Получена: 17 Мая 2024 / Принята: 29 Октября 2024 / Опубликована online: 30 Декабря 2024

DOI 10.34689/SH.2024.26.6.015

UDC 617-089.844

STUDY OF THE GUT MICROBIOTA COMPOSITION ROLE IN THE CONTEXT OF CHRONIC HEART FAILURE DEVELOPMENT: REVIEW OF CURRENT DATA

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Abstract

Background. Chronic heart failure (CHF) is a global health issue with high mortality rates. According to statistical data, in Kazakhstan, 4.7% of the population suffers from CHF, which amounts to approximately 320,000 people. In the United States, 6.7 million individuals are affected, with projections rising to 8.5 million by 2030. Despite advancements in treatment, mortality rates remain high. Recent studies highlight the role of gut microbiota in systemic inflammation, a key factor in cardiovascular diseases. Exploring the gut microbiota offers a novel perspective for understanding CHF pathogenesis and potential therapeutic interventions.

Aim. The review aims to explore the role of gut microbiota in the development and progression of CHF and examine new methods to improve the clinical status of patients through gut microbiota modulation.

Search strategy. A literature review was conducted using PubMed, Medline, Cochrane Central register of Controlled Trials database, Web of Science, Scopus, https://elibrary.ru, and Google Scholar over the past 10 years, providing information on the role of the gut microbiota in the development and progression of CHF. The review includes works published in Russian and English

Results. Disruption of the intestinal barrier allows endotoxins and microbial metabolites to enter systemic circulation, triggering systemic inflammation and endothelial dysfunction, exacerbating CHF. Gut hypoperfusion and increased permeability further contribute to the disease's progression. Microbial metabolites, such as trimethylamine-N-oxide (TMAO) and short-chain fatty acids (SCFAs), influence systemic inflammation. Elevated TMAO levels are linked to cardiovascular events, while SCFAs have protective effects but are reduced in CHF patients. Gut dysbiosis is prevalent in CHF, marked by altered microbiota composition, including decreased beneficial bacteria and increased pathogenic species. These changes correlate with systemic inflammation and disease severity.

Conclusions. The gut microbiota significantly impacts CHF pathogenesis through its influence on systemic inflammation and metabolic pathways. Modulating gut microbiota presents promising therapeutic opportunities, including dietary adjustments, probiotics, prebiotics, and fecal microbiota transplantation. Further research is essential to optimize interventions and explore the gut-heart axis's role in CHF progression and comorbidities.

Keywords*: cardiology, chronic heart failure, gut microbiome, TMAO, SCFAs, systemic inflammatory response.*

Резюме

ИССЛЕДОВАНИЕ РОЛИ СОСТАВА МИКРОБИОТЫ КИШЕЧНИКА В КОНТЕКСТЕ РАЗВИТИЯ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ: ОБЗОР СОВРЕМЕННЫХ ДАННЫХ

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Введение. Хроническая сердечная недостаточность (ХСН) представляет собой глобальную проблему здравоохранения с высокой смертностью. Согласно статистическим данным в Казахстане 4,7 % населения страдает от ХСН, что составляет примерно 320 тыс. чел. В США страдают ХСН 6,7 млн человек, к 2030 году прогнозируется увеличение числа пациентов до 8,5 млн. В целом глобальная распространенность ХСН варьируется от 100 до 900 случаев на 100 тыс. человеко-лет в зависимости от используемых диагностических критериев и исследуемой популяции. Несмотря на достижения в лечении ХСН, сохраняются высокая частота госпитализаций и смертность. Новые исследования уделяют внимание роли кишечной микробиоты в развитии системного воспаления, которое играет важную роль в патогенезе сердечно-сосудистых заболеваний. Изучение микробиоты открывает новые перспективы в понимании патогенеза ХСН и разработке терапевтических подходов.

Цель исследования. Исследовать роль кишечной микробиоты в развитии и прогрессировании ХСН, а также рассмотреть новые методы коррекции клинического состояния пациентов путем модуляции микробиоты.

Стратегия поиска. Поиск литературы проводился с использованием ресурсов PubMed, Medline, Центрального реестра контролируемых испытаний Cochrane, Web of Science, Scopus, https://elibrary.ru и Google Scholar за последние 10 лет, предоставляющий информацию о роли микробиоты кишечника в развитии и прогрессировании ХСН. Обзор включает работы, опубликованные на русском и английском языках.

Результаты. Нарушение барьерной функции кишечника способствует проникновению эндотоксинов и микробных метаболитов в системный кровоток, что вызывает системное воспаление и эндотелиальную дисфункцию, ухудшающую течение ХСН. Гипоперфузия кишечника и увеличение его проницаемости усугубляют прогрессирование заболевания. Метаболиты микробиоты, такие как триметиламин-N-оксид (ТМАО) и короткоцепочечные жирные кислоты (КЦЖК), участвуют в развитии системного воспаления. Высокий уровень ТМАО ассоциирован с сердечно-сосудистыми событиями, тогда как КЦЖК обладают защитным эффектом, но их уровень снижен у пациентов с ХСН. У пациентов с ХСН наблюдается дисбиоз кишечника, характеризующийся снижением числа полезных бактерий и увеличением патогенной флоры. Эти изменения коррелируют с системным воспалением и тяжестью заболевания.

Выводы. Кишечная микробиота играет значительную роль в патогенезе ХСН через влияние на системное воспаление и метаболические процессы. Модуляция микробиоты открывает перспективные терапевтические возможности, включая диетическую коррекцию, пробиотики, пребиотики и трансплантацию кишечной микробиоты. Для оптимизации подходов и дальнейшего изучения влияния «кишечник–сердце» требуется проведение дополнительных исследований.

Ключевые слова: *кардиология, хроническая сердечная недостаточность, кишечный микробиом, ТМА, ТМАО, КЦЖК, системная воспалительная реакция.*

Түйіндеме

СОЗЫЛМАЛЫ ЖҮРЕК ЖЕТІСПЕУШІЛІГІНІҢ ДАМУЫНДАҒЫ ІШЕК МИКРОБИОТАСЫ ДИНАМИКАСЫНЫҢ МӘНІ: ЗАМАНАУИ ЗЕРТТЕУЛЕР ШОЛУЫ

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Кіріспе. Созылмалы жүрек жеткіліксіздігі (СЖЖ) – жоғары өлім-жітім көрсеткіштерімен сипатталатын жаһандық денсаулық сақтау мәселесі. Статистикалық мәліметтерге сәйкес, Қазақстанда халықтың 4,7%-ы СЖЖ-мен ауырады, бұл шамамен 320 мың адамды құрайды. АҚШ-та 6,7 миллион адам осы дертке шалдыққан, ал 2030 жылға қарай бұл көрсеткіш 8,5 миллионға жетеді деп болжануда. Заманауи емдеу әдістерінің жетістіктеріне қарамастан, ауруханаға жатқызу және өлім-жітім деңгейі әлі де жоғары. Соңғы зерттеулер ішек микробиотасының жүйелік қабыну, жүрек-қан тамырлары ауруларының маңызды факторына айналған рөлін атап өтуде. Ішек микробиотасын зерттеу СЖЖ патогенезін түсіну мен жаңа емдеу әдістерін іздеуде жаңа бағыт ұсынады.

Мақсаты. Ішек микробиотасының созылмалы жүрек жеткіліксіздігі дамуындағы рөлін зерттеп, пациенттердің клиникалық жағдайын жақсартудың жаңа әдістерін қарастыру.

Іздестіру стратегиясы. PubMed, Medline, Cochrane орталық бақыланатын сынақтар тізілімі, Web of Science, Scopus, https://elibrary.ru және Google Scholar ресурстары арқылы соңғы 10 жыл аралығындағы әдебиеттерге шолу жасалды. Орыс және ағылшын тілдерінде рецензияланған мақалалар арнайы іріктеу және шығару критерийлері негізінде қаралды.

Нәтижелер. Ішек тосқауылының бұзылуы эндотоксиндер мен микробтық метаболиттердің жүйелік қан айналымына енуіне, нәтижесінде жүйелік қабынуға және эндотелий дисфункциясына әкеледі, бұл СЖЖ-ны нашарлатады. Ішектегі гипоперфузия мен өткізгіштіктің жоғарылауы аурудың асқынуына қосымша әсер етеді. Микробтық метаболиттер, мысалы, триметиламин-N-оксид (ТМАО) және қысқа тізбекті май қышқылдары (ҚТМҚ), жүйелік қабынуға әсер етеді. ТМАО деңгейінің жоғарылауы жүрек-қан тамырлары оқиғаларымен байланысты, ал ҚТМҚ қорғаныс қасиеттерге ие, бірақ СЖЖ пациенттерінде төмен деңгейде анықталған. СЖЖ пациенттерінде ішек дисбиозы жиі кездеседі, пайдалы бактериялардың азаюымен және патогендік түрлердің көбеюімен сипатталады. Бұл өзгерістер жүйелік қабынумен және аурудың ауырлығымен байланысты.

Қорытынды. Ішек микробиотасы жүйелік қабыну және метаболикалық жолдар арқылы СЖЖ патогенезіне айтарлықтай әсер етеді. Ішек микробиотасын модуляциялау диеталық түзетулер, пробиотиктер, пребиотиктер және нәжіс микробиотасын трансплантациялау сияқты перспективалы емдеу әдістерін ұсынады. Бұл бағыт бойынша қосымша зерттеулер жүргізу қажет, сонымен қатар ішек-жүрек осінің СЖЖ және қатар жүретін аурулардың дамуына ықпалын зерттеу маңызды.

Түйінді сөздер: *кардиология, созылмалы жүрек жеткіліксіздігі, ішек микробиомасы, ТМАО, ҚТМҚ, жүйелік қабыну реакциясы.*

For citation / Для цитирования / Дәйексөз үшін:

Bekbosynova M.S., Jetybaeva S.K., Aipov B.R., Nurlan K.R., Sailybaeva A.I., Taukelova A.T., Laiskanov I.A., Aldanysh Zh.Zh., Kushugulova A.R. Study of the Gut Microbiota Composition Role in the Context of Chronic Heart Failure Development: Review of Current Data // *Nauka i Zdravookhranenie* [Science & Healthcare]. 2024. Vol.26 (6), pp. 122-131. *doi 10.34689/SH.2024.26.6.015*

Бекбосынова М.С., Джетыбаева С.К., Аипов Б.Р., Нурлан К.Р., Сайлыбаева А.И., Тауекелова А.Т., Лаисканов И.А., Алданыш Ж.Ж., Кушугулова А.Р. Исследование роли состава микробиоты кишечника в контексте развития хронической сердечной недостаточности: обзор современных данных // Наука и Здравоохранение. 2024. Т.26 (6). С. 122-131. *doi 10.34689/SH.2024.26.6.015*

Бекбосынова М.С., Джетыбаева С.К., Аипов Б.Р., Нурлан К.Р., Сайлыбаева А.И., Тауекелова А.Т., Лаисканов И.А., Алданыш Ж.Ж., Кушугулова А.Р. Созылмалы жүрек жетіспеушілігінің дамуындағы ішек микробиотасы динамикасының мәні: заманауи зерттеулер шолуы // Ғылым және Денсаулық сақтау. 2024. Т.26 (6). Б. 122-131. *doi 10.34689/SH.2024.26.6.015*

Introduction

Over the past few decades, cardiovascular diseases (CVDs) have been recognized as the leading global cause of death with the highest morbidity and mortality rates worldwide [8,21,27,30,51,53]. According to the World Health Organization, in 2019, approximately 17.9 million deaths were attributed to cardiovascular diseases, accounting for 32% of total mortality, and this number is projected to increase [9,13,71]. Epidemiological data indicate a steady increase in the prevalence of CHF, reaching 1–2% in the general population and exceeding 10% among individuals over 70 years old [63].

Heart failure (HF) is a multifaceted clinical condition caused by various factors and underlying physiological mechanisms, characterized by dyspnea or limited tolerance to physical exertion due to impaired cardiac ventricular contractility [1]. HF manifests as a syndrome with specific symptoms and indicators resulting from heart function impairment, ultimately leading to reduced life expectancy. The pathophysiology of HF is typically described as myocardial dysfunction, which can be systolic, diastolic, or both. This dysfunction is often a consequence of underlying conditions such as coronary artery disease, hypertension, diabetes, dyslipidemia, and obesity [49]. HF can manifest in acute and chronic forms. The acute form of HF is associated with various markers of inflammation, while chronic heart failure is characterized by an abnormal inflammatory state involving pro-inflammatory agents that are considered key in the development of this condition [7,61].

Despite comprehensive attention from researchers and the effectiveness of modern treatment methods, there is still a high prevalence and socioeconomic significance of this disease. This trend highlights the need for comprehensive management strategies that not only incorporate advances in pharmacological therapy but also deepen our understanding of the underlying mechanisms of heart failure. One of the emerging approaches to understanding this issue is exploring the role of gut microbiota and its metabolites [29].

Currently, one of the new directions in studying the development of chronic heart failure is the investigation of the compositional makeup of the human gut and the products of their metabolism. Many authors increasingly mention the gut microbiota (GM) as one of the potentially modifiable factors involved in the pathogenesis of various diseases, including cardiovascular diseases [8,17,70]. The gut microbiota is the collection of microorganisms colonizing the gastrointestinal tract. The gut microbiota actively participates in the production of various metabolites acting as signaling molecules and regulators of vital processes [28]. Nowadays, changes in the compositional makeup of the microbiota and the role of gut flora metabolites in the pathogenesis of chronic systemic diseases and the

formation of various "axes" between the gut and the function of other internal organs are being increasingly studied [50,58]. Special attention is paid to the products of the intestinal flora metabolism such as trimethylamine‑N‑oxide (TMAO), lipopolysaccharide (LPS), and short-chain fatty acids (SCFAs) in the development of chronic systemic inflammatory reactions, the various concentrations of which can act as independent predictors or markers [45,60].

It is known that changes in the quantitative and qualitative composition of the gut microbiota are associated with the clinical course of various diseases - obesity, diabetes mellitus, bronchial asthma, and other allergic diseases, behavioral disorders, and nervous system development, as well as in the development and course of cardiovascular diseases [2,5,41].

The gut microbiota acts as one of the potentially modifiable factors involved in the pathogenesis of HF development. In everyday life, the microbiome contributes to the absorption of essential nutrients, acting as a barrier, participating in flora composition regulation, and suppressing excessive growth and colonization of potentially pathogenic bacteria. The composition of the gut microbiota can be influenced by many factors, including ethnic background, age, medication use, harmful habits, diet, obesity, comorbidities, and even in some studies, a correlation between emotional background and gut microbiota status is described [24,32,34]. Accordingly, potential therapeutic opportunities are opening up, including diet correction, probiotic and prebiotic use, fecal microbiota transplantation, and lifestyle changes - providing new possibilities for modulating the gut microbiota, thereby preventing the development or correcting chronic systemic inflammatory processes that affect multiple axes in the human body [19].

Aim of this review is to provide an understanding of the role of the gut microbiota in the development and progression of chronic heart failure (HF), as well as to explore new methods of correcting the clinical status of patients with HF.

Search strategy

The publication search was conducted using keywords relevant to the topic, utilizing resources such as PubMed, Medline, Cochrane Central register of Controlled Trials database, Web of Science, Scopus, https://elibrary.ru, and Google Scholar over the past 10 years, providing information on the role of the gut microbiota in the development and progression of CHF. However, articles from earlier years were included in the literature review due to their fundamental contribution to the study of this topic.

For this literature review, articles containing evidence-based experimental and clinical data on the most contemporary issues regarding the composition of the gut microbiome and its relationship with the development of chronic heart failure were used. The following keywords were used in the search process: "cardiology", "chronic heart failure", "gut microbiome", "trimethylamine N-oxide (TMAO)", "short-chain fatty acids (SCFAs)", "metabolites", "systemic inflammatory response".

All peer-reviewed published articles with relevant materials on the connection between the gut microbiota and CHF were considered suitable for inclusion. The review includes works published in Russian and English languages and specific inclusion and exclusion criteria are depicted in Figure 1.

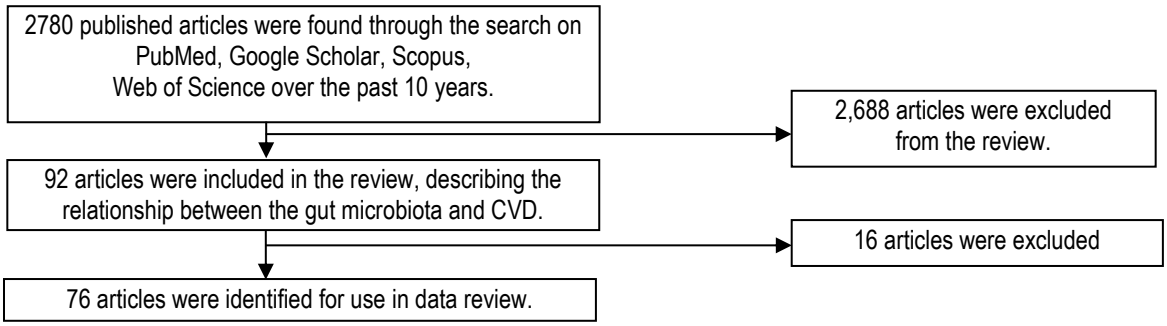

Figure 1. Data review.

Results

The Role of Intestinal Barrier in Heart Failure ("Barrier Hypothesis").

The mucosal multilayered epithelium of the intestine, together with the colonizing microbiome and some immune cells in the lamina propria of the intestine, are collectively referred to as the intestinal barrier, demonstrating some fundamental evidence of maintaining intestinal homeostasis [15]. The intestinal epithelium forms a critical protective boundary - a single-cell layer that separates the body from the contents of the intestines. This cellular barrier plays a vital role in defending against pathogens and preventing inflammatory responses, acting as the body's frontline defense system in the gut. [33]. In addition, the integrity of intercellular connections, the activity of cotransporters and various receptors are actively involved in strengthening and integrity of the intestinal barrier. [47].

Some studies emphasize the particular role of the intestinal barrier function, whereby the influence of mechanical and biological factors disrupts the barrier's integrity, leading to the penetration of endotoxins and microbial metabolites directly into the systemic circulation, resulting in the development of endotoxemia and, consequently, the amplification of cascades in the progression of chronic systemic inflammation [42,52]. Thus, the chain associated with disruption of the intestinal barrier function creates a vicious cycle by developing multiple complex immune-mediated pathways [50]. Microorganism migration through the intestinal wall is accompanied by the entry into the systemic circulation of endotoxins such as lipopolysaccharide (LPS) found in the outer membrane of many gram-negative bacteria, which in turn, through Toll-like receptor 4 (TLR4) of macrophages, adipocytes, and dendritic cells, induces the synthesis of pro-inflammatory

molecules (IL-6, TNF-α, IL-1, CRP, etc.), participating in the development of systemic inflammatory reactions and the formation of endothelial dysfunction, which plays a significant role in the development of cardiovascular diseases [64].

It is assumed that with a decrease in cardiac perfusion function, the hemodynamic balance is disturbed, leading to hypoperfusion of the gastrointestinal tract and stasis of blood flow, which causes hypoxia and stasis of the intestinal wall, especially the villi, which are more prone to ischemia. This condition of intestinal hypoperfusion leads to distortion of the intestinal mucosa and, ultimately, worsens the integrity of the intestinal barrier, resulting in the development of edema-ascitic syndrome [50, 57, 59, 72]. The presence of edema-ascitic syndrome in patients with HF, collagenous and thick mucous membrane deficiency, has shown higher concentrations of endotoxins and pro-inflammatory cytokines in the blood plasma, thereby leading to further increased intestinal permeability [50,59].

In many works, thickening of the intestinal mucosa wall, due to hypoxia, and the content of collagen proportionally correlated with the severity of HF and were characteristic features of this patient group [6,64].

On the other hand, with the development of hemodynamic imbalance, there is an increase in intestinal wall permeability, which creates an additional load on the pump function of the heart, due to the activity of the sodium-hydrogen exchanger-3 (NHE-3), when sodium and water absorption occurs through the transporter, thereby overloading the volume of the cardiac chamber, ultimately leading to earlier progression of heart failure [56].

An interesting regularity is described in one of the literature reviews, which note a correlation between the quantitative and qualitative compositions of the gut microbiota, the occurrence of small intestinal bacterial overgrowth (SIBO) syndrome, and the integrity of the intestinal mucosa [3]. The article mentions the work of E.C. *Lauritano E.C. et al.* [35], where increased intestinal permeability was observed in 11 out of 20 patients with SIBO, while in the control group; only 1 out of 21 patients had increased permeability. The development of this syndrome plays an important role in the growth of pathogenic microflora. A specific feature was identified in intestinal dysbiosis with an increase in the number of certain groups of microorganisms, in particular, species of Shigella, *Salmonella*, *Yersinia*, and *Candida* [55]. Moreover, in some studies, a significant decrease in the composition of normal flora was noted, including families *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae*, as well as *Blautia*, *Collinsella*, uncultured *Erysipelotrichaceae*, uncultured Ruminococcaceae, described in the works of *Huang Z et al.* when studying the microbial composition of patients with HF with preserved ejection fraction [26].

The statistical analysis of the microbial composition based on 16S rDNA revealed a decrease in the number of bacteria producing *Eubacterium Rectale* and *Dorea longicatena* in twenty-two hospitalized patients with HF [16,62].

Thus, another link in the chain of effects is revealed, where correction at the stage of heart failure onset will allow a comprehensive consideration of possible therapeutic approaches, thereby having the opportunity to break the vicious cycle of "gut-heart".

As previously mentioned, the current understanding of the heart-gut axis is incomplete, and there remains a lack of understanding of how gut dysbiosis and other related metabolic disturbances in gut microbiota contribute to both HF disease progression and the promotion of risk factors such as atherosclerosis and hypertension [42,46].

Intestinal Metabolites as Biomarkers of Systemic Inflammatory Response.

To date, the focus of study in the "gut-heart" axis has shifted towards metabolites in the development of neuroendocrine and metabolic disorders. In addition to the migration of endotoxins through the thin mucosal barrier of the intestine into the systemic circulation, the increasing attention is being paid to microbial metabolism products comprising the gut microbiome. The modern understanding of the role of the intestinal microbiome in the pathogenesis of HF is represented by the activity of such metabolites as Trimethylamine-N-Oxide (TMAO), short-chain fatty acids (SCFAs), and bile acids, which constitute the main groups of microbial products in the human intestine. Gut microbiota can transform various dietary nutrients into trimethylamine (TMA). [66,74].

Trimethylamine-N-Oxide (TMAO) is a metabolite of exogenous choline, phosphatidylcholine (lecithin), and L-carnitine, synthesized from trimethylamine (TMA), which is produced as a result of the metabolism of choline-rich foods such as egg yolk and red meat. TMA is secreted by the gut microbiota and then enters the bloodstream, where it is oxidized in the liver to TMAO. Previous studies have shown that TMAO can accumulate in the heart, kidneys, and other tissues, influencing various biological processes. These include promoting platelet aggregation, enhancing foam cell formation, triggering inflammatory responses, and impairing reverse cholesterol transport. Most part of TMAO eliminates by the kidneys, while the rest is reducing by the enzyme TMAO reductase in the gut to TMA [68]. TMAO has several ways which can cardiovascular system and heart function. TMAO can directly influence myocardial hypertrophy and fibrosis by activating the Smad3 signaling pathway [40]. Additionally, TMAO directly triggers an inflammatory response by activating signaling pathways like NF-κB and upregulating the expression of pro-inflammatory cytokines and chemokines [54]. Moreover, TMAO can promote the accumulation of mitochondrial reactive oxygen species (mtROS) by inhibiting sirtuin 3 (SIRT3) and superoxide dismutase 2 (SOD2). This, in turn, activates NLRP3 inflammasomes, leading to endothelial inflammation [12]. Additionally, TMAO has a significant impact on mitochondrial function. Prolonged exposure disrupts cardiac energy metabolism by impairing pyruvate and fatty acid oxidation, ultimately contributing to ventricular remodeling and the progression of heart failure [44]. The meta-analysis reported by *Heianza Y.* and colleagues in 2017, included with the results of 19 clinical trials, shows that elevated levels of TMAO may increase the risk of cardiovascular diseases, exacerbating atherosclerosis by activating inflammatory processes and impairing endothelial function. Elevated concentrations of TMAO and its precursors were associated with increased risks of MACE and all-cause mortality independently of traditional risk factors. These results were consistent across all populations studied [22]. According to literature data, TMAO exerts a pro-atherogenic

effect by affecting the reverse cholesterol transport from macrophages. Another meta-analysis in 2020, represents those random effects model analyses indicated that higher TMAO level also was associated with greater risk of MACEs in patients with heart failure and associated with poorer long-term prognosis for patients with heart failure, even after adjusting for renal dysfunction. However, the precise mechanism of this action is not fully understood. Increased circulating TMAO levels have been repeatedly associated with an increased risk of cardiovascular events (death, myocardial infarction, and stroke) [25,36,37,39]. However, the exact mechanisms involving TMAO in HF pathophysiology are not fully understood. *W.H. Wilson Tang* in 2014 first described the relationship between TMAO levels and mortality risk among HF patients [64,65]. *Li X. and* colleagues in 2019 described that the gut microbiota composition in people with heart failure differs from that in healthy Individuals, also mentioning the role of elevated TMAO levels in fibrosis, myocardial inflammation, and diastolic dysfunction. They also noted that a decrease in the number of microorganisms producing short-chain fatty acids may serve as an early predictor of HF development [38,75]. In one meta-analysis of 12 studies, was shown that an increase of Trimethylamine-N-Oxide levels may be a prognostic indicator and some kind of new marker of an unfavorable prognosis for patients with HF [73]. However, the obtained data demonstrate a certain "window of opportunity" for correcting the clinical condition and improving the prognosis of HF patients. Elevated TMAO levels in HF with reduced ejection fraction (HFrEF) have been significant both for diagnosis and prognosis, as observed by *Salzano A et al.* [58]. According to this, serum TMAO levels can be a pharmacological and dietary target for preventing HF progression [10,74].

A perspective direction is to stimulate the gut microbiota towards the formation of "beneficial" metabolic products. This group includes SCFAs and secondary bile acids, which are end products of dietary fiber fermentation. Short-chain fatty acids (SCFAs) are organic acids produced by the gut microbiota during the fermentation of dietary fiber. They play a role in various physiological processes and are known to have anti-inflammatory and metabolic properties. They are the most common products whose formation depends on the functioning of the gut microbiota in the intestinal lumen and serve as the main source of nutrition for colonocytes. SCFAs play a role in maintaining and altering the structure of the gut microbiota and influence the body's immune and metabolic processes. SCFAs are predominantly represented by acetate, propionate, and butyrate [11].

Significantly low levels of SCFAs were established among the first recruited patients with chronic heart failure, which is also associated with changes in the intestinal microbiome. Clinical application of SCFAs in various forms may be beneficial in inflammatory bowel diseases, providing protection of the intestinal mucosa and reducing intestinal inflammation [67]. One of the interesting remarkable results described in one article, which represents that the application of SCFA, protects against myocardial ischemia and reperfusion injury by inhibiting high mobility group box 1 protein in rats and particularly reduced infarct size [23].

Several studies have described the association of gut microbiota metabolites with various pathologies, including hypertension, atherosclerosis, HF, obesity, chronic kidney disease, and type 2 diabetes. These metabolites can be considered as biomarkers of gut dysbiosis and may serve as early predictors of systemic inflammatory reactions [16].

Key Representatives of the Gut Microbiome.

The gut microbiome is dynamic and constantly evolving, consisting of a multitude of bacteria from many taxonomic classifications. The main types observed in the healthy human intestine are predominantly constituted by the phyla *Firmicutes* and *Bacteroidetes*, although there is also a smaller contribution from other taxa such as Proteobacteria, *Actinobacteria*, and *Verrucomicrobia* [4,28,62]. Within these taxonomic groups, numerous genera and species perform various functions in maintaining gastrointestinal balance.

Representatives of *Bacteroides* are known for their important role in breaking down complex carbohydrates and synthesizing vital metabolites, such as short-chain fatty acids (SCFAs), especially butyrate [31]. *Firmicutes* carry out diverse activities, with individual species showing specialization in fermenting dietary fiber and producing SCFAs [31]. The *Prevotella* genus, typically associated with a plant-based diet, plays a significant role in carbohydrate metabolism. Conversely, *Proteobacteria* such as *Escherichia coli* can induce inflammation with an increase in their population [21,69]. *Akkermansia muciniphila* is known for its involvement in mucin breakdown and maintaining intestinal barrier integrity.

Several recent studies have identified the composition of the gut microbiome and found its association with heart failure (HF). *Hayashi T. et al*. in 2018 investigated the gut microbial composition of HF patients and an age-, sex-, and comorbidity-matched control group to assess differences between the two groups [20]. They performed 16S rRNA gene amplicon sequencing and found that HF patients had significantly increased relative abundance of the Bifidobacterium genus but decreased relative abundance of the *Megamonas genus* compared to the control group. *Bifidobacteria* are beneficial microbes with many physiological advantages, such as reducing harmful bacteria, modifying the host's immune system to prevent infection, and lowering pH and ammonia concentration in feces to improve gut environment. *Megamonas*, depleted in HF patients, produces SCFAs like propionate and acetate through glucose fermentation. Cui et al. evaluated and compared the fecal gut microbiome of chronic HF patients and healthy individuals from a control group using metagenomic analysis and observed a decrease in the abundance of *Faecalibacterium Prausnitzii* and an increase in *Ruminococcus gnavus* [14].

This finding was further supported by metabolomic analysis, which revealed gut microbial dysbiosis with decreased butyrate concentration but increased TMAO concentration in patients with ischemic heart disease [76]. Additionally, *Kamo T. et al.* in 2017 performed 16S rRNA gene sequencing from fecal samples and assessed differences in gut microbiome composition between HF patients and healthy individuals and also compared the composition of gut microbiota of 12 HF patients younger than 60 years of age with that of 10 HF patients 60 years of age or older. They found that the relative abundance of *Eubacterium rectale* and *Dorea longicatena* was lower in HF patients than in healthy individuals. Also

Faecalibacterium prausnitzii and *Clostridium clostridioforme* were less abundant in older HF patients than in younger patients. *Eubacterium rectale* and *Dorea longicatena* directly or indirectly produce the short-chain fatty acid butyrate as a major fermentation product. Butyrate exerts a variety of beneficial effects on the host, including acting as an energy source for intestinal epithelial cells, maintaining epithelial barrier integrity, and reducing both intestinal and systemic inflammation. [31,76].

Composite analysis of the gut microbiome in HF showed a predominance of *Firmicutes* and *Bacteroidetes* and a decrease in the abundance of *Actinobacteria*, *Fusobacteria*, and *Proteobacteria*. At the genus level, significantly high numbers of Streptococcus (7.0%), *Megamonas* (11.05%), and *Gemmiger* (3.2%) were observed in the patient group compared to the control group. At the class level, noteworthy changes included a significant increase in the number of Clostridia and *Coriobacteria* along with a decrease in the number of Bacilli. At the family level, significant changes occurred among members of *Ruminococcaceae*; *Rikenellaceae*; *Oscillospiraceae*; *Streptococcaceae*; *Coriobacteriaceae*; *Tannerellaceae*; *Bacteroidaceae*; *Lachnospiraceae*; *Veillonellaceae*; *Prevotellaceae* ($p \leq 0.0001$).

However, attention should also be paid to the role of external and internal factors in the development of this theory, such as various infections, medication use, diet, and acid-base imbalance, which contribute to shifting the degree of gut dysbiosis [48]. For example, in one study, it was found that medication groups such as alpha-glucosidase inhibitors and statins increased the level of molecular hydrogen in the intestinal lumen, suppressed oxidative stress reaction, thus providing additional pharmacotherapeutic effects [18]. However, a study by *Maier L. et al.* described that 24% of medications (out of 1000 studied) had the ability to alter the activity of one of the gut microbiota "representatives" in either a beneficial or detrimental direction [43]. These studies highlight important aspects of individual and more detailed approaches in patient therapy, emphasizing that the human microbiome can variably affect the effectiveness of medication use.

Conclusion

Based on the results of recent studies on the gut microbiota and its relationship with the human body, it can be concluded that the gut microbiome plays a significant role in the pathogenesis of systemic inflammatory reactions in patients with heart failure (HF), which allows us to view it as a new link and target in correcting the clinical status and treatment of HF patients. Thus, observing the complex interaction between the gut microbiota and the pathogenesis of HF can provide valuable insights into

1) prospective prevention and treatment schemes,
2) novel use of the gut microbiota as biomarkers, and
3) our understanding of HF.

Potential therapeutic opportunities include dietary interventions, such as incorporating supplements containing probiotics and prebiotics, in addition to fecal microbiota transplantation, antibiotics, and lifestyle modifications, which may contribute to modulating the gut microbiota. Furthermore, integrating such interventions into clinical practice can help revolutionize the quality of care provided to patients, thereby improving treatment outcomes for those suffering from such complex conditions. It is also important to acknowledge that understanding how medications affect the gut microbiota and the subsequent effects of such interventions can update strategies to ensure optimal treatment regimens. Further research is needed to understand how gut bacteria influence the body, how they can be controlled, and how they improve treatment outcomes for patients. More randomized controlled trials may shed light on the function of the gut microbiota in the genesis and progression of HF, as well as its interaction with cardiovascular medications. Additional research can explore the role of the gut microbiota in the etiology of various comorbidities exacerbating HF, while maintaining an understanding of the many processes involved in HF

Disclosure: *There are no conflicts of interest among all authors.*

Acknowledgments: *None.*

Funding: *This study was funded by the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan (IRN BR21882152). Sponsors played no role in the design of the study, data collection and analysis, decision to publish, or preparation of the manuscript.*

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