High Time for High-Flux Hemodialysis Mechanistic Studies

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In the current issue of *Blood Purification*, Dr. Chu and co-workers present their study 'The Effects of Low-Flux and High-Flux Dialyzers on Oxidative Stress and Insulin Resistance', showing an almost 50% reduction in insulin resistance (as assessed using HOMA-IR) in 20 patients randomized to 2 months of high-flux hemodialysis (HD). In contrast, 18 patients randomized to receive low-flux HD showed no reduction of insulin resistance.

After the HEMO trial [1] (the largest randomized and controlled trial to date designed to compare high- and low-flux HD) concluded that patients undergoing HD three times weekly appeared to have no benefit from the use of a high-flux membrane, many nephrologists despaired. If a larger dialysis dose and higher middle molecule removal were not of benefit to our patients, what was? However, subsequent analysis of the HEMO dataset [2] as well as other large datasets, including the USRDS [3] and the 4D Study [4], have all pointed to a potential lowering of both cerebrovascular and cardiovascular mortality in patients receiving high-flux dialysis. Perhaps of even greater interest, the recently finished MPO Study, not published yet but reported at both the EDTA 2007 and ASN 2007, shows a survival benefit for high-flux dialysis in incident European dialysis patients with S-albumin below 4 g/dl and not reusing their dialyzers.

While not designed to show any effect on mortality, the present study by Chu et al. adds to the small but growing body of mechanistic data supporting a beneficial ef-

fect of high-flux HD. Indeed, the HEMO Study showed that increasing small molecule removal does not appear to affect outcome [1]. Instead, more and more interest has focused on the ability of high-flux filters to remove middle molecules known to be associated with disease in uremia [5], including β_2 -microglobulin [6]. Indeed, the healthy kidney is likely an important organ for the metabolism of insulin and putatively also of other signaling molecules [7], while uremia is associated with markedly elevated levels of most cytokines and adipokines [8]. Thus, much needs to be done to understand the pathophysiological role of altered renal metabolism of middle molecules and polypeptides in the context of uremia and renal replacement therapy. Encouragement for this type of research may be found in a recent study by Haase et al. [9], who showed clearance rates of 14–75 ml/min for a number of cytokines during intermittent HD using a membrane with extended permeability in 10 septic patients with acute renal failure.

In conclusion, while validation of high-flux HD will remain the target of large, randomized and controlled trials, better understanding of what can be achieved with more permeable membranes in relation to the physiology of the healthy kidney will greatly aid us in selecting patients and outcomes to study in randomized and controlled trials. There is indeed a too low flux of mechanistic studies of high-flux dialysis!

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