Preservation of Residual Kidney Function and Urine Volume in Patients on Dialysis

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Chronic dialysis treatment usually starts before the development of anuria to prevent the major complications of the uremic syndrome. Consequently, most patients will still have urine production at this time. Hemodialysis (HD) has been the main dialysis modality for chronic kidney failure since its start in the early sixties of the last century. Clinical observations at that time showed that most patients became anuric while on dialysis treatment. As a consequence, the preponderance of outcome studies on the effect of HD dose on survival either excluded patients with urine production or assumed that none were present. This policy was also adopted in the guidelines on HD dose that were part of the Dialysis Outcomes Quality Initiative in 1997 (1). The stormy development of continuous ambulatory peritoneal dialysis (CAPD) in the late seventies enabled nephrologists to observe a better preservation of residual kidney function with CAPD compared with HD. This observation was first published from France in 1983 (2) and confirmed in many other studies since, including an analysis of The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) (3). This analysis also showed that BP and comorbidity were associated with residual renal function in the whole dialysis population investigated and that the rapid decline in the initial 3 months was associated with episodes of hypovolemia. Studies in patients treated with automated peritoneal dialysis (PD) have given variable results, but taking all of the results together, it can be concluded that its decline is similar to that in CAPD (4).

The excretory kidney function consists of glomerular filtration and tubular secretion and reabsorption. In the presence of normal kidney function, about 99% of the glomerular filtrate is reabsorbed. Consequently, urine production is not influenced by the GFR but is influenced by tubular transport mechanisms. A different situation is present in patients on PD. In these patients, urine volume accounted for one half of the variance in GFR (5). A relationship between urine production and GFR is also present in patients on HD (6). Here, the relationship between urine production and GFR in the interdialytic interval had an explained variance of 67%. Apparently, tubuloglomerular feedback mechanisms are disturbed or function differently in patients on dialysis. Inulin clearance is the gold standard for determination of GFR in humans, but its determination is cumbersome. Creatinine clearance overestimates GFR due to some tubular secretion, and clearance of urea gives an underestimation because of reabsorption, especially in the presence of hypovolemia. The mean of urea and creatinine clearance is closely related to inulin clearance in both patients on HD (6) and patients on PD (7). Therefore, the mean of the two clearances can be considered the reference method for GFR determination in patients on dialysis. This requires a timed and accurate urine collection. To overcome cumbersome urine collections, formulas have been developed for GFR estimation on the basis of plasma concentrations of creatinine and urea. The Modification of Diet in Renal Disease (MDRD) equation (8) is widely used and extensively validated but not in predialysis patients or patients on dialysis. It consists of sex and race in the numerator and creatinine and age in the denominator. Recently, a new equation aimed for use with patients on dialysis, $eGFR_{urea,creat}$ was developed by some of the same group (9). It consists of urea in the numerator and creatinine in the denominator. Also, serum concentrations of low molecular proteins that are removed from the body by glomerular filtration and subsequent reabsorption and breakdown in proximal tubular cells can be used for GFR estimation. β2-Microglobulin and cystatin C were related to residual urine production in both HD (10) and PD (11). Equations have been developed for GFR estimations from serum cystatin C in patients on HD and patients on PD (12). By using serum concentrations of low molecular weight proteins, it is assumed that GFR is the only determinant of these. The practical value of measurement or estimation of residual GFR or urine production is especially relevant when they are associated with the risk of death. A reanalysis of the Canada-USA Study performed on patients on incident PD showed that urine volume but not measured GFR was associated with a 36% reduction of the relative risk of death (13). The NECOSAD reported some similar results. Measured GFR was related to survival, whereas urine production only became significant after removal of GFR from the model (14). In HD, renal Kt/V_{urea} was evidently associated with survival (15). The importance of measured GFR (16) or urine production (17) for survival of patients on HD has been confirmed in other prospective studies. The performance of eGFR in the MDRD equation in patients just before the start of dialysis is different. A

number of studies, including an analysis by the European Renal Association-European Dialysis and Transplant Association Registry (18), reported a higher mortality on dialysis of patients who started dialysis with the highest eGFR values, despite extensive corrections for potentially confounding factors. The explanation for this unexpected finding is the dependency of plasma creatinine on muscle mass, which is, in a situation of dialysis initiation, more important for death than the effect of glomerular filtration (19).

A nationwide prospective cohort study (20) in 1946 patients on incident HD and patients on PD from Korea, published in this issue of the *Clinical Journal of the American Society of Nephrology*, shows that urine volume and, to a lesser extent, measured GFR were significantly associated with survival after adjustment for potential confounders but that $eGFR_{urea,creat}$ was not (21). In contrast, the association between eGFR on the basis of serum β2-microglobulin and survival was significant. This is the largest study on residual kidney function so far. It confirms that urine production is the most important kidney function parameter related to survival of patients on dialysis and also, that eGFR on the basis of plasma concentrations of small solutes only provides insufficient or even misleading information on this issue. Serum concentrations of small proteins may be an alternative but need more investigation.

The importance of urine volume requires a focus on the prevention of hypovolemia. However, hypervolemia should also be avoided, meaning that maintaining euvolemia can be regarded as sailing between Scylla and Charybdis. This difficult task for patients and doctors is easier in the presence of a substantial urine production. Despite the increased relative importance of glomerular filtration in the determination of urine volume in patients on dialysis, pharmacologic modifications of parts of the tubular system are still effective. This has been extensively shown for furosemide, and also recently, for tolvaptan, PD with icodextrin, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, although not very convincingly.

Furosemide should be given in high dosages, because the concentration in the urine of the proximal tubule determines its effect. Active secretion of furosemide into the lumen of the proximal tubule occurs by a transport mechanism that requires high plasma concentrations because of the impaired function of the proximal tubule. Farther distally, urine furosemide inhibits sodium reabsorption in the thick ascending limb of the loop of Henle. It is immediately effective in both patients on HD (21,22) and patients on PD (23), in whom it also increased the fractional excretion of sodium and potassium. Furosemide administration has no effect on GFR or its decline with time on dialysis (23,24). Tolvaptan has been studied extensively in patients on dialysis, but only one study has been published on its effect on urine production in a small number of incident diabetic patients on PD (25). After 1 year, urine volume and renal creatinine clearance had remained stable, whereas they decreased in the control group. It is well known that dialysis solutions containing icodextrin as an osmotic agent increase peritoneal ultrafiltration, especially during long dialysis dwells, but only one recent study reported an effect on the time course of urine volume without an effect on residual GFR (26). It is likely that circulating oligosaccharides generated by breakdown of absorbed icodextrin increase the osmotic load for the kidneys, leading to a higher urine production. A number of studies have been published on possible effects of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers on preservation of residual renal function but without consistent results (27).

Maintenance of euvolemia is the most important issue in prolongation of survival of patients on dialysis. Preservation of residual kidney function and especially, urine production has an important contribution to the prevention of overhydration. Using eGFR on the basis of plasma concentrations of creatinine and/or urea gives misleading information in patients on dialysis, which makes the use of timed urine collections unavoidable. The role of serum concentrations of low molecular weight proteins has not been established yet. Furosemide in high dosages is the only therapeutic intervention currently available to increase urine production, but it has no effect on the other aspects of residual kidney function.

Disclosures

None.

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