Editorial Comments

The importance of residual renal function for patients on dialysis

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It is the goal of every practitioner involved in the care of dialysis patients to maximize survival and quality of life. The last two decades have seen a plethora of investigations that have sought to determine how this goal can be achieved. The bulk of the studies have, unfortunately, concentrated on small solute clearance and outcome (measured principally as mortality). The HEMO [1] and ADEMEX [2] studies suggested that this is not a fruitful avenue of investigation. However, the residual kidney function in patients on dialysis, particularly in those on peritoneal dialysis (PD), has proven to be a consistent and powerful predictor of mortality.

We will review the evidence supporting the importance of residual renal function (RRF) on outcome, propose some explanations as to why this relationship exists, and suggest ways to prolong the renal function in dialysis patients.

The evidence

Maiorca and colleagues were among the first to examine residual kidney function as a separate variable in analysis of outcome. The cohort of surviving PD patients had a mean RRF of 2.73 ml/min, compared with those who ultimately died, where the RRF was just 0.33 ml/min ($P < 0.0005$) [3].

Diaz-Buxo et al. analysed the outcome of 1600 patients in the Fresenius database and reported that RRF, but not the dose of PD, predicted mortality [4]. Strikingly similar findings were seen in outcome studies around the world, including those from Hong Kong [5], The Netherlands [6] and a network registry from the USA [7], i.e. the ‘dose’ of PD, measured by small solute clearance, did not predict mortality, but the RRF did. This necessitated a re-examination of the widely held view that dose of PD strongly influenced survival. That view had derived from the original CANUSA study, where total (peritoneal and renal) small solute clearance strongly and significantly predicted mortality [8]. It was assumed that the peritoneal contribution must be important. Subsequently, a re-analysis of the CANUSA data showed that the predictive power lay exclusively in the RRF, and not in the peritoneal component [9].

Interestingly, there have been very few studies that have examined the contribution of RRF to outcome in haemodialysis (HD) patients. A paucity of studies have shown that persistence of RRF has been associated with higher serum albumin [10] and significantly improved outcome [11]. RRF does not appear to be on the ‘radar screen’ for those involved in HD outcomes. This may be because: (i) it is lost more quickly in HD patients than in PD patients [6,12]; (ii) it is more complicated to measure in HD patients, who are not in steady state; or (iii) those engaged in HD dosing focus principally on small solute prescription, and so the contribution of RRF would not, a priori, be obvious.

The preservation of RRF in PD patients, compared with those on HD, may ‘level the playing field’ in outcome studies of the two modalities. In other words, the continuous glucose loading, consequent hyperinsulinaemia and more atherogenic lipid profile seen in PD may be offset by persisting benefit of RRF in these patients, so that, in the end, survival of HD and PD patients is comparable.

Why is RRF important to outcome?

The additional contribution to small solute clearance afforded by RRF is probably the least important explanation for the reduction in mortality. The renal contribution to elimination of middle and larger molecular weight toxins is proportionately greater than the increment in renal urea clearance [13].
Unfortunately, there is so much focus on the small solute clearance as an index of blood purification that the role of middle and larger molecular weight uraemic toxins is underestimated. The renal clearance of these toxins may serve to improve survival in a manner not measurable by Kt/V urea.

The ongoing excretion of water and, more importantly, sodium, can mitigate hypervolaemia. This function could be particularly important for patients on PD, where ultrafiltration is not always simple. Given that the principal cause of death is the result of cardiovascular disease, it is reasonable to suggest that maintenance of euvolaemia is associated with survival. In the re-analysis of the CANUSA study [9], each 250 ml of daily urine output conferred a 36% reduction in mortality. Indeed, when renal small solute clearance was compared with volume of urine by multivariate analysis, the former lost statistical significance. Other studies have reported an association of RRF with normotension [14,15], euvolaemia [16] and a more normal left ventricular mass index [17]. These studies offer indirect evidence that ongoing renal salt and water excretion protects against the development of hypervolaemia.

Finally, a different thought: there is emerging evidence of an association between declining renal function and increased risk of death in the chronic kidney disease (CKD) population [18]. This observation has led to the proposal that patients who reach dialysis are ‘survivors’, i.e. they have beaten the odds that they were more likely to have died of cardiovascular events than to reach end-stage renal disease. Perhaps the risk of death associated with declining renal function does not stop at the start of dialysis. In other words, whatever it is about declining renal function that leads to decreased survival in the CKD population is also operative in the dialysis population.

Preserving RRF in the dialysis patient

One way to maximize survival of renal function is to place the patient on PD. Although the possibility of ‘informative censoring’ exists, wherein those on PD with rapid loss of RRF might intentionally be switched to HD [19], it is likely that RRF is indeed preserved longer on PD. This has been the basis for the advocacy of integrated care, or ‘PD first’. This philosophy is for a patient facing many years of dialysis, where the placement on PD may prolong the RRF (and limit lifetime demands on vascular access) with consideration of intentional modality switch if the patient loses RRF and encounters problems such as hypervolaemia. Using this approach, patients starting on PD and changing to HD have had improved survival compared with those starting, and remaining, on HD [20].

Avoidance of nephrotoxic drugs, such as anti-inflammatory agents or aminoglycosides, is a rational approach, although a recent study could not detect an association between the use of aminoglycosides and decline in RRF [21]. It is reasonable to assume that drugs that are risky in CKD will remain risky to RRF in dialysis patients.

A similar warning applies to the use of radiocontrast dye. It is advisable to ensure that there is a meaningful indication for the dye study, and that the patient is not volume depleted. The smallest volume and least toxic dye should be used. Despite the confusion regarding the usefulness of N-acetyl cysteine to abrogate deterioration of renal function, it is a low risk and inexpensive manoeuvre. If one is hopeful enough to use this agent in patients with CKD being exposed to dye [22], it should also then be used to protect RRF in dialysis patients.

Single-dose [23] and long-term [24] studies of diuretic therapy in PD patients suggest that these agents are effective in augmenting renal salt and water excretion, but do not change renal small solute clearance. The effect of diuretics on any volume-dependent excretion of larger molecular weight uraemic toxins has not been studied.

Patients with a failing transplant who return to dialysis routinely had their immunosuppressive drugs stopped, since residual transplant function was considered unimportant. It is unclear whether the transplant RRF is as life-prolonging as native kidney RRF in dialysis patients and, if so, whether it outweighs the risk attendant in ongoing immunosuppressive therapy. A recent decision analysis suggests that, on balance, non-calcineurin-based therapy may be warranted to maintain ongoing function of the failing allograft [25]. This suggestion remains to be borne out in clinical studies.

Finally, two recent randomized controlled studies have built on the observation from the USRDS [12] that angiotensin-converting enzyme inhibitor therapy is associated with preservation of RRF. Studies using ramipril [26] and valsartan [27] have shown both reduced progression to anuria and 1 ml/min improvement in glomerular filtration rate at the end of 1 year. While 1 ml/min may not seem such a remarkable result, extrapolating for the RRF studies discussed initially, this could translate into a possible 25% annual reduction in mortality.

Residual renal function is a valuable asset to those on dialysis, best demonstrated in PD. It is crucial to try to preserve this asset for as long as possible by re-educating ourselves, and our medical colleagues, that we still have to continue to think about protection of renal function, even in the dialysis patient.

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References

Do not be misguided by guidelines: the calcium $\times$ phosphate product can be a Trojan horse

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