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Narrative Review

Future Avenues to Decrease Uremic Toxin Concentration

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In this article, we review approaches for decreasing uremic solute concentrations in chronic kidney disease and in particular, in end-stage renal disease (ESRD). The rationale to do so is the straightforward relation between concentration and biological (toxic) effect for most toxins. The first section is devoted to extracorporeal strategies (kidney replacement therapy). In the context of high-flux hemodialysis and hemodiafiltration, we discuss increasing dialyzer blood and dialysate flows, frequent and/or extended dialysis, adsorption, bioartificial kidney, and changing physical conditions within the dialyzer (especially for protein-bound toxins). The next section focuses on the intestinal generation of uremic toxins, which in return is stimulated by uremic conditions. Therapeutic options are probiotics, prebiotics, synbiotics, and intestinal sorbents. Current data are conflicting, and these issues need further study before useful therapeutic concepts are developed. The following section is devoted to preservation of (residual) kidney function. Although many therapeutic options may overlap with therapies provided before ESRD, we focus on specific aspects of ESRD treatment, such as the risks of too-strict blood pressure and glycemic regulation and hemodynamic changes during dialysis. Finally, some recommendations are given on how research might be organized with regard to uremic toxins and their effects, removal, and impact on outcomes of uremic patients.
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INDEX WORDS: Uremic toxins; uremic toxin removal; dialysis adequacy; intestinal generation; microbiome; residual kidney function; dialysate; kidney failure; hemodialysis; end-stage renal disease (ESRD); review.

Raymond C. Vanholder, MD, PhD, was an International Distinguished Medal recipient at the 2015 National Kidney Foundation Spring Clinical Meetings. The International Distinguished Medals are awarded to honor individuals who have made significant contributions to the field of kidney disease and furthered the goals of the National Kidney Foundation.

The deterioration in kidney clearance capacity is associated with a progressive effect on almost every organ, resulting in uremic syndrome, which is intrinsically fatal when its final stages are untreated. This downward evolution parallels the accumulation of uremic solutes that are normally excreted by the kidneys; many of these uremic solutes exert biological activity (toxicity). Survival in the end stage becomes possible only when these solutes are removed by kidney replacement therapy, either dialysis or transplantation. Although many organ systems are affected by chronic kidney disease (CKD; Box 1), damage to the cardiovascular system, which results in substantial morbidity and mortality, is a matter of particular concern.[1,2] Unfortunately, none of the currently available kidney replacement strategies restore normal physiology. In addition, restoration of quality of life may be unsatisfactory.[3] These limitations of current therapies may be partly attributable to incomplete toxin removal.

An alternative explanation for the morbidity and mortality of dialysis patients is that they are due not to uremic toxicity, but rather arise from imbalances in sodium and fluid homeostasis imposed by the intermittent character of therapy.[4] The sawtooth management of volume status with intermittent dialysis is an undeniable source of complications. However, increased cardiovascular morbidity is already present before kidney replacement therapy is started, which is a stage before repetitive sudden volume changes can play a role. After dialysis therapy has been started, the intermittency of dialysis exerts its harmful effect in the context of the existing cardiovascular structural damage.

Because the toxicity of many uremic toxins follows a dose-response gradient,[5] further steps to decrease levels of uremic toxins appear to be necessary because mortality in end-stage renal disease remains unacceptably high. Selective removal would be desirable to avoid elimination of essential elements. However, in order to do this, we need to precisely define the most toxic compounds or groups of compounds. Another question that is unresolved is whether peak or trough toxin concentrations have

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Box 1. Affected Organ Functions in CKD

Anemia
Immune dysfunction
Osteodystrophy
Hyperparathyroidism
Insulin resistance
Malnutrition
Inflammation
Coagulation disorders
Skin atrophy
Pruritus
Gastrointestinal disturbances
Kidney tubular damage
Polyneuritis
Coordination disturbances
Tremor
Cognitive dysfunction
Cardiac failure
Loss of strength
Anorexia
Pericarditis
Hypertension
Fluid overload
Changes in metabolism
Vascular damage

Note: The italicized clinical problems directly or indirectly contribute to vascular damage.
Abbreviation: CKD, chronic kidney disease.

the most biological (toxic) impact. As with drugs, one may hypothesize that the answer may be different from compound to compound. However, dose-response curves usually suggest a straightforward relationship between concentration and effect. Because there could be a different reaction depending on the solute and in uremia a host of compounds is retained, it seems best to focus on decreasing overall concentration and especially on avoiding fluctuations in concentration. However, it is important to be careful when reducing concentrations of molecules for which a low concentration is also deleterious, for example, potassium.

Uremic toxins are traditionally subdivided according to their removal pattern by dialysis into small water-soluble compounds (such as urea), protein-bound solutes (such as indoles and phenols), and larger middle molecules (such as β_2-microglobulin).[6,7] Current evidence based on experimental studies and controlled outcome trials points to an effect of middle molecules and protein-bound solutes,[5,8] although some reports also suggest a role for small water-soluble compounds.[9-14]

In this review, we summarize potential options to decrease levels of uremic solutes, either by extracorporeal blood treatment or other strategies, for example, modifying gastrointestinal generation or preserving or improving residual kidney function (Fig 1). We do not intend to review in depth the extensive literature in some of these areas, but instead seek to summarize the different tracks that are currently being explored and may offer future solutions to the problem of uremia.

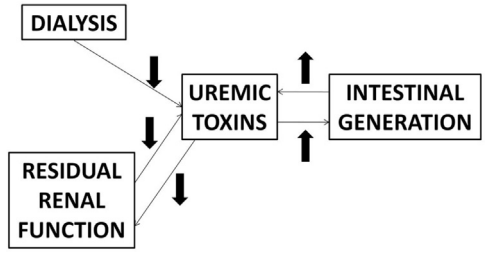

Figure 1. The components with potential impact on uremic concentration primarily focused upon in this review: metabolic and intestinal generation, (residual) kidney function, and kidney replacement therapy (if applied). The arrows point to the direction of the change in uremic toxin concentration, either a decrease or an increase.

EXTRACORPOREAL REMOVAL

Current Status

Small water-soluble compounds are easily removed by dialysis, even if the kinetics of urea and other solutes in this group are not necessarily concurrent.[15] All existing extracorporeal strategies have a high capacity to remove urea, but enhancing urea removal above what is now considered standard by major guidelines does not improve survival.[16,17] As shown in 1996 by Locatelli et al[18] in a longitudinal study, middle molecules can be removed efficiently only by dialyzers with a large pore size, which results in a survival advantage.[8] Adding convection to diffusion by applying hemodiafiltration further improves removal above dialysis,[19] and survival, if sufficient exchange volumes are pursued,[20] although studies may not be entirely free of bias.[21]

It is of note that since the longitudinal study by Locatelli et al,[18] the removal capacity of high-flux dialyzers has improved progressively.[19] With the recent introduction of filters with even larger pores, mainly for removal of light chains in multiple myeloma[22] or cytokines in septic patients,[23] the efficiency in removing a large array of solutes in the middle-molecular size range has been further increased.[24-26] The high cost of those filters is an obstacle to their large-scale use, and whether they offer a survival advantage still needs to be demonstrated. For instance, a 2-week randomized controlled trial (RCT) testing the effect of a high-cutoff dialysis membrane found that monocyte activation did not decrease despite significant cytokine removal,[25] possibly because not only proinflammatory but also anti-inflammatory cytokines were removed.

Protein-bound solutes are not easy to remove by any dialysis strategy.[19] Hemodiafiltration has greater capacity to remove protein-bound solutes compared with other options,[19,27] but the decrease in concentration is modest[28] and not unequivocal.[29]