Contributory Role of Gut Microbiota and Their Metabolites Toward Cardiovascular Complications in Chronic Kidney Disease

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Summary: The gut microbiome recently has emerged as a novel risk factor that impacts health and disease. Our gut microbiota can function as an endocrine organ through its unique ability to metabolize various dietary precursors, and can fuel the systemic inflammation observed in chronic disease. This is especially important in the setting of chronic kidney disease, in which microbial metabolism can contribute directly to accumulation of circulating toxins that then can alter and shift the balance of microbiota composition and downstream functions. To study this process, advances in -omics technologies are providing opportunities to understand not only the taxonomy, but also the functional diversity of our microbiome. We also reliably can quantify en masse a wide range of uremic byproducts of microbial metabolism. Herein, we examine the bidirectional relationship between the gut microbiome and the failing kidneys. We describe potential approaches targeting gut microbiota for cardiovascular risk reduction in chronic kidney disease using an illustrative example of a novel gut-generated metabolite, trimethylamine *N*-oxide.
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In the 1800s, the English physician Richard Bright established a relationship between chronic kidney disease (CKD) and the clinical abnormalities brought about in the uremic state or the residual syndrome, including cardiovascular disease (CVD).[1,2] It has long been postulated that such increased CVD risk in CKD patients is partly owing to a shared set of traditional risk factors such as diabetes, hypertension, albuminuria, dyslipidemia, and smoking.[3] However, such traditional risk factors do not entirely explain the accelerated progression of CVD in CKD patients. Because the large majority of morbidity and mortality of CKD remains CVD-related, elucidation of novel CVD risk factors may improve clinical outcomes of CKD patients.

The contribution of specific gut microbiota–generated metabolites toward uremia and poor outcomes have been documented in observational studies and associated with important clinical end points such as progression of renal failure, CVD events, and mortality.[4,5] Today, the perception of our microbiome has evolved from merely an inert set of microorganisms to a bona fide endocrine organ. Weighing in at approximately 2 kg, our intestinal microflora play a vital role to maintain a symbiotic relationship with its host.[6]

Multiple efforts such as the Human Microbiome Project and Metagenomics of the Human Intestinal Tract (MetaHIT) are cataloging the human microbiome.[7,8] At birth, the gut microbiome is relatively sterile. However, continuous exposure to the environment results in subsequent colonization of trillions of bacteria ($>10^{14}$).[9,10] This composition of bacteria is now believed to be a sensitive factor that alters our risk for disease. In the setting of CKD, a comparison of the gut microbiota composition between those with end-stage renal disease (ESRD) and healthy individuals showed the increased relative abundance of at least 190 bacterial operational taxonomic units.[11] The investigators then extended their findings to a model of 5/6 nephrectomized rats, which showed that a decrease in renal function also resulted in a distinct bacterial community.[11] In addition, the dialysis mode also can impact the gut microbiota composition.[12] Based on these environmental exposures, our gut microbiome can generate products that are dependent on renal clearance that are either beneficial and/or detrimental to our health. In fact, production of uremic toxins may involve several different sources, ranging from the body itself (without intestinal processing), unmodified absorption of dietary products (such as advanced end glycation products), to metabolites that are produced in the intestine from precursors originating from microbial fermentation[13]—all accumulating in the setting of impaired renal clearance.

HOW UREMIC SOLUTES AND METABOLITES IMPACT THE MICROBIOTA

Dysbiosis, or imbalance of gut microbial composition, can stem from many processes including an altered diet

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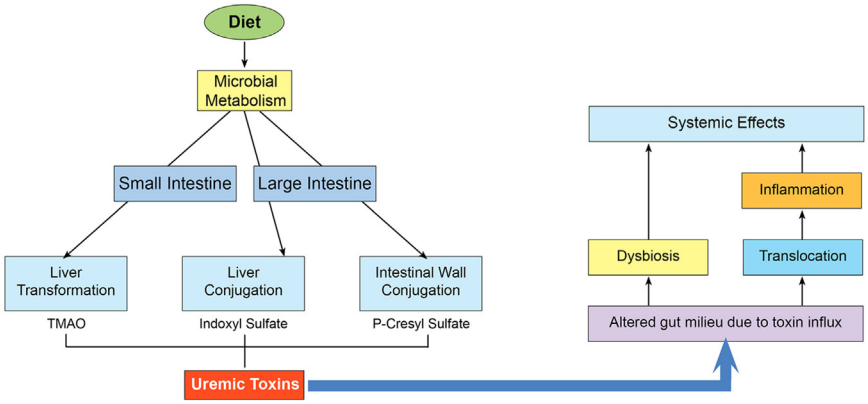

Figure 1. Dietary precursors are modified by the microbiota to generate an array of uremic toxins through multiple mechanisms at the level of the microbiota, intestinal wall, and liver. An influx of uremic toxins results in a microbiota imbalance along with bacterial translocation and inflammation. These factors contribute to the multitude of systemic effects covered in this review.

as well as colonic compensation for increased uremic toxins. Specifically, uremic metabolites and solutes are produced with contributions at many steps including direct microbiota transformation, intestinal wall conjugation, liver conjugation, or endogenous generation (Fig. 1). As the glomerular filtration and compensatory tubular secretion become impaired in CKD and tubular injury, increased nitrogen compounds such as urea and uric acid instead may be excreted via the intestines. As an example, increased urea secretion through the gastrointestinal tract is converted to ammonium, which then leads to increased intraluminal pH as well as mucosal damage.[14] This influx of nitrogen-rich compounds, along with the damage incurred by its metabolic byproducts, can lead to further gut dysbiosis. In the setting of increased uremic toxins, bacterial species that contain enzymes capable of metabolizing nitrogen compounds such as p-cresol and indole, urea, and uric acid, as sources for fermentation will out-proliferate bacteria such as *Lactobacillae* or groups that use dietary fiber to convert into short-chain fatty acids (SCFAs).[15] These functional changes have been reported by Wong et al[15] in which 19 families of bacteria containing urease, uricase, and indole or p-cresol–forming enzymes were identified predominantly in the setting of ESRD, whereas there were decreased bacterial families possessing SCFA butyrate-forming enzymes. Many other external factors also can influence gut microbial composition. For example, patients with CKD maintain a difficult balance between adequate nutrition to promote symbiosis while avoiding potassium and phosphorus overload.[16] Physiologic factors such as gut edema and reduced intestinal transit will influence the intestinal microflora. Patients with CKD often require chronic medications including phosphate-binding agents, iron supplements, as well

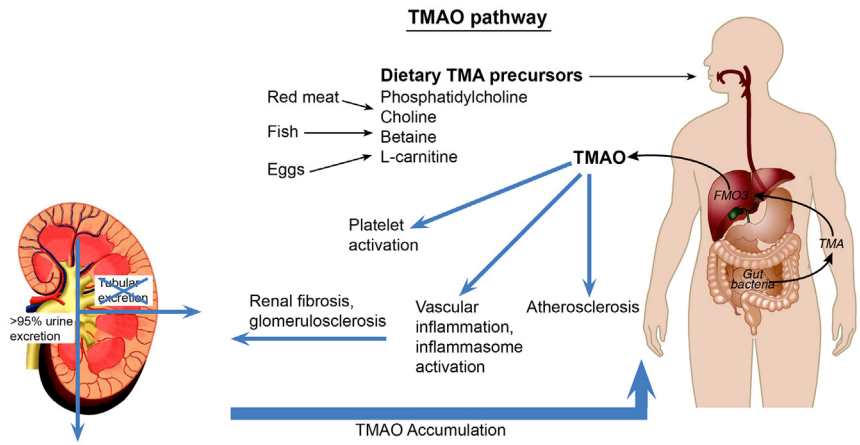

Figure 2. Overview of TMAO metabolism. Dietary precursors such as red meat, fish, and eggs contain compounds that contain the TMA moiety, which is released as TMA, absorbed into circulation, and converted to TMAO in the liver. Circulating TMAO has been implicated in processes such as atherosclerosis, platelet activation, as well as vascular inflammation. These processes contribute to the development of renal dysfunction. Destruction of tubular secretion mechanisms result in the accumulation of TMAO in the disease setting and contribute to a feed-forward cycle. Modified with permission from Tomlinson et al.[17]