

# Peritoneal Dialysis Adequacy: Not Just Small- Solute Clearance

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*Two indices of small-solute clearance, Kt/V urea and creatinine clearance, are widely used as markers of peritoneal dialysis (PD) adequacy. It has become clear, however, that increasing the small-solute clearance above a minimum level does not result in improved long-term PD outcomes. Several other factors may affect optimal dialysis outcome. These include, but are not limited to, ultrafiltration, inflammation, malnutrition, and mineral metabolism. In the present article, we briefly review data regarding the relationships between the foregoing factors and survival on PD.*

## Key words

Adequacy, ultrafiltration, malnutrition, inflammation, mineral metabolism

## Introduction

The word “adequate” originates from the Latin *adaequāt*, which means to make or become level or equal. Looking at the list of potential parameters of dialysis adequacy shown in Table I, it becomes immediately apparent that even the best dialysis does not equalize any of them. For example, where a peritoneal dialysis (PD) patient would be considered to be doing well with a weekly Kt/V urea of 2.0, a healthy individual with normal glomerular filtration rate has a weekly Kt/V urea of approximately 20! When considering dialysis “adequacy” a more pertinent question is this: Are there one or more parameters that, when a certain level is achieved, will predict improved survival as compared to survival in patients in whom these levels are not achieved?

In the present paper, we briefly examine whether small-solute clearance or other parameters may satisfy this condition.

## Discussion

*The rise (and fall?) of small-solute clearance as a marker of PD adequacy*

The urea-centric model for PD adequacy was originally bolstered by two longitudinal observational studies (1,2). In a relatively small study, Maiorca *et al.* demonstrated that 2-year patient survival was better in patients with a weekly Kt/V urea above 1.96 as compared with patients with a weekly Kt/V urea below 1.7 (1). The much larger CANUSA study showed that survival improved with a weekly Kt/V urea above 2.1 (2). Although reanalysis of CANUSA revealed that the improved outcomes in patients with a higher weekly Kt/V urea was attributable to residual renal function (3), a weekly Kt/V urea of 2.0 or higher became the accepted target for “adequate” small-solute clearance.

This small-solute dependent model for PD adequacy was challenged by the results of two randomized controlled trials (4,5). In the ADEMEX (Adequacy of PD in Mexico) trial, a total of 965 patients were randomly assigned to an intervention or a control group. Patients in the intervention group were prescribed progressive changes in their dialysis regimen to achieve a weekly peritoneal creatinine clearance (CCr) of 60 L/1.73 m<sup>2</sup> or more. Patients in the control group continued to perform 4 daily continuous ambulatory PD (CAPD) exchanges of 2 L each. The time-averaged total weekly Kt/V urea was

TABLE I Potential parameters of dialysis adequacy

Small-solute clearance
Blood pressure and volume homeostasis
Acid–base homeostasis
Control of lipids and cardiovascular risk
Nutrition
Ca, P, and bone homeostasis
Inflammation
Middle-molecule clearance

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2.27 in the intervention group as compared with 1.80 in the control group. Yet, upon 2-year follow up, no difference in mortality was observed between the two groups (4). Lo *et al.* performed a similar study in Chinese PD patients and found no difference in mortality between three groups with weekly Kt/V urea values ranging from 1.5 to more than 2.0 (5). Similarly, in the EAPOS (European APD Outcome Study) trial, no relationship was found between small-solute clearance and mortality (6). Furthermore, in NECOSAD (Netherlands Cooperative Study on the Adequacy of Dialysis), the risk of death in anuric PD patients increased only when weekly Kt/V urea was extremely low—less than 1.5 (7).

The foregoing studies all strongly suggest that there is more to PD adequacy than just small-solute clearance. We therefore briefly examine several of the other parameters that may potentially define PD adequacy.

#### *Ultrafiltration as a marker of PD adequacy*

The effect of ultrafiltration (UF) on mortality in PD patients has been examined in a few studies. The EAPOS study was a 2-year prospective multicenter study that enrolled a total of 177 anuric patients on automated PD (APD). The PD prescription was targeted to achieve a weekly CCr above 60 L/1.73m<sup>2</sup> and a daily UF of more than 750 mL. In addition to age older than 65 years, poor nutrition status, and presence of diabetes, multivariate analysis revealed that one of the baseline predictors of poor survival in these patients was a daily UF below 750 mL ( $p = 0.047$ ). However, on follow-up (and, admittedly, perhaps because of an inadequate sample size), the association between time-averaged UF and mortality failed to reach statistical significance ( $p = 0.097$ ) (6).

Similar data were obtained in NECOSAD, a prospective multicenter cohort study of 130 anuric PD patients (102 on CAPD, 28 on APD). When examined as a continuous variable, daily UF was significantly associated with 2-year survival ( $p = 0.04$ ). However, although patients in the lowest quintile of UF (<1.15 L daily) had a relative mortality risk of 3.41, that risk failed to achieve statistical significance. Likewise, when examined as a dichotomous variable (that is, a UF above or below a specific value) no significant relationship between UF and 2-year survival could be demonstrated ( $p > 0.1$  in all cases) (7). Once again, a small sample size may have limited the ability to achieve statistical significance.

In contrast, in another study performed in Turkey, 125 patients were followed for 3 years after starting PD. Using a Cox proportional hazards model, the investigators found that *total* sodium and fluid removal (urinary + dialysate) were both independent factors affecting survival: cumulative survival was lowest in the groups with lowest daily sodium removal (<130 mmol/1.73 m<sup>2</sup>) and lowest daily UF (<1265 mL/1.73 m<sup>2</sup>), both  $p < 0.01$  (8). Thus, the authors of the most recent International Society for Peritoneal Dialysis recommendations regarding dialysis adequacy and ultrafiltration concluded “from these data that no numerical target for ultrafiltration can be formulated” (9).

The cause of the potentially increased mortality associated with low ultrafiltration has generally been felt to relate to consequences of volume overload: congestive heart failure, increased left ventricular mass, hypertension, and other cardiovascular events. However, other possibilities must be considered as well. For example, in a study of 82 PD patients followed for a mean of nearly 1 year, Chung *et al.* observed that, among patients with elevated C-reactive protein (CRP) levels (>10 mg/L), a higher proportion of patients had low total fluid removal (<1000 mL daily) and increased mortality as compared with patients with low CRP levels (10). This observation suggests a possible association between inflammation and mortality that warrants further examination.

#### *Inflammation and PD adequacy*

The malnutrition, inflammation, and atherosclerosis (MIA) syndrome is increasingly recognized as a major cause of cardiovascular morbidity and mortality in dialysis patients. Peritoneal dialysis appears to be a less inflammatory modality than hemodialysis is. Haubitz *et al.* compared CRP levels between healthy volunteers, patients with chronic kidney disease (CKD) not on dialysis, and patients on either hemodialysis or PD. Levels of CRP were highest in the HD patients; the PD patients had levels comparable to those of the CKD patients not yet on dialysis (11). The question remains, however, whether within a population of PD patients, the degree of inflammation (or absence thereof) may be used as a marker for PD adequacy.

As previously mentioned, the study by Chung *et al.* demonstrated increased mortality (relative risk: 2.69;  $p = 0.01$ ) associated with inflammation (defined as CRP > 10 mg/L) as compared with no inflammation (10). Similar findings were obtained in a cross-sectional

study of 246 Chinese PD patients who were followed prospectively for an average of 20 months. In that study (12), a single measurement of high-sensitivity CRP (hsCRP) was found to be predictive of mortality: on multivariate analysis, each 1 mg/dL increase in hsCRP was associated with a 2% increase in all-cause mortality ( $p = 0.002$ ) and a 3% increase in cardiovascular mortality ( $p = 0.001$ ).

But CRP is not the only inflammatory marker associated with mortality. In yet another observational study, Stenvinkel *et al.* demonstrated that mortality increased as serum interleukin-6 (IL-6) levels rose. Furthermore, both serum IL-6 levels and mortality increased as the number of components of the MIA syndrome present in the patients increased (13).

These studies all suggest that *absence* of inflammation may be considered a component of “adequate” renal replacement therapy. However, no clear criteria emerged for ascertaining that inflammation is indeed absent. Furthermore, there are no specific guidelines regarding the best methods for monitoring or treating inflammation in these patients apart from treating infection, if present. Finally, as exemplified by the Stenvinkel *et al.* study (13), inflammation often coexists with malnutrition, suggesting that the potential role of nutrition as a marker for PD adequacy warrants closer scrutiny.

#### *Nutrition status and PD adequacy*

Malnutrition is very common in PD patients. In an international study, the prevalence of malnutrition measured by subjective global assessment (SGA), which has 21 components, was 40.6% (14). There are many different indices of malnutrition, including serum albumin, prealbumin, transferrin, anthropometric measurements, bioimpedance analysis, normalized protein catabolic rate, and multivariable methods such as SGA score and composite nutrition index (CNI: a function of SGA, albumin, and anthropometric measurements).

Several studies have demonstrated a relationship between one or more of these nutrition indices and mortality. For example, in the CANUSA study, each 1 g/L increase in serum albumin was associated with a 6% decrease in mortality, and a 1-unit increase in SGA score was associated with a 25% reduction in the relative risk of death (2). Lo *et al.* performed a cross-sectional study of 937 patients who had been on CAPD for at least 6 months and who were then followed for 24 months. Mortality was analyzed as a function of

both small-solute clearance and nutrition status as assessed by the CNI. As mentioned previously, they found no relationship between mortality and weekly Kt/V urea in the range of 1.5 to more than 2.0. In contrast, they found that patients with a better CNI enjoyed significantly greater 12-month survival ( $p = 0.0259$ ) did patients with a worse nutrition status (15). Similarly, in both EAPOS and NECOSAD, nutrition status independently predicted survival of PD patients at 2 years (6,7).

More recently, Avram *et al.* reported on the relationship between nutrition status and mortality in an observational study of 177 patients who started PD during 1991–2005. Bioimpedance analysis with determination of phase angle, and measurement of serum prealbumin and other indices of nutrition, was performed in subsets of these patients, who were then followed for up to 15 years (16). Phase angle may be understood to be a surrogate marker for the mass of cell membranes; healthy, well-nourished individuals should have a phase angle of 6 degrees or more. Indeed, over a period of 5 years, PD patients with a phase angle of 6 degrees or more at the time of entry enjoyed substantially improved survival ( $p = 0.036$ ) compared with those whose phase angle was less than 6 degrees. Similar findings were obtained when patients were stratified by entry prealbumin level: those with a level of 32 mg/dL or more enjoyed significantly superior survival ( $p = 0.032$ ) as compared with those with lower levels.

The cause of malnutrition in PD patients is multifactorial, including anorexia, protein loss into the PD fluid, hormonal derangements, and cytokine-induced cachexia (17,18). To date, no large-scale interventional trials have studied the relationship between nutrition status and mortality in PD patients. However, the available observational data suggest that, along with ensuring adequate small-solute clearance, efforts must be made to improve the nutrition status of our PD patients if they are to enjoy superior survival.

#### *Mineral metabolism and PD adequacy*

The past few years have seen substantial interest regarding a possible relationship between mineral metabolism—particularly that of phosphate—and mortality in PD patients. For example, Trivedi *et al.* followed 191 PD patients for an average of 21 months and examined predictors of mortality. On stepwise logistic regression analysis, they found that the

weighted time-averaged serum phosphate level was an independent predictor of death ( $p = 0.02$ ) (19). Similarly, Noordzij *et al.* reported NECOSAD data from 586 patients who started on PD between 1997 and 2004. Phosphorus levels above the Kidney Disease Outcomes Quality Initiative upper limit of 5.5 mg/dL were associated with increased cardiovascular mortality [hazard ratio (HR): 2.4;  $p < 0.01$ ] as was an increased Ca  $\times$  P product above 55 mg<sup>2</sup>/dL<sup>2</sup> (HR: 2.2;  $p < 0.01$ ) (20).

To date, no large database studies have looked at the effects of mineral metabolism on cardiovascular outcomes in the PD population. However, two recent abstracts from data obtained in a cohort of 7034 patients performing PD for at least 3 months do address this issue. Mehrotra *et al.* reported that, as compared with a reference group of patients with serum phosphorus ranging from 4.5 mg/dL to 5.5 mg/dL, patients with a serum phosphorus below 3.5 mg/dL experienced increased mortality (HR: 1.33;  $p = 0.003$ ). However, when the data were adjusted for the presence of confounders of the MIA syndrome (for example, albumin, total iron binding capacity, and lymphocyte count, among others), this relationship was no longer independently significant. In contrast, the presence of a serum phosphorus level above 8.5 mg/dL was associated with increased mortality (HR: 1.37;  $p = 0.03$ ), independent of any confounding variables (21). In another abstract based on this same database, Khawar *et al.* (22) reported that each 1 mg/dL increase in albumin-adjusted serum calcium above 9 mg/dL was associated with an increased risk of death (HR: 1.15;  $p < 0.0001$ ). It must be noted, however, that in the study by Noordzij *et al.* mentioned earlier, increased calcium levels were not associated with worsening mortality (20).

The exact mechanism or mechanisms whereby deranged mineral metabolism may lead to worse cardiovascular outcomes is currently uncertain. Some authors suggest that the relationship may be mediated by increased vascular calcification, which in turn culminates in worse cardiovascular outcomes. Further study of this important issue is clearly needed.

## Conclusions

The provision of “adequate” PD clearly requires much more than just obtaining a certain degree of small-solute clearance. More research is needed to determine which other parameter or parameters—including others not considered in this brief review (for example, middle-molecule clearance)—most closely correlate

with outcomes. Large randomized trials will then be needed to determine whether interventions targeted at optimizing these parameters will provide our patients with a significant survival benefit.

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