Uremic Retention Solutes: The Free and the Bound

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Many in the nephrology community were surprised when the Hemodialysis (HEMO) Study, completed in 2002, supported the null hypothesis for each intervention, suggesting ceiling effects for both the dose of dialysis and membrane permeability (1). Neither increases in the dose (expressed as the product of dialyzer urea clearance and dialysis time factored for patient size) nor an improvement in dialyzer membrane permeability or flux (expressed as β2-microglobulin clearance) improved patient survival or seven other prespecified outcome variables. In the HEMO Study, 1846 randomized patients were followed up to 7 yr, and the study was reasonably powered to detect a mortality improvement. Although outcomes were improved in subsets of the study population, the favorable effects were only suggestive, and the magnitudes were relatively small. What does this mean? Does it show that we have gone as far as we can with improving thrice-weekly dialysis or is there more to be done? The ongoing high high rates of mortality and cardiovascular disease, as well as uncontrolled data that show improvements in both of these outcomes by increasing dialysis frequency, suggest that the job is not yet done.

Nephrologists perhaps optimistically refer to dialysis as “renal replacement therapy,” and have focused measurement of dialysis adequacy on low molecular weight solute clearance, with urea as the predominant indicator solute. There is no question that small solute removal is vitally important. There is also no question that conventional thrice-weekly dialysis does not replicate the global ability of native kidneys to maintain homeostasis of the interior environment or to fully alleviate the uremic syndrome. Increasingly, data suggests that maintaining even minimal residual native kidney function in dialysis patients may be a more important determinant of patient outcome than dialyzer clearance (2). Endocrine function of the kidney is important but is unlikely to account for the magnitude of these effects. What else could account for failure of the artificial kidney to keep patients healthy, in contrast to the success of the native kidney?

Over the past four decades, several explanations and alternative approaches to improving dialysis outcomes have been suggested. Initial efforts focused on molecular size, as embodied in the term “middle molecule clearance” proposed by Babb et al. (3). These early pioneers envisioned that because the dialyzers in use at that time had an absolute molecular cutoff of about 10,000 Daltons and efficiently removed compounds up to only about 3000 Daltons, more toxic compounds would likely be found in the molecular weight range where dialytic removal was significant but incomplete, i.e. 500 to 5000 Daltons. They also hypothesized that molecular size could explain the success of peritoneal dialysis, because the peritoneal membrane leaks albumin and must therefore be more permeable to middle molecules. Vigorous attempts followed to improve the permeability of commercial dialyzer membranes and to improve removal of larger solutes through these same “high-flux” membranes by filtration instead of dialysis. After technical problems were resolved, these membranes gradually replaced the older, less permeable membranes. However, despite widespread application of these more permeable membranes, improvements in patient outcomes have been meager at best, and were not evident in the HEMO study.

Other potentially beneficial functions provided by the native kidney include selective reabsorption of solutes from the glomerular filtrate and active secretion of solutes from the peritubular circulation into the filtrate. Tubular secretion of solutes has long puzzled physiologists. The mechanisms, especially for secretion of organic anions, are extremely robust, such that Pitts postulated over 30 yr ago that the existence of some very toxic substances in the blood must be maintained at very low concentrations (4). Others have postulated that the vigor of the secretory mechanism is necessary to remove substances bound to circulating macromolecules, principally albumin, during its passage through the peritubular circuit (5). The low free concentrations available for diffusion through the capillary endothelium would require a robust transporter to maintain a maximal gradient for diffusion throughout the length of the peritubular capillary. The success of this postulated mechanism for stripping bound ligands from albumin has been demonstrated in vitro as well as in the isolated perfused rat kidney (6). In humans and whole animals, tubular secretion of phenol red results in >80% extraction during a single pass through the kidneys despite 90% binding to serum albumin (4). In uremic patients, albumin-binding sites are highly saturated as evidenced by relatively poor binding to exogenous ligands such as radiolabeled salicylate or phenytoin (7). Extensive studies in the late 1980s demonstrated that the binding defect is due to reversibly bound ligands. The albumin binding defect has long been recognized but relatively ignored as a potential mecha-
nism of toxicity in uremic patients. Carrying this concept a bit further one can postulate that serum albumin is an intrinsic part of the renal excretory mechanism, transporting toxic hydrophobic compounds to keep their concentrations low in the blood and interstitial fluid, and reducing volume of distribution for more efficient delivery to the kidney.

These considerations have raised the level of concern about protein-bound uremic solutes as a mechanism that could explain incomplete removal of toxic solutes by hemodialysis. In an earlier JASN publication, Meyer and colleagues demonstrated with the use of both in vitro dialysis and a mathematical model that increasing blood flow, as was done during the HEMO study to increase urea clearance, would have little effect on removal of bound toxins, but that increasing either dialyzer surface area or dialysate flow can improve toxin removal (8). Prolonging the treatment time would also be expected to enhance removal of bound solutes to a proportionately greater extent than removal of unbound small solutes, much as it does for solutes sequestered in the intracellular compartment (9). Hemofiltration is unlikely to improve removal of protein bound solutes above that which can be achieved by hemodialysis with an equal clearance of urea. The success of more frequent dialysis might also be explained by improved removal of toxins bound to macromolecules that diffuse slowly across the dialyzer membrane.

In this issue of JASN, additional studies by Meyer et al. show that adding charcoal as a sorbent to the dialysate during in vitro hemodialysis significantly enhanced removal of protein-bound solutes (10). The clearance of urea from a solution containing albumin was unchanged, but clearances of the protein-bound solutes indican, p-cresol sulfate, and p-cresol more than doubled under conditions of low blood flow. Analysis of the data using a mathematical model (11) suggested that the enhancing effect of the charcoal was likely caused by maintaining a higher gradient of unbound solute across the dialyzer membrane. The potential clinical importance of these findings is emphasized by a recent publication in which patient outcome was linked to the serum concentration of free p-cresol (12). The studies presented here by Meyer et al. focus attention on serum albumin and perhaps other binding macromolecules as possible missing pieces of the puzzle, and provide an avenue of investigation that has potential for improving patient outcomes.

Disclosures.

None.

References


