The Intestinal Microbial Ecosystem

Subjects: Allergy

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Cardiovascular diseases (CVDs) can refer to several conditions, including hypertension, heart failure, stroke, coronary artery disease, peripheral vascular disease, stroke, rheumatic heart disease, cardiomyopathies, and congenital heart diseases. Globally, CVDs are major contributors to a decreased quality of life and the principal cause of morbidity and mortality. In 2015, 422.7 million cases of CVDs were reported, with 17.92 million deaths due to CVDs.

dysbiosis   Firmicutes   Bacteroidetes   cardiovascular diseases   coronary artery disease

hypertension   heart failure   stroke   peripheral vascular disease   rheumatic heart disease

cardiomyopathies

1. Introduction

Cardiovascular diseases (CVDs) can refer to several conditions, including hypertension, heart failure, stroke, coronary artery disease, peripheral vascular disease, stroke, rheumatic heart disease, cardiomyopathies, and congenital heart diseases [1]. Globally, CVDs are major contributors to a decreased quality of life and the principal cause of morbidity and mortality. In 2015, 422.7 million cases of CVDs were reported, with 17.92 million deaths due to CVDs. Of all the causes, coronary heart disease was the major cause of CVDs worldwide [2]. As far as Middle Eastern countries are concerned, CVDs are responsible for 34% of all deaths, with coronary artery disease contributing to 44% of CVDs, followed by stroke with 35% of CVDs [3][4].

Hypertension (which is defined as systolic BP ≥130 mmHg and/or diastolic BP ≥80 mmHg) [5] is the third leading cause of years lost due to morbidity-related disabilities. It increases the risk of heart, kidney, brain, and other diseases. It can be easily diagnosed, treated, and controlled, thus reducing the morbidity and mortality. Globally, it is estimated to affect 1.13 billion people, with two-thirds of them living in developing countries. The global target is to reduce its prevalence by 25% by 2025. Globally, hypertension alone is responsible for 54% of stroke, 47% of coronary artery disease, and 13.5% of the total premature deaths (7.6 million) worldwide [6]. Heart failure (HF) is a disease that occurs due to a low cardiac output or an elevated ventricular-filling pressure with increasing prevalence; it is considered a global pandemic, affecting as many as 26 million people [7]. Data showing the prevalence of heart failure and associated mortality rate are deficient in Middle Eastern countries. However, a recent study published in Saudi Arabia showed the overall 30-day mortality rate for 1090 acute HF patients to be 7.5%. In the Sultanate of Oman, the prevalence of heart failure is 5.17 per 1000 individuals, which seems to be less than the prevalence recorded in some of the developed countries. Apparently, the analysis of the data was

taken from a single center. However, over the last decade, improved diagnostic methods, such as imaging, and the availability of new diagnostic indicators, therapeutic advances, and implantable devices have helped to delay the deaths of heart failure patients [8].

Recently, several studies have found that intestinal microbiota plays a critical role in the development of CVDs [9]. The term "Intestinal microbiota"' is commonly used for various groups of microorganisms that are living within the human digestive tract and help the host by virtue of various biochemical and physiological functions mediated by their metabolites [10]. There are four types of flora constituting the intestinal microbiota ecosystem: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Firmicutes and Bacteroidetes constitute a large proportion of the intestinal microbiota. The ratio of Firmicutes (F) and Bacteroidetes (B) (F/B) is regarded as an important biomarker for gut dysbiosis. Imbalances in the constitution of the intestinal microbiota (dysbiosis) have been linked to atherosclerosis, hypertension, heart failure, and other diseases [10]. Various factors, such as dietary habits, intestinal infection, and environmental factors, can change the balance of the intestinal microbial environment. Moreover, the intestinal microbiota can also produce trimethylamine (TMA) by metabolizing choline, phosphatidylcholine, and L-carnitine. The hepatic flavin monooxygenases (FMO3) enzyme then oxidizes TMA into trimethylamine N-oxide (TMAO). When TMAO is generated, several physiological processes can affect the host system by activating different signaling pathways. [10] Studies have shown that the elevation of TMAO can inhibit the transport of cholesterol and increase the accumulation of cholesterol in the macrophages, thereby accelerating the process of atherogenesis. Therefore, TMAO is pro-atherogenic, pro-thrombotic, and a contributor to ischemic heart disease; it is also linked to a bad prognosis in heart failure patients [10].

Intestinal microbiota also generates some short-chain fatty acids (SCFAs) that attach to G protein-coupled receptor 41 (GPR41) and vascular olfactory receptor 78 (Olfr78), producing hypertensive and hypotensive effects, respectively. Thus, these metabolites act as a unique target for the management of hypertension. Studies found an association between intestinal microbiota-mediated inflammatory and immune responses and HF. According to the "gut microbiota" hypothesis, the reduced cardiac output leads to diminished tissue perfusion and, consequently, leads to intestinal ischemia in HF patients. Subsequently, this alters the constitution of the microbiota ecosystem. The levels of TMAO are prognostic of the long-term risk of mortality in patients with HF. Additionally, the intestinal microbiota also produces p-cresyl sulfate (PCS) and phenylacetylglutamine by metabolizing aromatic amino acids and glutamine conjugation, respectively, which can indicate the risk of cardiovascular events [10]. The role of intestinal microbiota in cardiovascular diseases is illustrated in Appendix A Figure A1 .

2. Gut Barrier Function and Bacterial Component Translocation

Several trials have related bacterial alterations of the gut with epithelial barrier function [11][12]. Factors, such as unevenness, amid colonic epithelial cell apoptosis and proliferation and decreased tight junction protein expressions, such as zonula occludens-1 (ZO-1) and claudin-1, can lead to intestinal permeability [13][14]. The barrier function must remain proper for reducing the intestinal content translocation, including the entry of bacterial components into the circulation. Due to disruption of barrier function, an immune response is stimulated by the

pathogen-associated molecular patterns (PAMPs), leading to inflammation in the tissues. Thus, barrier function disruption due to dysbiosis is a major factor responsible for inflammatory processes and diseases linked to inflammation, such as obesity and diabetes [15][16]. Out of different microbial components recognized by the host's immune receptors, lipopolysaccharide (LPS) and peptidoglycan have gained much consideration in association to CVD risk.

LPS, present in Gram-negative bacteria, are one of the major PAMPs studied in relation to CVDs. The innate immune responses are activated by the LPS via Toll-like receptor 4 (TLR4) signaling pathways. In short, there is LPS movement from the colon by either transcellular or paracellular pathways into the small intestine lymphatics or portal vein, individually [17][18]. As the LPS reach circulation, they rapidly bind to LPS-binding protein (LBP) synthesized in the liver [19], enabling LPS to attach to the TLR4 receptor on desired cells and muscles. The TLR4 stimulates an intracellular signaling cascade which results in the transportation of NF-κB and enhancement of many proinflammatory target genes [20]. A high-fat diet is responsible for LPS absorption across the intestinal barrier via assimilation inside chylomicrons and negotiated functioning of the gut barrier, respectively [21][22]. In one study, it was confirmed that inherently overweight mice, which were fed a high-fat diet, exhibited a two to three times enhancement in LPS, a range demarcated as "metabolic endotoxemia" [21][23]. The increased level of LPS resulted in gut dysbiosis, an enhancement of intestinal wall permeability, and a consistent decrease in tight junction proteins. Numerous studies have confirmed that LPS may lead to increased CVD risk. Initially, the LPS level is elevated in at-danger individuals and envisages imminent CVDs [24][25][26]. Second, vascular cell development due to LPS provokes a response parallel to the one detected throughout atherogenesis with oxidative stress, macrophage activation, cell death, inflammation, and adhesion of monocytes [27][28]. Finally, LPS supplementation at a reduced dose in animal models at the same concentration that is detected in endotoxemia leads to inflammation and atherosclerosis [28]. Together, these reports strongly suggest that LPS is a significant factor relating dysbiosis of the gut to CVDs.

These are the chief components of the cell wall in the Gram-positive bacterial and negligible constituents in Gram-negative bacteria that may lead to CVDs. The fragments of peptidoglycan result in inflammatory gene transcription via MAPK and NF-κB signaling pathways [29]. Undeniably, peptidoglycans are detected inside atherosclerotic plaque cells in humans, which are linked with enhanced plaque inflammation [30].

3. Clinical-Trails and Animal Studies Demonstrated the Relationship between Dysbiosis and CVDs

Many trials have revealed a connection linking alterations in gut microbial composition and CVDs. Some of these clinical and animal studies are discussed below, and others are summarized in **Table 1** .

Table 1. Summary of trials explored connections between gut microbiota and CVDs.

		Clinical Studies		
CVD	No. of Patients	Change in Gut Microbiota Composition/Metabolites	Outcome	Reference
Atherosclerosis	332	Increased LBP	Increased carotid intima media thickness	[31]
CAD	4144	Increased TMAO	Increased atherosclerotic risk	[32]
	2255		Increased risk of artery infarction	[33]
	59	Increased L-carnitine	Increased TMAO in CAD patients	[34]
	126	Increased LPS	Increased inflammatory cytokines	[35]
	30	Reduced *Bacteroides vulgatus* and *B. dorei* and LPS	Increased lesions	[36]
CAD and artery stenosis	169	Increased TMAO	Increased risk of CAD and artery stenosis	[37]
Heart failure	122	Increased LPS	LPS translocation through leaky gut, resulting in inflammation	[38]
	452		Endotoxemia inflammation and oxidative stress	[38]
Heart attack	38	Increased proteobacteria LPS and leaky gut	Increased endotoxemia	[39]
Atrial fibrillation	912	Increased LPS	Increased platelet activation	[40]
		Animal studies		
CVD	Animal	Change in gut microbiota composition/metabolites	Outcome	Reference
Atherosclerosis	Mice	Increased LPS	Activation of NF-κB and JNK pathways	[41]
	Mice		Increased size of atherosclerotic	[42]

CVD	No. of Patients	Clinical Studies Change in Gut Microbiota Composition/Metabolites	Outcome	Reference
			lesions	
	Mice		Increased proinflammatory cytokines	[43]
	Mice		Nlrp3 inflammasome stimulation and endothelial dysfunction	[44]
	Mice	Increased TMAO	Increased plague area	[33]
			Increased expression of inflammatory genes	[33]
	Mice	Butyrate supplementation	Reduced cholesterol absorption and atherosclerotic lesion	[45]
	Mice	Reduced SCFAs and *Akkermansia*, *Clostridium*, and *Odoribacter*	Increased plague size	[46]
	Mice	Reduced *Bacteroidetes* and *Clostridia*	Increased dyslipidaemia	[47]
Heart failure	Mice	Increased TMAO	Increased severity of heart failure	[33]
Hypertension	Rat		Increased osmotic pressure and water reabsorption	[48]
Cardiomyopathy	Mice	Increased LPS	Increased inflammatory markers	[49]

CAD: Coronary artery disease; LPS: Lipopolysaccharides; TMAO: Trimethylamine N-oxide; LBP: Lipopolysaccharide binding protein; SCFAs: Short chain fatty acids; NF-κB:

Some trials have proved that plasma levels of TMAO are a risk factor for CVDs [50]. Nonetheless, in some clinical trials, these raised levels of TMAO have been autonomously related to the incidence of CVDs and risks of stroke, myocardial infarction (MI), and death; thus, further study is required for recognizing the existing mechanism [50][51]

[52][53][54]. Additional research has revealed that a TMA-containing nutrient (L-carnitine) present almost entirely in red meat acts as a nourishing pioneer to gut synthesis of TMA and TMAO in humans and mice [51]. While betaine, choline, and TMAO were linked with an enhanced risk of CVD in 1876 patients through a heart risk assessment [50], additional studies in cohorts revealed that the prognostic importance was regularly limited to the formation of TMAO, particularly from L-carnitine and choline [51][55]. In a prospective human trial of greater than 4000 individuals taking coronary angiography, increased TMAO levels produced the main adverse effects on the heart, including stroke and MI for a duration of 3 years.

Three current meta-analyses have recognized that raised plasma levels of TMAO are linked with enhanced risks of CVD and all-cause death [56][57][58]; yet, some condemnation occurs about the CVD and TMAO association as fish might hold larger TMAO and TMA concentrations [59]. Nevertheless, the intake of fish is good for cardiac health [60][61][62]. Similarly, there is a trial with no association between events of TMAO and atherosclerosis [63]. More randomized human studies with an increased number of subjects are required to elucidate if TMAO is a mediator or marker in CVD.

Current trials have linked increased TMAO concentrations to an enhancement of CVD risk and its sternness [64][65]. Consequently, TMAO concentration is connected with the size of atherosclerotic plaque and CVD proceedings [50] (Appendix A Figure A2).

4. Clinical Applications of the Drug-Gut Interactions

As we learn more about the scope and clinical relevance of drug–microbiota interaction, we realize that the gut microbiota not only affects drug absorption and distribution but can also metabolize drugs, thus altering their efficacy. The drug-induced alteration in the microbial composition and the microbial-induced alteration in the drug absorption and distribution have critical effects on the host system and the health outcome. We now understand that some anti-inflammatory medications, anti-hypertensive medications, and lipid-lowering medications can interact with the gut environment and have a positive or negative association with the microbiota composition. This raises awareness that when treating cardiovascular disease patients with these drugs, they need to be on probiotics or prebiotics or placed on special dietary and lifestyle changes [66]. It also highlights the effects of polypharmacy on the gut microbiota composition, and thus, providers should continuously monitor drug-associated effects in vulnerable patients where the microbiota ecosystem is already compromised. One approach to achieve that is through sequencing patient fecal samples, which serve as a proxy for the gut microbial composition, and then marking the absence or presence of a particular microbe or enzyme. Using this technique combined with a machine learning algorithm, one can predict drug safety, efficacy, and metabolism. Moreover, highlighting the current view of drug–microbial interactions creates a better understanding of internal factors that shape drug concentration and toxicity, which can affect the appropriate dose measurement per patient per condition [67].

Lastly, there is an increasing amount of evidence about the role of gut microbiota in predicting the prognosis and outcomes of cardiovascular diseases. Therefore, it is now regarded as a reliable target for disease management and prevention. Maintaining a balanced microbiota environment has been linked to improved lipid profiles, blood

pressure measurements, and improved BMI among patients with metabolic syndromes. Therefore, it is intuitive when treating patients with cardiovascular diseases to also target the gut microbial environment through dietary interventions to amplify treatment outcomes [68].

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