REVIEW ARTICLE

JOURNAL OF RARE CARDIOVASCULAR DISEASES

Microbiology and cardiovascular health: The gut-heart axis in focus

Ahmed Jalal Yousef[1,*], Shatha saadallah lafi[2] and Bassad Salem Mahmood[1]

[1]Diyala Health Directorate,Baqubah, Diyala Province, Iraq

[2] College of Dentistry, Albayan University, Baghdad, Iraq

Correspondance: (e-mail: ahmedjalal07729@gmail.com).

Received 21 September 2024 Revised 10 October 2024 Accepted 30 December 2024 Published 24 February 2025

ABSTRACT New studies show a strong connexion between the gut microbial community and cardiovascular system, recognized as the gut-heart axis. This review seeks to contrast and compare how the gut microbiota contributing to cardiovascular diseases (CVDs) mechanisms include microbial metabolites, immune response, and inflammation. In the section devoted to emerging therapies relevant to the microbiome, probiotics, prebiotics, diet, and pharmacological therapies that may influence the microbiome are described. The future directions underline the importance of individualization of the treatment and the quality of the trial to improve microbiome-directed strategies in CVD patients.

KEYWORDS microbiome, cardiovascular diseases, gut-heart axis, microbial metabolites, inflammation, probiotics, personalized medicine

1. INTRODUCTION

The World Health Organization global status manual recognizes cardiovascular diseases (CVDs) as the number one killer attributing 17.9 million deaths every year [1]. Besides these well-defined risk factors of hypertension, hyperlipidemia and diabetes, emerging data from the past have identified gut microbiota as another critical determinant of cardiovascular disease [2]. Unlike the well-studied and better understood blood circulatory system and the endocrine system [3], the gut microbiota consists of trillions of microorganisms, which control a number of metabolic as well as immunological functions that are not confined to the digestive system alone. This review aims to discuss the GHA, its functional processes, consequences, and potential targeting for CVDs control.

2. MICROBIAL CONNEXION TO CARDIOVASCULAR DISEASE

The term, gut-heart axis, illustrates a reciprocal relationship between gut microbiota and the function of the heart via microbial-derived metabolites, inflammation, and immune signaling [4], [5].

1) Microbial Metabolites Gut microbiota produce metabolites such as short-chain fatty acids (SCFAs) and Trimethylamine-N-oxide (TMAO), which significantly impact cardiovascular health:

- SCFAs: SCFAs (acetate, propionate, butyrate) generated from dietary fibre fermentation are known to possess anti-inflammatory effects, alter the blood pressure and improve endothelial function [6], [7].
- TMAO: Derived from choline and l-carnitine in the diet, TMAO accelerates the formation of atherosclerotic plaques through boosting cholesterol loading and platelet hyper aggregation. High TMAO is associated with an increased risk of acute myocardial infarction, ischemic stroke [8]–[10].

2) Immune Modulation Dysbiosis is a condition characterised by microbial imbalance and leads to LPS and other microbial products that enhance inflammation causing endothelial dysfunction and atherosclerosis. Fourthly, changes in gut permeability promoted bacterial translocation and enhance inflammatory cytokines [11].

3. CARDIOVASCULAR DISEASES AND DYSBIOSIS

1) Atherosclerosis Gut dysbiosis has been suggested to play a role in atherogenesis by the DCA formation and inflammation [12]. Research shows elevated TMAO levels in patients with CAD and play a crucial step in plaque development and progression [13].

2) Current Availability of SCFA modification and the link between reduced SCFA and increased gut permeability to hypertension has been identified [14]. Research done on animals has shown that the SCFA supplement helps maintain blood pressure and decrease the inflammation of blood vessels [15].

3) Heart Failure Patients with heart failure had severe impairment of gut permeability, bacterial endotoxins, and inflammation [16]. TMAO which is a predictor of adverse clinical outcomes has been observed to be at high levels in patients with heart failure and, more so, high levels were found to be

associated with increased mortality [17].

4. HOW SOME THERAPEUTIC APPROACHES AIM AT THE MICROBIOME?

1) Probiotics and Prebiotics Probiotics that include Lactobacillus and Bifidumi bacterium help regain proper balance of the gut bacteria while prebiotics including inulin help with the growth of the good bacteria [18], [19]. A review of randomized placebo controlled clinical trials concerning the effects that probiotics and prebiotics have on CVD risk factors reported decreases in inflammatory markers and favorable changes in lipid profile [20].

2) Dietary Interventions Plant-based diets, especially those providing large amounts of fiber and polyphenols, promote beneficial bacterial growth, increase mucus SCFA and therefore decrease TMAO [21]. Mediterranean diets have been postulated with protective effects against CVDs through alterations of gut microbiota [22], [23].

3) Pharmacological Interventions Thus, new cardiovascular risk reducing strategies include therapies that target microbial enzymes involved in the synthesis of TMAO. For instance, inhibitors of trimethylamine-lyase have shown promise in earlier research work in the regulation of TMAO levels [24].

4) Faecal Microbiota Transplantation (FMT) FMT process involves transferring of microbial contents of stool from a suitable donor to a patient with dysbiosis. There is some preliminary evidence of its ability to rebalance the microbiome and decrease systemic inflammation relevant to CVD situations [25].

5. FUTURE DIRECTIONS AND CONCLUSION

Recent developments in metagenomics and metabolomics studies have helped elucidating complex relations between microbiota and cardiovascular status [26] (Supporting Information S2). However, it means that these findings should be implemented into clinical practice on a large scale and patients should be treated individually [27].

Gut-heart axis is a relatively recent advance in cardiovascular disease research holding significantly higher potential for future prevention and intervention. Further research on different microbiome interventions may lead to a shift in the CVD approach and an overall increase in global health [28].

REFERENCES

[1] Wang, Zeneng, et al. "Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease." *Nature* 472.7341 (2011): 57-63.

[2] Tang, WH Wilson, et al. "Intestinal microbiota in cardiovascular health and disease: JACC state-of-the-art review." *Journal of the American College of Cardiology* 73.16 (2019): 2089-2105.

[3] Portincasa, Piero, et al. "Gut microbiota and short chain fatty acids: implications in glucose homeostasis." *International Journal of Molecular Sciences* 23.3 (2022): 1105.

[4] Marques, Francine Z., Charles R. Mackay, and David M. Kaye. "Beyond gut feelings: how the gut microbiota regulates blood pressure." *Nature Reviews Cardiology* 15.1 (2018): 20-32.

[5] Devkota, Suzanne, and Eugene B. Chang. "Interactions between diet, bile acid metabolism, gut microbiota, and inflammatory bowel diseases." *Digestive Diseases* 33.3 (2015): 351-356.

[6] Koeth, Robert A., et al. "Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis." *Nature Medicine* 19.5 (2013): 576-585.

[7] Kummen, Martin, et al. "Gut microbiota signature in heart failure defined from profiling of 2 independent cohorts." *Journal of the American College of Cardiology* 71.10 (2018): 1184-1186.

[8] Fischer, Monika, et al. "Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: a promising treatment approach." *Gut Microbes* 8.3 (2017): 289-302.

[9] Sonnenburg, Justin L., and Fredrik Bäckhed. "Diet–microbiota interactions as moderators of human metabolism." *Nature* 535.7610 (2016): 56-64.

[10] Qin, Junjie, et al. "A metagenome-wide association study of gut microbiota in type 2 diabetes." *Nature* 490.7418 (2012): 55-60.

[11] Wang, Peng-Xu, et al. "Gut microbiota and metabolic syndrome." *Chinese Medical Journal* 133.07 (2020): 808-816.

[12] Ridaura, Vanessa K., et al. "Gut microbiota from twins discordant for obesity modulate metabolism in mice." *Science* 341.6150 (2013): 1241214.

[13] Holmes, Elaine, et al. "Therapeutic modulation of microbiota-host metabolic interactions." *Science Translational Medicine* 4.137 (2012): 137rv6-137rv6.

[14] Battson, Micah L., et al. "The gut microbiota as a novel regulator of cardiovascular function and disease." *The Journal of Nutritional Biochemistry* 56 (2018): 1-15.

[15] Clemente, Jose C., et al. "The impact of the gut microbiota on human health: an integrative view." *Cell* 148.6 (2012): 1258-1270.

[16] Poll, Brian G., Muhammad Umar Cheema, and Jennifer L. Pluznick. "Gut microbial metabolites and blood pressure regulation: focus on SCFAs and TMAO." *Physiology* 35.4 (2020): 275-284.

[17] Smits, Samuel A., et al. "Seasonal cycling in the gut microbiome of the Hadza hunter-gatherers of Tanzania." *Science* 357.6353 (2017): 802-806.

[18] Turnbaugh, Peter J., et al. "An obesity-associated gut microbiome with increased capacity for energy harvest." *Nature* 444.7122 (2006): 1027-1031.

[19] Gregor, Margaret F., and Gökhan S. Hotamisligil. "Inflammatory mechanisms in obesity." *Annual Review of Immunology* 29.1 (2011): 415-445.

[20] Kelly, John R., et al. "Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders." *Frontiers in Cellular Neuroscience 9* (2015): 166028.

[21] Doroszkiewicz, Julia, Magdalena Groblewska, and Barbara Mroczko. "The role of gut microbiota and gut–brain interplay in selected diseases of the central nervous system." *International Journal of Molecular Sciences* 22.18 (2021): 10028.

[22] Li, Jing, et al. "Gut microbiota dysbiosis contributes to the development of hypertension." *Microbiome* 5 (2017): 1-19.

[23] Estruch, Ramón, et al. "Primary prevention of cardiovascular disease with a Mediterranean diet." *New England Journal of Medicine* 368.14 (2013): 1279-1290.

[24] Desai, Moreshwar S., et al. "Bile acid excess induces cardiomyopathy and metabolic dysfunctions in the heart." *Hepatology* 65.1 (2017): 189-201.

[25] Marchesi, Julian R., et al. "The gut microbiota and host health: A new clinical frontier." *Gut* 65.2 (2016): 330-339.

[26] Tang, WH Wilson, Takeshi Kitai, and Stanley L. Hazen. "Gut microbiota in cardiovascular health and disease." *Circulation Research* 120.7 (2017): 1183-1196.

[27] Jie, Zhuye, et al. "The gut microbiome in atherosclerotic cardiovascular disease." *Nature Communications* 8.1 (2017): 845.

[28] Brown, J. Mark, and Stanley L. Hazen. "Microbial modulation of cardiovascular disease." *Nature Reviews Microbiology* 16.3 (2018): 171-181.