Novel Approaches for the Removal of Uremic Solutes

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Dialysis is frequently referred to as kidney replacement therapy, yet suboptimal outcomes for patients on dialysis call into question the extent to which human kidney function can be sufficiently replaced by a machine. The filtration, secretion, and selective reabsorption of solutes by native kidneys have been difficult to recapitulate, and the inadequate removal of select substances that accumulate during kidney failure (“uremic solutes”) is generally viewed as an important limitation of current dialytic approaches. Enhancing extracorporeal removal of toxic solutes is an attractive strategy to improve dialysis outcomes, but such efforts are hampered by our limited understanding of which of the scores of analytes we can now measure actually cause harm. Randomized human studies are needed to definitively establish a direct causal role for any given solute and clinical outcome, and the ability to modulate putative toxins is a prerequisite. To date, studies targeting urea kinetics, using higher-flux dialyzers, and increasing the frequency or duration of hemodialysis treatments have shown these strategies to be inadequate at removing several well-described uremic solutes, particularly protein-bound ones (1–3).

In recognition of these challenges, more innovative efforts to increase the clearance of protein-bound uremic solutes have emerged. Early-stage studies have used a competitor substance to displace solutes from their binding sites on albumin, as well as used changes to the physical conditions within the dialyzer to increase the free fraction of protein-bound solutes (e.g., modifying osmotic conditions, temperature, or pH within the dialysis circuit) (4). Preventative strategies targeting intestinal microbiota and colon-derived uremic solutes, such as indoxyl sulfate (IS) and p-cresol sulfate (PCS), have also been seen increased focus. For example, interventions including prebiotics, probiotics, and oral adsorbents have been studied (4).

In this issue of CJASN, Lee et al. (5) expand our knowledge of the armamentarium to reduce various uremic solutes, particularly protein-bound ones, by focusing on dialysate. When solute concentrations in dialysate reach plasma-free concentrations (typically low for protein-bound substances), further removal of that solute down its concentration gradient is hindered. Thus, the authors ran several in vitro metabolic experiments to show how processing dialysate through activated carbon blocks can affect solute concentrations in dialysate and, consequently, plasma solute clearance. First, to determine if activated carbon adsorbs uremic solutes, the investigators collected spent dialysate from a small number of patients on hemodialysis and assessed pre- versus post-metabolite levels when passing the spent dialysate through an activated carbon block. Of 264 uremic solutes profiled using mass spectrometry, the majority were taken up by the carbon block, although 45 went unchanged and three increased after passage through the block. Importantly, as more of the spent dialysate was passed through the block, there was less uptake and eventual release of several solutes. When close to 190 L of spent dialysate had been processed, 18 uremic solutes, the majority of which had been taken up when a lesser amount of dialysate had been processed, showed increases exiting the block (notably, 20 solutes not classified as uremic also increased).

They next tested if dialysate processing using activated carbon could increase plasma clearance of protein-bound solutes. They used in vitro dialysis experiments measuring solute clearance from artificial plasma run through a dialysis circuit with two dialyzers in series (with dialysate flowing in the countercurrent direction). The dialysate either flowed directly from the first to the second dialyzer or passed through a carbon block inserted between the two dialyzers. For these experiments, they added physiologic concentrations of commonly studied protein-bound uremic solutes (PCS and IS) as well as phenylacetyl glutamine (PAG), an organic acid that is not protein bound. Although the introduction of the carbon block to the circuit did not greatly affect the removal of urea, it did increase clearance of PCS, IS, and PAG. Given that PCS and IS are tightly protein bound, it is notable that their clearances were increased by >70% with the introduction of the block, whereas the clearance of largely unbound PAG increased by only 30%. These results were in accordance with mathematical model predictions and showed that the midpoint carbon block “regenerated” the dialysate to a near-zero solute concentration, allowing additional protein-bound solute removal from plasma. Because much larger amounts of unbound solutes were removed even without a carbon block, clearance was not able to be enhanced much for those solutes when regenerating the dialysate. Also notable, the fraction of PCS and IS removed from the dialysate by the carbon...
block was reduced at higher dialysate flow rates (600 versus 200 ml/min), suggesting that sorbent cartridges must be designed to match dialysate flows rates. Changes to dialysate flow showed less effect on the clearance of unbound solutes, and such findings may have implications for “lower-flow” dialysis (e.g., home and portable systems) and dialysate use in general.

Interestingly, a sorbent dialysis system was previously available in the 1970s and 1980s; the “REcirculating DialYsate” (REDY) system used a cartridge containing activated carbon to aid solute clearance while requiring relatively small dialysate volumes (approximately 6 L versus typically hundreds of liters used in conventional hemodialysis) (6). Because effluent in such systems repetitively recirculates across a sorbent column adsorbing solutes, an ultrapure solution is continuously regenerated, and only a small dialysate volume is required. Manufacturing of the REDY system was discontinued due to cartridge costs and concerns around aluminum release from the sorbent, but a redesigned sorbent unit was incorporated into the Allient dialysis system years later (6). Commercial development was again abandoned, and it was not widely studied (6). Today, sorbent technologies are regenerating enthusiasm, partially fueled by growing interest in home and portable dialysis as well as calls to reduce the environmental effect of dialysis. It has long been recognized that the hundreds of liters of dialysate required per treatment influences financial and environmental costs as well as the feasibility of where treatments can occur (e.g., such high volumes are not suitable for wearable dialysis devices and pose challenges to home dialysis). Mechanisms to recycle or regenerate a smaller pool of dialysate are of increasing interest, and sorbent technology utilizing activated carbon is a prominent area of focus. Lee et al. (5) now show us the effect that such technology can have on the metabolome as well.

The investigators should be commended for carefully demonstrating that dialysate exposure to activated carbon blocks can enhance solute clearance, particularly for protein-bound solutes. The approach favored lower dialysate flows and effectively reduced dialysate concentrations of several solutes to zero (i.e., regenerating the dialysate to allow more solute clearance along a favorable concentration gradient). If such clearance improvements translate to clinical benefit, sorbents seem attractive as their integration into existing dialysis circuits is straightforward to conceive. Indeed, the authors have previously demonstrated that simply adding activated charcoal to dialysate in vitro enhanced clearance of protein-bound solutes (7). Carbon block technology is considered relatively inexpensive (relative to high-volume water treatment costs in conventional hemodialysis), which could improve cost efficiencies (6). These enticing findings, however, must be weighed against other considerations. Reporting of relative concentration changes is difficult to interpret without absolute quantitation of analytes (e.g., large relative changes in very small quantities of metabolites may be clinically insignificant). The release of substances from the carbon block will require careful assessment to determine cause and any health risks. Similarly, at higher dialysate rates or volumes of exposure, the benefits of activated carbon may diminish, and this could limit the therapeutic range with which the technology could be applied. More broadly, as alluded to earlier, precisely which solutes should be targeted and what the clinical benefit of their enhanced clearance will actually be remain critically unanswered. Also, similar to other efforts to increase solute clearance with dialysis, advantageous adsorptive characteristics may be offset by the simultaneous adsorption of beneficial factors (the many solutes profiled still cannot be considered exhaustive). Additional research is needed.

This study and our discussion thus far have focused on small molecules. Further highlighting the complexities of optimizing clearance on hemodialysis is the issue of larger “middle molecules.” To improve the clearance of middle molecules, hemodiafiltration has been established, adding convection to diffusion and using membranes with high sieving coefficients to allow for the passage of larger solutes. A recent summary of hemodiafiltration studies revealed variable results, and any benefits likely stem from reduced cardiovascular events (8). Even so, a new dialysis membrane, the medium cutoff (MCO) dialyzer, has been designed to expand the efficient clearance of middle molecules while minimizing albumin loss. Initial studies suggest that MCO dialysis efficiently increases the clearance of a wide range of middle molecules, such as free light chains, complement factor D, and β2-microglobulin, without significant risk of hypoalbuminemia (9). Larger randomized clinical trials are being conducted to assess the effect of MCO dialysis on patient symptoms and long-term clinical outcomes.

From MCO dialyzers to dialysate processing with sorbents, each of these finite improvements to solute clearance on hemodialysis, if proven safe and effective, will hopefully see benefits magnified when used synergistically. Lee et al. (5) took great efforts and succeeded in adding important incremental knowledge to this field while further highlighting how daunting the task of genuinely creating “kidney replacement” through dialysis can be.

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See related article, “Removal of Uremic Solutestes from Dialysate by Activated Carbon,” on pages XXX–XXX.