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Feed your microbiome and your heart: The gut-heart axis

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1. ABSTRACT

Cardiovascular and metabolic diseases are the leading causes of disability, morbidity, and mortality worldwide. Genetics plays an important role, but environmental factors change the game and hold the potential for prevention, reversibility, and applied therapy. Nutrition, phenotype, and behavior of microorganisms, intestinal eco-events, and intestinal permeability play a crucial role in the induction of diseases. The present mini-review summarizes nutrients, diets, microbial manipulations, and tight junction function modifiers that might prevent, modulate, or treat certain diseases.

2. INTRODUCTION

The natural history of scientific interests is quite dynamic and sometimes stormy, acting as a pendulum between booms and ebbs. However, the gut microbiome is here to remain (1). To such an extent, Fernández-Real J-M *et al*. coined: "They were here before us...and hosted us!" (2). It is generally accepted that bacteria have evolved over billions of years. Only 1-2 million years ago, they inhabited the human intestine, making them much more flexible and adaptable and resistant to an extreme or changing environment (3). Those prokaryotes inhabited an ideal compartment to thrive, proliferate, multiply, and perform their metabolic functions while fighting the enteric and systemic protective barriers to achieve a state of tolerance. The commensals enjoy continuous food supply, ideal temperature and humidity, extreme density to conjugate, and constant mixing of the content by slow intestinal motility. Those ideal exogenous and endogenous Physico-chemical conditions allow them to stay in the bay, all along human life (4).

Despite recent advances in medicine and therapeutic strategies, mortality and morbidity associated with cardiovascular disease (CVD) remain very high. Several approaches are investigating the underlying pathogenesis of CVD. However, there is still a need for more specific and complementary therapeutic options.

3. THE DYSBIOME IMPACTS ON CARDIOVASCULAR DISEASES

Changes in the composition of the intestinal microbiota, known as dysbiosis, play a crucial role in the development of various diseases, including CVD. The reduced cardiac output associated with CVD, which leads to intestinal wall edema and intestinal ischemia, can change the structure and function of the intestine. These changes would promote bacterial

translocation and exacerbate CVD pathology, at least in part, by activating systemic inflammation. Current and future preventive and therapeutic strategies against CVD by adequate modulation of the microbiome and its derived metabolites are under discussion. The high mortality rate partly reflects the possibility that current therapeutic options do not cover critical pathogenic mechanisms. Other factors, such as intestinal microbial dysbiosis, have been included as significant risk factors for the development of the CVD. In many respects, the homeostasis of the intestinal microbiota is essential for maintaining human health, digesting indigestible nutrients, producing vitamins and hormones, shaping the development of the mucosal immune system, and preventing colonization by pathobionts. From the gut prospective, reduced cardiac output in CVD can lead to a decrease in intestinal blood flow, mucous degradation, cellular, and tissue ischemia, resulting in a disorder of the intestinal mucosa. These changes in intestinal barrier function may lead to increased intestinal permeability, intestinal dysbiosis, bacterial translocation, and increased circulating endotoxins that may contribute to the underlying inflammation associated with CVD. The challenge is to go beyond the primordial role of bacteria and move from previous associative studies to those that clarify the cause-effect relationship between microbial intestinal dysbiosis and CVD. Recent studies have shown that the intestinal microbiome can influence host processes and the development of diseases via bioactive metabolites that could be absorbed into the body's circulation.

4. MICROBIAL MOBILOME AFFECTS CARDIOVASCULAR HEALTH

For the last several years, the topic of enteric eco-events that irradiate peripherally to impact remote organs functions, in health and disease, is expanding (5). On the same topic, the gut-cardiovascular axis is gaining attention, and several observations, reviews, and editorials reinforce the cross-talk between nutrition, microbiome, and its mobilome, intestinal permeability, and locally induced immune responses that affect cardiac homeostasis or promote CVD (6-12). To this end, Lässiger-Herfurth A. *et al*., in a most recent review paper on this topic, have summarized the metabolites of the intestinal microbiota that influence the development of arterial thrombosis and atherosclerosis as well as CVD (13). Trimethylamine (TMA), short-chain fatty acids (SCFA), lipopolysaccharides (LPS), lipoteichoic acid (LTA), serotonin, secondary bile acids, and some other microbial constituents and products, derived from the microbiome, were described in detail. The mucosal host's immune system is activated via the microbial-associated molecular patterns (MAMPs) and the above mentioned microbial mobilomic cargo.

Further down, the liver converts some of the molecules into trimethylamine N-oxide (TMAO), intercellular adhesion molecule-1, and the prothrombic von Willebrand factor, thereby enhancing blood hypercoagulation, platelet hyperactivation, and increased aggregation and pro-adhesive phenotype of the vessel lining (13). There is no doubt that enteric dysbiota plays a central role in CVD, hypertension, atherosclerosis, hypercoagulability, and thrombosis as well as in cardiac metabolic diseases such as obesity, diabetes, dyslipidemia, hypercholesterolemia, and liver steatosis (8). However, based on the current knowledge, the well life-long established composition, diversity, and resilience of the microbiome and the unresolved debate between association and causality, the nutrition impact on heart health is gaining importance and therapeutic potentials (14- 18). The present narrative review aims are to expand on the dietary solution as a potential therapy to fight chronic heart conditions and to stimulate the scientific community to study those strategies in humans. It intends to supplement Lässiger-Herfurth *et al*. review (13), highlighting the nutritional and intestinal events that affect cardiovascular health.

5. THE HEART'S NUTRIENTS

Multiple studies explored the effects of specific nutrients on heart health. Most agree that phosphatidylcholine metabolites such as choline, TMA, which is converted to TMAO in the liver,

Table 1. Effects of various diets on the microbiome, TMAO levels and cardiac health in human

Type of diet	Potential effect	Other consequences	Change	Remarks	Cardiovascular health
High fiber	eubiosis	TMAO, less calories, weight loss, improved intestinal motility	Decreased	Vegetarian diet	beneficial
High fat	dysbiosis	TMAO, metabolic syndrome, CVD	Increased	Western/ketogenic diet	detrimental
Low fat	eubiosis	TMAO, weight loss	Decreased	High carbohydrates	beneficial
High protein		TMAO	Increased	Western, meat consumers	detrimental
Low protein		TMAO	Decreased	Meat avoiders	beneficial
Vegetarian	eubiosis	TMAO	Decreased		beneficial
Low trimethyllysine	eubiosis	TMAO	Decreased	Carrot, white onion, cucumber, tomato, whole milk, chicken	beneficial
High trimethyllysine	dysbiosis	TMAO	Increased	Egg, shrimps, goat, beef, veal, turkey, tuna, cheese	detrimental
Low choline	eubiosis	TMAO	Decreased	White onion, cucumber, tomato, whole milk	beneficial
High choline	dysbiosis	TMAO	Increased	Beef liver, egg, salmon, beef, goat, turkey, lamb, pork, veal	detrimental
High carnitine	dysbiosis	TMAO	Increased	Beef, deer, lamb, goat, veal,	detrimental
Low choline	eubiosis	TMAO	Decreased	Cucumber, white onion, carrot, tomato, butter, beef liver, salmon, cheese	Beneficial
Abbreviations: TMAO: trimethylamine N-oxide, CVD: cardiovascular disease, Adapted with permission from (1, 6-8, 17-21)					

carnitine, and betaine are potential predictors of CVD and related diseases (1, 7-8, 14, 16-19). Table 1 summarizes different types of diet, their possible effects on the gut microbiome and TMAO levels, and their cardiovascular health effects.

6. LEAKY GUT IN CARDIOVASCULAR CONDITIONS

Increased intestinal permeability is a dominant factor in the control of chronic diseases, and the compromised tight junctions allow pathogenic, toxic, immunogenic, allergic, inflammatory, and auto immunogenic factors to internalize and activate the local and systemic immune system. Cardiovascular and associated conditions are not an exception. Increased enteric permeability was described in CVD, coronary artery disease, heart failure, gut ischemia, gut dysbiosis, hypertension, type 2 diabetes, obesity, and in the elderly. Besides, to prevent or treat those conditions, a practical way might be to consume nutrients that improve the permeability and/or avoid those that breach tight junction integrity. Table 2 describes those nutrients. It should be emphasized that most of the effects were shown on human gut-originated cell lines or animal models but not in humans. It seems that the nutritional and bacterial cardiogenic factors like choline, carnitine, and TMA, LPS, and the liver originated TMAO were not specifically evaluated for their effects on human intestinal tight junction performances.

7. ADDITIONAL ENTERIC-HEART POTENTIAL PATHWAYS

Finally, several luminal eco-events that may impact the intestinal contribution to CVDs should be highlighted:

1. Post-translational modification of naïve proteins is constantly operating in the lumen (4). The microbiome enzymatic cargo is turning environmental naïve proteins to immunogenic/path-ogenic ones. Celiac disease and rheumatoid arthritis are some of the examples (26-28). A plethora of

Table 2. Nutritional factors that improve or breach tight junction integrity and change intestinal permeability

Change in gut permeability
Increased
• High fat diet
• High carbohydrate/sugar diet
• Vitamin A, D and zinc deficiency
• Fructose
• Gluten
• Process food additives: sugar, organic acids, salt, • emulsifiers, nanoparticles, microbial transglutaminase
• Medium chain fatty acids; capric acid, lauric acid
• Acyl carnitines
• Glutamine deprivation
• Ethanol
• Chitosan
• Capsianoside
Decreased
• Prebiotics: galacto/fructooligosaccharides
• Short chain fatty acids: Butyrate, acetic acid, propionic acid
• Glutamine
• Poly unsaturated fatty acids
• Zinc, Vitamin A & D
• Propolis
• Green tea, coffee, berries, grapes, and other fruits/vegetables
• Polyphenols: Quercetin, Kaempferol, Genistein, Curcumin
• Tryptophan
• β-casein, β-lactoglobulin
Adapted with permission from (22-25)

nutritional and microbial proteins, some of them have the cardiogenic, atherosclerotic, diabetogenic, hypertensive or coagulatory capacity (choline, TMA, betaine, carnitine, LPS, etc.), reside in the lumen. The enzymatic modification can break the tolerance toward those proteins that contribute to cardiovascular pathology. Since choline and carnitine are major dietary precursors of TMA in the human gut, their enzymatic modifications are crucial to drive the cardiovascular pathology (29). In this light, microbial transglutaminase, a heavily used food additive is a universal cross-linker of proteins. In the presence of an acyl donor (glutamine) or an acyl acceptor (lysine), the enzyme can cross-link the proteins/peptides, thus, change their naïve profile to a pathogenic profile (30-32). Since the luminal cardiogenic proteins/peptide can potentially harbor acyl donors/acceptors, the microbial transglutaminase can cross themselves or with other compounds, thus affecting their toxicity and pathogenicity. Alternatively, choline, carnitine, and TMA-degrading enteral bacteria can be identified, thus lowering the risk for CVD (29). The human tissue transglutaminase represents an additional aspect of detrimental protein modifications. It is not only the autoantigen of celiac disease, but appears to play an active role in inflammation, autoimmunity, and hypertension (33, 34). Since all those three

phenomena are essential in CVD evolvement, and since specific inhibitors can block the enzyme, it can represent a potential preventive or therapeutical modality for CVDs.

2. A powerful survival mechanism exists in the enteric luminal microbiome in order to face the constant environmental changes, namely, the horizontal gene transfer (35). Recently, we have hypothesized that an increasing foreign genetic load presented by altered environmental factors is transferred to the enteric microbiome by horizontal gene transfer, leading to chronic human diseases. The gut microbiome responds to those recent changes by a genetic restructuring of the enteric dwellers, driven via horizontal gene exchange. Multiple of those exchanged hostile genes can shift physiological microbiota to a pro-cardiogenic dysbiota. Diet composition, including a gluten-free diet (Table 1, 36), a nutrient that increases gut permeability (Table 2), can drive those changes. Transient bacteria or probiotics carrying hostile genes (35, 37) or enhancing the luminal microbiome that increase the local load, generating choline (29, 38), TMA (39, 40), carnitine (29, 41, 42) and ethanol (43), can be detrimental. The opposite holds for the cardio- beneficial short-chain fatty acid. In this regard, the strain, family, and genus of the intestinal microbiome that secretes acetate, propionate, and butyrate are continuously elucidated, and the genes involved are studied (43).

3. The contribution of the enteric virome genetic cargo, their bacterial lysis or synergy, and their important role in determining the microbiota/dysbiota ratio were scarcely studied in CVDs (44). The gut phageome might have a crucial role in heart pathology evolvement (45, 46).

4. Finally, the “French paradox” can teach us how a society that consumes a lipid-rich diet and fatty foods have relatively decreased morbidity and mortality from CVDs (47). It was suggested that the polyphenol-rich diet, containing indigestible fibers, whole grains, wines, teas, juices, fruits and vegetables provides health-promoting phytonutrients and phytochemicals that can prevent CVDs. By their lowering intestinal permeability, antioxidant and anti-inflammatory capacities they can prevent and treat those chronic heart diseases (22, 24, 48).

8. SUMMARY

It seems that the lateral gene transfer of harmful cardiovascular genes, the post-translational modification of unfriendly cardiogenic products, and the enteric phageome in the intestinal compartment should be studied and explored more deeply. It can be concluded that the present review, based on nutrition, microbiome, luminal protein modifications, and lateral gene transfer in the human intestinal compartment, highlights additional aspects that may affect CVDs. In a more holistic view, chronic inflammation drives chronic human diseases, including CVDs and its associated conditions (49). Understanding the mechanisms and pathways might unravel novel therapeutic strategies to prevent, lower the incidence, morbidity, and mortality of those conditions.

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Abbreviations: cardiovascular disease –CVD, Trimethylamine -TMA, short-chain fatty acids-SCFA, lipopolysaccharides-LPS, lipoteichoic acid (LTA), microbial-associated molecular patterns MAMPs, trimethylamine N-oxide-TMAO

Key Words: Heart, Gut, Microbiome, Cardiovascular Disease, Nutrition, Mechanisms, Pathways, Review

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