Innovations in approaches to remove uraemic toxins

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Kidney failure is associated with the retention and subsequent accumulation of uraemic toxins, which have detrimental effects on various physiological processes. The removal of these toxins by current dialysis modalities is inadequate, highlighting the need for innovative approaches to enhance their clearance and/or suppress their generation to improve outcomes for patients with kidney disease.

> “removal of clinically relevant levels of solutes will require any future kidney replacement therapy to incorporate an active secretory component”

The term uraemia, which in Greek means urine poisoning or ‘urine in the blood’, was introduced as early as the eighteenth century following the discovery that urea is filtered from blood into urine and that failure of this process led to serious disorders. We now know that the kidneys have an essential role not only in this filtration process but also in active secretion, and that kidney failure leads to the retention of endogenous waste products, termed uraemic toxins and the consequential development of severe co-morbidities. We also know that many uraemic toxins exist in addition to urea. One database, compiled by the European Uremic Toxin Work Group currently lists >150 solutes that accumulate in the plasma of patients with kidney failure. Research in the field of nephrology has led to important advances in treatments for kidney disease, including the development of dialysis, which is now used regularly by more than 2.5 million people worldwide. However, the morbidity and mortality of patients on dialysis remains high, and the therapy has limited effects on quality of life.

One reason for these poor outcomes is the persistence of uraemic toxins resulting from their incomplete removal by current dialysis devices. The inability of current dialysis modalities to remove these toxins is a consequence of two factors. First, some of these toxins, such as indoxyl sulfate and *p*-cresyl sulfate, are likely to be actively secreted by the kidneys rather than filtered. Because these solutes are highly protein-bound in plasma, they are not removed by current dialysis approaches that mimic glomerular filtration only. Second, while both peritoneal dialysis and haemodialysis can remove free fractions of small uraemic toxins, their ability to remove middle-sized and large uraemic toxins, or protein-bound uraemic toxins, is limited, as these are too large to pass through the pores of the dialysis membrane. A 2020 study found that lower renal clearance of uraemic solutes that are known to be highly protein bound, is associated with kidney disease progression and all-cause mortality after adjustment for estimated glomerular filtration rate, albuminuria and other confounders[1]. These limitations in current dialysis modalities have spurred the development of new approaches to improve the removal of protein-bound uraemic toxins.

For example, a newly developed bioelectronic system incorporates carbon nanotubes onto conventional polyethersulfone dialysis membranes, enabling electrically triggered dissociation of protein-bound toxins[2]. A dialysis device that incorporates such a system could increase uraemic toxin removal with minimal protein loss. In separate work, based on the observation that the ability of uraemic toxins to bind plasma proteins depends on the ionic strength of plasma, other researchers have shown that increasing the sodium concentration in the pre-dialysate fluid and thus the ionic strength of plasma efficiently increases the free fraction of uremic toxins, enabling their removal through dialysis. Retention of plasma sodium is a limitation of this approach, however, and needs to be addressed[3]. Alternative approaches to the removal of protein-bound uraemic toxins include infusion of a binding competitor into the arterial blood line during haemodialysis, which competes with the uraemic toxins for the albumin binding sites, thereby increasing their free fraction. The promise of this approach has been demonstrated clinically whereby infusion of ibuprofen as a competitor increased dialytic removal of indoxyl sulfate and *p*-cresol sulfate in patients with kidney failure[4].

The development of portable and wearable dialysis systems has potential to improve outcomes for patients with kidney failure by facilitating more frequent, longer, dialysis sessions. However, the portable nature of these devices requires highly efficient membranes and a dialysate regenerating system. The regeneration of spent dialysate for reuse is challenging given the accumulation of ions, urea and organic solutes in a relatively small volume. Strategies for the purification of spent dialysate include the enzymatic hydrolysis of urea by urease, electro-oxidation to convert urea into gaseous products (nitrogen, hydrogen and carbon dioxide) and

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sorbent technologies, such as activated carbon[5]. Wearable dialysis systems will also require dialysis membranes to be extremely thin to maximize the surface-to-area ratio, and have sufficient strength and pore sizes to enable removal of middle-sized molecules, such as provided by, for example, nanoporous silicon-nitride-based membranes[6]. Other types of advanced membranes contain carbon-based sorbents with well-defined dual porosity (micropores (<2 nm) and mesopores (2–50 nm)) for the selective and efficient removal of larger protein-bound uraemic toxins as well as smaller cytokines[7].

The use of adsorbents has gained attention not only in the context of dialysis devices, but also as an oral treatment. A systematic review of eight studies found that oral administration of the carbonaceous adsorbent AST-120 reduced serum levels of the uraemic toxin indoxyl sulfate but did not consistently slow disease progression or reduce all-cause mortality among patients with chronic kidney disease (CKD)[8]. The lack of effect on disease outcomes highlights the complex pathophysiology of CKD and the need to achieve more than removal of a single uraemic toxin.

We propose that removal of clinically relevant levels of solutes will require any future kidney replacement therapy to incorporate an active secretory component, which mimics tubular secretion, in addition to a filtration component. In support of this proposal, we have demonstrated that tubule epithelial cells can sense plasma levels of indoxyl sulfate and respond by accelerating its removal[9]. These cells are equipped with transporters that selectively take up the protein-bound toxins from blood, enabling them to be actively secreted in urine in an efficient and concerted manner. Free toxins bind and are translocated by membrane transporters, in general with a higher affinity than their binding to plasma proteins, thereby favouring cellular uptake as an essential step in the excretion process. The development of biohybrid devices that combine cellular components that mimic the uptake of uraemic toxins by tubular epithelial cells with a membrane haemofilter is encouraging, although such devices are in early stages of development. Pre-clinical studies using small functional units demonstrated active secretion of protein-bound indoxyl sulfate. Future in vivo research should provide proof of efficacy and safety of such a bioartificial kidney system.

While promising, the approaches described may not be sufficient to improve clinical outcomes and could be complemented by alternative approaches. One suggestion is that emphasis should be placed on approaches to reduce the production of uraemic toxins in parallel with approaches to enhance their clearance. These retention solutes mostly originate from gut microbial metabolism of nutrients in conjunction with human metabolism and enrich the human metabolome. Bacterial metabolites in particular — that is, the phenols, indoles and amines, precursors for their human end-products, such as indoxyl sulfate and *p*-cresol sulfate, are believed to be toxic. Moreover, uraemia is associated with alterations in the composition of the gut microbiome, as well as altered microbial metabolism, further stimulating the production of uraemic toxins. Finally, the uraemic toxins that accumulate in plasma might also directly affect the intestinal barrier, which can promote the translocation of bacterial components into the circulation, with inflammatory consequences[10]. How we might influence the gut microbiome and metabolome composition to reduce the production of toxic solutes and minimize disease burden in patients with kidney failure is at this stage unclear. However, greater understanding of the pathways that can be manipulated through nutritional or pharmacological means will likely help us to achieve this aim.

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Competing interests
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