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Commentary

Uraemic toxins: Time for a paradigm shift

Louis L. Huang and Lawrence P. McMahon*

Department of Renal Medicine, Eastern Health Clinical School, Monash University, Victoria, Australia

DESCRIPTION

The poisonous milieu created by the accumulation of toxins in End-Stage Kidney Disease (ESKD) is associated with extremely poor patient outcomes. Yet, despite the institution of maintenance dialysis in these patients (eGFR <15 mL/min/1.73 m^2), life expectancy remains similar to that of metastatic malignancy. This grim comparison provides the impetus to reassess our understanding of what comprises a true uraemic toxin and why we have not done better for our patients. Do we have the wrong targets, or are we barking up the wrong molecular tree?

Traditionally, water-soluble, low molecular weight toxins - typically, creatinine and urea-have been used to determine dialysis adequacy. In peritoneal dialysis, this has led to a targeted creatinine clearance target of >50 L/week/1.73 m^2 and a urea-based target of >1.6 for weekly Kt/V. Clinicians have adjusted dialytic prescriptions based on these targets for several decades. However, supporting evidence that these are of benefit has been slim, as a number of randomised controlled trials have not demonstrated better patient survival or quality of life by more efficient or effective removal of creatinine and urea.

The consistency of these findings has slowly led-as yet with limited evidence-to a change in clinical practice, moving from small solute clearance to a more complete approach that encompasses such aspects as patient symptoms, quality of life, volume and nutritional status, and alternative laboratory targets. Extending Koch's postulates for the validation of a pathogenic organism, first published in 1890, a uraemic toxin must be chemically quantifiable, display elevated concentrations in the setting of kidney disease, have deleterious biologic effects - and health must be restored with its removal. Based on the last criterion in particular, both creatinine and urea fall well short of the necessary requirements.

An alternative family of putative toxins that has garnered interest in the past decade is a group of molecules, heavily protein-bound, which originate in the colon. Generated from metabolism of aromatic amino acids by the microbiota, they are collectively known as protein-bound uraemic toxins (PBTs) and include molecules such as p-cresyl sulphate and indoxyl sulphate. Like urea and creatinine, they have a molecular weight usually <500 Da. However, being highly albumin-bound, they are poorly removed by conventional dialysis and thus behave akin to larger molecules. Concentrations of PBT increase with progression of kidney disease and are associated with adverse biologic effects through activation of pro-inflammatory (NF-kB and plasminogen activator inhibitor-1 activation) and pro-fibrotic pathways (*via* TGF-b1 and epidermal growth factor receptor activation), culminating in tissue inflammation, endothelial dysfunction and fibrosis. At end organ level, these pathologic processes promote the development of atherosclerosis, arteriosclerosis, kidney and cardiac fibrosis, resulting in cardiovascular morbidity and further functional kidney loss. Prospective observational studies in patients with kidney disease have demonstrated an association between higher PBT levels and mortality, both cardiovascular and other, the effects of which have stood firm even after adjustment for the traditional Framingham cardiovascular risk factors.

Before being considered a true uraemia toxin, however, it must be determined whether PBT removal restores a measure of health and wellbeing, and whether it improves patient mortality. Currently, the only meaningful and enduring method of reducing PBTs is through kidney transplantation, which augments renal tubular secretion of PBTs. Traditional dialytic methods such as peritoneal dialysis and high-flux haemodialysis only remove the free, unbound PBTs, while approximately 95%is left bound to albumin - inaccessible to either diffusion or convection. Novel methods of PBT-lowering currently being investigated include adsorptive strategies (including activated charcoal or cellulose polymers) in conjunction with haemodialysis; use of a displacer agent, such as non-steroidal anti-inflammatory drugs and Shen-Shuai-Ning, that competes with PBTs for the albumin binding sites, thereby potentially increasing dialytic clearance; and lastly, reducing colonic PBT generation, where precursors to molecules such as p cresyl-sulphate and indoxyl sulphate are generated. Studies of these PBT-lowering options not only need to demonstrate the reversal of the pathologic effects of PBTs *in vitro*, they will also need to establish a solid link with better health, one that is associated

Correspondence to: Louis L. Huang, Department of Renal Medicine, Eastern Health Clinical School, Monash University, Victoria, Australia, E-mail: Louis.Huang@easternhealth.org.au (or) Lawrence.McMahon@easternhealth.org.au

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with a reduced mortality and symptom burden, and a better quality of life compared with the standard of care dialysis treatment.

The benefit of adhering to traditional markers of uraemic toxicity has proven futile and the search for relevant toxins must continue. Early indications suggest that PBTs could be one, possibly a major, contributor to the toxic uraemic milieu, and this family of small molecules requires further study and appraisal. Whether toxin removal, once conclusively identified, can be sufficiently efficient to restore health and wellbeing for patients with ESKD is a further step along the way and, like the infamous Grail itself, could prove a step too far. In the meantime, rigorous scientific studies must continue, and we must be prepared to change our targets and practices for the betterment of our patients.