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EDITORIAL

Urea: Surrogate or toxin?

Patients who develop progressive renal failure retain solutes normally excreted by healthy kidneys. The resulting uremic syndrome eventually leads to clinically apparent deterioration in biochemical, physiologic and cellular function. Uremia also results in dysfunction of a wide variety of specific organ systems, most notably neurologic, cardiovascular, hematologic, immunologic, and endocrinologic abnormalities [1]. Left unchecked, uremia ultimately results in death from metabolic and cellular dysfunction. Fortunately, the past four decades in clinical medicine have been witness to the development of dramatic therapeutic interventions to ameliorate the uremic syndrome, including the widespread use of renal replacement therapies such as dialysis and renal transplantation.

Almost since the initial recognition of the uremic syndrome, there has been a search for "the uremic toxin." The search for uremic toxins has been complicated by both philosophical and technical issues. Philosophically, it is doubtful that any single compound is responsible for inducing most uremic cellular injury; more likely, injury occurs as a result of cumulative retention of a multitude of compounds. From a technical standpoint, a myriad of compounds can be identified from both uremic ultrafiltrate and serum using techniques such as high performance liquid chromatography. However, alterations in electrostatic charge, protein binding, and molecular configuration as a consequence of uremia may alter chromatographic behavior and make identification difficult. Furthermore, *in vitro* assays that relate retention of solutes in uremia to actual cellular toxicity have not been standardized. Of most importance, the dialytic clearance characteristics of most putative uremic toxins have not been correlated with morbidity and mortality for patients with renal failure.

The most abundant solute that accumulates as a by-product of protein metabolism is urea. For over two decades, quantitation of the dialytic clearance of urea has been utilized to measure the adequacy and efficacy of dialysis therapy [2]. Urea has been the solute of choice for quantifying dialysis therapy because of its abundance in plasma, its low molecular weight and uncharged chemical structure, and the similarity of its volume of distribution to total body water. Both urea clearance and the time average concentration of urea in the plasma of patients on dialysis have been correlated with patient outcomes in well-designed clinical studies [3, 4].

Despite the ubiquity of urea kinetic modeling as a measure of dialysis therapy, urea has generally been considered to be relatively non-toxic, functioning more as a surrogate for other unidentified low molecular weight uremic toxins [5]. The study by Moeslinger et al in this issue of *Kidney International* [6], as well as several other recent investigations [7] may cause us to rethink this assumption. Moeslinger and colleagues hypothesized that elevated levels of urea, by increasing macrophage proliferation and inhibiting macrophage apoptosis, could contribute to the accelerated atherogenesis frequently seen in patients with renal failure. Using a mouse-derived monocyte/macrophage cell line, the authors demonstrate that high concentrations of urea induce macrophage proliferation via inhibition of inducible nitric oxide synthesis (iNOS). The critical role of iNOS in mediating urea-induced macrophage proliferation was further demonstrated with experiments using both NO scavengers and donors.

Does urea really contribute to uremic toxicity, or is it merely a surrogate for other toxins? The provocative study by Moeslinger and colleagues needs to be interpreted with caution. The concentration of urea required to induce macrophage proliferation in these experiments was generally higher than that seen clinically in well-dialyzed patients with renal failure. Caution must also be used in extrapolating the results of *in vitro* experimentation with cell lines to biologically complex *in vivo* complications. Despite these limitations, the authors of this study are to be congratulated for exploring and extending our understanding of uremic toxicity. Further experimentation using other specific assays of cellular activation and dysfunction may help clarify the role of urea in the uremic syndrome.

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