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Introduction to the Critical Balance – Residual Kidney Function and Incremental Transition to Dialysis

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Obsession with dialysis adequacy is the prevailing dogma in the management of patients with end-stage renal disease (ESRD) and has overshadowed the needed attention to personalized dialysis treatment and preservation of residual kidney function (RKF). As dialysis therapy emerged in 1960's and early 1970's, a thrice-weekly hemodialysis schedule was laid down by the dialysis pioneers as the "standard of care" – one that would prevent uremic symptoms and offer "the best compromise" by permitting the treatment of many patients with limited resources.¹ The rapid (but now stalled) technological progress in hemodialysis therapy has been beneficial, but the many attempts to improve patient outcomes by increasing dialysis dose and frequency have failed to show definite clinical benefits. Recent reports from the Frequent Hemodialysis Network (FHN) Trial group have suggested mixed and even contradictory effects of frequent vs. thrice-weekly in-center hemodialysis on patient survival in that mortality was reduced in the FHN Daily Trial while increased in the FHN Nocturnal Trial.^{2,3}

What might account for such a difference in the effect of dialysis frequency within the same study group? The key may lie in the different characteristics of participants, in particular their RKF. The FHN Daily Trial included mainly long-term hemodialysis patients of whom two thirds were anuric,⁴ while the patients recruited for the FHN Nocturnal Trial were relatively new to dialysis with half having urine volumes of 500 ml/d or more.⁵ Hence, RKF may have obscured the benefit of dialysis dose or frequency,⁶ considering its pivotal role in maintaining fluid and metabolic homeostasis even at the low levels present in ESRD patients.⁷ Indeed, residual kidney clearance is more strongly associated with survival among both ESRD patients on hemodialysis and peritoneal dialysis than is dialytic urea clearance.^{8,9} Interestingly, the above mentioned FHN Nocturnal Trial showed faster RKF decline in the frequent hemodialysis group¹⁰ which may at least partly explain the unexpected higher mortality in this group.¹¹ Frequent hemodialysis also led to worse vascular access outcomes.¹²

Technological advances have made hemodialysis treatments more efficient, effective, and less costly, allowing for an expansion of the eligibility for dialysis treatment such that the percentage of patients with an estimated GFR of >10 mL/min/1.73m² at dialysis initiation in

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the U.S. has increased from 13% in 1996 to 40% in 2013.¹³ The elderly population is also increasing, and almost a quarter of incidence ESRD patients were aged 75 years in 2013. Growing heterogeneity in this population clearly warrants individualized treatment, rather than the one-size-fits-all approach. “Personalized dialysis” may offer more favorable clinical outcomes, better quality of life, and yet more cost-savings.

To that end, an emerging strategy is incremental dialysis. While an incremental approach has commonly been employed among patients transitioning to peritoneal dialysis, the vast majority of maintenance hemodialysis patients in developed countries are initiated abruptly with thrice-weekly treatments irrespective of their RKF. This is despite the 2006 Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines suggesting less frequent hemodialysis schedules among patients with “substantial” residual renal urea clearance (i.e., $K_{ru} > 3.0 \text{ mL/min/1.73m}^2$).¹⁴ This gap between guidelines and clinical practice may be attributed to the misconception that RKF would invariably decline rapidly and quickly become clinically irrelevant after hemodialysis initiation, a belief based on old and inconclusive data from early studies comparing changes in RKF between patients on hemodialysis vs. peritoneal dialysis.^{15–18} Some – but not all – studies suggest that the current use of biocompatible dialysis membranes have been associated with the slower rate of decline in RKF.^{19,20} Hemodialysis patients may, contrary to widespread belief, have similar rates of decline to patients on peritoneal dialysis if ultrapure dialysate or on-line hemodiafiltration is used.^{21–24}

Less frequent hemodialysis (including twice-weekly treatment) has been criticized and labeled as inferior or inadequate dialysis.²⁵ While we agree that dosing may be “inadequate” by conventional measures when infrequent hemodialysis is used in palliative dialysis strategies,^{26,27} that critique is unwarranted in other settings. Major knowledge gaps have persisted until very recently pertaining to the multitudes of advantages of an incremental approach to dialysis initiation and the criteria to identify those who would benefit the most from this and other less frequent hemodialysis regimens.

In this issue of *Seminars in Dialysis*, we have assembled a group of opinion leaders in dialysis to address several important and emerging topics related to the interplay between RKF and incremental dialysis. We commence our discussion with Ghahremani et al. providing us the first reported experience in any North American center in implementing incremental hemodialysis in a case-series of 13 new ESRD patients who incrementally transitioned to full dose dialysis therapy. They explore the criteria used to decide on implementing twice-weekly hemodialysis and the methodology for the incremental transition to more frequent dialysis at a major University of California program. We then join Kalantar-Zadeh et al. in discussing renal replacement therapy including the incremental hemodialysis approach in the large and growing United States Veterans population with advanced CKD. The report is worth noting when considering that dialysis therapy in Veterans Affairs medical centers has demonstrated better outcomes than other centers.

Yan et al. explore the China’s experience in incremental dialysis. They have gathered the studies and patient characteristics that are important in that they will help practitioners implement incremental dialysis treatment strategies. Then, Locatelli et al. bring us their

experience from Italy in discussing the role of nutrition and, specifically, a low protein diet in preserving RKF in incident ESRD patients transitioning to incremental dialysis as well as the key factors for successful implementation of this program in their patient population.

Chin et al. then bring us a practical approach to adequacy assessments for incremental dialysis that includes RKF. This approach allows us to provide customized individual patient care. Tangvoraphonkchai and Davenport then bring us the European perspective on incremental dialysis and its clinical benefits, considerations and current practice implementation. Lastly, Shafi et al. describe the lessons they learned in their studies on incremental dialysis and RKF by their application in home hemodialysis and personalized dialysis care.

We would like to thank our invited authors, who include some world's most renowned experts and opinion leaders in the field, for their important contributions to this novel and fast emerging area. We believe that the readers of this issue will gain much knowledge on the critical roles of RKF and potential impact of incremental dialysis on the health care system and patient quality of life. It is likely that with these and other contributions, incremental dialysis will become the standard of care in the coming years and that preservation of RKF will become a high priority goal that will be linked to quality of care incentives. We look forward to exciting future of personalized dialysis.

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