Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

The role of gut microbial symbiosis in Heart Failure: A systematic review

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Abstract:

Heart failure (HF) is a significant factor in the global burden of cardiovascular health. Recent studies have revealed that patients with heart failure exhibit distinct alterations in their gut flora, which in turn impact immunological balance and metabolism. This systematic literature review aims to determine the influence of gut dysbiosis on heart failure. We employed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria to carry out our systematic review. We conducted a comprehensive search of the literature using databases such as PubMed, PubMed Central (PMC), and Medline. A total of ten papers were selected for the purpose of review. Heart failure shown notable disparities in the composition of the gut microbiota. The Ruminococcus gnavus, Escherichia Shigella, Streptococcus sp, Veillonella sp, and Actinobacteria are relatively more abundant, while Eubacterium, Prevotella, Faecalibacterium, SMB53, and Megamonas are more depleted. The composition differed based on age, stage of heart failure, and extent of decompensation. The composition remained unchanged in relation to the ejection fraction. There was an upregulation of genes involved in the metabolism of amino acids, carbohydrates, choline trimethylamine-lyase (TMA-lyase), lipopolysaccharide (LPS) production, tryptophan, and lipid metabolism. The resulting alterations impacted the concentrations of metabolites, including trimethylamine N-oxide (TMAO), indoxyl sulfate (IS), and LPS, as well as inflammatory markers in both feces and plasma, hence contributing to the development of heart failure. These biomarkers associated with heart failure could be utilized as focal points for the prevention and treatment of heart failure. Individuals suffering from heart failure possess a distinct combination of gut bacteria that directly impact the development and progression of heart failure. Additional research is required to comprehend the causal connection between dysbiosis and heart failure.

Background

Heart Failure (HF) is a significant global public health issue, affecting about 23 million

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

individuals worldwide (1). In India, the accuracy and reliability of the prevalence and incidence estimates of HF are compromised due to the inadequate monitoring methodologies used to collect this data(2). The process of industrialization, urbanization, and economic growth in India has led to transformations that have increased the risk of heart failure. Cardiovascular disease (CVD) is the leading cause of mortality in India, and its incidence is projected to rise. In 2000, the number of patients with CAD in India was approximately 30 million. The annual occurrence of heart failure (HF) due to coronary artery disease (CAD) varies between 0.4% and 2.3%(2).

In India, the incidence of additional risk factors was also on the rise. In addition to the process of becoming older, it is projected that the number of people affected by hypertension (HTN) will increase from 118 million in 2000 to 214 million in 2025. Based on estimations from the year 2000, the incidence of heart failure (HF) resulting from hypertension (HTN) during a five-year period might range from 590,000 to 3.5 million cases. With a death rate of around 50% at five years, the prevalence of HF caused by HTN is predicted to be between 295,000 and 1.8 million cases. Furthermore, it is projected that the incidence of DM in India will increase from 32 million in 2000 to 70 million by 2025 (3). Research has demonstrated that the occurrence of heart failure (HF) rises from 2.3 cases per 1000 person-years for individuals with a HbA1c level below 6% to 11.9 cases per 1000 person-years for those with a HbA1c level above 11.9%.Based on the assumption of ideal glucose control, the estimated yearly incidence of heart failure (HF) caused by diabetes mellitus (DM) may rise from 73,600 cases in 2000 to 161,000 cases in 2025. Based on diabetes estimations from the year 2000, the incidence of heart failure (HF) during a five-year period might result in a total of 368,000 individuals. Assuming a 50% mortality rate within five years, the prevalence of HF specifically caused by diabetes could be calculated at 184,000. However, this is likely to be a low estimation, as a result of cautious assessments of HbA1c (2).

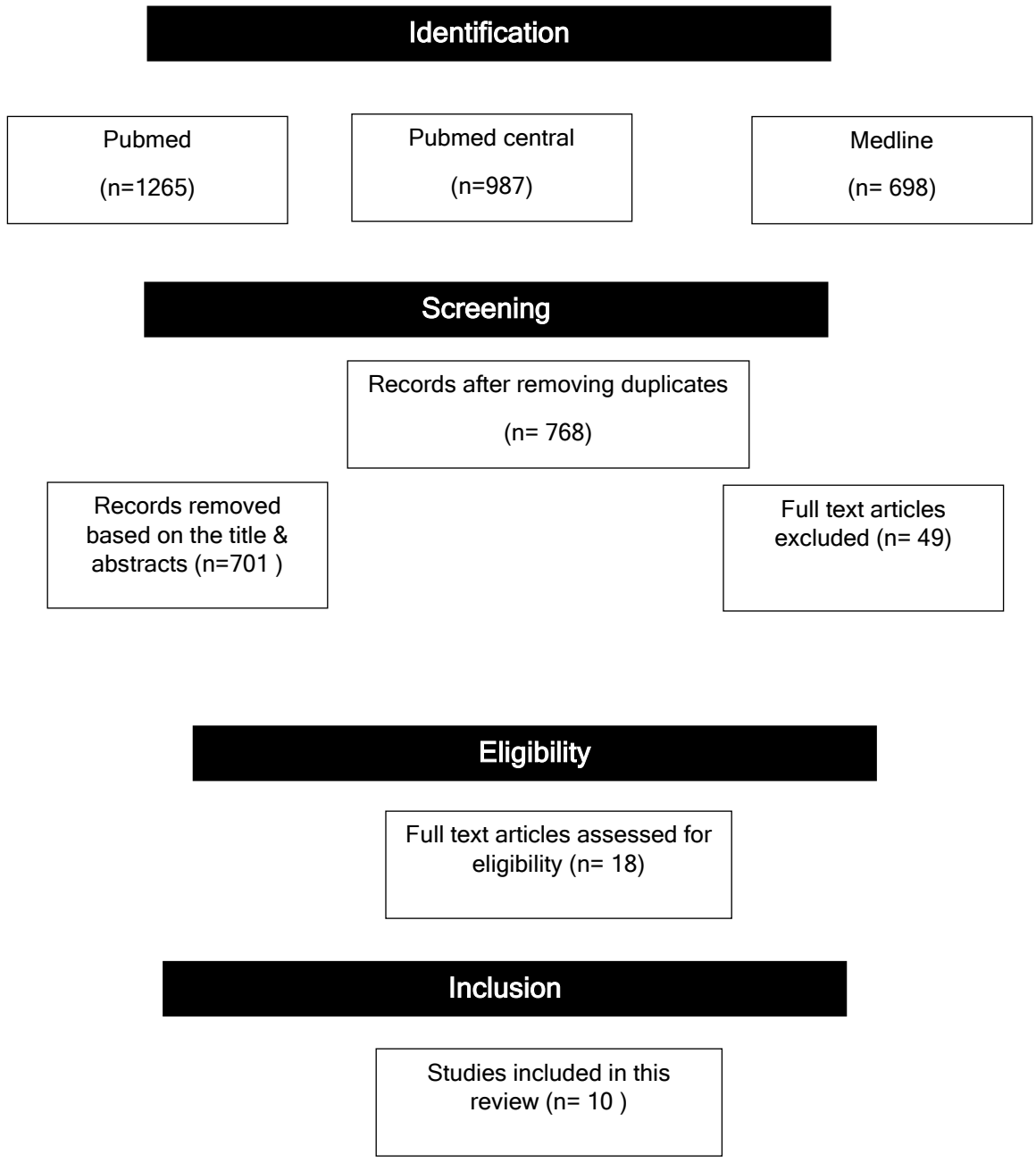
Heart failure (HF) is a condition that occurs when the heart is structurally or functionally damaged as a result of many causes, leading to its end-stage consequences. Heart failure is categorized into systolic heart failure, which is characterized by a reduced ejection fraction, and diastolic heart failure, which is characterized by a retained ejection fraction. Irrespective of the cause and category, heart failure is linked to widespread inflammation, presence of endotoxins in the bloodstream, and increased oxidative stress. These procedures ultimately impact the advancement, intensity, and consequently, the forecast of heart failure. The gut microbiome has recently been recognized as a significant factor in the development of chronic heart failure, as it has diverse impacts on the body, especially the immune system. The connection between the digestive system and the cardiovascular system is referred to as the gut-heart axis. The human body harbors a diverse range of microbial species, collectively referred to as the human microbiome, which are grouped into specific groups such as the oral, vaginal, gastrointestinal, and skin communities(4), (5), (6), (7). They play a role in maintaining general balance in the human body and in the development of diseases. Culture-independent analyses

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

employing advanced technology have been utilized to study the composition of the human microbiome (7). Dysbiosis, which is the modification of the makeup of these communities, is believed to be involved in the development of several disorders (4). Studies have also shown that the populations of microorganisms associated with the host can heighten the host's vulnerability to inflammatory bowel disease(8),type1diabetesmellitus(9), Cancer(10) and allergies(11). The gut microbiome has garnered significant attention in recent times due to its crucial function in preserving the immune system(12), (13),has the potential to impact different systems and organs in the body, which includes the musculoskeletal system (14)pulmonary systems (15),endocrine(16), (17), and central nervous(18).There is an increasing interest in assessing the connection between an imbalance in the gut's microbial community and the occurrence of cardiovascular illnesses, specifically atherosclerosis & chronic heart failure. Recent studies have observed the microbial breakdown of nutritional phosphatidylcholine into a metabolite called trimethylamine N-oxide (TMAO), which has been linked to the development of cardiovascular conditions like coronary artery disease as well as heart failure among individuals with intestinal dysbiosis(19). Although there is increasing interest in this area, the precise correlation among the gut microbiome & heart failure remains inadequately researched. Thus far, only a few restricted, small-scale investigations have been carried out to discern distinctive alterations in the gut microbiota composition along with metabolic profiles in individuals with heart failure. While research has shown that people with heart failure possess a unique group of microorganisms, it remains unclear whether these alterations are a direct cause or a result of heart failure. It is imperative to establish a cause-and-effect connection between gut dysbiosis along with heart failure in order to find precise fecal biomarkers that can be targeted for therapeutic purposes in the prevention and treatment of heart failure. This literature review provides a comprehensive analysis of the connection and significance of dysbiosis in individuals suffering from chronic heart failure. Additional research is necessary to establish a cause-and-effect relationship, if any, between dysbiosis & heart failure.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

Methodology:



ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

Figure 1: PRISMA flowchart

We conducted this systematic review in strict accordance with the most recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective of our investigation was to determine whether there is a correlation between gut microbial dysbiosis & chronic heart failure.

Search strategy:

In order to find studies that investigated the connection among intestinal microbial dysbiosis & chronic heart failure, we conducted a comprehensive search across three databases: Pubmed, PubMed Central (PMC), and Medline. For the purpose of extracting all of the pertinent articles for study, a methodical search technique that makes use of medical subject headings (MeSH) words and phrases was devised. "Chronic heart failure" "Heart failure" "Cardiac failure" "Gut microbiome" "Dysbiosis," "Intestinal dysbiosis" and "Intestinal microbiome" were some of the keywords that were used. In order to retrieve all of the relevant articles from the databases, we utilized the Boolean approach, as well as the MeSH strategy and keywords.

Our systematic reviewadhered to the PRISMA guidelines. The methodology was structured to comprehensively identify, screen, assess eligibility, and include studies pertinent to our research question. The following is a detailed description of each step in the process.

Identification:

A systematic literature search was performed across three databases: PubMed, PubMed Central, and Medline. The search was designed to include all relevant studies published up to the date of the search. The initial search yielded 1265 records from PubMed, 987 from PubMed Central, and 698 from Medline.

Screening:

All identified records were collated, and duplicates were removed, resulting in 768 unique records. These records were screened by reviewing titles and abstracts.

Eligibility:

The full texts of the remaining 18 articles were then assessed for eligibility based on predefined inclusion and exclusion criteria.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

Inclusion:

After a thorough assessment, 10 studies were found to meet all the eligibility criteria and were included in the final review.

Each step of the selection process was conducted independently by two reviewers, with discrepancies resolved through discussion or consultation with a third reviewer.

Results:

Study selection

In the beginning of our search, we looked through a total of 9845 articles that were present in the PubMed, PubMed Central (PMC), and Medline databases. After removing duplicates and studies that were published more than ten years ago and concentrating on pediatric patients, we were able to consist of 865 articles that were selected for additional screening. There were 768 papers that were not included after screening based on the titles, abstracts, & the criteria for inclusion and exclusion. In addition, we did not include any publications that were not observational studies & did not fulfill the requirements during the quality assessment process utilizing the JBI tool. The final selection for the review consisted of ten different articles. Observational studies with a cross-sectional design were all included in the papers. (Fig.1)

Study population

The patients who were included in the study were those who were experiencing either stable chronic heart failure, acute de novo heart failure, or acute decompensation of chronic heart failure. In order to have a better understanding of the effects that ejection fraction has on the gut microbiome, patients with heart failure who had low ejection fraction as well as those who had retained ejection fraction were incorporated in the study. Patients who were in various stages of heart failure were also included in the study. These patients included those who were in New York Heart Association (NYHA) classes I-IV, patients who had a left ventricular assist device (LVAD), and patients who had received a heart transplant (HT).

Gut composition

The approach of 16S rRNA gene amplification & sequencing was utilized in eight different research to investigate the changes in the microbiome's composition as well as its functional characteristics. An alternative study, on

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

the other hand, utilized the 16S rDNA gene amplification & sequencing technique. After cultivating the colonies on a particular type of agar, the remaining study discovered the colonies through the use of colony-forming units (CFU).

Nine of the ten papers examined the differences and similarities between the gut microbiota makeup of patients had clinically confirmed heart failure and that of controls. There was a considerable difference in the beta diversity (inter-individual diversity) between the two groups, according to the findings of all of these research. The effects of various phases of heart failure (NYHA classes I-IV, LVAD, and transient ischemic heart failure) on beta diversity were investigated in one of ten investigations.

Functional and metabolic changes

In patients who were diagnosed with heart failure, four of the ten papers investigated the functional changes that occurred in the gut's metagenome, and five among the ten publications investigated the alterations that occurred in the metabolites found in the feces and plasma.

Discussion

Over the past few years, there has been a growing interest in the interaction between the microbiota of the gut and other organ systems throughout the human body, including the circulatory system. This is mostly due to the potential role that these microbiota could have in the pathogenesis along with prognosis in heart failure. The purpose of this systematic review was to investigate the variety of gut microbes, changes in composition, and the functional & metabolomic changes that are related with cardiovascular disease in patients who have chronic heart failure.

Gut microbial richness and diversity in heart failure

A diversified gut microbiome is made up of millions of different species of microorganisms, each of which makes a distinct contribution to the preservation of homeostasis and coexists in a peaceful and mutually beneficial relationship with the host's digestive tract. The overall number of species is referred to as the alpha diversity, which is a measurement of intra-individual diversity. On the other hand, beta diversity refers to the specific species that are present in the gut at any given time, as well as the abundance of those species (a measurement of inter-individual diversity). We will now discuss the ramifications of the changes in gut microbial composition that are observed in patients with CHF. These changes will be detailed over the following few paragraphs.

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

Studies involving patients with systolic and diastolic heart failure

The interaction that occurs between the circulatory system and the digestive system has recently become a topic of interest for a great number of people. Wang et al. discovered that overall diversity and richness of bacteria among individuals with persistent CHF was much lower than in controls. This was the observation made by the researchers. (20).Patients with congestive heart failure were shown to have an overgrowth of pathogenic bacteria which include Escherichia coli, Klebsiella, and Haemophilus, in addition to a substantial enrichment of Ruminococcus gnavus. Ruminococcus gnavus was especially intriguing due to the fact that it had also been found to be increased in a previous investigation(21). In a previous study, it was demonstrated that it possesses pro-inflammatory capabilities. As a result, it has the potential to contribute to the development of an inflammatory response in chronic cardiac failure, which would then have an effect on the severity of the condition as well as its prognosis (22). Despite the fact that this study provides additional support for the findings of a number of earlier studies, it is impossible to disregard the fact that this was a relatively small investigation(20). Additionally, the individuals were not categorized according to the kind of heart failure, which include systolic and diastolic heart failure conditions. A previous study that was carried out by Hayashi and colleagues has disproved the notion that ejection fraction has a role in dysbiosis. However, additional large-scale longitudinal investigations are required in order to rule out the possibility that LVEF% has an effect on gut dysbiosis(23).

According to the findings of a new study, the most significant alteration in the gut microbiome of patients with heart failure is the reduction in the number of Eubacterium & Prevotella on network analysis (23). Within the digestive tract, these genera are responsible for a major portion of the production of critical amino acids. Aside from the fact that it was conducted not too long ago, the most significant advantage of the study was that it included patients who had heart failure with reduced ejection fraction (HFrEF) as well as those with heart failure with preserved ejection fraction (HFpEF). The researchers found that the alterations in the composition of the gut microbiome did not differ significantly between the two groups when compared to the controls. On the basis of these information, it is possible to deduce that the ejection fraction does not play a substantial role in the gut dysbiosis that is observed in individuals who have CHF.

Despite the fact that patients with heart failure had a lesser proportion of Eubacterium rectale & Dorea longicatena, a study of a small number found that there were no variations in the alpha diversity of the patients having heart failure. After additional investigation, they discovered that older patients with

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

heart failure had a smaller percentage of Bacteroidetes and a greater proportion of Proteobacter compared younger individuals with the same cardiac condition. In addition, the feces of elderly individuals included a higher concentration of Lactobacillus and a lower concentration of Faecalibacterium prausnitzii & Clostridium clostridiidioforme. In elderly individuals with heart failure, the depletion of Eubacterium rectale & Faecalibacterium prausnitzii results in a decrease in the generation of butyrate in the gut, which in turn has an effect on the integrity of the gut and creates a situation that is detrimental to inflammation. Even though they have shed light on the connection between dysbiosis and age, the most significant weakness of their research is that it does not take into account the potential confounding influence that aging as a natural process, drugs, nutrition, and comorbidities can have on the microbiome of the gut. The research was unable to demonstrate a temporal connection between the progression of age in patients with heart failure and gut dysbiosis. It is recommended that long-term longitudinal studies be conducted in order to gain an understanding of specific aging changes in order to develop individualized treatment strategies that are depending on the age of the patient (24).

On top of that, a study discovered that individuals with heart failure had a non-significant expansion of dangerous bacteria in their guts, but it also discovered that the overall amount of microbes in their bodies had decreased significantly. It was shown that the number of genera belonging to the Blautia, Collinsella, unclassified Erysipelotrichaceae, & unclassified Ruminococcaceae families had significantly decreased. In addition, they hypothesized that the depleting of Collinsella was unique to heart failure because it was found to be present even in individuals who had heart failure in addition to concomitant conditions such as diabetes mellitus , ischemic heart disease (25). There was also recent research that suggested that Blautia have anti-inflammatory potential. Therefore, the fact that its depletion has been established may be a factor in a pro-inflammatory condition, which further exacerbates the severity of heart failure and accelerates its progression. There is a possibility that a constellation of these alterations is a particular finding of heart failure, and this possibility needs to be investigated further in large-scale, multi-centric longitudinal investigations.

Studies involving patients with only systolic heart failure

Cui et al. conducted research on the beta diversity of the samples (using the Bray Curtis distances as their basis). They discovered that the composition of the microbiome was considerably different among individuals with HFrEF, and this effect was independent of whether or not the patients were taking statins or PPIs. In contrast, there was no discernible variation in the beta diversity between individuals with ischemic cardiomyopathy (ICM) and those with

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

dilated cardiomyopathy (DCM), leading to the conclusion that the alterations in beta diversity are not dependent on the underlying cause of heart failure with reduced ejection fraction (HFrEF). The most important characteristics were an increased representation of Ruminococcus gnavus and a decreased representation of Faecalibacterium prausnitzii, both of which were measured in the feces. Due to the fact that it plays a role in the formation of butyrate, Faecalibacterium prausnitzii has been investigated for its potential to contain anti-inflammatory properties(26). However, limiting the number of bacteria that produce butyrate is a contributor for the pro-inflammatory state that is present in CHF. This is due to the fact that butyrate plays a crucial function in avoiding inflammation of the body as well as damage to the gut. It has been postulated that the functional & metabolic alterations that occur in children with congestive heart failure are caused by the interaction between microorganisms that affect the homeostasis of butyrate in the body. As a result, we advise conducting additional research to find these derangements as potential therapeutic targets in order to prevent the progression and inflammation that are associated with CHF. Despite the fact that this was a multi-center study that focused on those who had systolic dysfunction, the majority of the participants were hospitalized patients who had impaired cardiac function (NYHA classes III & IV). As a result, it is possible that stable people who had systolic heart failure were not well represented in the study. In addition, neither the patients' diets nor their exercise routines were taken into consideration.

Patients with systolic heart failure did not have a substantial decline in the overall variety of the species (alpha diversity) compared to the controls, according to the findings of another study that investigated the range of species in HFrEF patients. However, these patients did have notable changes in the content of the microbiome. The researchers found that the relative abundance of bacteria belonging to the phylum Actinobacteria and the genus Bifidobacterium was higher, whereas the quantity of Megamonas bacteria was lower (27). They hypothesized that the interaction between these bacteria was responsible for the development of a pro-inflammatory state in systolic heart failure; similar changes have been found in individuals with Behcet's illness in the past(28). On the other hand, this study had a number of shortcomings, including a limited sample size, a study conducted at a single center, and an inability to rule out the possibility of confounding impacts of physical activity and diet on the stomach. Another study that investigated the changes in the makeup of the gut microbiome in patients with heart failure with reduced ejection fraction (HFrEF) came to the conclusion that although overall alpha diversity didn't vary substantially across groups, beta diversity did differ, even after taking into account factors such as age, renal function, and drug usage

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

(29).In patients with heart failure with reduced ejection fraction (HFrEF), there was a decrease in the number of SMB53 and an increase in the number of Streptococcus and Veillonella species.

An investigation carried out on individuals with systolic heart failure revealed a notable proliferation of harmful microorganisms, including Campylobacter, Shigella, Salmonella, Yersinia, and candida, in patients with HFrEF(30). Similarly, a study found an excessive proliferation of harmful Enterobacteriaceae, particularly in the Escherichia/Shigella clusters. However, the amount detected did not reach a statistically significant level (25).Patients who were diagnosed with heart failure also exhibited elevated levels of intestinal permeability (IP), right atrial pressure (RAP), and C-reactive protein (CRP). The pathogenic gut flora overgrowth, IP, RAP, and CRP were all examined by Pasini et al., who were the first to come to the conclusion that they were connected. In addition, they highlighted that the severity of heart failure was correlated with an increase in these parameters, as shown by the NYHA classes(31).Reduced intestinal blood circulation & inflammation, which leads to an expansion of pathogenic organisms, are the causes of increased intestinal permeability (IP) when RAP levels are high (32). This pathogenic growth ultimately hinders the generation of important intestinal chemicals that include short chain fatty acids (SCFA), which results in the development of a condition that is supportive of inflammation and has an impact on the function of the cardiovascular system as well as the progression of CHF(33). There is a need for additional research to determine whether or if the re-establishment of gut microbiota can stop the progression of chronic heart failure (CHF).

A large-scale study was carried out by Yuzefpolskaya and colleagues in order to determine the variation in gut composition that occurs across the several stages of heart failure, which include NYHA Class I-IV, LVAD, & HT. They noticed a decline in the diversity of the gut across all stages, beginning with NYHA class I and continuing through class IV. In addition, the diverse characteristics among individuals with LVAD & HT remained very low. This decrease in diversity was mostly caused by a specific group of taxa that had characteristics that promote anti-inflammatory responses (34).

Studies involving patients with only diastolic heart failure

Although other studies had been carried out on patients with HFrEF in order to assess gut dysbiosis, the research that was carried out by Beale et al. was one of a kind due to the fact that it only included patients who were suffering from diastolic heart failure. The purpose of the investigation was to determine

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

whether or not patients with HFpEF had gut microbial dysbiosis. As a result of their investigation, they came to the conclusion that individuals who had HFpEF had a different alpha and beta diversity when compared with the control group. According to their findings, the most important factor that contributed to the difference in beta diversity consisted of a considerable reduction in the number of microorganisms that produced SCFA, in particular Ruminococcus(31).

Recently, research has been conducted to investigate the relationship that exists between SCFAs, the circulatory system, and the immune system of the body. By influencing a wide range of parameters within the body, including insulin resistance, management of diabetes, obesity, hypertension, and cardiac hypertrophy and fibrosis, depletion of short-chain fatty acids (SCFAs) plays a role in the pathophysiology and prognosis of heart failure with preserved ejection fraction (HFpEF). Consequently, Beale et al. postulated that the bacteria within the gut that produce SCFA could be possible targets for avoiding the development of the further development of heart failure with preserved ejection fraction (HFpEF). It was also found in this study that the modifications in beta diversity that occurred in patients with heart failure with preserved ejection fraction were not influenced by dietary variables. The participants in this study were limited to those who had heart failure with preserved ejection fraction (HFpEF). Therefore, it is not possible to apply the knowledge gained about the impact of dietary variables on the stomach to all patients who have heart failure.

Functional and metabolomic alterations in heart failure

Along with the research of the composition of the gut microbiome in patients with CHF, it is also important to uncover the consequences of those alterations on the physiological expression of genes as well as metabolic pathways in order to gain a more in-depth understanding of the influence that dysbiosis has.

There have been two studies that have concentrated on the subject of interest in recent times. The levels in the blood of the inflammatory markers (IL-6, IL-8, TNF-a, & IL-10) were investigated by Wang et al. as they were found in patients who were experiencing stable chronic heart failure(20). Research conducted in the past has shown that an increase in intestinal permeability and amplification of pathogenic bacteria in the gut are connected(30). Leakage of substances from the microbiota of the gut into the circulatory system and into the bloodstream is caused by inflammation. These compounds ultimately enter the bloodstream. Wang et al. found that patients had an elevated level of inflammatory mediators such IL-6, IL-8, & TNF-a compared to controls. This

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

was based on the concept that was presented earlier. In addition to this, they found that the amount of IL-10 found in their serum had reduced. On top of that, the patients' CRP levels were much higher than average(20).These findings lend more support to the idea that chronic heart failure (CHF) is characterized by increased intestinal permeability as a result of dysbiosis in the gut, as well as the role that inflammation plays in the etiology of heart failure. All of the patients who participated in this study were of advanced age and were in a stable clinical state. In light of this, the findings of this study can't be extrapolated to patients who are either clinically unstable or young and who are experiencing an aggravation of heart failure respectively. In addition, the LVEF percentage of the individuals in question has not been characterized in a precise manner.

A study that was quite similar to this one was carried out largely on patients who were experiencing systolic heart failure at different stages. The researchers came to the conclusion that the levels of inflammation, including IL-6, CRP, adiponectin, endothelin, & TNF-a, as well as oxidative stress, including isoprostane, increased in tandem with progression of heart failure. In the long run, they decreased in patients with LVAD and heat stroke(20). It is therefore possible to comprehend whether inflammation plays a crucial part in the growth of systolic heart failure through the progression of the disease. Since the rate of ejection improved following the placement of the assist device and the heart transplantation, the enhanced circulation in the gut alleviated dysbiosis, and as a result, the inflammation decreased over time. On the other hand, they additionally noticed the level of the biomarker of endotoxemia, known as LPS, remained raised after both LVAD and HT. On the other hand, sCD14 remained elevated exclusively after LVAD and reduced in HT(20). These discoveries shed light on the dynamic relationship that exists between the decreased ejection fraction, the increased gut permeability, the gut dysbiosis, and the inflammation.
In the year 2021, Hayashi and colleagues conducted research to study the connection between dysbiosis in the gut and alterations in the metabolism of amino acids. The researchers found that the abundance of genes responsible for degradation was higher at the metagenome level, whereas the quantity of genes responsible for the production of essential amino acids was lower. Consequently, the amounts of important amino acids, such as branch-chain amino acids, alanine, and histidine, are seen in the blood of patients who are suffering from heart failure. In addition, they found that there was a positive association between the genes responsible for essential amino acid production in microorganisms and the levels of branch-chain amino acids in plasma(23).While the study found a connection among dysbiosis and metabolic

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

changes, it did not show a clear cause-and-effect relationship among dysbiosis-driven metabolic changes and the onset of heart failure. Priorly, a comparable investigation likewise documented a notable disparity in the prevalence of genes accountable for the metabolic processes of amino acids, xenobiotics, carbohydrates, and vitamins(29).

The impact of TMAO on the cardiovascular system has undergone extensive investigation in recent times. An increase in the expression of genes encoding choline trimethylamine-lyase (TMA-lyase) and lipopolysaccharide (LPS) production was detected in a group of patients with heart failure with reduced ejection fraction (HFrEF)(21). One of the enzymes that is responsible for the production of TMAO is called TMA-lyase. It has been established that TMAO is directly associated with the advancement of CHF due to the effects that it has on the kidney, which results in renal tubulointerstitial fibrosis and dysfunction(35). Furthermore, there is a decrease in the expression of genes responsible for butyrate acetoacetate CoA transferase, amino acid synthesis and transport, nucleotide sugar biosynthesis, iron transport system, and short-chain fatty acid metabolism. Butyrate exhibits anti-inflammatory properties and confers a protective effect on the intestines. Reducing the activity of genes involved in the production of butyrate leads to a decrease in the amount of butyrate in the host, which in turn promotes a state of inflammation that may exacerbate the degree of heart failure. The metabolomic analysis also identified a dysregulation of many metabolites, with the most prominent being the elevation of sphingosine 1-phosphate(21). It has been demonstrated that sphingosine 1-phosphate is responsible for cardiac dysfunction and remodeling, in addition to playing an active part in a number of other pathological processes that are associated with the cardiovascular system (36).

On the other hand, an enhanced expression of TMA-lyase & tryptophanase genes was detected in patients who were suffering from decompensated heart failure(27).A higher level of TMAO would be observed in these patients, which could potentially have a role in the advancement of heart failure. Furthermore, they found that there was a positive correlation among the concentrations of indoxyl sulfate and TMAO and the quantity of Escherichia and Shigella. The cardiovascular system is known to be negatively affected by indoxyl sulfate, which is a uremic toxin that is dependent on microorganisms. A higher level of tryptophanase gene expression in the microbiota during the decompensated phase is responsible for the formation of indoxyl sulfate in the host bacteria. They also

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

hypothesized that there is an inverse association connecting the abundance of the genus Bifidobacterium and the levels of plasma indoxyl sulfate, indicating that it may have a cardioprotective impact in people who have hearts that are not functioning properly(27).

Limitations& future perspectives

In the first place, the majority of the studies that were included were single-centered, small-sized studies that involved a limited number of patients. There are a number of factors that can influence the microbiota in the gut, such as the patient's age, the presence of comorbid disorders, nutrition, drugs, and physical activity. Dietary and exercise histories were not taken into consideration in the majority of the trials that were included. On top of that, there was a notable disparity between the patients and the control individuals in terms of the amount of medication that they took. According to the findings of none of these research, there is no correlation between gut dysbiosis and heart failure in terms of time. For this reason, large-scale, multi-center longitudinal studies need to determine whether or not there is a causal association between the two variables.

Conclusions

A significant shift can be seen in the richness and composition of the microbiome that is present in the stomach of individuals who are suffering from heart failure. This change can be noticed. Additional changes in composition can be seen depending on characteristics such as age, the severity of heart failure, and the stage of the condition where it is occurring. In addition, the presence of dysbiosis in the gut has an effect on the metabolic equilibrium of the host. This syndrome causes a disruption in the equilibrium of essential metabolites in plasma and feces, including TMAO, indoxyl sulfate, amino acids, and inflammatory indicators. This condition is characterized by the presence of inflammatory markers. These metabolic anomalies are a contributing factor in the formation of a pro-inflammatory state, which in turn has an extra impact on the severity of heart failure and the evolution of the condition. Specifically, the biomarkers of heart failure that are being reviewed here are those that are found in the feces and the plasma. These indicators have the potential to become essential targets for the prevention of heart failure and the improvement of patient prognosis in the event that heart failure occurs. In accordance with our proposition, it is recommended that additional large-scale

ISSN: 0975-3583,0976-2833 VOL15, ISSUE 02, 2024

longitudinal studies be carried out in order to ascertain whether or not there is a temporal connection between gut dysbiosis and heart failure.

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