Rev Esp Cardiol. 2017;70(10):799–800

Editorial

The Role and Impact of Gut Microbiota in Cardiovascular Disease

Impacto de la microbiota intestinal en la enfermedad cardiovascular

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Article history:
Available online 18 May 2017

The human gut harbors more than 100 trillion microbial cells, which intricately regulate the normal development and function of mucosal barriers. Over the past decade, we have discovered the substantial inter- and intra-individual variation and versatility of the gut microbiome profile and changes in health and various disease states. Although it is clear that the composition of gut microbiota can be significantly altered in patients with cardiometabolic diseases (also known as "dysbiosis"), much of the data remain largely associative in nature. Thus, the path to further understanding the role of the gut microbiome in health and disease remains exceedingly challenging. Recent studies have identified the gut microbiota as playing a critical role in the pathophysiology of cardiovascular disease (CVD) and chronic kidney disease (CKD). Given that the primary role of the kidneys is to remove metabolites and toxic compounds to maintain body homeostasis, impaired renal function can lead to increased levels of such unwanted compounds. These organic compounds with adverse biological activity are often referred to as "uremic toxins," such as advanced glycation end products and tryptophan-based metabolites (eg, p-cresyl sulfate and indoxyl sulfate).[1] Indeed, altered profiles of gut microbiota composition have been associated with increased production of indoxyl sulfate and p-cresyl sulfate, which is directly associated with endothelial dysfunction, inflammation and oxidative stress, and increases in the incidence of CVD and mortality.[2] These data support a gut-renal axis hypothesis contributing to the progression of CVD and CKD.

The gut microbiota interacts with the host via the intestinal mucosal surface, and intestinal epithelial barrier function is maintained by a well-balanced gut microbiota through several mechanisms, including restoration of protein tight junction structure, upregulation of mucin genes, and competition with pathogenic bacteria to bind epithelial cells.[3] In the setting of impaired cardiac and/or renal function, intestinal wall edema due to systemic congestion and intestinal wall ischemia may reduce intestinal blood flow, which can result in structural disruption of the epithelial mucosal barrier and increased permeability.[4] In addition to hemodynamic deterioration, gut dysbiosis is associated with the production of unwanted toxins and the promotion of a leaky intestinal barrier.[5] The disruption of intestinal barrier function allows the translocation of endotoxins, microbial components, and microbial metabolites to enter the systemic circulation, which can induce immune responses and lead to systemic inflammation. Circulating bacterial lipopolysaccharide levels increase with CKD stages and have been associated with a higher mortality risk. Furthermore, bacterial DNA is also detected in the blood of patients with both CVD and CKD.[6,7] Plasma inflammatory markers, such as high-sensitive C-reactive protein and interleukin-6 levels, were higher in patients with bacterial DNA in the blood than in those without.[8] In a recent study, a corresponding increase in the amount of fecal intestinal bacteria and fungi has been observed with increasing intestinal permeability in patients with heart failure.[9]

The discovery of trimethylamine *N*-oxide (TMAO) production and the development and progression of cardiovascular risk adds another dimension to this complex interplay between gut microbiome and its human host, whereby dietary intake (a form of environmental exposure) interfaces with gut microbiota to generate metabolites that may serve as promoters of cardiorenal diseases. Indeed, circulating TMAO levels have consistently been observed to be elevated in patients with CKD as well as in those with atherosclerotic burden, and have been associated with the development and progression of heart failure and CKD.[10,11] We and others have observed that increased dietary-induced TMAO generation in animal models has been associated with myocardial and renal tubulointerstitial fibrosis.[11] Microbial taxa belonging to the *clostridiaceae* and *peptostreptococcaceae* families are positively associated with blood levels of TMAO in humans.[12] Given the high choline-induced gut microbiota-dependent production of trimethylamine (TMA) and TMAO,[13] reduced intake of dietary precursors of TMAO is a potential approach to reduce CVD. We have recently reported that 3,3-dimethyl-1-butanol (DMB), which is a structural analog of choline and an inhibitor of TMA formation through inhibition of microbial TMA lyases, inhibited choline diet-enhanced endogenous macrophage foam cell formation and atherosclerotic lesion development without alterations in circulating cholesterol levels.[14] DMB was detected in some balsamic vinegars, red wines, and olive oils, which may in part potentially explain the cardiovascular benefits of the Mediterranean diet.

Besides identifying gut microbiota-derived metabolites that can lead to disease progression, various other metabolites may

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http://dx.doi.org/10.1016/j.rec.2017.04.007

promote cardiovascular benefits. For example, a connection between blood pressure regulation and microbial short chain fatty acids (SCFAs) has also been gathering attention. Hypertension was associated with changes in the microbiota as well as in SCFAs.[15] SCFAs were shown to act through both olfactory receptor 78 (Olf78), which increases blood pressure, and G-protein-coupled receptor 41, which lowers blood pressure.[16] High-fiber diets, which increase microbial SCFA production, lowered blood pressure.[17] Individuals with lower microbial SCFA levels had higher blood pressure.[18] In addition, SCFAs also reduced acute kidney injury and intestinal mucosal injury in an ischemia-reperfusion mouse model.[19,20] Further studies are needed to investigate whether and how changes in SCFA-producing microbiota truly translate into changes in plasma levels of SCFAs.

Because gut microbiota plays a role in systemic inflammation, metabolic syndrome, vascular dysfunction and atherosclerosis, modulating gut microbiota and its metabolites is a possible therapeutic strategy. Prebiotics are nondigestible ingredients that selectively alter the growth or activity of certain species of the intestinal microbiota. The reduction of p-cresyl sulfate and indoxyl sulfate was observed in hemodialysis patients receiving inulin.[21] Probiotics, organisms in food and dietary supplements that can confer health benefits on the host, reduced uremic toxins in the gut through several mechanisms including enhancement of epithelial barrier function, the production and secretion of mucin, inhibition of pathogenic bacteria adhesion, regulation of epithelial homeostasis, and increased cell survival.[22] The administration of a probiotic bacterial formulation in CKD patients was associated with a significant decrease in blood urea nitrogen levels and significant improvement in the quality of life and serum creatinine and uric levels.[23] Targeting healthy reactive oxygen production in the gut with probiotics was beneficial for the prevention of CKD progression.[23] Meanwhile, direct removal of gut-derived toxins has also been a focus in the treatment of patients with CKD.[4] However, we have yet to see concrete evidence on the benefits of gut dysbiosis manipulation or interventions targeting gut microbiota in patients with cardiovascular or cardiorenal syndrome.

In summary, multiple factors link the gut and cardiorenal pathophysiology. In particular, the metabolic potential of gut microbiota has gained much attention as a contributing factor in the development of CVD and CKD. Gut microbiota and cardiorenal syndrome can potentiate each other, leading to a vicious cycle. Further understanding of these gut-cardiorenal interactions may result in novel diagnostic and therapeutic approaches as well as improve the long-term clinical care of these patients. This exciting new area of gut-cardiorenal interaction needs further investigation, and long-term intervention studies are warranted to clarify potential benefits of such strategies in modulating gut microbiota.

FUNDING

W. Tang is supported by grants from the National Institutes of Health (NIH) and the Office of Dietary Supplements (P20HL113452, R01DK106000, R01HL126827) related to the content of this article.

CONFLICTS OF INTEREST

None declared.

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