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The Intricate Gut-Heart Connection; Role of Gut Microbiota in the Pathogenesis of Cardiovascular Disease

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Abstract

The human intestines are home to a complex community of bacterial organisms known as the gut microbiome. The composition of the microbiome is susceptible to modifications triggered by environmental factors and lifestyle choices made by the host. The interactions between the gut microbiome and the host have a crucial role in regulating human health and can influence various metabolic pathways, leading to potential health consequences. One such consequence is cardiovascular disease (CVD), which is the leading cause of death worldwide. CVD encompasses any disease process affecting the heart or blood vessels and has been shown to be affected by microbial imbalances in the gut. Specifically, conditions such as atherosclerosis, hypertension, and heart failure have been linked to dysbiosis within the gut microbiome. Specific by-products of microbial metabolism, including trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids (BAs), are contributors to this imbalance. TMAO is a proatherogenic metabolite that is derived from the breakdown of dietary choline and L-carnitine and has been found to cause abnormalities in platelet function and lipid levels, as well as increases in oxidative stress.

SCFAs are produced when the gut microbiome ferments carbohydrates. This article will focus on three specific SCFAs: butyrate, acetate, and propionate. Butyrate has anti-inflammatory properties in the body, while acetate and propionate play roles in cholesterol production. Additionally, propionate may also contribute to vascular dysfunction, hypertension, and hypertrophy. The gut microbiome can convert primary bile into secondary BAs. These secondary BAs have been linked to higher levels of cholesterol and the development of CVD. By understanding the connection between CVD and the gut microbiome, we can decipher the mechanisms that contribute to heart disease. In this article, we will examine how these microbial-synthesized metabolites impact CVD and explore potential treatments for gut dysbiosis such as microbial transplants and probiotics.

Keywords: Gut microbiome; cardiovascular disease (CVD)

Introduction

The physiologic connection between gut microbiota and the host has garnered significant attention in recent years. Gut microbiota not only extracts nutrients from ingested food but also generates a vast array of bioactive metabolites and signaling molecules, exerting a profound influence on host physiology, particularly in CVD. The gut microbial community comprises

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microbial species and plays a crucial role in protecting the host against pathogenic microbes, modulating immunity, and regulating metabolic processes [1,2]. The growing interest in the relationship between gut microbiota and CVDs is fueled by advancements in metagenomic sequencing and metabolomics [3,4]. These scientific tools have allowed researchers to gain a deeper understanding of the complex interplay between gut microbial communities and cardiovascular well-being. The findings suggest that gut microbiota may play a crucial role in the development of various CVDs, providing a promising avenue for therapeutic interventions and prevention strategies.

The gut microbiome can be altered by environmental factors throughout a host's lifetime, which in turn can affect the host's overall health [5]. Significant alterations in the gut microbiome can lead to dysbiosis, which is characterized by an imbalance in bacterial species found in the gut [6,7]. Studies have shown that one of the health effects of gut microbiome dysbiosis is CVD which is the dominant cause of death world-wide, and it is largely caused by atherosclerosis [8,9,10]. Atherosclerosis is the formation of plaque on arterial walls which can cause obstruction and stenosis of vessels [11]. The Other risk factors for CVD include chronic inflammation, elevated cholesterol, hypertension [12,13,14], and myocardial infarction [15]. Considering the high incidence of CVD, it is imperative to understand how gut health affects the cardiovascular system. Previous studies have shown multiple pathways of gut microbiome contributions to CVD development. Three of the better understood microbial-synthesized metabolites that contribute to CVD are TMAO, SCFAs, and BAs. This paper explores the impact of these three agents on the genesis of cardiovascular diseases and examines potential therapies for correcting imbalances in the gut microbiome.

The gut microbiota and TMAO

Dietary choline and L-carnitine are essential nutrients for humans. Dietary choline is ingested through foods such as meat, nuts, beans, and dairy products [16] and is a necessary component of cell membranes and the formation of the neurotransmitter acetylcholine [17]. L-carnitine is primarily ingested through red meat and high-fat dairy products [18] and is needed for mitochondrial fatty acid transportation [19,20].

1a. TMAO formation and thrombosis potential

Human gut microbiota converts dietary choline and L-carnitine into trimethylamine (TMA) [21]. The hepatic enzyme flavin monooxygenase (FMO) then oxidizes TMA, forming TMAO. This is a proatherogenic metabolite [22]. Therefore, although they are essential nutrients, excess amounts of choline and L-carnitine in the diet can lead to increased levels of TMAO and thus the development of CVD. A clinical cohort study revealed a dose-dependent association between elevated levels of choline, betaine, and TMAO with the presence of CVD, including peripheral artery disease, coronary artery disease, and myocardial infarction [23].

To confirm the relationship between gut microbiota and CVD seen in the clinical cohort, an experiment was performed in which mice were given either a diet supplemented with 1% choline or a control diet with 0.08% choline. Half of the mice were additionally placed on an antibiotic to reduce gut microbiota. Mice on the supplemental choline diet showed a rate of atherosclerosis almost three times that of the mice on the control diet. Mice that were given the antibiotic, however, showed complete inhibition of dietary choline induced atherosclerosis [23,24].

In a separate study assessing humans, it was found that upon introduction to antibiotics, plasma TMAO levels decreased. Once the patients were taken off the antibiotics, their plasma TMAO levels increased again. It was also found that the risk of a major adverse cardiovascular event was increased in the presence of an elevated plasma TMAO level [25].

Both studies linked the prevalence of atherosclerosis and adverse cardiovascular events to increased TMAO levels, which indicates that an increased level of plasma TMAO increases the risk of CVD. These studies also showed that the introduction of antibiotics decreased levels of TMAO-producing organisms in the gut, which decreased total plasma levels of TMAO. Gut microbiota were thus confirmed to be a predominant factor in determining the formation of the proatherogenic metabolite TMAO. When atherosclerotic plaques rupture, they cause thrombus or embolus formation. Thromboses and embolisms can cause life threatening events such as myocardial infarction or acute ischemic stroke [26]. To assess the relationship between TMAO and thrombus formation, Zhu et al. [27] conducted a study that examined thrombosis potential in the setting of increased TMAO and choline intake. Mice were placed on either a control diet of 0.08% choline or an experimental diet consisting of 1% choline or 0.12% TMAO. Then, a carotid artery FeCl3 injury model was used to assess thrombosis potential. In this model, an injury to the carotid artery was made using FeCl3 and thrombosis potential was measured by using the time it took for blood flow to cease in the carotid artery. Their results showed a shortened blood flow cessation time for the mice on the choline and TMAO supplemental diets, indicating a higher thrombosis potential in those groups.

1b. TMAO and platelet hyperactivity leading to CVD

The mechanism by which TMAO promotes thrombus formation involves its ability to activate platelets via multiple pathways as shown in figure 1. Platelets play a vital role in both controlling bleeding and impacting inflammation and

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atherosclerosis. Inflammation can be intensified by the release of various cytokines from platelets, ultimately contributing to the advancement of atherosclerotic lesions. Activated platelets can promote the attachment of leukocytes to the endothelium, fostering inflammation and the formation of atherosclerotic plaques [28,29]. In a study, increase in platelet count did not lead to a higher thrombosis potential among the mice, but an increase in platelet hyperreactivity did [27]. To elucidate the mechanism behind the observed platelet hyperreactivity, Zhu et al. used donor platelets and a calcium-selective dye to examine calcium release. Platelet activation is largely dependent on intracellular calcium levels, and an elevation in intracellular calcium upon blood vessel injury is one of the mechanisms responsible for platelet activation [30]. This experiment showed that platelet reaction time was faster in the presence of TMAO due to enhanced calcium release [27]. Upon investigation of microbial species, Zhu et al. also found that a choline-rich diet is associated with an increase in microbial taxa that produce TMA. There was also increased activity of TMA lyase, an enzyme important for the synthesis of TMA from choline [27]. These results indicate that choline causes dysbiosis by altering the gut microbiome to favor the production of TMA and subsequently the production of TMAO. The consumption of choline supplements led to an increase in macrophage scavenger receptors, which are linked to atherosclerosis. This indicates a clear association between choline intake and the development of this condition [31]. Similarly, dietary choline was linked to abdominal aorta calcification in older adults. The metabolic pathway from choline to TMAO is crucial, as TMAO has been linked to inflammation and foam cell formation, which are key factors in the development of atherosclerosis [32,33]. These studies demonstrate the crucial role of the gut microbiome in the conversion of dietary choline to TMAO. The relationship between platelets and pro-inflammatory cytokines, such as TNF-α and IL-1, is intensified through the stimulation of additional cytokine release and the promotion of a pro-inflammatory environment [34]. TMAO-induced oxidative stress can hinder platelet function, causing greater aggregation and the release of inflammatory substances [35]. This chain of events highlights the crucial role that TMAO plays in connecting gut microbiota, oxidative stress, cytokine release, and platelet function regarding atherosclerosis. These provide evidence that dysbiosis within the gut microbiome can lead to serious repercussions, such as cardiovascular disease, as it promotes a higher risk of atherosclerosis and thrombosis.

1c. TMAO and endothelial injury leading to CVD

TMAO can prevent endothelial nitric oxide synthase (eNOS) activity, resulting in reduced production of nitric oxide [36]. Inhibition of eNOS, coupled with increased reactive oxygen species (ROS) production, results in a vicious cycle that exacerbates endothelial dysfunction and promotes the development of hypertension. Additionally, TMAO has been shown to induce oxidative stress in various cell types, leading to apoptosis and further vascular damage [37]. Surprisingly, despite TMAO being commonly linked to negative impacts on cardiovascular well-being, several research studies propose its potential antioxidant capabilities under specific circumstances [38]. Despite potential protective roles, current evidence strongly suggests that the pro-oxidative and pro-inflammatory effects of TMAO far surpass any beneficial effects [39]. The relationship between TMAO and homocysteine is of particular interest due to their combined impact on endothelial dysfunction. Both metabolites have been independently linked to this condition, but when present together, they may have a synergistic effect. For instance, TMAO-induced oxidative stress can worsen the effects of homocysteine on endothelial cells, leading to an increased risk for vascular injury [40]. High levels of homocysteine, often caused by insufficient choline intake, are an independent contributor to the development of atherosclerosis. This is supported by research from Van Parys et al. [41] and Zhou et al. [42]. Choline acts as a source of methyl groups in converting homocysteine to methionine, and deficiency in choline can lead to elevated levels of homocysteine, which in turn increases the risk for cardiovascular disease. Studies have demonstrated that interventions aimed at lowering TMAO levels can enhance endothelial function and decrease inflammation which could potentially alleviate the negative impacts of elevated homocysteine [43].

TMAO promotes oxidative stress and inflammation, which are key drivers of atherosclerosis development. Studies indicate that TMAO can induce oxidative stress by promoting the production of ROS and activating inflammatory pathways, including the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines [45,46]. Oxidative stress has been linked to endothelial dysfunction, which serves as a warning sign for the development of atherosclerosis. Additionally, recent research has linked TMAO to changes in synaptic plasticity and overall brain health, indicating that its impact goes beyond just affecting the heart [46].

The gut microbiota and SCFA

Gut microbiota use fermentation process to convert carbohydrates that would otherwise be indigestible into SCFAs [47]. SCFAs are saturated fatty acids with anywhere from one to six carbon atoms [5]. Butyrate is anti-inflammatory and has been shown to slow the progression of atherosclerosis [48]. The major SCFAs produced from fermentation by gut microorganisms are butyrate, propionate, and acetate [49]. Both acetate and propionate have functions in cholesterol production [49], but propionate additionally decreases vascular dysfunction, hypertension, and hypertrophy [12]. Butyrate is an important SCFA produced by the gut microbiota through the fermentation of dietary fibers [50]. Butyrate is primarily metabolized by the colonic commensal bacteria, which plays a pivotal role in regulating cell growth

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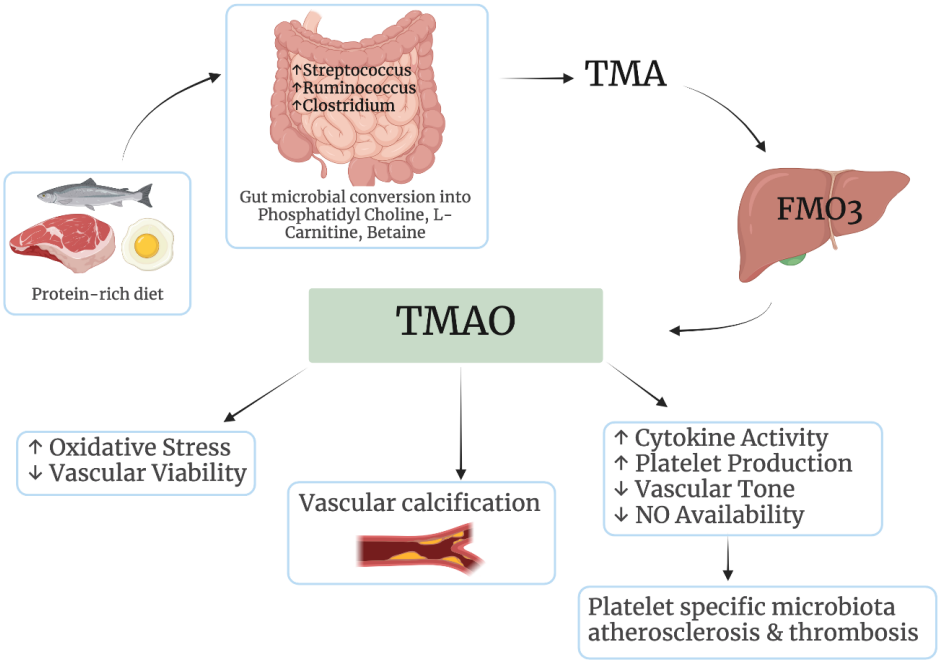

Figure 1. Provides an overview of TMAO's role in endothelial dysfunction. The gut microbiota produces trimethylamine N-oxide (TMAO) from dietary precursors, including phosphatidylcholine, betaine, and L-carnitine. The TMA is then absorbed into the bloodstream and undergoes oxidation in the liver by flavin monooxygenases (FMO3), resulting in the formation and release of TMAO into circulation. Also, as a result the platelets secrete a diverse range of growth factors, including platelet-derived growth factors, vascular endothelial growth factor, and platelet-derived pro-inflammatory cytokines, which promote smooth muscle cell proliferation and the progression of atherosclerosis. The growth factors, membrane particles, and cytokines secreted by platelets play a significant role in the progression of atherosclerosis by promoting smooth muscle cell proliferation. TMAO promotes the activation of mitogen-activated protein kinase signaling cascade, which exacerbates oxidative stress and inflammation in endothelial cells, leading to vasoconstriction. Elevated TMAO levels have been associated with increased vascular inflammation and smooth muscle cell senescence, which contribute to vascular calcification. Reduction in nitric oxide (NO) availability can exacerbate endothelial dysfunction, contributing to increased vascular resistance and hypertension, and eventually developing cardiovascular diseases.

and differentiation [51]. It has gained significant attention for its potential role in protecting against CVD. Recent research has shown that individuals with CVD have lower levels of butyrate, making it a potential biomarker for assessing their risk and highlighting its distinct impact on the development of CVD [52]. One key feature that sets butyrate apart is its anti-inflammatory effects, which have been shown to be effective in reducing chronic inflammation caused by lipopolysaccharide (LPS), a major culprit in the development of atherosclerosis. This suggests that butyrate has not only the potential to prevent CVD, but also to mitigate its progression [53].

Atherosclerosis, chronic inflammation, elevated cholesterol, and hypertension are all contributing factors to CVD [12,54]. It is therefore important to understand the role that SCFAs play in the occurrence of these risk factors. In a study performed by Jie et al. [22], stool samples were analyzed from healthy individuals and people with atherosclerotic cardiovascular disease (ACVD) to investigate the integrity of the gut microbiome of both groups. Strains of microorganisms were identified along with their functional gene modules. The results of this study indicated major differences in the gut microbiome of the two sample groups.

2a. Bacterium capable of producing SCFAs

Earlier studies have highlighted that bacterium capable of producing SCFAs, such as Faecalibacterium prausnitzii and Roseburia hominis, are significantly less prevalent in hypertensive patients [55,56]. Zhang et al. [57] observed a significant decrease in the relative abundance of F. prausnitzii among hypertensive patients, suggesting a potential connection between reduced SCFA production and the development of hypertension. Similarly, R. hominis, another important SCFA-producing bacterium, has been linked to anti-inflammatory effects and enhanced gut barrier function, which are compromised in individuals with hypertension [58]. Stool samples from the ACVD group showed a higher prevalence of Ruminococcus gnavus than the control group. R. gnavus is a bacterium that has been linked to low gut microbial richness. Thus, the elevated level of R. gnavus in ACVD stool indicates gut microbiome dysbiosis of those individuals. The prevalence of Eggerthella lenta was also higher in stool samples from ACVD individuals. Interestingly, E. lenta is a bacterium known to have enzymes that deactivate the antiarrhythmic drug digoxin.

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Stool samples from the ACVD group also showed a lower prevalence of Roseburia intestinalis and Faecalibacterium cf. prausnitzii, both of which are bacteria that produce butyrate, an anti-inflammatory SCFA. Since a decrease in these bacteria causes a decrease in butyrate, this indicates a pro-inflammatory gut microbiome in ACVD patients. It was also found that a functional gene module that synthesizes propionate was less abundant. No changes in acetate synthesis were noted. Overall, this study concluded that with ACVD, the gut microbiome is more inflammatory and less fermentative [30], which can promote CVD [24].

A study conducted by Pluznick et al. [59], revealed the importance of propionate in blood pressure regulation. This study found that an olfactory receptor expressed in the renal juxtaglomerular apparatus, Olfr78, induces renin secretion upon interaction with SCFAs like propionate. Renin is a key factor in the renin-angiotensin system that induces a cascading mechanism that can increase blood pressure. When administered propionate, the blood pressure of mice dropped in a dose dependent manner, but this effect was rapidly mediated by the Olfr78 receptor with the release of renin. This suggests that although propionate decreases blood pressure, its effects are counteracted by Olfr78 receptors.

Recent research has shown that antibiotics have a considerable influence on the relationship between gut microbiota alterations and physiological outcomes, such as increased blood pressure in mice lacking Olfr78 receptors [60]. The researchers determined that because there was an elevated blood pressure response in the absence of both Olfr78 receptors and sufficient microbiota (and thus propionate), there must be another mechanism other than Olfr78 to increase blood pressure [59]. Regardless of this, the study provided evidence supporting the key role of SCFAs in blood pressure regulation. Since elevated blood pressure is a risk factor for CVD, it is important to understand its etiology in relation to the gut microbiome.

Antibiotics have the potential to disrupt the balance of bacteria in the gut, leading to dysbiosis, which can have systemic effects on various bodily functions. They can cause metabolic and inflammatory changes that may impact blood pressure regulation. The consequences of antibiotics include reducing the diversity of gut bacteria, which is essential for maintaining overall health and metabolic stability [61]. This reduction in diversity may contribute to an increase in pathogenic bacteria and contribute to conditions like hypertension as shown in Figure 2.

2b. Role of SCFAs in microbiome imbalance leading to hypertension:

Dysbiosis, characterized by an imbalance in gut microbiota composition, has been associated with the development of hypertension [62]. This condition is characterized by a decrease in beneficial microbial populations and an increase in pathogenic ones. This imbalance can lead to altered metabolic profiles and the production of various metabolites, including SCFAs [61].

Dysbiosis and hypertension are closely related, and this relationship can be attributed to several mechanisms linked to SCFAs. One notable mechanism is the ability of SCFAs to activate G protein-coupled receptors (GPCRs), specifically GPR41 and GPR43, which are expressed in vascular tissues.

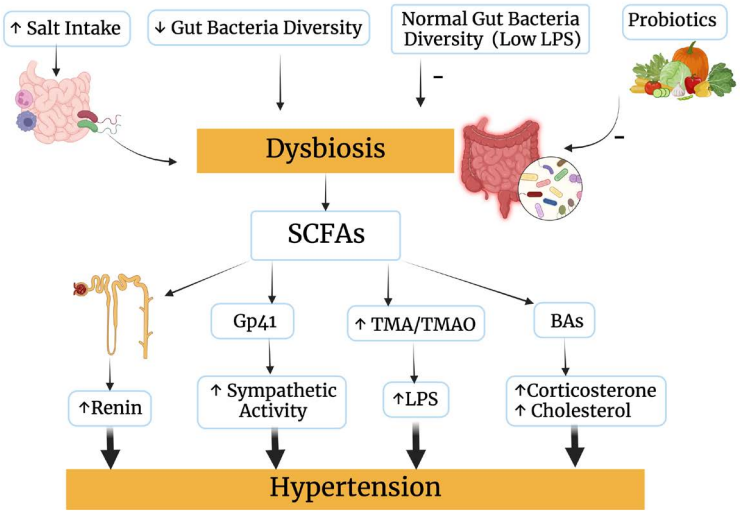

Figure 2: Illustrates the connection between gut dysbiosis and hypertension, where various mechanisms work in tandem to contribute to elevated blood pressure. The gut microbiota produces microbial metabolites, specifically short-chain fatty acids (SCFAs) and trimethylamine (TMA), which act as ligands for G protein-coupled receptors like GPR41 and olfactory receptor 78 (Olfr78). These receptors are in the vascular endothelium and smooth muscle, and their activation by SCFAs can stimulate renin release through afferent arterioles, ultimately causing an increase in blood pressure.

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These GPCRs have been shown to evoke vasodilatory effects, thereby lowering blood pressure [63]. Activation of these receptors can lead to an increase in NO production, promoting vasodilation and thereby lowering blood pressure. However, dysbiosis often results in reduced SCFA production, which can impair these protective mechanisms and contribute to hypertension. Dysbiosis can disrupt the renin-angiotensin system, a critical regulator of blood pressure. Changes in gut microbiota composition can result in increased production of angiotensin II, a potent vasoconstrictor, which can contribute to elevated blood pressure [64]. Also, SCFAs and BAs are key players in the regulation of cholesterol metabolism and corticosterone levels. They are intricately linked to gut microbiota composition and can be influenced by dietary factors [65].

2c. SCFA and TMAO contributing to hypertension

TMAO has been shown to promote angiotensin II-induced vasoconstriction, which can also contribute to hypertension. Decreased gut bacterial diversity can lead to imbalances in microbial metabolites such as SCFAs and TMAO, which can activate the sympathetic nervous system and contribute to hypertension. LPS is an essential constituent of the outer membrane in gram-negative bacteria. It is made up of lipids and sugars. The gut-blood barrier serves as a protective mechanism against LPS entering the bloodstream. However, when there is dysregulation in the barrier, LPS can leak into the bloodstream, leading to its activation and subsequent initiation of NF-κB signaling [66]. This results in the release of pro-inflammatory cytokines. plasma LPS concentration was positively correlated with hypertension. High-salt intake was linked to alterations in the gut microbiome, characterized by an increase in Firmicutes, Proteobacteria, and genus Prevotella bacteria [67].

The gut microbiota and BAs

BAs are important compounds for lipid metabolism. In the liver, primary BAs are synthesized and then transported to the intestine. In the intestine, primary BAs can be converted into secondary bile acids by bacteria [68]. In a study conducted by Liu et al. [68], germ-free mice on a high-fat diet were colonized with microbiota extracted from patients with coronary artery disease (CAD). After receiving the CAD microbiota transplant, the mice showed an increased diversity of bile acids due to an increased ability to synthesize secondary BAs. The increased level of secondary BA synthesis inhibited the production of hepatic primary BA synthesis, which resulted in elevated serum cholesterol levels.

It was additionally found that 7-alpha-dehydroxylation was increased in the CAD microbiota transplant mice. 7-alpha-dehydroxylation is a process involved in the synthesis of secondary BAs, suggesting it may be a contributing factor to elevated secondary BA synthesis. Furthermore, CAD transplant mice had higher levels of Clostridium symbiosum and Eggerthella, both of which have functions in secondary BA biotransformation [68].

Another study performed by Le Roy et al. [69] also demonstrated interesting findings in relation to microbiota transplants. In this experiment, mice were given antibiotics to suppress their endogenous microbiota. These mice were then either given a microbiota donation from a human with a healthy cholesterol level, or a donation from a human with an elevated cholesterol level associated with CVD risk. Mice that received a microbial donation from people with abnormal cholesterol levels showed elevated cholesterol [69]. These results further show the importance of lipid metabolism as it relates to BA synthesis, gut microbiome health, and CVD risk. Collectively, the results of this study indicate that the gut microbiome plays a key role in cholesterol regulation and that gut microbiome dysbiosis can cause the overproduction of secondary BAs, resulting in elevated serum cholesterol levels. Elevated cholesterol is a major risk factor for CVD, so this study highlights the importance of BAs in cardiac health. As previously mentioned, the interaction between the gut microbiota and BAs is a complex process that involves bidirectional communication. This dynamic relationship has a significant impact on host metabolism and immune function. The liver synthesizes BAs from cholesterol, and their modification by the gut microbiota plays a crucial role in altering the composition and function of microorganisms in the gut.

3a. Gut Microbiota modulation of BA metabolism

The presence of BAs within the intestinal lumen can influence the composition of microbial communities through selective pressure. Notably, specific BAs, including secondary ones, have been found to impede the growth of bacterial populations such as Clostridium difficile [70]. Additionally, BAs can stimulate the growth of beneficial bacteria such as Bacteroides and Lactobacillus, which are known to have protective effects against harmful bacteria [71]. On the other hand, gut microbiota plays a vital role in the metabolism of BAs, converting primary BAs produced by the liver into secondary BAs through processes like deconjugation and dihydroxylation. This microbial conversion is crucial in regulating both the size and composition of BA pools, which ultimately affects various metabolic pathways and signaling mechanisms [72]. For example, studies have shown that gut bacteria can convert cholic acid into deoxycholic acid, leading to improved energy extraction from dietary fats [73].

3b. BA Metabolism and innate immune system

The BAs play a role in the innate immune system and bacterial defense mechanisms. They can regulate the expression of key immune receptors, such as the farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5

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(TGR5), that play a critical role in controlling inflammatory responses [74]. BAs can stimulate these receptors, resulting in the production of antimicrobial peptides and cytokines [75]. This process not only affects the composition of the gut microbiota but also strengthens the host's ability to defend against harmful pathogens.

3c. Mechanism of bile salt hydrolysis

The metabolism of BAs heavily relies on the conversion of these compounds by bacterial bile salt hydrolase. This process is crucial for maintaining gut health and overall host metabolism. Certain bacterial species, including Lactobacillus, Clostridium, Enterococcus, and Bifidobacterium, are crucial in facilitating this conversion process. This is achieved through the enzymatic activity of bile salt hydrolase (BSH), which breaks down conjugated BAs into their free form [76]. These free BAs can then undergo further modifications by gut microbiota, including deconjugation and dehydroxylation. The activity of BSH not only impacts the composition of BAs but also influences their biological functions in processes such as lipid metabolism and signaling pathways [77].

3d. Gut microbiota interactions with BAs and heart failure

There is a correlation between altered BA profiles and heart failure [78]. This concept is visually represented in Figure 3. An important observation is the elevated secondary to primary BA ratio detected in the serum of individuals diagnosed with chronic heart failure. This rise in secondary BA levels has been linked to a decrease in overall survival rates. BAs are known to interact with specific receptors, including the farnesoid X receptor (FXR) and the Takeda G protein-coupled receptor 5 (TGR5) [79]. These receptors are expressed in cardiac tissues and play a crucial role in the heart's response to stress. The activation of these receptors has been shown to have cytoprotective effects on the heart, resulting in improved myocardial responses [80]. BAs are essential in regulating inflammatory responses, which play a critical role in understanding the pathogenesis of heart failure. These acids possess the ability to control the production of pro-inflammatory cytokines and chemokines, both of which are significant contributors to heart failure progression [81]. By regulating these inflammatory molecules, BAs contribute to the development of cardiac dysfunction. Moreover, BAs also impact lipid metabolism and energy homeostasis, further influencing cardiac function. Metabolites produced by gut microbiota, including BAs, have been shown to modulate lipid metabolism and affect energy balance in the heart [82]. Imbalances in BA metabolism have been linked to cardiomyopathy and metabolic dysfunctions in the heart, emphasizing the importance of maintaining a well-balanced gut microbiota for optimal cardiovascular health [83]. Recent research has shed light on the role of BAs in various physiological processes, particularly their impact on inflammatory responses, lipid metabolism and the development of cardiomyopathy and metabolic dysfunction in the heart [84,85,86]. As depicted in Figure 3, there exists a complex interplay between the gut microbiota and BAs that can contribute to ischemic injury and cardiac remodeling through dysbiosis.

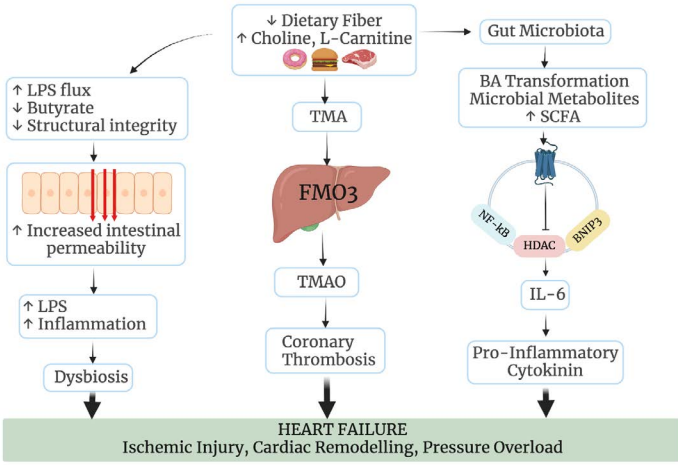

Fig 3: The interplay between SCFAs, bile acids, and gut microbiota

Figure 3: Dysbiosis is marked by a decline in beneficial bacteria, resulting in elevated levels of lipopolysaccharides (LPS) in the bloodstream. A lack of butyrate can weaken the tight junctions between epithelial cells, making it easier for LPS to enter the body's circulation. This increase in intestinal permeability has been associated with cardiac remodeling and heart failure. Dysbiosis can lead to an overproduction of secondary BAs, which may exacerbate inflammation and trigger heightened secretion of IL-6. The vital transcription factor NF-κB controls the expression of various inflammatory cytokines and mediators that contribute to heart failure. Increased activation of NF-κB due to inflammatory stimuli can result in cardiac remodeling and dysfunction. Histone Deacetylases (HDACs) work to suppress NF-κB activity and regulate inflammatory responses. Disruption in HDAC function has been linked to the development of heart failure as they play a role in gene expression regulation. Elevated TMAO levels have been shown to promote oxidative stress, which is a key factor in the pathogenesis of atherosclerosis.

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Treatments for Gut Microbiome Dysbiosis

The treatment of gut microbiome dysbiosis has garnered significant attention as a promising research area due to its implications for various health conditions. Specifically, gastrointestinal disorders and cardiovascular diseases are among the key areas being studied. This research focuses on dietary modifications, diet and lifestyle changes, probiotics, prebiotics, antibiotics, and fecal microbiota transplantation (FMT).

FMT has emerged as a potential treatment for severe dysbiosis, particularly in cases of recurrent Clostridium difficile infection [87]. It involves transferring fecal material from a healthy donor to a recipient, aiming to restore a healthy microbiome. Studies have demonstrated the effectiveness of FMT in improving gut health and reporting positive outcomes in conditions like inflammatory bowel disease and metabolic syndrome [88]. The potential for microbial transplants in protecting against atherosclerosis was found in a study conducted by Gregory et al. [89] which investigated the transmission of atherosclerotic susceptibility with cecal microbial transplants. Atherosclerosis-prone mice and atherosclerosis-resistant mice acted as microbial donors. Mice that received the transplanted cecal microbes were first given antibiotics to suppress their endogenous microbes. Mice that received cecal microbes from atherosclerosis-prone donors showed a higher level of atherosclerosis than mice that received atherosclerosis-resistant microbes. These results suggest that recipient mice received anti-atherosclerotic microbial taxa that protect against atherosclerosis from the atherosclerosis-resistant mice [89]. This study shows potential for microbial transplantation as a therapy for protecting against atherosclerosis, because the transplant of microbes seems to transfer phenotypic outcomes.

Another potential therapy for regulation of the gut microbiome to protect against CVD is the use of probiotics. A meta-analysis conducted by Mo et al. [90] analyzed the effect of probiotics on serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels in hypercholesterolemic adults. Elevated total cholesterol is a risk factor for CVD [90]. The results of this study showed a significant decrease in serum cholesterol levels with the use of probiotics. Probiotics are therefore a potential treatment and preventative measure in protecting against CVD.

Although probiotics were found to be useful in lowering serum TC, different strains of bacteria have differing levels of effectiveness. Strains that significantly reduced serum TC were Lactobacillus acidophilus, Lactobacillus plantarum, and Lactobacillus reuteri. Strains that significantly lowered LDL-C levels were Lactobacillus plantarum and a mixture of Lactobacillus helveticus and Enterococcus faecium. No significant reductions in serum TC or LDL-C levels were found with the use of Lactobacillus fermentum, Lactobacillus rhamnosus and mixtures of Lactobacillus acidophilus and Bifidobacterium spp. [90].

It was also found that probiotic effectiveness varied with duration of use. There was a greater hypocholesterolemia effect with use lasting more than six weeks as compared to use lasting less than six weeks [90]. Both prospective treatments show enormous potential for treating CVD, but more research is needed to further develop the ideas. In the case of microbial transplants, the mentioned study was conducted on mice, not humans. Thus, more studies in humans are needed to fully understand the effectiveness of the treatment in people. Regarding probiotics, the difference in effectiveness among probiotic bacterial strains and duration of use shows that the effects of varying strains over a longer period must be investigated.

Conclusion

In conclusion, the reviewed studies collectively illustrate the complex interactions of the gut microbiome and cardiovascular disease. The three metabolites, TMAO, SCFAs and BAs, produced by the gut bacteria play integral roles in CVD manifestation. Even though these metabolites and their effects are becoming more apparent, their mechanisms remain unclear. More research is needed to elucidate why these compounds increase the risk of CVD by examining the precise mechanisms driving them in relation to gut microbiome dysbiosis. Furthermore, most studies have investigated the gut microbiome and CVD relationship in mice, but few studies have sufficiently evaluated this relationship in humans. More human trials are thus needed to strengthen the claims that gut microbiota dysbiosis is a significant contributing factor for CVD. The pathways leading to CVD are crucial to fully understanding the disease since it is the leading cause of death in the world. Doing so will allow for the development of effective treatments. Although some potential treatments have been suggested, they have not been sufficiently evaluated. A key priority is to gain a comprehensive understanding of the pathogenesis of CVD by thoroughly examining dysbiosis pathways. This knowledge is crucial in developing more precise and effective therapeutic approaches.

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