Nonextracorporeal Methods for Decreasing Uremic Solute Concentration: A Future Way To Go?

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Summary: The uremic milieu is consequential to a disrupted balance between availability of retention solutes and the excretory capacity of the kidneys. Although metabolism is the prime contributor to the internal milieu, a significant fraction of uremic retention solutes originates from other sources. The main route of entrance is via the intestinal tract, directly from the diet and indirectly from commensal microbial metabolism. This latter dynamic interplay between the intestines and kidney has been coined the gut–kidney axis. This review summarizes current understanding of the gut–kidney axis and explores the impact of dietary and other nonextracorporeal therapeutic interventions in patients with chronic kidney disease.
Semin Nephrol 34:228-243
Keywords: Uremic retention solutes, intestine, diet, microbiome, metabolism

Accumulation of uremic retention solutes (URS) is consequential to a disrupted balance between exposure to waste products mainly coming from the diet, their subsequent metabolism, and the excretory capacity of the kidneys (Fig. 1).[1] These URS constitute a long and ever-expanding list of molecules. A widely accepted classification, endorsed by the European uremic toxin (EUTox) Work Group, divides all known URS into three groups according to characteristics affecting their removal pattern during dialysis.[2] This physicochemical classification categorizes URS into the following: (1) small water-soluble molecules (<500 Da) that readily pass any dialysis filter; (2) larger molecules (≥ 500 Da), for which passage through a dialysis filter may be limited and dependent on membrane characteristics (this group is often referred to as *middle molecules*); and (3) protein-bound molecules, for which dialysance largely depends on the equilibrium between the bound and free fractions. An update of this classification recently was published.[3] Representatives of these groups are discussed in more detail in this issue.[4–8]

Alternatively, uremic retention solutes can be classified according to their origin (Table 1).[9] Obviously, the majority of URS originate endogenously from mammalian metabolism. Exogenous dietary URS also may be an important additional source of URS, such as oxalate[10] and advanced glycation end products.[11,12] Apart from these well-recognized sources of URS, nowadays it is clear that intestinal microbial metabolism also results in the generation of numerous URS.[9,13] Classifying the URS according to their site of origin may be of great help to identify therapeutic options beyond extracorporeal removal and should be considered complementary to the EUTox Work Group classification (Table 1). We focus on the nonendogenous (ie, exogenous molecules and microbial metabolites) URS to explore nonextracorporeal methods to reduce their uremic serum concentrations.

THE GUT–KIDNEY AXIS

It has long been accepted that the principal role of the colon is to absorb salt and water, and to provide a mechanism for the orderly disposal of waste products of digestion. We now understand that the advantages of microbial metabolism to the host are manifold, including energy harvesting by fermentation of dietary carbohydrates resistant to digestion in the small intestine (eg, dietary fibers and nonstarch polysaccharides), the formation of essential molecules such as several vitamins and the development and modulation of the human gut immune system.[14] Untargeted metabolomic analyses show that the gut microbiota contribute substantially to the mammalian metabolome and that at least part of these metabolites are unique microbial metabolites that otherwise would not be part of the human metabolome.[13,15] In general, the relation between host and bacteria is considered symbiotic. Nonetheless, the microbial metabolism also may lead to the production of potentially detrimental molecules. Bacterial metabolism of phosphatidylcholine (lecithin),

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Financial support: Supported by a fellowship of the Research Foundation-Flanders (grant 11E9813N to R.P.).

Conflict of interest statement: Björn Meijers has received consultancy fees from Bellco (Belgium).

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0270-9295/ - see front matter

http://dx.doi.org/10.1016/j.semnephrol.2014.02.012

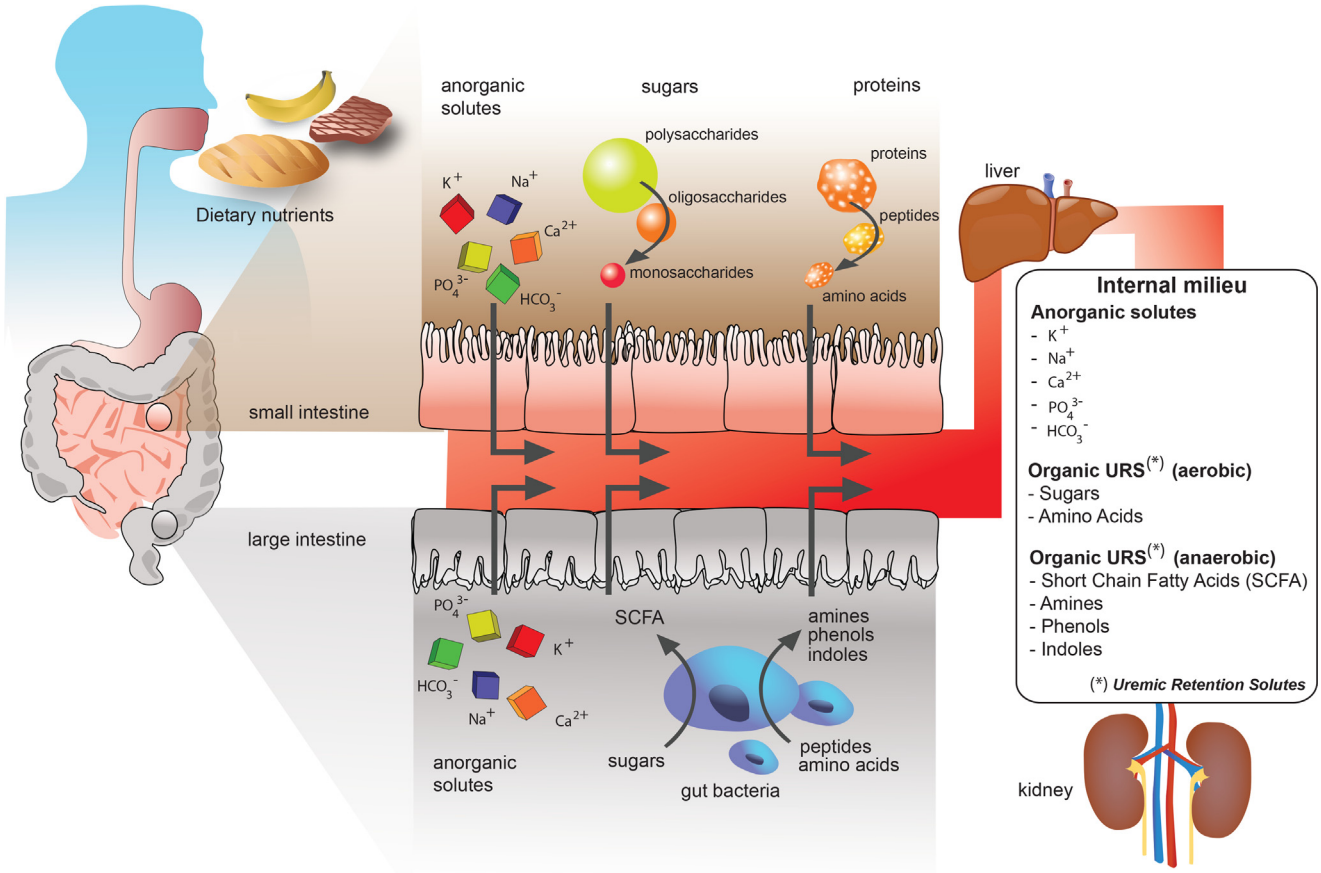

Figure 1. Schematic overview of the gastrointestinal tract metabolism contributing to the internal milieu. In patients with kidney disease, the gastrointestinal uptake outweighs the renal excretory capacity, leading to retention of so-called URS. This altered composition of the internal milieu contributes to the uremic syndrome. Retention of anorganic electrolytes may lead to hyperkalemia and hyperphosphatemia. Organic uremic retention solutes include the indoles (eg, indoxyl sulfate), phenols (eg, *p*-cresyl sulfate, phenyl acetic acids), and the amines.

particularly present in eggs and processed foods, and of L-carnitine, particularly present in red meat, leads to the bacterial production of trimethylamine, which after intestinal absorption is metabolized further toward trimethylamine-oxide.[16,17] Accumulation of trimethylamine-oxide induces atherosclerosis in animal models and serum concentrations of trimethylamine-oxide are linked with cardiovascular events in a dose-dependent manner.[18]

In 1870, Jaffe[19] suggested the intestine to be the source of some metabolites excreted in the urine when he wrote "und bei der nahen Verwandtschaft, welche zwischen indigo und indican besteht, darf man somit vermuten, daβ das bei der Verdauungsthätigkeit im Darm auftretende indole eine der Quellen der Indican bildung ist" (which translates to, "taking into account the close relationship between indigo and indoxyl sulfate, it is quite conceivable that the indole produced by intestinal digestion is one of the origins of [urinary] indoxyl sulfate"). One of the first experimental studies on the interaction between the gut microbiome and kidney function of the mammalian host was the observation that although survival of germ-free rats under starvation conditions was shorter than their conventional counterparts (longer survival by the presence of gut bacteria in animals with normal kidney function), the survival advantage was reversed when uremic rats were starved to death (shorter survival by the presence of gut bacteria in animals with uremia).[20] Over the years, several URS derived from microbial metabolism were identified. Bacterial metabolism of tryptophan under anaerobic conditions leads to the formation of indole, which after intestinal absorption is oxidized to indoxyl and finally is sulfated to indoxyl sulfate.[21,22] Likewise, bacterial fermentation of tyrosine results in *p*-cresol, which after intestinal absorption is sulfated, resulting in the formation of *p*-cresyl sulfate.[23,24] Apart from sulfate conjugation as a major pathway, to a lesser extent other phase II reactions also take place, including glucuronidation, resulting in, for example, the formation of *p*-cresyl glucuronide and indoxyl glucuronide.[25,26]