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EDITORIAL COMMENTARY

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Adequacy of dialysis in children: does small solute clearance really matter?

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Abstract Measurement of dialysis adequacy relies on an assessment of small molecule clearance during the dialysis procedure. However, recent adult studies (HEMO and ADEMEX) that pushed clearance to maximally achievable levels within practical constraints of thrice-weekly hemodialysis or four times daily continuous ambulatory peritoneal dialysis failed to demonstrate improvements in patient outcome above current guidelines. The relatively low incidence of pediatric compared with adult end-stage renal disease limits large-scale study of pediatric dialysis. Several single-center pediatric studies demonstrate a lack of association between small solute clearance alone and patient growth. The aim of the current article is to review the relevant pediatric and adult studies of small solute clearance and put them in the context of optimal dialysis provision. While small solute clearances do indeed matter, clearance is not all that matters. Our quest to provide optimal dialysis requires that we also focus our attention on patient nutritional status, increased dialysis delivery (daily/nocturnal hemodialysis), and adjunctive dialysis modalities (hemofiltration and renal tubular replacement therapy).

Keywords Adequacy of dialysis · Continuous ambulatory peritoneal dialysis · Small solute clearance

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Introduction

The concept of dialysis adequacy was born nearly 30 years ago from the National Cooperative Dialysis Study (NCDS) [1], which aimed to control for dialysis treatment dose in adult patients and correlate a particular dose with patient outcome. The mechanistic analysis of the NCDS [2], performed by Gotch and Sargent, revealed that the relationship between dialysis dose and outcome was not linear. An almost fourfold increase in hospitalization/death rates occurred in patients receiving less than 50% urea clearance compared with patients receiving greater than 50% urea clearance during each dialysis treatment. Thus, the resultant concept of "adequate" dialysis was created to define a *minimum* hemodialysis dose, below which occurs a clinically unacceptable rate of negative outcome.

Over the ensuing 20 years, both pediatric and adult dialysis adequacy study focused mainly on deriving the most accurate mathematical formulae for quantifying urea clearance during hemodialysis or peritoneal dialysis [3, 4, 5, 6]. While these studies led to more interest in the kinetics of dialysis and the creation of published national standards for adequate provision of hemodialysis, few studies have attempted to determine if higher urea clearance targets result in improvement in adult patient survival or morbidity. Results from two prospective and comprehensive dialysis adequacy studies reported in the last 2 years, the ADEMEX study for peritoneal dialysis [7] and the HEMO study for hemodialysis [8], suggest that increasing urea clearance above currently accepted target ranges does not lead to improved patient outcome. Since the pediatric nephrology community lacks prospective randomized pediatric dialysis patient outcome trials, we must extrapolate results from adult studies. The aims of the current editorial are to review studies that evaluate the effect of dialysis dose on patient outcome and assess the potential implications on the current and future management of pediatric dialysis patients.

Prospective dialysis adequacy outcome studies

Despite the enormous cost and high mortality rates associated with the United States adult dialysis program [9], only four large-scale and adequately powered, prospective trials have been conducted to assess the impact of dialysis dose on patient morbidity and mortality—the NCDS and HEMO study for hemodialysis patients and the CANUSA [10] and ADEMEX studies for peritoneal dialysis patients.

The NCDS randomized patients to one of four groups using a 2×2 matrix based on treatment duration (2.5 versus 4 h) and the level of chronic uremia, categorized as a time averaged urea concentration of 50 versus 100 mg/dl. The mechanistic analysis of the NCDS provided mathematical tools, termed urea kinetic modeling (UKM), to calculate the delivered dose of dialysis that accounted for small solute clearance achieved by both diffusion- and ultrafiltration-driven convection.

The initial analysis of the NCDS showed that 57% of patients receiving a Kt/V of less than 1.0 died or were hospitalized during the course of study, whereas only 13% of patients receiving a Kt/V >1.0 died or were hospitalized. The impact of these NCDS results upon hemodialysis patient care cannot be overestimated. The observation of a non-linear relationship between hemodialysis dose and the degree of improvement of patient outcome between groups was not only unexpected, but also led to fundamental reassessment of the impact of dialysis treatment on patient morbidity and a resulting paradigm change in hemodialysis practice. Once the NCDS results were widely understood and accepted, thrice-weekly hemodialysis and routine monitoring of delivered dialysis dose became an international standard of care for hemodialysis patients. In addition, while the NCDS results produced the hemodialysis adequacy concept, it also spawned creation of the optimal hemodialysis concept, a hemodialysis dose above which no significant reduction in negative outcomes or improvement in positive outcomes occur. Thus, the early sentiment that hemodialysis patients were destined to poor medical outcomes slowly became replaced by significant clinical research efforts to assess for improvements in hemodialysis patient health-related quality of life resulting not only from increased delivered dose of dialysis, but also from improvements in patient nutritional status, renal osteodystrophy status, and management of anemia.

One decade after the NCDS mechanistic analysis, Bloembergen et al. [11] and Held et al. [12] furthered research into the effect of dialysis dose on the overall and cause-specific mortality of hemodialysis patients. These retrospective studies of more than 2,000 adult hemodialysis patients demonstrated significant reductions in overall patient mortality and cardiovascular, cerebrovascular, and infection-related mortality for each 0.1 Kt/V increase up to a certain point. No improvements in mortality were observed for patients receiving a Kt/V greater than 1.3 or a urea reduction ratio greater than 70%. These studies produced both theoretical implications and further refined the basis for national clinical guidelines of hemodialysis adequacy. The mortality of hemodialysis patients was now demonstrated to result not just from one cause, but from a number of pathophysiological causes, which implied that lower dialysis doses could promote atherogenesis, infection, malnutrition, and failure to thrive. The improvement in hemodialysis patient mortality up to a Kt/V of 1.3 argued for a minimum dialysis dose above that generally prescribed at that time. This was the basis for the Dialysis Outcomes Quality Initiative Hemodialysis Adequacy Guidelines, which recommended prescribing a Kt/V of 1.3 to ensure delivery of a Kt/V of 1.2 [13].

In the 1990s, many investigators became concerned about the accuracy of single-pool kinetic modeling and its potential overestimation of the urea mass removed during a dialysis treatment. Kt/V calculation is based upon obtaining a pre- and post-treatment blood urea nitrogen (BUN) level. As the BUN rises with equilibration post hemodialysis, the resultant calculation of Kt/V yields lower values. Numerous equations were created to estimate equilibrated Kt/V (eKt/V) [4, 15]. However, until the HEMO study, few studies investigated an association between increased eKt/V and patient outcome.

The HEMO study stratified patients into one of four groups based on delivered eKt/V to account for diffusive clearance, and high or low flux to assess for an impact of convective middle molecule clearance on adult patient mortality. Patients were randomized to receive thrice-weekly delivered eKt/V of 1.05 versus 1.45 and a β2-microglobulin clearance of less than 10 ml/min versus greater than 20 ml/min.

The strongest predictors of death were patient age, serum albumin level, race, and years on dialysis at time of entry into the study. However, these predictors transcended all four of the dialysis dose groups, and no improvement in patient mortality was observed for the high-dose group versus the low-dose group or the high-flux group versus the low-flux group.

Ten years after the mechanistic analysis of the NCDS, the first large-scale multi-center trial was performed to assess for an impact of small solute clearance of peritoneal dialysis upon adult patient outcome. The CANUSA study was a prospective cohort trial that examined factors affecting 2-year survival rates. Patients with a weekly continuous ambulatory peritoneal dialysis (CAPD) Kt/V <2.0 had significantly worse survival (74%, 71%, and 66% for Kt/V 1.9, 1.7, and 1.5, respectively) than patients with weekly CAPD greater than 2.0 (78% and 81% for Kt/V of 2.1 and 2.3, respectively). An essential component for peritoneal adequacy measurement is the contribution of residual renal function to small solute clearance. The CANUSA study initially proposed that renal small solute clearance and peritoneal dialysis small solute clearance might be equivalent. However, since the CANUSA trial was a prospective cohort trial and declining renal small solute clearance was not replaced by increasing peritoneal clearance, it was not designed to substantiate this claim. In fact, re-analysis of

the CANUSA data by the original investigators [16] clearly demonstrates the dominant role of residual renal clearance in improving survival of peritoneal dialysis patients.

The ADEMEX (ADEquacy of PD in MEXico) trial was specifically designed to assess if increasing peritoneal dialysis small solute clearance would lead to an improvement in patient outcome. ADEMEX subjects in the control group continued to receive four daily 2-l CAPD exchanges, whereas subjects in the intervention group received peritoneal dialysis prescription modifications to achieve a peritoneal dialysis creatinine clearance of 60 l/week per 1.73 m^2. After initiation of the study and for the entire 2 years of study, control subjects maintained their baseline clearance values. The intervention group had a mean peritoneal creatinine clearance of 57 l/week per 1.73 m^2 with 59% of intervention patients receiving a peritoneal creatinine clearance >60 l/week per 1.73 m^2 and 78% a total creatinine clearance (peritoneal plus residual renal clearance) >60 l/week per 1.73 m^2.

ADEMEX trial results failed to demonstrate a significant improvement in patient survival between the control and intervention groups. The control groups exhibited 1- and 2-year survival rates of 85.5% and 68.3% and the intervention group had 1- and 2-year survival rates of 83.9% and 69.3%, respectively. Similar to the CANUSA study, patient age, diabetes, and malnutrition conferred greater mortality risk irrespective of delivered small solute clearances. Thus, the main message of the ADEMEX study is that increasing peritoneal small solute clearances did not lead to improved survival of peritoneal dialysis patients.

What about children?

The pediatric nephrology community will never be able to perform studies that approximate the magnitude of the HEMO and ADEMEX trials. For example, fewer pediatric patients in the United States currently receive hemodialysis than were entered into the HEMO study. However, several pediatric dialysis studies have assessed the effects of dialysis dose on outcome.

Schaefer et al. [17] prospectively studied 213 pediatric patients who received peritoneal dialysis over an 18-month period to assess potential relationships of peritoneal transport characteristics by peritoneal equilibration tests (PET), residual renal, and dialysis small solute clearances upon growth and nutrition. In this study, declining residual renal small solute clearance was replaced with increased peritoneal urea and creatinine clearance to maintain a mean total weekly Kt/V of 2.42±0.7 and a creatinine clearanceof 55±21 l/1.73 m^2. Interestingly, patients exhibiting high peritoneal transport characteristics by PET had a significantly increased risk of worsening height standard deviation score (SDS) over the study period, which corroborates data from adult studies linking high transporter states with morbidity and mortality. While the authors observed that neither weekly urea nor creatinine clearances correlated with growth rates in a univariate analysis, multivariate analysis controlling for PET characteristics showed a weakly positive association between small solute clearance and growth. Finally, residual renal function correlated only with mean height SDS and not with change in height SDS in this study, demonstrating that residual renal function affects the degree of growth retardation but not catch-up growth.

Although most other pediatric dialysis outcome studies that quantify dialysis dose are single center in design, they lend insight into the relative importance of small solute clearance. Fortunately, as pediatricians, our community has always placed a great emphasis on nutritional status [18] and has the crude but quantifiable outcome measure of growth by which to assess our interventions. As such, measures of nutritional status are assessed in nearly every pediatric dialysis outcome study. Although we cannot recreate the HEMO or ADEMEX trials for children, nor should we since most pediatric patients with end-stage renal disease (ESRD) are treated with renal transplantation, work performed to validate methods of small solute clearance measurement in children receiving dialysis allow for clinical investigators to control for and assess the impact of dialysis dose. Tom et al. [19] demonstrated improved growth without use of growth hormone in a group of pediatric hemodialysis patients who received significantly greater than the recommended daily allowance (RDA) of calories and protein and a thrice-weekly Kt/V of 2.0. This provides strong support for adequacy measurement in children, and this study produced the novel physiological concept that children provided with enough nutrition and concomitant removal of waste products will demonstrate improvement in a fundamental pediatric outcome measure, and could not have been performed without methods to measure delivered dialysis dose.

Holtta et al. [20] provided an excellent example of state-of-the-art care of pediatric peritoneal dialysis patients by demonstrating improved clinical outcome over the 9-month period after dialysis was initiated and achievement of small solute clearance objectives (weekly Kt/V 3.2±0.5, creatinine clearance 68.8±16.6 l/1.73 m^2). Although the authors did not show a correlation between small solute clearance and growth, their data provide one of the first analyses since the publication of K/DOQI guidelines of improved growth, renal osteodystrophy status, and anemia status in well-dialyzed pediatric patients receiving peritoneal dialysis.

Chadha et al. [21] assessed a 24 pediatric patient cohort for potential associations between small solute clearance, nutrition, residual renal function, and growth. While small solute clearance and nutritional provision were much higher than K/DOQI guidelines (mean weekly Kt/V 3.45±0.73, creatinine clearance70.3 l/1.73 m^2, protein intake 213±65% RDA), they did not differ between patients with positive versus negative height SDS during the study period. However, residual renal function was present in 78% of patients with positive height SDS

versus only 33% of patients with negative height SDS ($P<0.03$). Similar to the CANUSA and ADEMEX studies, these data suggest that peritoneal and residual renal small solute clearances are not equivalent.

Bakkaloglu et al. [22] assessed the impact of increasing dialysis dose upon cardiac function in 18 pediatric peritoneal dialysis patients. Increasing weekly Kt/V and creatinine clearance were positively correlated with improved cardiac function (ejection and shortening fractions) and negatively correlated with cardiac structural parameters (left ventricular end diastolic and systolic dimensions). While these data are unique for the pediatric population and certainly provocative, multivariate analyses of this and future populations are required to assess the impact of hypertension, years on dialysis, and residual renal function in order to substantiate the effect of small solute clearance on cardiac function.

Editorial

Given that both the HEMO and ADEMEX trials fulfilled the null hypothesis, and since no pediatric study has yet shown a significant positive correlation between small solute clearance and growth, one could be tempted to wonder if small solute clearances really matter with respect to dialysis patient outcome. There are two potential interpretations of the HEMO and ADEMEX trials. One is blind to the NCDS and CANUSA data and expects that urea clearance (as a surrogate for small solute clearance) should be the only variable to impact upon dialysis patient outcome. The other incorporates evaluation of the entire clinical ESRD picture and suggests that current recommendations with respect to dialysis delivery reveal the limitations of small solute clearance on outcome.

Numerous authors have addressed the relevance of current dialysis adequacy consensus guidelines [23, 24, 25], which are mostly based upon the adult outcome data reviewed in the current article, to the pediatric dialysis population. Such guidelines, including the K/DOQI guidelines and European Paediatric Peritoneal Dialysis Working Group recommendations [26], are crucial because they provide a starting point for all future investigations. In that sense, these guidelines demonstrate that pediatric dialysis outcome research is still in its infancy. Prospective randomized multi-center trials will be crucial to assess the impact of particular interventions on pediatric outcome. However, we should heed the lessons of the ADEMEX and HEMO trials, as well as the preliminary pediatric trials, and not expect dialysis small solute clearance at or above current prescription guidelines to be the only factor affecting patient outcome. In his review of pediatric peritoneal adequacy, Sharma [24] clearly recognizes the need to incorporate the results of previous pediatric outcome studies when designing future studies. Sharma [24] advocates a 2×2 factor analysis that assesses both total solute clearance and residual renal function. Using data from his previous study [22], he noted that a total of 140 pre-pubertal pediatric patients would be required for a study of sufficient power to identify a 0.3 height SDS difference. Such a study would require significant effort, but would clearly be worthwhile to determine if manipulation of dialysis prescription alone can lead to improvement in pediatric patient outcome. In any case, assessment of small solute clearance is required to control for dialysis dose in any outcome study.

Investigators from the HEMO or ADEMEX trials and authors who have interpreted trial data in various editorials have advocated that HEMO and ADEMEX argue for provision of less dialysis. In what has seemed to be a "monotheistic" drive to search for the "Holy Grail" equating adequacy levels to patient health, some important "secondary" data from all these trials have been neglected. In both the peritoneal dialysis patient trials, patient pre-morbid conditions, especially malnutrition, were powerful predictors for mortality and hospitalization. The mechanistic analysis of the NCDS also showed that malnutrition, as evidenced by a low protein catabolic rate (nPCR), seemed to have a negative impact on patient outcome. However, this observation appeared as an afterthought. The HEMO study also noted that baseline nutritional status, as measured by serum albumin level, was a strong predictor of death. However, ongoing measures of nPCR or albumin were not provided. While further analysis of the HEMO study revealed an association between malnutrition and poor physical functions and health-related quality of life [27, 28], it would be interesting to learn whether a decline in patient nutritional status over the course of study was associated with increased mortality.

The HEMO and ADEMEX trials suggest that if significant improvement in patient morbidity and mortality are to be realized, dialysis patient care may need to experience the first major paradigm shift since the NCDS. Clearly, no one could suggest, given 1- and 5-year dialysis patient mortality rates of 25% and 70% from the United States, that the majority of American dialysis patients are receiving optimal dialysis. However, financial and quality of life issues make provision of more hemodialysis treatment time on a thrice-weekly daytime basis or more than 15 l/day of CAPD impractical. Large-scale comparative trials of alternative treatment regimens need to be conducted that include, but are not limited to, daily and nocturnal dialysis [29], addition of hemofiltration to enhance middle molecule clearance, and new therapies that replace the tubular function lost in ESRD [30]. More-aggressive preventive measures to disrupt the inter-related development of cardiovascular calcifications and atherosclerosis, malnutrition, and inflammation would likely improve survival of dialysis patients.

In summary since the NCDS, while all dialysis outcome trials fail to demonstrate improved patient outcomes at readily achievable small solute clearance, these studies are of great importance in that they show the limitations, not the irrelevance of small solute clearance on dialysis patient outcome. HEMO and ADEMEX are milestones in that they complete one part of a nearly 30-

year quest to assess the impact of dialysis dose on patient outcome. The lesson we should learn from HEMO and ADEMEX is that our clinical and scientific excursions need to extend beyond small solute clearance.

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