ZARĘBSKA, Julia, KRASNOBORSKA, Julia, SAMOJEDNY, Sylwia, SUPERSON, Maciej, SZMYT, Katarzyna, SZYMAŃSKA, Katarzyna, WALCZAK, Kamil, WILK-TRYTKO, Klaudia and ZARĘBSKI, Łukasz. Gut Microbiota and Its Implications for Cardiovascular Diseases – a Review. Journal of Education, Health and Sport. 2024;62:143-157. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.62.009
https://apcz.umk.pl/JEHS/article/view/48312
https://zenodo.org/records/10692079

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 24.01.2024. Revised: 15.02.2024. Accepted: 22.02.2024. Published: 22.02.2024.

Gut Microbiota and Its Implications for Cardiovascular Diseases – a Review

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Abstract

Background: The symbiotic relationship between the gut microbiota and cardiovascular health has become a main point in contemporary research, offering valuable insights into the pathogenesis of cardiovascular diseases (CVDs). This review aims to comprehensively examine the bidirectional communication between gut microbial communities and the cardiovascular system, explaining the intricate mechanisms that connect gut dysbiosis to the initiation and progression of CVDs.

Material and Methods: A systematic literature review was conducted to compile and analyze relevant studies investigating the impact of the gut microbiota on cardiovascular health. Emphasis was placed on explaining the molecular and physiological mechanisms underlying the interaction between gut microbes and cardiovascular function.

Results: Our review confirmed evidence linking gut microbiota-derived metabolites, such as short-chain fatty acids, trimethylamine N-oxide and lipopolysaccharides to vascular function and inflammation. Additionally, we explored the modulation of host metabolism and immune responses by gut microbes, providing insights into their roles in atherosclerosis and hypertension. The review also highlighted the influence of diet and lifestyle on shaping the gut microbiome and, consequently, cardiovascular outcomes.

Conclusions: Gut microbiota plays a crucial role in cardiovascular health and is involved in the start and development of various heart diseases. The identified molecular and physiological mechanisms highlight the need for complete understanding of the gut-cardiovascular axis. Moreover, the review emphasizes the potential of microbiota-targeted interventions, including probiotics and fecal microbiota transplantation, as innovative strategies for preventing and managing CVDs.

Keywords: Gut microbiota; Cardiovascular diseases; Dysbiosis

1. Introduction

The gut microbiota constitutes a complex ecosystem of microorganisms, including bacteria, viruses, and fungi, that colonize the gastrointestinal tract. Research on gut microbiota has significantly advanced in recent years, leading to the discovery of its role in maintaining health and contributing to the development of various disorders. In this article, we will focus on current research describing the significance of gut microbiota in the context of cardiovascular diseases (CVDs) and discuss therapeutic implications arising from these findings. The aim of this work is to provide a thorough analysis of the current state of knowledge regarding the influence of gut microbiota on the development of cardiovascular diseases.

2. Composition and dynamics of intestinal microflora

The composition of the gut microbiota is diverse and changes changes under the influence of various factors. Prominent bacterial strains include Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria which dominate in the intestinal microenvironment [1]. The balance between these microorganisms is crucial for maintaining host health and homeostasis. Firmicutes is a major phylum of bacteria in the gut, and it includes many gram-positive bacteria. Some well-known genera within Firmicutes are Clostridium, Lactobacillus, and Streptococcus. These bacteria are involved in the fermentation of dietary fibres and the production of short-chain fatty acids (SCFAs) [2]. Bacteroidetes is another predominant phylum, consisting mainly of Gram-negative bacteria, which are efficient in breaking down complex polysaccharides and producing SCFAs like acetic and propionic acids [3]. Actinobacteria constitute a smaller portion of the gut microbiota but are important contributors. Genus Bifidobacterium, belonging to Actinobacteria, is well-known for its beneficial effects, such as aiding in the digestion of dietary fibres and promoting immune system health [4]. Proteobacteria is a diverse phylum that includes various pathogenic and commensal bacteria. While they form a smaller proportion of the gut microbiota, certain members can become prominent during dysbiosis, potentially contributing to inflammation and other health issues [5]. These phylogenetic differences represent just the tip of the iceberg, and the role of specific bacterial types remains not fully understand.

The gut microbiota undergoes constant fluctuations influenced by various internal and external factors. Changes in diet, antibiotic use, or even stress can lead to shifts in the composition of microorganisms in the intestines [6]. This phenomenon is called dysbiosis, a disturbance in the microbiotic balance closely linked to various disorders, including cardiovascular diseases [7]. Reduced bacterial diversity, increased pathogenic strains, and a decrease in beneficial bacteria can contribute to inflammation, insulin resistance, and an

elevated risk of CVDs [8]. A fibre-rich diet promotes the growth of bacteria that ferment fibre and produce beneficial SCFAs [9]. Conversely, diets rich in saturated fats and chlorides are associated with dysbiosis and an increased risk of CVDs [10]. With advances in science, it becomes clear that the gut microbiota undergoes dynamic changes throughout an individual's life. Children are born with a relatively poor microbiota, and the bacterial composition evolves as the child develops. Over time, microbial diversity increases, reaching stability in adulthood [11]. The impact of antibiotics on the gut microbiota is also well-documented. Although essential for treating bacterial infections, antibiotics simultaneously disrupt the microbiotic balance, often leading to dysbiosis [12]. This disruption can have serious consequences for health, including an increased risk of CVDs.

3. Pathomechanisms of cardiovascular diseases in the course of intestinal microflora dysfunction

The proper functioning of the circulatory system is directly linked to the interaction of gut microbiota, which exerts a significant influence on metabolic processes, inflammatory status, and immune function of the organism. Undoubtedly an important mechanism related to gut microbiota and cardiovascular health is the production of metabolites, such as SCFAs. SCFAs, including acetic, propionic, and butyric acids, are produced from the fermentation of dietary fibre by gut bacteria. SCFAs, have lot of positive effects on cardiovascular system. By acting as histone deacetylase (HDAC) inhibitors SCFAs demonstrate anti-inflammatory properties [13]. By inhibiting HDAC activity, particularly butyrate and propionate, SCFAs promote histone acetylation, leading to an open chromatin structure and enhanced transcriptional activity of anti-inflammatory genes [13]. This epigenetic modification suppresses pro-inflammatory cytokine production and modulates immune responses within the vascular endothelium, contributing to the attenuation of chronic inflammation associated with atherosclerosis [14]. Acetate and propionate serve as substrates for hepatic lipogenesis,

influencing lipid metabolism. Through the activation of G protein-coupled receptors (GPCRs), such as GPR43 and GPR41, SCFAs modulate adipocyte function and energy metabolism [15]. Propionate, in particular, has been implicated in reducing lipogenesis and adipose tissue inflammation [16]. The intricate interplay between SCFAs, GPCRs, and metabolic pathways underscores their potential in ameliorating dyslipidemia, a key risk factor for CVDs.

Another important metabolite gaining significance in the context of CVDs is trimethylamine N-oxide (TMAO). The mechanism of TMAO formation begins in the intestines, where bacteria transform dietary compounds such as choline, phosphatidylcholine and carnitine into trimethylamine (TMA) [17]. Subsequently, TMA reaches the liver, where it is oxidized into the biologically active form, TMAO. This compound exhibits several harmful effects on the circulatory system. One of the key mechanisms through which TMAO influences cardiovascular health is its modulation of lipid metabolism. TMAO has been shown to enhance the accumulation of cholesterol in macrophages, a process integral to the formation of atherosclerotic plaques [18]. The upregulation of scavenger receptors, such as CD36 and SR-A1, by TMAO exacerbates the uptake of oxidized low-density lipoprotein (LDL) by macrophages, promoting foam cell formation—a hallmark of early atherogenesis [18]. TMAO's impact extends beyond lipid metabolism to inflammatory pathways and endothelial dysfunction. Elevated TMAO levels have been linked to increased expression of inflammatory cytokines, such as interleukin-1β (IL-1β) and tumor necrosis factor-alpha (TNF-α) [19]. These inflammatory mediators contribute to the activation of endothelial cells, impairing nitric oxide bioavailability and promoting a pro-thrombotic and pro-inflammatory vascular environment [20]. The microbial origins of TMAO bring the gut microbiota into focus as a critical player in CVDs pathophysiology. Specific bacterial species, such as those belonging to the genera Clostridium, Enterobacter, and Escherichia, are key contributors to TMAO production [17]. Understanding the compositional shifts in the gut microbiota that

favor TMAO generation provides a potential avenue for therapeutic interventions aimed at modulating cardiovascular risk.

Metabolites known for their harmful effects on the cardiovascular system include lipopolysaccharides (LPS). These endotoxins, originating from the outer cell membrane of gut bacteria and released during bacterial breakdown, influence the inflammatory state by activating signalling pathways [21]. LPS strongly stimulate the immune system by interacting with cell receptors, primarily lipopolysaccharide receptors (CD14/TLR4) [22]. Activation of these receptors leads to the release of pro-inflammatory cytokines such as interleukins (IL-1β, IL-6) and tumor necrosis factors (TNF-α) [22]. Consequently, an inflammatory state is induced, contributing to the damage of blood vessel endothelium and promoting atherosclerotic processes [23]. This process also disrupts the balance between pro-inflammatory and anti-inflammatory factors, inducing further changes in vessel walls. Additionally, LPS is described to influence the regulation of smooth muscle cell function, a significant component of blood vessel walls. Activation of these cells by LPS can lead to excessive blood vessel constriction, increasing the risk of arterial hypertension [24].

4. Gut microbiome as a potential therapeutic target in the treatment of cardiovascular diseases

The gut microflora has emerged as a compelling and innovative therapeutic target in the treatment of CVDs. The intricate crosstalk between the gut microbiota and the host has been recognized for its clear influence on various physiological processes, including inflammation, metabolism, and immune responses.

4.1 Probiotics

Probiotics, as microorganisms conferring recognizable health benefits, serve as active modulators of the gut microbiota, and their intricate influence extends to cardiovascular

homeostasis [25]. Principal among probiotic genera are Lactobacillus and Bifidobacterium, instrumental in promoting a symbiotic microbial community within the gastrointestinal environment [26].

At the fundamental level, probiotics are responsible for reconfiguration of gut microbiota dynamics. This modulation prominently features the augmentation of beneficial taxa and the concurrent suppression of potentially harmful microorganisms. This microbial curation induces the production of bioactive metabolites, which have garnered attention for their immunomodulatory and anti-inflammatory properties [27].

Probiotics, due to their assimilative capacity, contribute to the sequestration of cholesterol within their cellular matrices. This sequestration, coupled with the biosynthesis of compounds inhibiting intestinal cholesterol absorption, supports the observed reduction in serum low-density lipoprotein cholesterol levels [28]. Such reduction holds enormous significance in mitigating atherosclerotic proclivities and ameliorating the risk of coronary artery disease [29].

Moreover, probiotics exhibit an ability to attenuate oxidative stress, which is crucial in endothelial dysfunction and atherosclerotic progression [30]. Through the amelioration of oxidative stress, probiotics contribute to the preservation of endothelial integrity, thus mitigating a key precipitant in cardiovascular pathogenesis.

4.2 Prebiotics

Prebiotics, non-digestible fibres that selectively stimulate the growth and activity of beneficial bacteria in the gut, play a crucial role in shaping the composition and functionality of the gut microbiota. These compounds, often derived from plant sources such as chicory, garlic, onions, and certain grains, serve as substrates for fermentation by specific microbes, promoting the proliferation of beneficial species [31]. During fermentation, beneficial bacteria metabolize prebiotics to produce SCFAs which contributes to the overall metabolic and

immunomodulatory effects associated with a healthy gut [32]. Moreover, these SCFAs have been shown to influence lipid metabolism by inhibiting cholesterol synthesis in the liver. By modulating lipid levels in the bloodstream, prebiotics may contribute to the prevention of atherosclerosis, a key pathology underlying many cardiovascular conditions [33].

The gut barrier serves as a protective interface between the internal environment of the body and the external environment of the gut. Maintaining the integrity of this barrier is essential for preventing the translocation of harmful substances and bacteria into systemic circulation, a phenomenon known as "leaky gut". Prebiotics, by promoting the growth of beneficial bacteria and the production of SCFAs, contribute to the maintenance of gut barrier function [34]. This protective effect has implications for preventing the entry of inflammatory agents into the bloodstream, thereby positively influencing cardiovascular health.

Recent studies suggest a potential link between prebiotics and blood pressure regulation. Certain prebiotics, such as oligofructose and inulin, have shown theirability to lower blood pressure [35]. While the precise mechanisms are not fully explained, it is hypothesized that the effects are, in part, mediated by the modulation of gut microbiota and the subsequent production of bioactive metabolites [36].

4.3 Fecal Microbiota Transplantation (FMT)

FMT emerges as a therapeutic modality, presenting important implications for cardiovascular well-being. This procedure enable a transfer a diverse microbial consortium from a healthy donor to a recipient. Initially introduced for the management of recurrent Clostridium difficile infections [37], FMT has recently expanded its therapeutic indications. The rationale underlying FMT rests on the premise of rectifying dysbiosis, by instating a more resilient and balanced microbial ecosystem [38]. Clinical investigations exploring the application of FMT in individuals with risk factors for CVDs, such as obesity and metabolic syndrome, are

underway. Preliminary results indicate that FMT may influence metabolic parameters and attenuate inflammation, offering therapeutic potential of manipulating the gut microbiota for cardiovascular benefits [39]. While the application of FMT in cardiovascular contexts is an area of ongoing exploration, its capacity to rectify dysbiosis and instigate a positive microbial shift underscores its potential as a novel therapy.

4.4 Dietary Modifications

Numerous studies have underscored the impact of diet on the composition and diversity of the gut microbiota, establishing a link between dietary patterns, microbial balance, and cardiovascular outcomes [40], [41], [42]. For instance, a diet abundant in diverse plant-based fibers serves as a reservoir for prebiotic substrates, fuelling the growth and activity of beneficial microbes. Foods rich in soluble fibres, such as oats, legumes, and certain fruits, provide fermentable substrates that support the production of SCFAs [43]. Conversely, diets characterized by high levels of saturated fats and refined sugars are associated with dysbiosis, a disruption in the balance of gut microbial communities [44]. For example, excessive intake of processed foods, sugary beverages, and saturated fats can lead to an overabundance of pro-inflammatory bacteria and a reduction in beneficial strains [10], [45]. This dysbiotic state is linked to systemic inflammation, insulin resistance, and dyslipidaemia, all precursors to CVDs [46].

Precision dietary modifications, tailored to an individual's microbial profile, hold great promise. Analysing an individual's gut microbiota composition can inform personalized dietary recommendations, optimizing the intake of specific nutrients that promote the growth of beneficial microbes [47]. Examples include incorporating fermented foods like yogurt and kimchi for their probiotic content or increasing the consumption of fibre-rich foods like whole grains, vegetables, and fruits to support a diverse and flourishing gut microbiota [48].

Furthermore, the concept of "nutritional psychiatry" underscores the bidirectional communication between the gut and the brain, influencing not only cardiovascular health but also mental well-being [49]. Diets rich in omega-3 fatty acids, found in fatty fish, flaxseeds, and walnuts, contribute to a favourable gut microbiota composition and have been associated with reduced cardiovascular risk. Nutritional strategies to optimize the gut microbial ecosystem showcases the potential to mitigate the risk factors associated with cardiovascular diseases and pave the way for a more personalized and effective approach to maintaining heart health.

5. Conclusions

The relationship between the gut microbiota and cardiovascular health is not completely explored yet. Imbalances in gut bacteria, known as dysbiosis, are linked to heart diseases, highlighting the potential of focusing on gut health to improve heart conditions. Approaches like adjusting diet, using probiotics, and other gut-focused treatments show promise in addressing heart disease by improving gut health, signaling a new direction in how we might approach heart care more effectively and personally.

Disclosures

Authors do not report any disclosures.

Authors contribution

Conceptualization: Julia Zarębska, Julia Krasnoborska; Methodology: Sylwia Samojedny, Maciej Superson; Validation: Katarzyna Szymańska, Kamil Walczak, Łukasz Zarębski; Formal analysis: Katarzyna Szmyt; Investigation: Julia Krasnoborska, Klaudia Wilk-Trytko, Maciej Superson; Resources: Sylwia Samojedny; Writing – Original Draft Preperation: Julia Zarębska, Kamil Walczak, Julia Krasnoborska, Katarzyna Szmyt; Writing – Review & Editing: Łukasz Zarębski, Maciej Superson, Katarzyna Szymańska, , Klaudia Wilk-Trytko

All authors have read and agreed with the published version of the manuscript.

Funding

This research received no external funding.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

Not applicable.

Conflicts of Interest

The authors declare no conflict of interest.

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