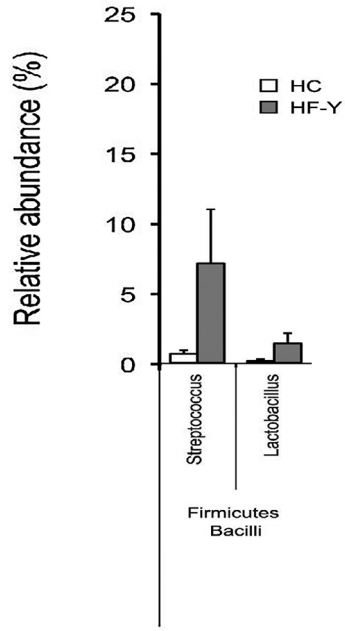
The Relative Abundance of Bacterial Genera in Healthy Individuals (White) and Young Heart Failure Patients (Aged <60 Years Old) (Grey) (Modified from Kamo et al., 2017)



Note. Overall decrease in bacterial genera that produce butyrate in patients with HF.

Figure 6

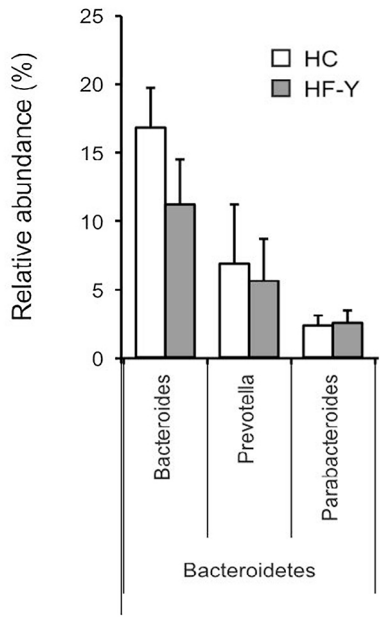
The Relative Abundance of Bacterial Genera in Healthy Individuals (White) and Young Heart Failure Patients (Aged <60 Years Old) (Grey) (Modified from Kamo et al., 2017)



Note. Overall increase in bacterial genera associated with pathogens in patients with HF.

Figure 7

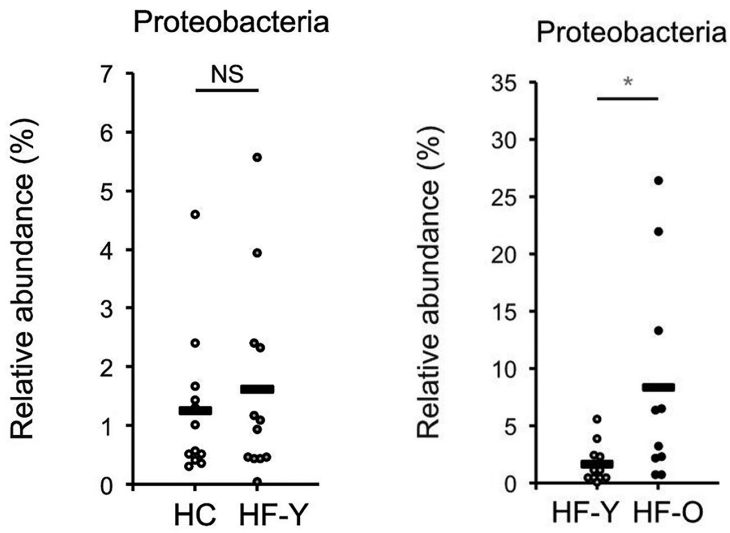
The Relative Abundance of Bacterial Genera in Healthy Individuals (White) and Young Heart Failure Patients (Aged <60 Years Old) (Grey) (Modified from Kamo et al., 2017)



Note. Overall decrease in bacterial genera that produce SCFAs in patients with HF.

Figure 8

Left: The Relative Abundance of Bacterial Genera in Healthy Individuals (HC) and Young Heart Failure Patients (Aged <60 Years Old) (HF-Y)
Right: The Relative Abundance of Bacterial Genera in Young Heart Failure Patients (Aged <60 Years Old) (HF-Y) and Older Heart Failure Patients (Aged >60 Years Old) (HF-O) (Modified from Kamo et al., 2017)



Note. Slight increase (not significant) in Proteobacteria in patients with HF compared to healthy control (left) and significant increase in Proteobacteria in older patients with HF compared to young patients with HF (right).

Diet

Diet plays a significant role not only in the overall health of an individual, but also in the overall health of the individual's GM. Diet supplies the GM with precursors that are needed to produce SCFAs and TMAO. The precursors to SCFAs are found in plant-based foods that are high in dietary fiber—such as fruits, vegetables, whole grains, legumes, nuts, and seeds (Mayo Clinic). The precursors to TMAO—choline, carnitine, and phosphatidylcholine—are found mainly in animal-based foods, like red meat, seafood, dairy, and eggs. If these precursors needed to produce SCFAs and TMAO are manipulated through diet modification, then the GM can be tailored because a lack of precursors would result in reduced food available for the bacteria that produce SCFAs and TMAO. Thus, diet can be used to potentially induce favorable changes in the GM that can reduce the risk of HF. Given this, the following hypothesis was suggested: following a diet high in plant-based foods will increase the bacteria responsible for producing SCFA—Clostridia and Bacteroidetes—and low in animal-based foods will decrease the bacteria responsible for producing TMAO—Firmicutes and Proteobacteria—and thus, can be used to reduce the risk of developing HF.

Dietary Fiber Supplementation

Li et al. (2017) demonstrated that supplementing a diet of red meat with dietary fiber in mice can induce changes to the GM. C57BL/6 mice (a common genetically equivalent mouse model) were fed various diets supplemented with dietary fiber in the form of natural wheat bran. The control (C) was fed a standard mouse diet, the positive control was fed only a diet of red meat

(RM), and the experimental groups were fed red meat and a form of supplementary dietary fiber. One of the experimental groups was fed a diet of high dose natural wheat bran (HN) and another was fed a diet of high dose steamed wheat bran (HE). Steaming the wheat bran processes the dietary fiber more, which makes it easier for the GM to metabolize (Koc et al., 2022).

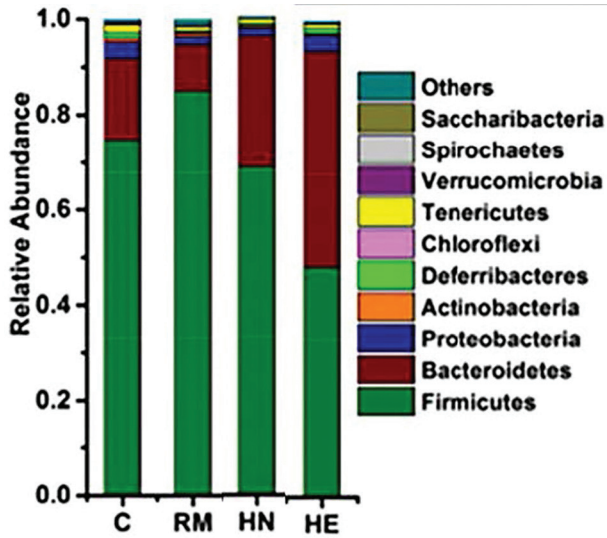
After being fed this diet for four consecutive weeks, the mice were euthanized, and an abdominal dissection was performed. The contents of the cecum were extracted and analyzed for bacterial DNA by using 16S rRNA sequencing. The levels of SCFAs and TMA/TMAO were also analyzed in each dietary group.

The red meat group had an increased abundance of Firmicutes compared to the control group (Figure 9). The red meat group also had a significant increase in TMA/TMAO compared to the control group. Both changes were expected given what is currently known about relationship between red meat, TMAO, and Firmicutes. Li et al. (2017) demonstrated that there was a positive correlation between the abundance of Staphylococcus (Firmicutes) in the red meat group and a negative correlation in both the HN and HE groups, which demonstrates that Staphylococcus is associated with the production of TMAO. Introducing dietary fiber into a diet of red meat can reduce the production of TMAO by reducing bacteria associated with TMAO production, like Staphylococcus (Li et al., 2017).

Both wheat bran groups (HN and HE) saw a drastic decrease in Firmicutes and an increase in Bacteroidetes compared to both the red meat group and control group (Figure 9). There was a more significant decrease in Firmicutes and increase in Bacteroidetes in the steamed wheat bran group (HE) compared to the natural wheat bran (HN). Both groups also had an increased SCFA production compared to the red meat group; specifically, there were increased levels of acetate, butyrate, and isobutyrate in the intestinal digesta. The supplementation of dietary fiber increases the bacteria responsible for the production of SCFAs, and thus increases the production of SCFAs, which is beneficial to heart health (Li et al., 2017).

Figure 9

Control Diet (C), Red Meat Diet (RM), Red Meat Supplemented with Natural Wheat Bran (HN), and Red Meat Supplemented with Steamed Wheat Bran (HE) (Modified from Li et al., 2017)



Note. Relative abundance of bacterial phyla after a four-week diet.

Bacterial Differences Between Omnivores and Vegetarians

A study by Matijašić et al. (2013) classified the GM of 31 vegetarians (20 of whom were vegan) and 29 omnivores. To be included in the study, the participants had to have been following their respective diets for at least a year and could not have had any antibiotic or chemotherapy use within a month of the stool sample collection. The fecal matter was analyzed using 16S rRNA sequencing to determine the microbial makeup of the participants. It was found that the microbial community of vegetarians did differ from that of omnivores. There was an increased abundance in Bacteroidetes and Clostridium (SCFA producing bacteria) and a decrease in Streptococcus (typical pathogenic bacteria) when comparing vegetarians to omnivores (Figure 10). While SCFA and TMAO levels were not studied, it is likely that because the bacterial species associated with their production were modified, that the GM metabolite levels would also be modified.

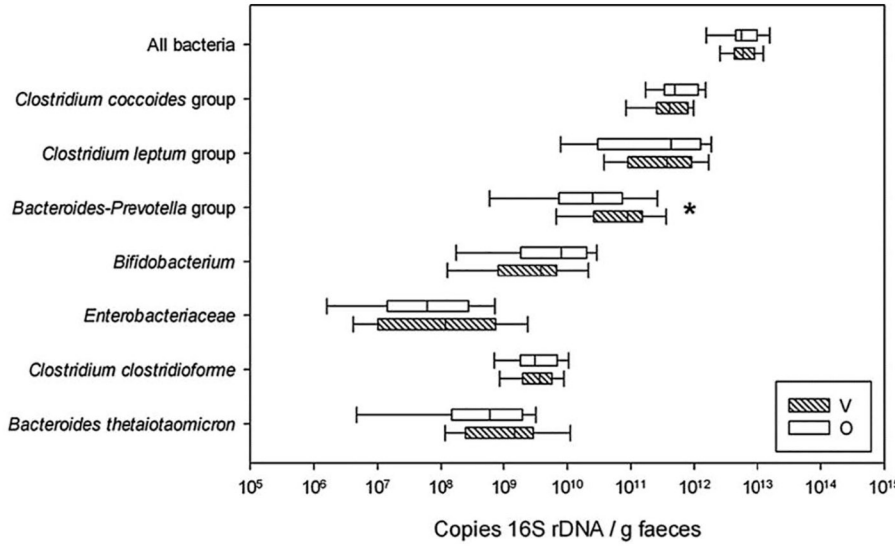
Conclusion

There are specific metabolites produced by the GM that are associated with an increased risk for developing HF. Having decreased levels of SCFAs and increased levels of TMAO are linked to health issues that can lead to the progressive development of HF. These GM metabolites can be influenced via diet. It is known that diet is an important factor in the microbial makeup of the GM and it plays a significant role in the development of HF. There are specific changes in the GM that are seen with people suffering from HF. Most notably, there is an increase in Firmicutes and Proteobacteria, and a decrease in Bacteroidetes. These changes in the GM can potentially explain the differences in the GM metabolites seen in patients with HF.

It has been demonstrated that diet can be used as a mechanism to modify the GM and its associated metabolites. Following a diet high in plant-based foods can increase the bacteria responsible for producing SCFA (like Bacteroidetes and Clostridia) and thus increase the production of SCFAs. An increase in SCFAs is

Figure 10

The Copies of 16S rDNA/g Feces of Various Bacterial Groups in Vegetarians (V)—Including Vegans—and Omnivores (O) (Matijašic et al., 2017)



Note. Bacterial abundance in vegetarians and omnivores.

linked to decreased blood pressure and cholesterol and reduced inflammation—all of which are important for preventing HF. Diets that are lower in animal-based foods (like a vegetarian diet) are linked to decreased abundance of bacteria that negatively affect health (like Streptococcus) and an increase in Bacteroidetes and Clostridium. While it was shown that diet can modify the GM makeup which in turn can alter the production of GM metabolites, the actual changes of these metabolites levels was not explicitly shown. However, it can be concluded that diet modification that induces changes in the GM would also induce changes to the GM metabolites accordingly. Therefore, diet can be used to modify the GM metabolites by modifying the GM itself. These modifications can potentially decrease the risk for developing HF or potentially slow the progression of HF since HF is associated with a decrease in SCFAs and an increase in TMAO.

Discussion

There are numerous limitations when it comes to analyzing how diet can be used to modify the GM and induce favorable changes in GM metabolites to reduce the risk of HF. First off, the GM does not exist in a vacuum—it is an ecosystem. Therefore, there are numerous factors that can affect the microbial communities present in the gut. Some of these factors can be controlled for (like antibiotic and chemotherapy use) while others are nearly impossible to control for (like individual genetic diversity). Every person has an individually unique and diverse GM and thus what affects one individual, might not affect another. In addition, the age of the person can play a role in the microbial makeup, as seen with Kamo et al. (2017). Gender also has the potential of affecting the GM, as well (Matijašić et al., 2017).

While diet is an important aspect that affects the GM, currently most strategies involving the GM remain untargeted. Rather than focusing on how manipulating diet changes the GM, most studies focus on elimination-based tactics through antibiotics or restoration-based tactics through fecal transplants. Therefore, it is hard to determine how diet really impacts the GM when most research studies combine diet modification with elimination-based or restoration-based strategies.

The clinical diagnosis of HF is also a complex process. While there are measurements that can be indicative of HF, it is a progressive disease. Diet has the potential to reduce certain GM metabolites associated with increased risk for HF, but it is difficult to classify the reduction in risk for developing HF. One aspect for this is it is difficult to directly measure the effects that diet has on developing HF and progressive HF. There are many factors that contribute to HF, so it is hard to definitively say that diet—and diet alone—is responsible for reducing the risk of developing HF. Plus, there are no studies that show that diet alone is enough to curb the progression or prevent the development of HF.

The study by Matijašić et al. (2017) included vegans in the same category as vegetarians, which makes it harder to determine the full extent that a plant-based diet has on the microbial makeup of the GM. It can be expected that the GM differences seen between the vegetarian group (which included vegans) and the omnivore group would be less pronounced if the vegetarian and vegan diets were compared separately. The vegetarian diet should theoretically be in-between the omnivore and vegan group, with the vegan group showing the most drastic GM differences.

The study by Matijašić et al. (2017) also only compared different diets from individuals that had been following that specific diet for at least a year. While GM shifts were recorded between the two groups, it is unclear how long it takes for diet to induce these changes. It would have been better to do a longitudinal study in which multiple fecal samples were collected and analyzed

over a longer period rather than just collecting one sample. It would also be interesting to see if following a plant-based diet has the same effects on the GM and health on the short-term as it does on the long-term. Is there a point where the GM is no longer able to change from diet alone and if so, at what point is that? Would it be better to also supplement with pro-and prebiotics at that point to continue to induce favorable changes in the GM? While there are still many questions to be answered in regards to the ability of diet to induce favorable changes in the GM as a means to prevent the development or progression of HF, the current research indicates that diet can induce changes to the GM and that these changes are associated with reduced risk of HF.

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