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Exploring the Significance of Gut Microbiota in Cardiovascular Health

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Abstract: Cardiovascular disease (CVD), comprising heart and blood vessel disorders, persists as the foremost contributor to global morbidity and mortality. In modern times, the intricate composition of gut microbiota has garnered significant focus, particularly for its varying impact on diverse ailments. Perturbations in gut microbiota and consequent dysbiosis have demonstrated connections with the advancement and origin of CVD, including conditions like atherosclerosis, hypertension, and heart failure. This comprehensive review delves into the pivotal role of gut microbiota in maintaining cardiovascular well-being.

Keywords: cardiovascular health; gut microbiota; microbiome; dysbiosis; atherosclerosis

1. Introduction

The gut microbiota, a diverse and dynamic collection of microorganisms found in the human GI tract, has a significant impact on the host both in times of homeostasis and disease. The human body is home to trillions of microorganisms, which work together to create a dynamic ecosystem both within and outside of the body [1]. This ecosystem's alterations and interactions have an impact on human health and sickness [2]. This complex ecosystem, which is made up of a wide variety of bacteria, viruses, fungus, and other microbes, was originally only marginally related to digestion. The gut microbiota, sometimes referred to as the "forgotten organ," is now understood to be a dynamic colony of bacteria that is essential to preserving our general health [3]. From the modulation of neuronal transmission to the digestion of complex polysaccharides, the gut microbiota is crucial to a wide range of physiological activities. It has gained increasing attention in recent years due to its link to a wide range of diseases, including Type 1 diabetes [4,5], reproductive health [6–10], autoimmune disease rheumatoid arthritis, inflammatory bowel disease [11], metabolic disorders like diabetes and its complications, cardiovascular disease (CVD), obesity, cancer [12], and sexual disorders [13–16], as well as neurodevelopmental disorders like autism and neurodegenerative diseases like Alzheimer's disease.

Cardiovascular diseases (CVD) leading cause of death in 2015, followed by cancer fatalities (595,930), making it one of the two biggest causes of death in the US since 1975 (633,842 deaths, or 1 in every 4 deaths) [17]. According to the World Health Organization (WHO), CVD is also the leading

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cause of death worldwide, accounting for 17.7 million fatalities in 2015. With estimated indirect costs of $237 billion annually and a projected increase to $368 billion by 2035, CVD is considered the most expensive disease, even more so than diabetes and Alzheimer's disease [18,19].

While we've long known that the gut plays an important role in digestion and nutrient absorption, the scope of its influence has grown substantially. Scientific advances in microbiology and health studies have revealed a surprising link between the gut microbiota and the cardiovascular system. What was long thought to be two distinct domains – the gut and the heart – is now acknowledged to be a dynamic interplay of signals, chemicals, and influences that can have a considerable impact on our cardiovascular health. In this article we will encompass the various facets such as intricate mechanisms that link gut health to inflammation and blood vessel function, how gut microbes can influence blood pressure regulation and lipid metabolism[20,21]. We'll also explore how the gut microbiota affects metabolic health and how it contributes to the onset of atherosclerosis, the condition that is the root of CVD[22].

2. Diversity and Composition the Gut Microbiota

Around 100-trillion microorganisms (bacteria, fungi, viruses, protozoa, and viruses) are found in the human gut. The microbiome has nearly 3 million genes that produce thousands of metabolites that have an impact on human health, compared to the 23,000 genes that make up the human genome [1]. A number of variables, including as food, demographics, medication use, health status, and environmental elements influencing the gut environment, have an impact on the composition and metabolism of adult gut microbial populations[23–25]. The Human Microbiome Project Consortium found that 208 donors represented 226 bacterial species in the total fecal microbiota richness [3,26].

3. Emerging Insights: Gut Microbiota and Cardiovascular Health:

3.1. The Inflammation: Unveiling the Role of Gut Health in Cardiovascular Diseases

Inflammation, often act as defense mechanism of the body, known as double-edged sword. Chronic inflammation can become a silent enemy, wreaking havoc on our health and laying the groundwork for a number of chronic diseases, including cardiovascular disorders, even while it is essential for warding off infections and encouraging healing. Our gut health is a surprise factor in this inflammatory cascade, according to recent studies. Inflammation is a key mechanism of cardiovascular diseases. It is an integral part of atherosclerosis and a major contributor to the occurrence of cardiovascular events. Inflammation has been observed that patients with heart failure have higher levels of inflammatory cytokines [27]. Redox and inflammatory signals can affect permeability pathways, and this is shown in CVD [28]. Changes in the composition of gut microbiota known as Gut dysbiosis (Figure 1) can lead to a decrease in hazardous bacteria (including Collinsella, Proteobacteria, and Enterobacteriaceae) and an increase in helpful bacteria (Bacteroidetes and Firmicutes). High quantities of lipopolysaccharide (LPS) are produced in the dysbiotic gut by Gram-negative pathogens such Escherichia coli, which then cause atherogenesis and systemic inflammation (endotoxemia) [29]. The intestinal mucosal epithelial barrier, which guards the internal milieu from the hostile external environment, is kept in place by the development of tight junctions (TJs, a complex made of intramembranous proteins, occludin, and several molecules from the claudin family of proteins), which spread between the epithelial cells and create a semi-permeable seal [30] . In a sick state, this barrier ceases to serve as a barrier, increasing intestinal permeability, particularly to LPS generated locally by the gut bacteria. Prior until recently, it was believed that certain pathological conditions were the source of leaky gut, however a number of studies have suggested that the pathological illnesses are not the cause of leaky gut [31]. One of the main factors leading to arterial plaque and blockages can be inflammation from leaky gut [32]. In actuality, patients with heart disease exhibit higher rates of leaky gut than people without heart disease. On the artery walls, inflammation causes lesions. With cholesterol, the body "bandages" them, and the result is plaque. Atherosclerosis is the term for this process [33,34].

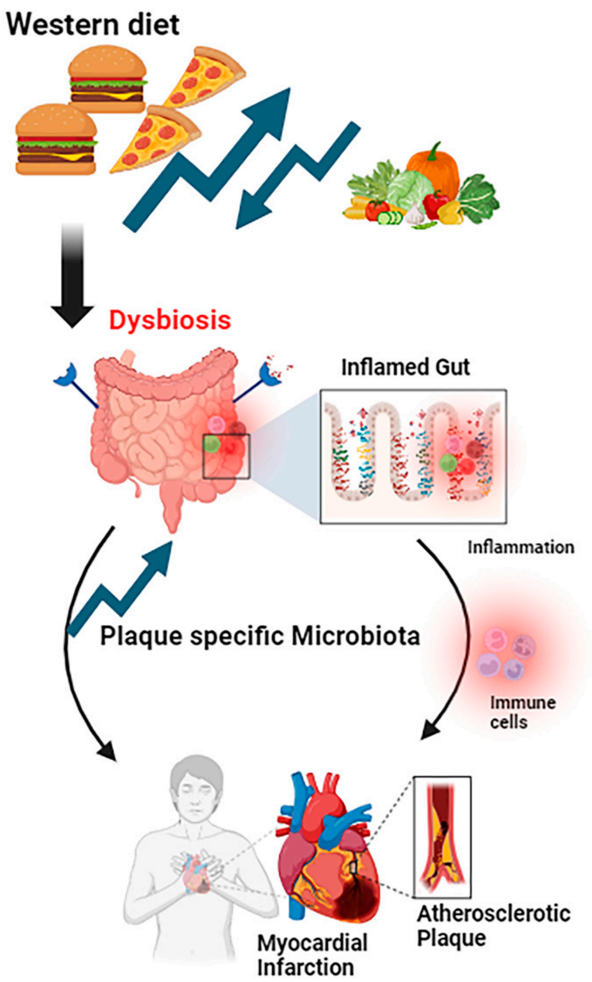

Figure 1. Mechanism of atherosclerosis due to gut dysbiosis.

Plaque in the arteries is encouraged by inflammation, but it is also less stable due to inflammation. To prevent heart attacks, plaque stability is essential [35] . Plaque ruptures, causing it to become loose and clog the artery, depriving the heart of blood and resulting in a heart attack. It is well known that a leaky gut is a major contributor to the chronic inflammation that can inflame and clog your arteries [36].

3.2. Microbial Architects of Cholesterol: Gut Microbiota's Influence on Lipid Metabolism

An international investigation found that of all modifiable risk factors for cardio vascular disease, elevated serum cholesterol levels were linked to the highest attributable risk for developing CVD, particularly ischemic heart disease [37]. Studies suggest that high serum total cholesterol (TC) is the primary factor causing coronary atherosclerosis, and it is widely known that elevated TC is linked to an increased risk of CVD [38]. Numerous epidemiological and interventional investigations have determined that LDL-C is the primary risk factor for CVD since it is a crucial factor in the development of atherosclerosis [39,40].

A sizable portion of patients cannot stop the progression of atherosclerosis despite effective cholesterol-modulating therapy (such as statins). It is well known that bile acids, which are the primary form in which cholesterol is excreted from the body by the liver [41]. The liver converts cholesterol into the amphipathic molecules known as bile acids. For the breakdown of hepatic cholesterol, bile acid production is a key route. It is vital for the biliary secretion of free cholesterol, endogenous metabolites, and xenobiotics that bile flow is produced through bile acid production. Biological deodorants called bile acids make it easier for lipids and fat-soluble vitamins to be absorbed by the digestive tract. Bile acids may be crucial metabolic regulators of lipid, glucose, and energy homeostasis, according to recent studies [42].

Gut microbiota plays a vital role in Deconjugation, dehydroxylation, and reconjugation of these molecules result in the biotransformation of BA [43]. The possibility that gut microorganisms could affect cholesterol levels was emphasized by a ground-breaking study that appeared in the journal Nature. In the study, scientists gave mice with altered cholesterol metabolism gut bacteria from human donors. The results were startling; animals given microbiota from donors with high cholesterol had higher levels of LDL cholesterol, indicating a clear link between the gut microbiota and cholesterol management [44].This expanding knowledge of the gut microbiota's function in lipid metabolism is changing how we think about cholesterol control and opening up new treatment possibilities.

A group of researchers from Broad Institute of MIT, revealed the function of the gut microbiota in bile acid metabolism, a crucial aspect of controlling cholesterol. A probable mechanism by which these bacteria may lower host serum cholesterol levels is that the presence of coprostanol-forming bacteria in stool samples is related with lower levels of fecal cholesterol. This observation emphasizes not just the sophisticated enzymatic capabilities of gut bacteria, but also their ability to influence host cholesterol pathways [45].

Wang and colleague observed that, the gut microbiota modulates mammalian lipid absorption, metabolism, and storage. The study found that different microbial populations can considerably influence the absorption of dietary lipids and cholesterol, hence influencing their incorporation into lipoproteins. Microbiota alters intestinal lipid metabolism in mice by suppressing the expression of Snhg9 (small nucleolar RNA host gene 9) in small intestinal epithelial cells [46].

A study published in the European Heart Journal highlighted the potential of probiotics in modifying cholesterol metabolism. The study focused on Lactobacillus reuteri, a probiotic strain, and found that it might lower LDL cholesterol levels in mice by transforming cholesterol into a less absorbable form. This work demonstrates the potential of using probiotics to alter lipid profiles, yet it calls for additional clinical studies using human participants [47].

3.3. Gut microbiota obesity, a major risk factor for heart disease

Obesity raises the risk of cardiovascular disease (CVD), especially heart failure (HF) and coronary heart disease (CHD). Changes in body composition that might impact hemodynamics and change the anatomy of the heart are among the ways through which obesity raises CVD risk [48]. Adipose tissue produced pro-inflammatory cytokines can cause can cause cardiovascular dysfunction and encourage the development of atherosclerotic plaques [49].

A Scientific Statement from the American Heart Association in 2021 discussed Independent of other cardiovascular risk factors, obesity increases the risk of developing cardiovascular disease and dying from it [49,50].

The gut microbiota exerts direct effects on the digestion, absorption and metabolism of food. Furthermore, the gut microbiota shows a miscellany of protective, structural and metabolic effects both on the intestinal milieu and peripheral tissues, thus affecting body weight by modulating metabolism, appetite, bile acid metabolism, and the hormonal and immune systems.

Investigations into the connection between the microbiota and body weight management have not revealed a clear causal relationship or association between these two factors [51], but it is believed that the composition of bacterial species varies depending on whether or not obesity is present.

A metagenomic and biochemical analyses study by Turnbaugh et al, observed Obese people's microbiomes can extract more energy from their diet which results increase the total body fat [52]. A group of researcher from Washington University School of Medicine, observed that, obesity has a microbial component, which could be a potential target therapeutic implications [53]. Proceedings of the National Academy of Sciences published an article in 2004, changes in microbial ecology affects predisposition toward energy storage and obesity [54]. Another Study from Academic Medical Center Amsterdam, The Netherlands observed that the alterations in intestinal microbiota are associated with obesity and insulin resistance [55].

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4. Impact of gut microbiota on Blood Pressure Regulation:

4.1. The connection between gut bacteria and blood pressure (BP) regulation

The connection between gut bacteria (microbiota) and blood pressure regulation is a relatively new and intriguing area of research. A huge number of studies have suggested that there is a two-way communication between the cardiovascular system and the gut bacteria, including the regulation of blood pressure.

a. **Short-Chain Fatty Acids (SCFAs):** Short-chain fatty acids (SCFAs) are a class of gut microbial metabolites known to activate multiple signaling pathways in the host. Short-chain fatty acids (SCFAs) are a result of the fermentation of dietary fiber by gut bacteria. Blood vessel relaxation and blood pressure reduction have both been linked to SCFAs. SCFAs enhance the production of nitric oxide that helps dilate blood arteries, boosting blood flow and lowering blood pressure [56].

b. **Inflammation and Immune Response**: Chronic inflammation as a result of dysbiosis might contribute to the development of hypertension. The immune system's reaction is regulated by the gut microbiota, and inflammation is controlled, both of which have been linked to indirect effects on blood pressure. National Center for Cardiovascular Diseases of China has done a study in 2017 to observe, how Gut microbiota dysbiosis contributes to the development of hypertension [57]. They observed, dysbiosis an important pathogenic factor for the high BP of the host. To further investigate the precise processes underlying the impact of gut microbiome in BP regulation, bacteria including *Prevotella, Klebsiella, Enterobacter,* and *Fusobacterium* are potential candidates for further bacteria transfer research [58].

c. **Salt Sensitivity**: According to several research, a person's sensitivity to dietary salt (sodium) may be influenced by the bacteria in their stomach. The development and treatment of hypertension are significantly influenced by salt sensitivity [59].

4.2. Production of nitric oxide by gut bacteria in maintaining healthy blood vessels

Nitric oxide is a biological substance that dilates blood vessels, increases hormone release, modulates neurotransmission, and functions as a signaling molecule. Nitric oxide is produced by both NOS-dependent and -independent pathways [60]. Nitric oxide supplementation improves cardiac health, increases exercise performance, lowers high blood pressure during pregnancy, lowers erectile dysfunction, and improves healing and respiratory responsiveness [61,62]. Here's how the production of nitric oxide by gut bacteria can help maintain healthy blood vessels:

a. **Dietary Nitrate Conversion**: Dietary nitrate, which is widely found in vegetables such as spinach, beetroot, and lettuce, can be converted into nitrite by particular gut flora. Nitrite can then be further converted into nitric oxide under certain conditions, such as tissue hypoxia. This conversion is mediated by gut enzyme [63–65].

b. **Influence on Nitric Oxide Synthase (NOS) Activity:** Endothelial nitric oxide synthase (eNOS), an enzyme that generates nitric oxide in blood vessel walls, may be affected by certain gut flora [66]. Shandong Provincial Key Laboratory of Animal Cell and Developmental Biology conduct a study on how Gut Microbiota Homeostasis effects on Nitric Oxide Synthase (NOS) activity. They observed, the concentration NOS in the gastrointestinal tract were increased significantly in shrimp infected with *Vibrio anguillarum.* A gut microbiota dysbiosis situation [67].

c. **Anti-Inflammatory Effects:** A healthy gut microbiota composition helps to minimize inflammation, which is essential for maintaining healthy blood vessels. Chronic inflammation has been linked to endothelial dysfunction. The inflammatory mediators enter into the bloodstream, through the blood–intestinal barrier which results effects on circulatory system including stiffness of the vessel due to inflammatory reponse. These results increase the blood pressure [68,69]. NO reduced inflammation which indirectly helps blood pressure regulation.

d. **Gut-Endothelium Axis:** Gut-endothelium axis, or connection between gut microbes and the endothelium, involves a variety of signaling molecules, including those involved in NO generation [70].

5. Diet, Lifestyle, and Gut Health

Intake of nutrients alters the makeup of the gut microbial community and produces metabolites that have an impact on the physiology of the host. Dietary patterns, such as macronutrient balance and feeding/fasting cycles that can be modified with dietary plans based on calorie restriction periods, have an effect on the microbial ecosystem in the gut, which affects homeostasis in that region [71].

a. **Consumption of Fiber rich diet:** Dietary fiber can have a significant impact on the diversity, richness, and composition of the microbiome by offering a wide range of substrates for fermentation events carried out by particular microbe species that have the enzyme machinery required to break down these complex polysaccharides. [72]. A prebiotic is a compound that feeds the healthy bacteria in the gut, and fiber is one such material. In the process of fermenting dietary fiber, these bacteria create short-chain fatty acids (SCFAs), which have a number of health advantages, including enhancing gut health and lowering inflammation [73].

b. **Plant-Based vs. Animal-Based Diets:** A plant-based diet rich in vegetables, fruits, whole grains, and nuts promotes a more diversified and healthier gut flora. Animal-based diets, especially those heavy in saturated fats and processed meats, might result in unfavorable alterations in gut microbial composition [74,75].

c. **Probiotic and Fermented Foods:** Probiotics are advantageous, active bacteria that colonize the human intestines and alter the flora in specific regions of the host. Probiotics may improve or prevent gut inflammation and other intestinal or systemic disease phenotypes by restoring the composition of the gut microbiome and introducing beneficial functionalities to gut microbial communities [76].

d. **Sugar and Refined Carbohydrates:** Excess sugar consumption has been associated to increased morbidity and mortality and has been connected to the development of numerous illnesses, including metabolic, cardiovascular, neurological, and even some malignancies [77,78]. sugars in the form of nutritious and non-nutritional sweeteners consumption have negative effects on the gut microbial ecosystem, including abnormal short-chain fatty acid synthesis, altered intestinal barrier integrity, and chronic inflammation, which frequently fuels a variety of metabolic conditions [79].

e. **Mediterranean Diet:** A gut microbiome composition linked to superior health outcomes, including decreased inflammation and improved cardiovascular health, has been found to be connected with the Mediterranean diet, which is high in vegetables, fruits, whole grains, lean proteins, and healthy fats like olive oil [80]. The Mediterranean diet produces gut microbiome regulation in rodents, nonhuman primates, and human subjects, and the potential function of gut microbiota and microbial metabolites as one of the key catalysts mediating the host's many favorable health benefits is discussed [81,82].

f. **Food Additives:** In today's world, the use of food additives in food manufacturing is unavoidable. Some food additives and emulsifiers included in processed meals have been demonstrated to have a deleterious impact on gut flora and gut barrier integrity [83]. Artificial sweeteners are most likely to damage glucose tolerance and promote weight gain by negatively altering microbiota. The majority of sugar alcohols are fermentable by bacteria and may have qualities comparable to prebiotics[84] .

6. Future Implications and Research Directions

There is a clear correlation between gut bacteria and cardiovascular health, according to research. The gut microbiota is involved in various pathways that can affect cardiovascular outcomes, including inflammation, metabolism, and bioactive chemical synthesis. Although much of this research is still in its early phases, manipulating the gut microbiota has emerged as a promising avenue for enhancing cardiovascular health.

a. **Diet Modification:** Plant-based diets that were processed or ultraprocessed were not connected with healthy clusters of gut bacteria. When selecting foods, think about whether they are processed or unprocessed, as well as if they are plant or animal food. Emphasizing minimally processed plant foods allows the gut microbiome to thrive, providing protection against, or decreasing the risk of, chronic diseases such as heart disease, diabetes, metabolic disease, and obesity. Certain diets, such as those high in fiber and plant-based foods, can help good gut flora proliferate. These bacteria may create short-chain fatty acids (SCFAs), which have anti-inflammatory properties and may benefit cardiovascular health [85].
b. **Probiotics and Prebiotics:** Several human and animal research have explored the molecular mechanisms underlying the therapeutic benefit of various probiotic and prebiotic substances for gut health. Fibers like inulin and galactomannan have both independent and synergistic health benefits [86].
c. **Fecal Microbiota Transplantation (FMT):** FMT includes transferring healthy donor feces to a recipient in order to restore a balanced gut flora. The treatment of recurrent Clostridium difficile infection with FMT has been proven effective [87]. There are early signs that it may potentially have therapeutic potential for other illnesses such obesity, metabolic syndrome, inflammatory bowel disease, and functional gastrointestinal disorders [88].
d. **Stem cell Therapy:** In several disorders, including ulcerative colitis[89], acute liver injury [90], hypoxia-induced pulmonary hypertension, chronic hypoxia, and diabetes [91], which causes gut dysbiosis, researchers have discovered that MSC therapy may be related to the gut microbiota.

7. Conclusion

The gut microbiota is a novel research topic with important applications in human health, particularly in the creation of novel diagnostic and therapeutic techniques for preventative and curative outcomes**.** Manipulation of gut bacteria via diet, probiotics, and novel approaches may open up new possibilities for enhancing heart health. While the research is still in its early stages, further investigation and collaboration could pave the door for tailored treatments, changing cardiovascular care.

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