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Intestinal dysbiosis in heart failure - modulation of dysbiosis as a potential therapeutic target

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Abstract

The last decade has provided extensive information on the human gut microbiota. The microorganisms populating the gastrointestinal tract play important roles in maintaining the body's homeostasis. It turns out that the intestinal microbiota can affect many diseases from various branches of medicine. The importance of the function of the microflora can also affect cardiovascular diseases (CVD), including heart failure (HF). The microflora influences among other things, nutrient digestion, vitamin production or the production of bioactive metabolites including trimethylamine/trimethylamine *N-oxide*, short-chain fatty acids and bile acids.

Therefore, changes in the composition of the intestinal microflora, defined as dysbiosis, have become one of the key pathogenic factors in many diseases. There is emerging evidence of a strong correlation between gut microflora and the occurrence of cardiovascular disease. In patients with cardiovascular disease and corresponding risk factors, the composition and proportions of the intestinal microflora differed significantly from healthy subjects.

Differences in microbial composition and marked fluctuations in the levels of biomarkers such as TMAO, zonulin, LPS, SCFAs may become helpful in the diagnosis of cardiovascular diseases. For this reason, the intestinal microflora and its metabolic pathways have recently become the subject of numerous studies. A very important issue is the fact that it is possible to regulate the intestinal microflora through diet, the use of prebiotics, probiotics or influence through a much larger intervention - for example, fecal mass transplantation. These possibilities have become new strategies in the treatment of HF. The main purpose of this review is to summarize recent studies that illustrate the complex interactions between the microbiome and the occurrence of HF.

Conclusions. The gut microbiota is a complex ecosystem of microorganisms that live in the human gut.

The gut microbiota plays an important role in maintaining the body's health, including the cardiovascular system. Dysbiosis, or an imbalance in the gut microbiota, has been linked to the development of heart failure. Gut microbiota metabolites, such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids, can have harmful effects on the heart. Diet, probiotics, and fecal microbiota transplantation (FMT) are all potential interventions for improving gut microbiota and reducing the risk of heart failure. More research is needed to fully understand the role of gut microbiota in heart failure and to develop effective treatment strategies.

Keywords: heart failure, gut microbiota, biomarkers of heart failure, intestinal dysbiosis.

Introduction

In recent years, knowledge of the human gut microbiota and its potential impact on cardiovascular disease, in particular on heart failure (HF), has increased. HF is a significant problem in the healthcare setting, with a high mortality rate [1–4]. HF is defined as the inability of the heart muscle to pump blood, the chambers lose their ability to diastole and contract properly resulting in inadequate blood perfusion for the body's needs. As the degree of myocardial damage increases, the patient's quality of life deteriorates [5].

Risk factors for HF include obesity, hypertension, diabetes, or smoking [6,7]. Contemporary studies recognize intestinal dysbiosis as an element that is associated with HF [8].

In a study already conducted in 2007 by Sandek et alia, it turned out that patients with chronic heart failure (CHF) showed increased intestinal wall thickness, greater intestinal permeability and a decrease in D-xylose absorption, which would indicate intestinal ischemia. These studies suggested that increased intestinal permeability and increased bacterial biofilm may contribute to chronic inflammation and malnutrition. The hypothesis that assumes the involvement of the gut microbiota in the pathogenesis of HF is known as the “gut hypothesis of HF” [9]. Unfortunately, despite significant advances in medical therapies, more than 40 million people worldwide struggle with the intractable symptoms of HF [6]. That is why it is so important to look for other factors that may influence the disease. In this work, we focus on gut microbiota and its role as a possible therapeutic target in HF.

Physiological Aspects of Gut Microbiota

The human gastrointestinal tract contains more than 100 trillion microbial cells [10] and it is populated by several viruses, bacteria and fungi that make up the intestinal microbiota. The most important microbial representatives in the gastrointestinal ecosystem are bacteria [11].The fundamental building blocks of the microbiota include the cluster *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria* and *Verrucomicrobia* [1,12] This complex ecosystem is subject to constant change in human life. The microbiota functions in conjunction with the host's defenses and immune system to protect against colonization and invasion by pathogens [13]. The composition of the intestinal microbiota is regulated by factors such as diet, gender, lifestyle, pharmacotherapy and past treatments [4,8]. The gut microbiota influences many aspects of human physiology that interact with each other. It has metabolic, trophic and immunological functions in the human body. (Fig. 1) [14]. Ultimately, the functioning of the intestinal microflora depends on many of the host's vital functions, so the intestinal microflora affects homeostasis. Dysbiosis of the intestinal microflora can induce, far-reaching health consequences. The altered composition of the intestinal microflora is often the cause of many chronic diseases such as colorectal cancer, obesity, diabetes and cardiovascular disease. In recent years, the intestinal microbiome has become the subject of research due to potential links between the occurrence of cardiovascular disease and dysbiosis of the intestinal flora [8,15].

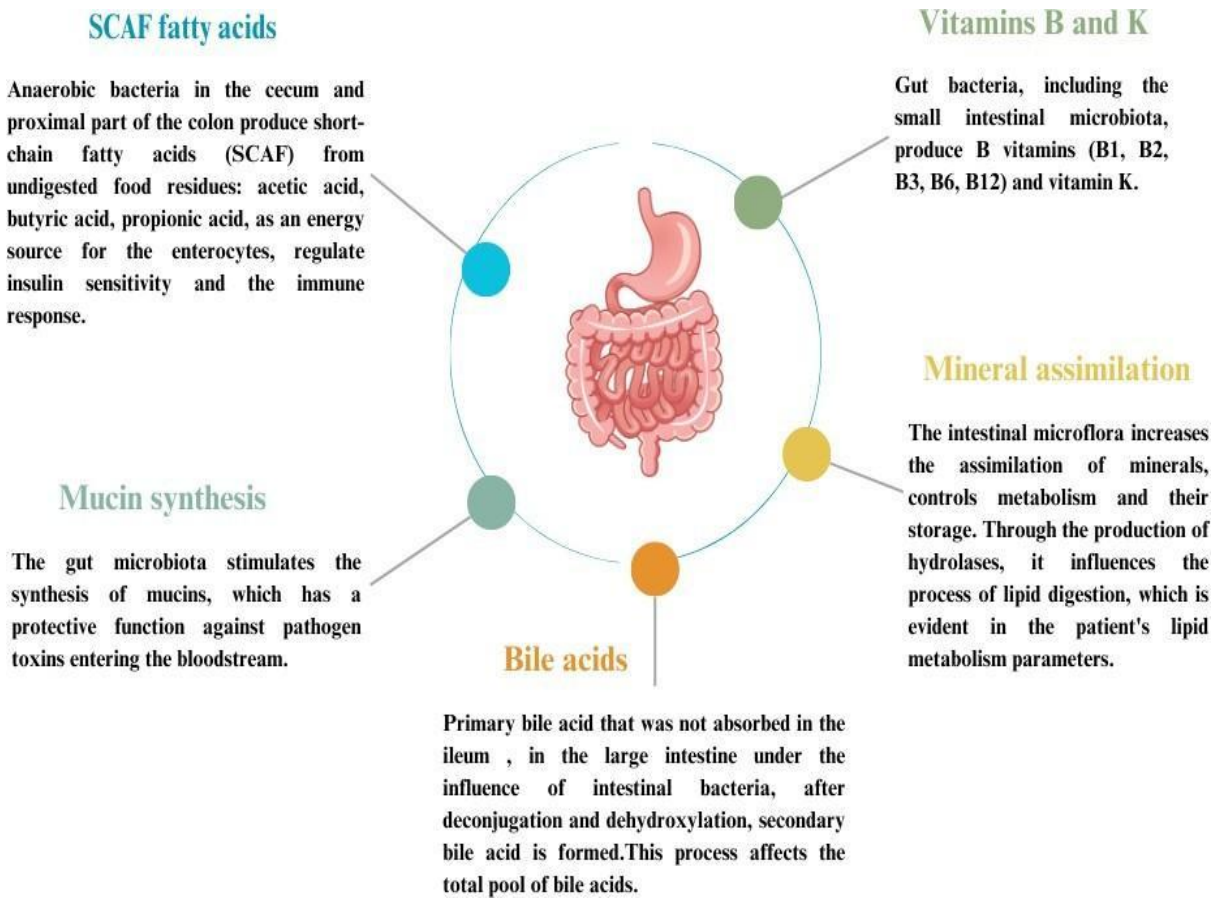

Fig. 1. Selected functions of intestinal microflora based on [16–21].

Dysbiosis in Heart Failure

Several exogenous and endogenous factors influence the existing differences in the proportions of microorganisms building the intestinal microflora. Exogenous factors include diet, medications, past treatments or age while endogenous factors include impaired intestinal perfusion, chronic inflammation, autoimmune diseases. These factors can significantly reduce the diversity of intestinal flora [6,21,22]. The overall richness and diversity of bacteria were observed to be altered in patients with HF. Wang et al [23] studied a group, of elderly patients with chronic HF. According to the researchers, the abundance of pathogenic microorganisms increases in importance: *Escherichia Shigella* , *Klebsiella* and *Haemophilus.* They also noted abnormalities in the profile of serum metabolites. The study indicates that there is no correlation between *Escherichia* , *Shigella* spp. and riboflavin and biocytin. In the case of *Haemophilus* species, a lack of disaccharide correlation was noted with cellobiose, alpha-lactose, lactose, isomaltose, sucrose, or melibiose, among others. In contrast, *Klebsiella* species were associated with

ethyl salicylate and bilirubin, and showed no association with hexanocarnitine, citramalate, isovaleryl carnitine, inosine, methylmalonate and riboflavin. Another study confirming the diversity of the intestinal microbiota in patients with HF was conducted by Hayashi, T et al. Particular differences can be seen in the reduction in the abundance of *Eubacterium* and *Prevotella*. This disproportion mainly affected the impairment of amino acid biosynthesis in the gut. Moreover, it was noticed that gut microbial compositions were similar between patients with reduced ejection fraction (HFrEF) and preserved ejection fraction (HFpEF) [24]. Brand Ludde et al. first analyzed the gut microbiome of HF patients using 16S rRNA gene sequencing. They showed a significant decrease in the bacterial diversity of *Blautia* and *Collinsella* bacteria, as well as bacteria belonging to the *Erysipelotrichaceae* and *Ruminococcaceae* families, compared to the control group. Interestingly, the study jumps to the specificity of this type of gut microbiota diversity for HF due to the absence of such relationships in other disease entities [25]. Kamo T et al. also used the 16S ribosomal RNA sequencing method. They collected fecal samples from subjects with known HF disease and from healthy subjects to analyze the composition of the intestinal microflora [26]. The study shows that the composition of the intestinal microflora in people with HF significantly differs from that of healthy people. There is a clear decrease in the abundance of *Dorea longcatena and Eubacterium rectale* in people with HF. Moreover, it has been observed that the intestinal dysbiosis associated with HF changes with the age of patients**.** The intestinal bacterial flora of elderly people with HF is characterized by a decreased percentage of *Bacteroides* and *Faecalibacterium*. On the other hand, an increase in Proteobacteria and *Lactobacillus has* been noted. In a study by Li et al, patients with HF showed reduced amounts of *Faecalibacterium prausnitzii and Roseburia intestinal* bacteria responsible for SCFA butyrate production, and elevated levels of several species and genera of *Streptococcus* from the *Enterobacteriaceae* family [27]. A very significant issue was observed in the study by Cui et al. In a pool of 53 patients with chronic heart failure (CHF), there were reduced levels of *Faecalibacterium prausnitzii and Ruminococcus gnavus.* There was a decrease in the number of gut microbes involved in the metabolism of protective metabolites such as butyrate. In contrast, there was an increase in the percentage of microorganisms responsible for the metabolism of harmful metabolites, such as N-oxide in patients with CHF [22].

There is a growing body of evidence that points to a link between the occurrence of HF and intestinal dysbiosis. Patients with HF in many cases have been observed to have an altered composition of their gut microbiota compared to healthy individuals.

Biomarkers of intestinal dysbiosis

Under the influence of dysbiosis of metabolites such as trimethylamine N-oxide (TMAO), short-chain fatty acids (SCFAs), circulating LPS or zonulins are released, which are its biomarkers [1,28]. Trimethylamine N- oxide (TMAO) is one of the dietary components belonging to the group of amino oxides [29]. TMAO is formed in the liver by oxidation of the gut microbe's trimethylamine (TMA) metabolite, which is produced by the fermentation processes of dietary substances such as choline, L-carnitine, phosphatidylcholine, lecithin, and betaine [30]. These substances come from a variety of sources, including fish, peanuts, red meat, soy, brassica vegetables, and eggs [31]. Dysbiosis of the intestinal microflora has been shown to occur with increased levels of circulating TMAO. In cardiomyocytes, TMAO activates TGF-β1/Smad3 and p65 NF-κB signaling pathways and has inhibitory effects on mitochondrial function and energy metabolism. Trimethylamine N-oxide decreases pyruvate and fatty acid oxidation and stimulates the release of IL-1β and IL-18 in epithelial cells, which consequently disrupts endothelial function, resulting in the degradation of the intestinal epithelial barrier [30,32]. Numerous studies have found TMAO to be an optimistic marker of cardiovascular risk as an indicator for predicting adverse effects in patients with HF [7,29,33], (Table 1).

Zonulin is a peptide produced in the liver and intestinal cells that regulates the protein complex of tight junctions between small intestinal epithelial cells and enterocytes [34]. Bacteria and gliadin are the main inducers of its secretion. As a result of zonulin, the intestines become permeable by opening enterocytes [35]. Intestinal dysbiosis interferes with normal secretion of zonulin, increasing its induction and resulting in loss of intestinal barrier function, followed by transport of antigens and endotoxins from the microbiome causing a pro-inflammatory microenvironment [36], (Table 1).

Short-chain fatty acids SCFAs are formed by bacterial fermentation of dietary fiber substances. SCFAs are absorbed by collenocytes or enter the portal vein and are used as energy deposits for liver cells [37,38]. SCFAs have beneficial effects on intestinal function, producing mucus, maintaining the integrity of the intestinal barrier and also protecting intestinal cells from inflammation [38]. SCFAs show beneficial protective effects against HF. Short-chain fatty acids are an effective source of energy in HF, as they stabilize heart contractions [37]. A decrease in the production of short-chain fatty acids (SCFAs) by companion flora (e.g., Lachnospiraceae) has been observed in HF patients [22] (Table 1).

Table 1. Biomarkers for the identification of intestinal dysbiosis in HF based on [22,36,41–43].

Biomarkers of intestinal dysbiosis	
Including N-oxide-trimethylamine (TMAO)	Increased levels in circulating blood increase the risk of developing heart failure, which can result in serious cardiovascular events.
Zonulin	Elevated levels of zonulin are associated with increased intestinal permeability.
Circulating LPS	Activate the immune system in people suffering from chronic heart failure.
Short-chain fatty acids (SCFAs)	People with heart failure have been shown to have reduced levels of.

LPS is an endotoxin that is found on the outer membrane of Gram-negative bacteria [39]. Increased permeability of the intestinal villi increases the permeation of LPS derived from the intestinal microflora from the gut into the bloodstream [40]. CHFpatients have been shown to have increased plasma concentrations of LPS and cytokines following acute exacerbation of edema, which may indicate that endotoxins activate the immune system in patients with CHF [41] (Table 1).

Adjusting dysbiosis as a prospective therapeutic focus in heart failure

The intestinal microflora plays an important role in maintaining the body's homeostasis and is a key element in maintaining health. Due to the possibility of conducting studies to obtain characteristics of the disproportion of bacteria colonizing the gut, the composition of the intestinal microbiota can be influenced in a controlled manner [1,22].

A major determinant of the structure and function of the gut microbiota community

appears to be diet [44]. There are many links between the Mediterranean diet (MD) and its beneficial effects on the microbiome. MD provides large amounts of various fractions of dietary fiber, polyunsaturated fatty acids, and polyphenols. The Mediterranean diet increases SFCA, increases bacterial diversity and stability, and decreases TMAO content [45–47]. Another diet that positively influences the diversity of intestinal microflora is a diet rich in fiber. Fructooligosaccharides present in products such as artichokes, onions, leeks grains and honey cause an increase in: *Lactobacilus sp*., *Prevotella sp,* Bacteroides *sp.*, *Bifitobactefia sp.,* raising metabolism and consequently strengthening the intestinal barrier [1,44]. Increasing fiber intake correlates with lowering blood pressure and reducing the incidence of cardiovascular risk [48]. For this, the Western diet is characterized by a high content of unsaturated fats. Compared to a diet rich in saturated fats, a diet high in unsaturated fats induces an increase in *Bacteroidetes*, a decrease in *Firmicutes* and *Bilophila wadsworthia* - microorganisms that affect sulfate reduction. Consequently, this can lead to an increase in LDL cholesterol and *B. wadsworthia*, resulting in dyslipidemia and increased inflammation [49,50]. A very important aspect in the diet is the regulation of protein and fat supply. In high-protein and high-fat diets, an increase in the percentage of *Ruminococcus* bacteria and reduced numbers of *Bacteroidetes, Clostridium coccoides, Bifidiobacterium, E. rectal, Akkermansiamuniciphil* have been observed [3,51].

In their study, Wilck et al. demonstrated that increased salt intake affects the gut microbiome, especially a decrease in Lactobacillus murinus, which consequently increases Th17 cells and exacerbates hypertension [52]. Continuing with the natural regulation of the bacterial microbiome, it is worth mentioning probiotics and prebiotics [53]. Probiotics and prebiotics are essential elements for controlling the microbiome to improve function [54]. Probiotics are considered to be live cultures of microorganisms that, when supplied in adequate amounts, provide the host with positive health effects. Prebiotics, on the other hand, do not contain microorganisms, but only substances that stimulate their growth.

Prebiotics can be obtained from a variety of resources, including breast milk, soy, and unprocessed oats, but the most common prebiotics include oligosaccharides found in plants [55,56]. Using them is a method of providing the body with specific beneficial bacteria, such as bifidobacteria, to improve the physiological balance of the intestinal flora [53]. In a rat study, the probiotic Lactobacillus rhamnosus GR-1 was shown to

restore systolic and diastolic cardiac function in rats after six weeks of sustained coronary embolism [57]. In contrast, another study found that endotoxins and opportunistic pathogens decreased in mice with cardiac anemia that were treated with prebiotic agents [58].

The use of pharmacotherapy in the form of antibiotics has become a rather questionable form of attempting to modulate intestinal dysbiosis. A study by Viviane et al. showed positive results. Patients with CFH received two antibiotics at a dose of 800 mg of polymyxin B and 320 mg of tobramycin. As a consequence of the therapy, there was a normalization of intestinal Gram-negative bacilli and a decrease in pro-inflammatory cytokines [59]. Vancomycin also emerged as a beneficial antibiotic for the intestinal microbiome. Through the action of vancomycin, the level of chenodeoxycholic acid increased, thus acting as a bactericide against *Clostridium* species [60]. However, an increasing number of studies suggest that the balance and composition of the intestinal microflora is altered under the influence of antibiotic therapy. In the publication of Wong et al. proved a correlation between the use of clarithromycin within 2 weeks and the incidence of myocardial infarction (MI), and arrhythmia compared to the use of amoxicillin. However, it was not associated with long-term cardiovascular risk [61].In addition, when prescribing antibiotic therapy, it should be taken into account that they act not only against pathogenic pathogens. The use of antibiotics leads to a disproportion between intestinal pathogens and probiotics or prebiotics, which consequently leads to cardiometabolic episodes [62–65].

A more invasive effect on the microorganisms populating the gut is fecal microbiota transplantation (FMT). FMT is the procedure of transferring the entire bacterial biomass of the stool from a healthy donor to the recipient's digestive system to normalize or correct the properties and functions of the intestinal microbiota [66]. FMT therapy is particularly useful in patients suffering from chronic *Clostridioides difficile* infection [67]. In terms of treating patients with HF FMT is considered a possible complementary therapy [53].

Gut microbiota dysbiosis is a common finding in patients with heart failure (HF). Dysbiosis is characterized by a decrease in the diversity of the gut microbiota and an increase in the number of pathogenic bacteria. Dysbiosis may contribute to the development of HF in several ways.

First, dysbiosis can lead to an increase in the production of trimethylamine N-oxide (TMAO), which is associated with an increased risk of cardiovascular disease. TMAO is

produced by gut bacteria from choline and carnitine, which are found in animal products.

Second, dysbiosis can lead to an increase in intestinal permeability, which can allow harmful substances to leak into the bloodstream. These harmful substances can then damage the heart and blood vessels.

Third, dysbiosis can lead to a decrease in the production of short-chain fatty acids (SCFAs), which are important for heart health. SCFAs are produced by gut bacteria from undigested carbohydrates. SCFAs help to reduce inflammation and improve heart function.

Gut microbiota dysbiosis is a potential therapeutic target in HF. Clinical trials have shown that modulation of dysbiosis can improve outcomes in patients with HF. For example, one study showed that supplementation with probiotics, which are live bacteria, improved heart function and reduced the risk of death in patients with HF.

Dysbiosis is a complex phenomenon, and there are likely multiple factors that contribute to its development in patients with HF.

The gut microbiota is not static, and it can be influenced by a variety of factors, including diet, medications, and lifestyle.

There is a growing body of evidence to suggest that gut microbiota plays a role in the development of a variety of diseases, including HF.

Further research is needed to better understand the role of gut microbiota in HF, and to develop effective interventions to improve the gut microbiota in patients with HF.

Gut microbiota dysbiosis is a potential therapeutic target in HF. Clinical trials have shown that modulation of dysbiosis can improve outcomes in patients with HF. For example, one study showed that supplementation with probiotics, which are live bacteria, improved heart function and reduced the risk of death in patients with HF.

The authors raise some important points about the potential therapeutic targets for HF that involve modulation of the gut microbiota. We believe that this is an area of active research, and We are hopeful that we will see some promising developments soon.

Conclusions

This paper aimed to summarize the latest research on the characteristics and potential impact of the intestinal microbiota on HF. Recently, more and more studies have confirmed that gut microbiota plays an important role in the pathogenesis of HF. Changes in the diversity and abundance of microorganisms inhabiting the gut, as well as the accumulation of metabolites they produce, are associated with HF. On the other hand,

research on intestinal microflora may help in the development of new therapeutic methods. Bacteria that stimulate physiological and pathophysiological processes in the human body can successfully play a therapeutic role in HF. The composition of the intestinal microflora is constantly changing. Therefore, future research efforts should be directed at enriching the existing knowledge of gut microflora in the development of HF pathogenesis. It is also worth seeking new therapeutic interventions targeting the gut microbiota in HF.

Highlights are the following key points:

More research is needed to fully understand the role of gut microbiota in heart failure.

Diet, probiotics, and fecal microbiota transplantation (FMT) are all potential interventions for improving gut microbiota and reducing the risk of heart failure.

New therapeutic interventions targeting gut microbiota in HF are worth seeking.

Statements:

Conceptualization, JO, ŁW; methodology, JO, ŁW; software, JO, ŁW, XŻ, DF, AJ, KG, AS, GG; check, JO, ŁW, DF, AJ, KG, AS, GG; formal analysis, JO, ŁW, AJ, KG, AS, GG; investigation, JO, ŁW, XŻ, DF, AJ, KG, AS, GG; resources, JO, ŁW, XŻ, DF, AJ, KG, AS, GG; data curation, JO, ŁW, KG, AS, GG; writing - rough preparation, JO, ŁW, XŻ, DF, AJ, KG; writing - review and editing, JO, ŁW, XŻ, DF, AJ, KG, AS, GG; visualization, JO, ŁW, XŻ, DF, AJ, KG, AS, GG; supervision, JO, ŁW, GG; project administration, JO, ŁW, GG; receiving funding, JO, ŁW, XŻ, DF, AJ, KG, AS, GG. All authors have read and agreed with the published version of the manuscript

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