Toxic microbiome and progression of chronic kidney disease: insights from a longitudinal CKD-microbiome study

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The gut microbiome is essential for human health and disease, acting in a symbiotic relationship with its host. In chronic kidney disease (CKD), this relationship is commonly disrupted, leading to an overgrowth of dysbiotic bacteria and the production of potentially harmful compounds.[1] Key drivers of dysbiosis in CKD include slow intestinal transit, impaired protein digestion, low dietary fibre, iron therapy and frequent antibiotic use. Impaired gut barrier function in CKD further enables the systemic translocation of gut-derived uraemic toxins.

There is evidence that uraemic toxins contribute not only to uraemic symptoms and CKD comorbidities, such as cardiovascular disease, but also to the progression of CKD itself.[1 2] Several protein-bound uraemic toxins have been implicated in promoting inflammation and fibrosis in CKD.[2] In *Gut*, Laiola *et al*[3] present a series of studies that aimed to clarify the relationships among gut microbiome composition, diet and the progression of CKD.

The investigators first analysed the gut microbiome of 240 patients with non-dialysis CKD from the Chronic Kidney Disease - Renal Epidemiology and Information Network and Nephrology (CKD-REIN) cohort by shotgun metagenomics, and compared these findings to healthy controls from the *Milieu Intérieur* cohort, and further validated in an independent Belgian cohort. They found marked alterations in the microbiota of patients with CKD, particularly an increased abundance of species that generate uraemic toxin precursors. Plasma levels of multiple uraemic toxins were strongly associated with microbiome composition, confirming that microbial metabolic activity is a major determinant of toxin accumulation in CKD.

The investigators then performed faecal microbiota transplantation from patients with CKD into antibiotic-treated CKD mice, which led to increased serum uraemic toxin levels and slight but measurable kidney fibrosis. Although the fibrotic changes were modest and tended to diminish with time, these results reinforce the notion that microbiome alterations can accelerate kidney damage at a rate consistent with typical CKD progression.[3 4]

Next, the investigators categorised the patient cohort into fast and slow progressors. Gut microbiome-derived metabolites were found to be associated with rapid kidney function decline, independent of traditional risk factors like albuminuria.[3] In a supplementary analysis of 3-year follow-up data from 103 patients, patients' microbial communities shifted toward generating toxin precursors, and this trend was mitigated by a plant-based, low-protein diet. It is important to note that, however, 'fast progressors' were defined in this study as those experiencing a sustained 30% decline in estimated glomerular filtration rate (GFR) or kidney failure. While this definition is commonly used in nephrology clinical trials, it differs from the KDIGO (Kidney Disease: Improving Global Outcomes) guideline for rapid progressors (ie, GFR≥5 mL/min per year).[4] Although the definition in this study is conventional and generally reliable, it may introduce bias by disproportionately affecting patients with a lower baseline GFR. An alternative approach would be to calculate the slope of GFR decline. Although the authors planned such an analysis, they did not present the details.

Despite some minor technical nuances, this study robustly corroborates that (1) CKD alters the gut microbiome; (2) these changes drive accumulation of uraemic toxins; and (3) both dysbiosis and resulting toxins can directly exacerbate CKD progression. The question is: which toxins drive CKD progression? This study measured 10 prominent toxins, including trimethylamine N-oxide, kynurenine, kynurenic acid, hippuric acid, phenylacetylglutamine, indoxyl sulfate, p-cresyl glucuronide, p-cresyl sulfate, indole-3-acetic acid and 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid, plus the precursors tyrosine, tryptophan and phenylalanine.[3] Some, like indoxyl sulfate and hippuric acid, originate mainly from gut microbiota; others, such as kynurenine, are actually human metabolic by-products.

We have summarised their biological properties and likely clinical effects in table 1. In essence, indoxyl sulfate and p-cresyl sulfate are leading potential candidates for CKD progression. Indoxyl sulfate induces tubular cell death, increases oxidative stress, stimulates transforming growth factor beta-1 (TGF-β1) production and promotes fibrosis,[5 6] while p-cresyl sulfate drives oxidative injury and activates profibrotic and pro-hypertensive pathways.[6 7] However, current evidence suggests that these toxins alone may not fully explain the microbiome's impact on CKD; their clinical effect is significant but incomplete, and additional mechanisms likely contribute.

What are the other potential mechanisms? One hypothesis is that dysbiosis triggers persistent gut and systemic inflammation, activating leucocytes that can migrate to and injure the kidney.[8] However, not all progressing patients with CKD show local inflammation histologically—and this was not assessed by Laiola *et al*.

On the other hand, recent research revealed that olfactory receptors (ORs), beyond their traditional sensory roles, regulate physiological processes in non-sensory tissues, including the kidney.[9] Intra-renal chemical sensing of bacterial products has emerged as a likely link in the gut-kidney axis. Renal ORs play important roles in blood pressure regulation and glucose homeostasis.[9] For example, OLFR78 is expressed in renal blood vessels, and activation of this receptor in the renal afferent arteriole increases renin release. Likewise, OLFR558 is found in renal blood vessels and is involved in the regulation of blood pressure. Importantly, the ligands for OLFR78 are the short-chain fatty acids (SCFAs) acetate and propionate, while OLFR558 is activated by the SCFA butyric acid; all of these SCFAs are primarily produced by gut microorganisms.

The logical message that follows is that alterations in gut microbiota may affect the kidney not only by the active production of organic toxins, but also by the reduction of beneficial molecules, for example, SCFAs. Further studies are certainly needed to define the panel of beneficial molecules

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Table 1 Uraemic toxins and microbiota-derived metabolites tested by Laiola *et al*[3]

Compound	Origin	Physiological function	Role in diseases
TMAO	Metabolic product of choline, trimethylglycine and L-carnitine from ingested meat	Stabilise proteins and modulate their function in marine animals	Association with all-cause mortality and cardiovascular diseases
Kynurenine	Metabolite of tryptophan, mostly from liver	For the production of niacin	Increased production associated with worsening depressive symptoms and cognitive dysfunction
Kynurenic acid	Metabolite of tryptophan (via kynurenine)	None reported	Antagonist of glutamate receptors and NMDA receptor; affect synaptic function
Hippuric acid	Formed from gut microbiota by the combination of glycine and benzoic acid (the latter via the consumption of phenolic compounds, such as in fruit juice, tea and wine); also produced in the liver and kidneys	None reported	A marker for Parkinson's disease
Phenyl-acetyl-glutamine	Metabolite of the degradation of phenylacetate in the liver; also produced by gut microbiota; excreted in urine	None reported	Possible marker for cardiovascular disease
Indoxyl sulfate	Metabolite of tryptophan from gut microbiota	None reported	Stimulates glomerular sclerosis and renal interstitial fibrosis; contributes to CKD progression; also a predictor of cardiovascular disease
P-cresyl sulfate	Metabolite of aromatic amino acids from gut microbiota	None reported	Contribute to CKD progression
P-cresyl glucuronide	Metabolite of aromatic amino acids from gut microbiota	None reported	None reported
Indole-3-acetic acid	Plant hormone, also produced by some bacterial species	Gene regulation in plant	Developmental toxicity and immunotoxin in animals
CMPF	Endogenous metabolite of furan fatty acids in diet; also produced from gut microbiota	Affect fatty acid metabolism of liver	May induce kidney cell apoptosis or ferroptosis
Tyrosine, tryptophan and phenylalanine	Amino acids	Protein synthesis and generation of other metabolic intermediates	None reported

.CKD, chronic kidney disease; CMPF, 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; NMDA, N-methyl-D-aspartate; TMAO, trimethylamine N-oxide.

produced by normal gut flora, and the methods to preserve or replace these missing helpers in disease conditions.

In conclusion, the work by Laiola *et al*[3] significantly advances our understanding of the gut-kidney axis in CKD, demonstrating that gut microbiota dysbiosis contributes to uraemic toxin accumulation and CKD progression. The findings underscore the potential of dietary interventions, such as plant-based, low-protein diets, to mitigate these effects. However, critical questions remain. Further research is needed to pinpoint which uraemic toxins are primary drivers of CKD progression and to elucidate mechanisms of uraemic toxins, particularly regarding inflammatory triggers and intrarenal chemical sensing via olfactory receptors.

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