Editorial Reviews

When to initiate dialysis—is an early start always better?

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Abstract

The question when to initiate dialysis is attracting increasing attention. In recent years, there has been a tendency to initiate dialysis earlier in terms of estimated glomerular filtration rate (eGFR) in an attempt to achieve better patient outcomes. However, several observational studies and one randomized controlled trial have found no benefit for early dialysis initiation. On the contrary, they have found that starting dialysis with a higher eGFR is associated with increased mortality. These studies need to be carefully interpreted in light of their reliance on eGFR to estimate kidney function at dialysis initiation. The decision to start dialysis should not be based solely on a predefined eGFR value, but more importantly on a careful clinical assessment of the individual patient.

Keywords: dialysis; eGFR; survival

Introduction

In the 1960s and 1970s, dialysis facilities were limited and treatment was started late in patients with symptomatic uremia. With increasing availability and technical improvements, the aim of therapy gradually shifted from merely prolonging patients’ lives until transplantation was possible to achieving the best possible outcome in terms of survival and quality of life. As utilization has expanded with inclusion of older patients with significant comorbidities, this aim has become more difficult to achieve, and the resultant mortality on dialysis, although improving, has remained disappointingly high. The importance of predialysis care has been recognized, and early referral to a nephrologist and a specialist care team has been linked to better patient outcomes [1,2]. This approach enables not only superior outcomes of conservative treatment of chronic renal failure, with wide employment of antihypertensive medications, phosphate binders and erythropoiesis stimulating agents, but also allows predialysis education to facilitate the patients’ role in dialysis modality selection and timely access creation [3,4]. There has also been a tendency both in Europe and the US to initiate dialysis earlier, in some cases well before the symptoms of uremia develop [5,6]. Although this approach has been driven by the expectation of achieving better patient survival, scientific evidence supporting it is limited [7]. Additionally, with the increasing cost of renal replacement therapy, the question of when to initiate dialysis has important financial implications for health care providers [8].

Current trends in starting dialysis

Despite the lack of randomized controlled trials, several guidelines on the timing of dialysis initiation have been published. Firstly in the series was the National Kidney Foundation-Disease Outcomes Quality Initiative (NKF-DOQI) guidelines based predominantly on the Canada-USA (CANUSA) study, which suggested a survival benefit in incident peritoneal dialysis patients with combined peritoneal and renal weekly Kt/V over 2.0 [9]. In accordance with the results of this study, it was recommended that dialysis should be initiated before renal Kt/V falls below this limit, unless normalized protein nitrogen appearance was >0.8 g/kg and patient had stable weight and good appetite. Although direct conversion is not possible, it is estimated that Kt/V of 2.0 is equivalent to a creatinine clearance of ~10 to 14 mL/min/1.73m². In 2006, these guidelines were revised and it was stated that ‘at chronic kidney disease Stage 5, when the estimated glomerular filtration rate (eGFR) is <15 mL/min/1.73m², nephrologists should evaluate the benefits, risks and disadvantages of beginning renal replacement therapy’ [10]. In agreement with this, guidelines of the Canadian Society of Nephrology did not set any strict threshold value of eGFR to initiate dialysis and suggested that patients with eGFR <20 mL/min/1.73m² may require dialysis when symptoms of uremia or deteriorating nutritional status are present [11]. Importantly, the European Best Practice Guidelines, published in 2005, recommended that when estimation of kidney function was needed to guide initiation of dialysis, GFR should be...
evaluated from the mean of urea and creatinine clearance performed by urine collection (measured creatinine clearance). It was advocated that patients with GFR <15 mL/min/1.73m² should be evaluated monthly, and at this point, dialysis access should be planned. To prevent an overdue start, a threshold GFR level of 6 mL/min/1.73m² for initiating dialysis was recommended. However, to achieve this goal, it was suggested that initiation of dialysis should be strongly considered when the GFR level fell to 8–10 mL/min.

It is difficult to assess whether these recommendations had a significant impact on the observed tendency to initiate dialysis earlier. Nevertheless, early initiation has been observed both in Europe and in the US. According to the United States Renal Data System, in 1996, 15% of patients started dialysis with eGFR 10–14.9 mL/min/1.73m² and only 4% with eGFR >15 mL/min/1.73m², while a decade later, these percentages had more than doubled (30 and 15%, respectively). This phenomenon is more prominent in the elderly dialysis population [5]. In Europe, the average eGFR at dialysis initiation rose from 7.9 to 8.6 mL/min/1.73m² between 1999 and 2003 [6]. Our own data from the 2.2 million population of the Pomerania Region in Poland indicate a similar trend (Figure 1). Potential reasons for the observed earlier dialysis commencement remain speculative. It cannot be excluded that, at least in some registries, this trend may be due to the increasing number of diabetics and the elderly, although this may not be the case in the US, where the percentage of these populations in recent years has been relatively stable. The financial incentive for doctors or health care providers does not seem to be a major factor as the trend is observed in countries where dialysis is run predominantly on a nonprofit basis. Another possible explanation is a heavier reliance of the nephrologists on eGFR values with a reduced emphasis on the clinical condition. The conservative management of clinical problems related to advanced renal failure, like fluid overload, anemia or electrolyte disturbances may pose more difficulty and require more intensive and frequent individualized adjustment in an outpatient setting where monitoring may not be available, in comparison to dialysis therapy. In facilities that lack dedicated predialysis care programs, physicians may insist on early dialysis initiation where care is structured and patients are seen frequently and as a consequence regarded as more ‘safe’ in comparison to less closely supervised medical management.

**Effect on survival**

Does the practice of earlier dialysis initiation have an impact on patient outcomes? This question should be answered with evidence in regard to patient survival, functional status and quality of life. Importantly, if patient survival is assessed, lead time bias needs to be taken into consideration. Lead time bias is related to the time of treatment initiation in the natural history of the disease. In general, the earlier the disease is diagnosed and treated, the longer the survival may be expected, irrespective of the treatment employed. Thus, it is important to estimate survival from a defined point in the disease progression (renal function) and not just from the time when certain therapy is commenced. Unfortunately, most renal replacement studies are observational in nature and survival is usually assessed from the time of initiation of dialysis not accounting for lead time bias. In the Netherlands Cooperative Study Adequacy of Dialysis (NECOSAD) cohort, survival on dialysis of the patients started in a timely fashion (i.e. dialysis initiated according to the first K-DOQI guidelines) versus late starters was insignificantly longer with an estimated survival benefit of 2.5 months. However, it was estimated that the average delay in dialysis initiation in the late start group was at least 4.1 months [7]. Thus, the gain in survival on dialysis related to earlier initiation was more than counterbalanced by the survival time before dialysis initiation in the late starting patients. The importance of lead time bias in dialysis was demonstrated directly in the study by Traynor et al. [13] where survival of patients starting dialysis early or late was measured retrospectively from the time of dialysis initiation and also from the time point when the eGFR of these patients was 20 mL/min/1.73m². It has been elegantly demonstrated that while survival measured from the start of dialysis was better in patients who had started earlier, there was no evidence of a survival benefit for earlier dialysis initiation when patients were assessed from the same timepoint of equivalent renal function. Furthermore, it could be assumed that the time gained from the judicious delay of renal replacement therapy might offer the patient better quality of life, as it is free from the burdens of chronic dialysis.

A number of studies have compared patient survival with respect to the timing of dialysis initiation. In over 300,000 US incident patients commencing dialysis in 1996–1999, a higher eGFR at the start of dialysis was linked to increased risk of death, both in high- and low-risk populations [14]. In a more recent paper, these observations were confirmed in a database of >800,000 patients observed for over 10 years [15]. Four other observational studies have been published linking kidney function at initiation of dialysis to survival in large cohorts of European, Canadian and Asian patients [6,16–18]. These studies also found that starting dialysis with low eGFR (late start) was associated with improved survival. Importantly, in a study from Taiwan comprising of >23,000 incident patients, the average eGFR at dialysis initiation was much lower than in European and US patients (4.7 mL/min/1.73m²). Nevertheless, the quintile which started dialysis at the lowest eGFR value (<3.23 mL/min/1.73m²) still had the best survival [6,16–18].

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**Fig. 1.** Estimated GFR (MDRD4) in patients starting dialysis in Pomerania Region in Poland.
In all these studies, the four variable Modification of Diet in Renal Disease (MDRD) equation was used to estimate the kidney function. This equation may not be precise in advanced renal failure, when dialysis initiation is considered. Although it is well validated in moderate and severe impairment of kidney function, in end-stage renal disease, the serum creatinine concentration is relatively more influenced by the muscle mass thus diminishing the reliability of the MDRD equation. It should be noted that in the original MDRD publication, the two regression curves for black and white patients became more divergent at low eGFR. Importantly, the main reason for different GFR MDRD estimation formulae was the racial difference in relative muscle mass [19]. The MDRD formula does not include any anthropometric measurement which might be used as a surrogate measure of nutrition or muscle mass. In this respect, previous studies have linked survival in incident peritoneal dialysis patients to 24-hour urinary creatinine, used as a crude measure of muscle mass [20] and our own study found an association between survival and peritoneal creatinine excretion in anuric female patients [21]. Thus, solely due to the use of MDRD equation for eGFR estimation, malnourished fragile patients with low muscle mass with or without obvious comorbidities and with potential low survival may start dialysis with a high eGFR due to low creatinine appearance. On the other hand, ‘healthy’ well-nourished patients with high muscle mass will have a higher serum creatinine and lower eGFR but a relatively low mortality risk. In the recent NE COSAD incident cohort, MDRD estimation of GFR was compared to GFR measurement based on the creatinine and blood urea nitrogen clearance studies [22]. Importantly, the averages of these estimates did not differ significantly. However, while MDRD eGFR at dialysis start stratified patients with respect to their survival, as was demonstrated in previous studies, this effect was lost when GFR was measured by clearance studies.

Almost all of these studies were retrospective and observational in design [6,14–18]. Irrespective of the method of estimation of renal function, most patients start dialysis because of clinical indications not just because they have reached a given eGFR value. Thus, studies are confounded by the fact that patients in a compromised clinical condition with comorbidities have, as a consequence, lower potential survival and tend to start dialysis earlier, with an apparent relatively higher GFR. Age and clinical condition strongly determine the decision to start dialysis treatment as is illustrated (and, at least in part, may be corrected for in the multivariate analysis) by the increasing prevalence of comorbid conditions in subgroups of patients with rising eGFR at the start of dialysis in the reported studies. In all studies, correction for these factors weakens the association between timing of dialysis initiation and survival. Nevertheless, even after adjustments for the recorded demographic factors and comorbidities, the association between eGFR at dialysis initiation and survival remains significant.

In the light of these unexpected findings, should we ask the question, whether early dialysis initiation could be harmful and what are the possible mechanisms through which that might occur?

One of the reasons for the potential increased mortality on dialysis may be complications directly related to the dialysis therapy. Nowadays, hemodialysis appears to be a very safe procedure and potentially fatal complications like air embolism or massive hemolysis are very rare. Infectious complication, however, seems to be an important source of morbidity and mortality. Septicemia rates related to vascular access are rising, especially in the older population, where central catheters are used increasingly. This issue seems to be most alarming in the US, where ∼80% of patients start hemodialysis with the use of central catheters [15,23]. Other potential sources of morbidity and mortality are hypertensive episodes during hemodialysis, especially in patients subjected to rapid ultrafiltration, with potential cardiac and neurologic complications. It could be argued that rapid deterioration of residual renal function related to the initiation of hemodialysis may be responsible for the observed excess mortality in the patients starting dialysis early [24,25]. It could be assumed that, due to slower loss of renal residual function and lower incidence of infectious complications [26], the effect of initiating dialysis early may be different in peritoneal dialysis patients. However, recently published data does not support this hypothesis. In this respect, in the study of Wright et al. [15], in the subcohort of over 63,000 patients treated by peritoneal dialysis, starting dialysis at higher eGFR had a similar deleterious effect on survival as in hemodialysis patients.

A recently published study of initiation of dialysis in elderly nursing home residents has linked initiation of dialysis not only accelerated mortality but also to rapid deterioration of the functional status of the patients [27]. As a result, >70% of the patients have and only ∼15% maintained functional status after a year from dialysis initiation. In this study, the causal relationship between starting dialysis and deteriorating functional status or mortality has not been proven, but the time coincidence makes it a likely possibility.

All cited studies linking survival to kidney function at dialysis initiation present very similar data, where earlier dialysis initiation is related to increased mortality. However, they are all observational in design and thus subject to many biases, most importantly to lead time bias and confounding by unreported selection bias due to the fact that clinical condition influence the decision to start dialysis. This problem could only be resolved by a randomized controlled trial, where patients are randomized to start dialysis at different GFR values. The IDEAL (Initiating Dialysis Early and Late) study, a randomized controlled trial, was started in Australia and New Zealand in 2000 in an attempt to overcome the shortcomings of observational studies. Over 800 patients were randomized to start dialysis at eGFR 10–14 or 5–7 mL/min/1.73m² (as estimated by the Cockcroft–Gault formula) and followed for >3.5 years. Its results have recently been published [28]. Importantly, there was no difference in patient survival between early- and late-start groups. However, as many as 76% of patients in the ‘late start’ group did not reach the target GFR and started dialysis earlier by the decision of the caring physicians. As a result, the mean difference in eGFR at dialysis initiation was only
2.2 mL/min/1.73m² (9.2 versus 7.0 mL/min/1.73m² by the MDRD equation) and, on average, dialysis was postponed by 5.6 months in the late-start group. It is worth noting that the eGFR values at dialysis initiation, even in the ‘late start’ group, were similar to that reported in the observational studies from the US and Europe [6,17,29]. Despite these shortcomings, the IDEAL trial has clearly shown that early initiation of dialysis in patients with Stage 5 chronic kidney disease is not associated with an improvement in survival.

Conclusions

The evidence presented does not support the current practice of earlier dialysis initiation based on eGFR and contradicts its potential role in achieving better patient outcomes. In analyzing the evidence, it would appear that the decision to initiate dialysis should be based on the clinical judgment of the nephrologist with the assent of the patient and takes into consideration not only the measured kidney function but primarily the patient well-being, nutritional status, signs of fluid overload and metabolic disturbances related to uremia. Structured specialist predialysis programs encompassing both patient education and meticulous clinical care may be a valuable alternative to the early initiation of dialysis therapy. These programs may be especially important in elderly populations where, on average, progression of chronic kidney disease is slower than in younger patients [30]. As this population seems to be especially vulnerable to the untoward effects of dialysis, cautious delay and continuation of scrupulous outpatient medical care may be beneficial in terms of survival, quality of life and cost of therapy. As far as estimation of kidney function is concerned in the context of dialysis initiation, we would like to point out that although MDRD GFR estimation is very easy to perform, both DOQI [9] and European Best Practice Guidelines [12] recommend the use of urine collection to measure renal function. The decision to initiate dialysis should be based on the clinical assessment of the individual patient, with estimation of kidney function relegated to a secondary role.

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Kidney paired donation

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Abstract

Kidney paired donation (KPD) was first suggested in 1986, but it was not until 2000 when the first paired donation transplant was performed in the USA. In the past decade, KPD has become the fastest growing source of transplantable kidneys, overcoming the barrier faced by living donors deemed incompatible with their intended recipients. This review provides a basic overview of the concepts and challenges faced by KPD as we prepare for a national pilot program with the United Network for Organ Sharing. Several different algorithms have been creatively implemented in the USA and elsewhere to transplant paired donors, each method uniquely contributing to the success of KPD. As the paired donor pool grows, the problem of determining allocation strategies that maximize equity and utility will become increasingly important as the transplant community seeks to balance quality and quantity in choosing the best matches. Financing for paired donation is a major issue, as philanthropy alone cannot support the emerging national system. We also discuss the advent of altruistic or non-directed donors in KPD, and the important role of chains in addition to exchanges. This review is designed to provide insight into the challenges that face the emerging national KPD system in the USA, now 5 years into its development.

Keywords: allocation; incompatible kidney transplantation; paired kidney exchange; transplantation policy; transplant finances

Introduction

Kidney transplantation has been established as the best treatment for patients suffering from end stage renal disease (ESRD). Patients fortunate enough to receive a kidney transplant, on average, live 10 years longer than those who remain on dialysis [1], and it is now clear that a living donor kidney transplant is better than a kidney from a deceased donor. The average deceased donor kidney transplant will function for 8.6 years, while a living donor kidney provides an average of >16 years of dialysis-free survival [2]. Sadly, the demand for a kidney transplant far exceeds the supply that can be met by deceased donors, so much so that roughly 19 patients die each day in the USA, while waiting for a kidney donation [3]. Unfortunately, all too often, a willing living donor is deemed incompatible due to blood type or unacceptable donor-specific antibodies. Kidney paired donation (KPD) provides a solution to this dilemma by pairing two incompatible pairs together to facilitate an exchange between the willing donors’ kidneys. KPD was first suggested by Felix Rapaport in 1986 [4] (See Figure 1) and in 1991, the first kidney exchange was performed in South Korea [5]. Several years later, in 1999, the first paired exchange in Europe took place at University Hospital in Basel, Switzerland [6]. The next year, the first KPD transplants were performed in the USA in 2000, first in New England then followed by the Johns Hopkins team [Ratner L. (personal communication)] [7]. KPD has grown rapidly since then, utilizing advanced matching algorithms that identify both simple exchanges and more complex chains of transplants to increase the number of transplants achieved. As of the third quarter of 2010, >1000 KPD transplants have been performed in the USA (see Figure 2) [3].

There are still many obstacles in most countries, including the USA, preventing widespread and national implementation. The Netherlands, however, set a precedent in 2004 by successfully launching the first national KPD program in the world [8]. New approaches incorporating