Factors influencing dialysis outcome: the dialysis dose in perspective

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Introduction

The nature of renal replacement therapy (RRT), the term applied to dialysis and transplantation, has changed dramatically in the past decade. The number of units offering RRT has multiplied in all European countries and beyond. These serve areas in which there may earlier have been little or no opportunity to treat patients in renal failure. At the same time, the stock of patients on RRT has altered in composition as older and more clinically compromised subjects have entered the treatment programmes.

None of these changes is uniform, and from country to country, or even within a given country, the delivery of RRT differs. So even though there have been, overall, improvements in service delivery with concomitant benefits for survival, it is hardly surprising to find that the survival characteristics of the RRT population are themselves not uniform, but the reasons for this are complex. Despite the intense interest in the challenge of improving survival on dialysis, it has remained difficult to explain why the results are better in some centres and regions than in others. This report addresses salient issues.

General considerations

It might be expected that the survival of a given patient group would have improved over the years. This is the case, for example, for patients with autosomal dominant polycystic kidney disease (ADPKD). Many are transplanted and, when the data for the years 1979–1982 and 1989–1992 are compared, patients with ADPKD or with ‘standard’ primary renal diseases have clearly better survival in the later cohort.

These data illustrate one of the less easily quantifiable parameters in comparing survival on RRT between different centres. The selection procedure for transplantation favours those patients in whom comorbidity, if present, is not such as to compromise survival, so the survival of patients who are transplanted may be better than that of patients who remain on dialysis. In a centre or country in which there is a vigorous transplantation programme, ‘dialysis alone’ survival is not strictly comparable with that obtained if there is little or no transplantation.

A point at once obvious and too little addressed in the literature is the glomerular filtration rate (GFR) at which dialysis is commenced. In countries or regions where facilities are scarce or where the referral to nephrologists is very late in the course of end-stage renal failure (ESRF), this is often at the terminal stage. Elsewhere, there may be considerable renal function and the patient is relatively well clinically and reasonably nourished. Outcome findings are not readily comparable in such circumstances. Furthermore, the management of late presenting, ill and malnourished patients in terms of the ‘dose’ of dialysis needed and the medical problems which must be defined and dealt with is quite different from that of better analysed patients who enter RRT before terminal renal failure has occurred.

Clearly, such considerations may account in part for discrepancies in the survival on dialysis of patients in different centres. When any attempt is made to study the influence of a given factor on survival, it becomes obvious that even more qualifications apply.

Underdialysis and its consequences

Over the past two decades, nowhere was the development of new facilities more striking than in the US. There, the number of patients on RRT has increased dramatically, as has the number of dialysis facilities recorded in the US renal data systems. Reports in the early 1990s indicated that the management of RRT in these emergent centres did indeed differ, and that the survival of patients from centre to centre was not uniform. Furthermore, it became clear that although the number of patients accepted for treatment was so substantial, the increase in workload may not have been accompanied by sufficient attention to the amount of haemodialysis (HD) given.

It became evident that patients in the US who regularly received HD at a dose which did not clear 50% of the body urea load \( \frac{Kt}{V} \) for urea of 0.8–1.0,
adjusted urea removal rate (URR) of 45% or less] effectively remained uraemic and had high mortality. For example, the National Co-operative Dialysis Study (NCDS), [1,2] established that many patients were receiving only 9 h HD weekly, and so were ‘underdialysed’ by these criteria, with an adjusted URR of <45%, or a KT/V of no more than 1. Mortality was strikingly increased in these patients. Lowrie et al. [3,4] and others essentially confirmed these findings. Furthermore, Hakim [5] demonstrated a reduction in mortality from 22.8 to 9.1% following an increase in KT/V from 0.82 to 1.18.

Given that the need to account for body habitus and protein intake in any formula for determining the ‘adequacy’ of HD in this way has been assimilated gradually in subsequent studies, there seems little doubt that this broad concept is valid.

One of the most damaging consequences of uncontrolled, terminal uraemia is the excess saline retained. This aggravates hypertension and increases the left ventricular load. Since in such patients, the anaemia will also be uncorrected, it is unsurprising that recorded mortality from cardiac causes is high in the first year of RRT.

One of the consequences of too little regular HD is that the saline overload is insufficiently corrected. Left ventricular load is greater than necessary and there is hypertension. This is likely to have contributed to the poor survival noted for such patients in the NCDS study, but must remain inferential in the absence of definitive data on the achievement of ‘dry body weight’ and of the precise causes of death in the differently dialysed patients. ‘Dry body weight’ has been surprisingly difficult to define. Zucchelli and colleagues [6] argue persuasively that the attainment of ‘dry body weight’, a prerequisite for salt and water control and so for minimizing the load imposed on the heart by excess volume, is not achieved as often as it could be. They have examined various technical and laboratory methods for assessing it, but believe that these are not in themselves accurate enough to be relied on alone. They stress the need for careful attention to clinical parameters and perhaps the use of a scoring system.

Even in units in which there has been a particular interest in hypertension in dialysis patients, 15–25% of patients need hypotensive drugs, and this may rise to 50% in other units. The higher figures suggest that there has been inadequate salt and water removal during HD and that patients have not controlled their intake sufficiently between dialysis sessions. The fact that, even when this has apparently been achieved, hypotensive drugs may be needed in a quarter of patients, while in Tassin (see below) they are hardly employed raises the possibility that longer hours on dialysis may confer an as yet undefined advantage.

Certainly, the Tassin patients achieved adequate fluid and solute removal by virtue of the long time available for this in each dialysis session, but it is accepted that this can be achieved in a shorter time and is not in itself a reason for advocating sessions of 8 h three times weekly. Thus, further evidence is needed before one can be sure that short dialysis regimes are intrinsically linked to (higher blood pressures and so to) potentially shortened survival. Indeed, in Parma, Cambi (personal communication) has obtained survival similar to that reported by the Tassin group using 12 h HD weekly.

Dialyser membranes and sterilization techniques

Since it is important that the dialysis filter is efficient and does not cause untoward reactions, and that HD fulfils its intended purpose, the influence on survival of the size and composition of dialysis filters, of the regime employed to sterilize reused dialysers and of the length of dialysis sessions have been studied. There is little doubt that leucocytes and platelets adhere to the older, cellulose-based membranes and that as a result there is cytokine release, with activation of the platelet cascade. Membranes made of non-cellulose materials, which do not interact with blood products (‘biocompatible’ membranes), are less likely to induce these effects. These may not be as important clinically as was thought initially. For example, in a recent study [7], there was no difference in terms of morbidity or mortality over a 5 year study in patients being dialysed using cellulose or using ‘biocompatible’ membranes.

With regard to the size of the filters and the length per se of each dialysis session, Held et al. [8] concluded that the better survival on HD in Europe was associated with the use of larger dialysers (20% greater surface area) and 23.5% longer dialysis sessions. Charra et al. from Tassin [9] demonstrated that long HD of some 24 h weekly using the ‘old fashioned’ Kiil dialyser was associated with prolonged survival, only 1.6% of their initially 445 patients were on antihypertensive drugs, the haemoglobin was maintained without erythropoietin and by surrogate analysis (albumin and cholesterol levels) patients were adequately nourished.

At present, the type of sterilization regime used in a dialysis reuse system has not been shown convincingly to be a factor in survival on dialysis, as it has proved difficult to separate such an individual influence from the multitude of variables which affect patients on RRT [10].


Is the concept of optimal dialysis achievable?

The reasons for the higher mortality when the Kt/V or an equivalent measure is low, are not clear-cut. Certainly, underdialysis results in residual uraemic features such as anorexia and metabolically compromised anabolism, and is often accompanied by inadequate fluid removal. While these and their surrogates of plasma albumin, serum creatinine and fluid overload are linked statistically to increased mortality on dialysis [3], taken in isolation, these are not convincing as being the reasons for such striking mortality, which is
from many causes. This is important, since the next step after awareness of the overall consequences of underdialysis is to examine what level of dialysis is optimal.

Owen *et al.* [2], in a retrospective analysis of 13 473 patients on HD have suggested that a URR of 65–70% (Kt/V of 1.3–1.6) was associated with a significantly lower risk of death. This might lead to the view that at least this amount of dialysis should be delivered, but is not a general conclusion. For example, Collins *et al.* [11] suggested that only in patients with diabetes or other co-morbidity does a Kt/V of >1.0 reduce mortality. They found no such effect in non-diabetic ‘no-risk’ patients.

While it is possible to adjust the dose of HD to take account of body habitus, it remains uncertain whether or not this will be possible in continuous ambulatory peritoneal dialysis (CAPD). Absolute values for Kt/V between HD and CAPD are not directly comparable, because of the differences between continuous and intermittent removal in terms of the prevailing extracellular concentration of ‘uraemic’ solutes. It has been suggested that a weekly dose of CAPD of Kt/V of 1.7–2.0 is needed to equate to that achieved in Groups I and III of the NCDS [12]. This may not be possible in men of >70 kg who no longer have any residual renal function.

Indeed, the relationship between solute clearance and survival has been unclear. In the CANUSA study [13], in which, in contrast to smaller studies, there were sufficient and prospective data to make possible a proportionate hazard approach to address the variables monitored, there was a relationship between the weekly Kt/V and death; this increased by 6% for each 0.1 fall in Kt/V.

Renal solute clearance in the months or years before it is lost may exert a greater impact on survival than dialysis dose in CAPD patients. Initially, patients entering CAPD retain their residual function to a greater degree than do patients entering HD [14]. The CANUSA study demonstrated that the progressive loss of residual renal function is key to the longitudinal change in total clearance achieved on CAPD, and so underlines this inherent limitation of the technique. Over the medium term, an ‘adequate’ target Kt/V may not be achievable in the absence of residual renal function. The CANUSA study underlines this limitation of CAPD in that, over the medium term, an ‘adequate’ target Kt/V may not be achievable in the absence of residual renal function.

The study did not define a causal link between solute clearance and mortality because its design did not include randomization to different dialysis doses at onset or during follow-up. Frail patients deemed likely to do badly may have been prescribed less dialysis exchanges or volumes out of consideration for their quality of life.

**Haemodialysis, CAPD and nutrition**

Despite significant amelioration of uraemia by dialysis, protein/calorie malnutrition continues to be reported [15] in 18–56% of CAPD patients and 23–76% of maintenance HD patients. While there is a broad consensus that the presence of malnutrition exerts a substantial impact on dialysis-associated mortality [16], it remains difficult to pinpoint how this operates. The nutritional surrogates cited as evidence for the relationship between malnutrition and mortality are not precise, and prospective studies are scarce and small.

Serum albumin is not a particularly sensitive nutritional index. A low serum albumin is a late manifestation of malnutrition since it takes months of malnutrition to override the large hepatic capacity to synthesize it as a physiological priority [17]. Albumin also exhibits poor and often contradictory correlations with other nutritional markers, especially muscle mass and dietary protein intake [18], and its plasma concentration is influenced both by the extracellular fluid volume and by its distribution between extravascular and intravascular compartments.

The normalized protein catabolic rate (nPCR) is used as a measure of nutrition. The NCDS study found that a low nPCR was strongly associated with the probability of treatment failure [19]. In another study, it was reported that patients with an nPCR <0.65 g/kg/day had a substantially higher mortality rate than those patients with an nPCR of 1.2 g/kg/day [20].

Certainly, both serum albumin and the nPCR are low in those patients who are seriously malnourished and who ‘require’ protection of their depleted protein stores. It must be emphasized that both are late markers of malnutrition. It is hardly surprising that studies which have used these parameters have reported that dialysis patients who have a low serum albumin level and/or a low nPCR are at risk. Indeed, it may be said that the clinician who examines his patient should not need to look at such markers to know that the patient is malnourished and should have taken steps to ensure good nutrition well before such abnormalities supervened.

It has become obvious that such clinical assessment, especially of centre HD patients, has been deficient. Judged, for example, by the findings of Lowrie and Lew, who, in a study of >12 000 HD patients, found that the mortality rate was five times greater for those with serum albumin between 30 and 35 as compared with those with serum albumin levels between 40 and 45 g/l [3], avoidable and potentially fatal malnutrition has occurred frequently.

Similar findings have been observed in CAPD patients in whom both initial and average albumin levels over the period of observation appear to predict subsequent mortality [21,22]. In a recent study of 680 CAPD patients, a 1 g/l lower serum albumin was associated with a 6% increase in the relative risk of death [23].

A relationship between nPCR and mortality has not been demonstrated convincingly in CAPD patients [24]. Furthermore, it has been shown that the nPCR is a questionable nutritional surrogate in CAPD as a...
reciprocal correlation exists between the nPCR and established measures of body composition [25].

Whilst not denying the evidence linking a low serum albumin with an increased risk of mortality, one must question whether this relationship demonstrates a link between nutrition and mortality. Studies have shown that serum albumin only predicts mortality when considered independently of existing co-morbid conditions [11,26]. Such data suggest that serum albumin may simply be a marker of the malign effects of co-existing illness both on nutritional state and on survival.

Although nutritional state has been linked to survival in dialysis patients, no study to date has adequately determined whether this is a causal relationship.

A large number of dialysis patients have additional medical illnesses which, as in the case of cardiovascular and peripheral vascular disease, have been linked specifically to malnutrition and death [27]. Such co-existing disease may itself result in impaired nutrition and survival, with death occurring in the context of, but not as a consequence of, malnutrition.

**Towards optimal renal replacement therapy; the role of co-morbidity**

However, when the question is modified, and one attempts to determine how best to restore the patient to optimal health, quite different considerations arise. In patients in ESRF, artificially removing sufficient solute waste to restore appetite and alertness and enough fluid to maintain a ‘dryish’ body weight, together with correction of renal hormone deficiencies, is essentially different from restoring normal health in both objective and subjective terms. This remains the true aim of the treatment; it cannot be achieved by ‘adequate’ dialysis alone. While there are many variables to consider, age, the cause of renal failure, the mental and physical preparedness of the patient for RRT and co-morbidity are dominant in determining outcome.

The clinical state in which the patient enters and then is maintained on RRT is a major determinant of outcome. If renal failure is caused by a systemic condition which involves other major organ systems, such as diabetes mellitus or atheromatous disease, it is the damage caused by the underlying disease which is the dominant influence on survival.

At all ages, assessment shows that patients with ADPKD, essentially an isolated renal disease, have the benchmark prognosis. Because diabetes is such a common cause of ESRF, the morbidity associated with it has a bearing on the whole RRT programme. However measured, the message is the same. Patients with diabetes on RRT do less well and live for a shorter time. Both hazard rates and the relative risk [28,29] of death in patients with diabetes are about three times higher compared with glomerulonephritis and polycystic disease as causes of ESRF. Wood *et al.* [30] have demonstrated that for the British population, which is likely to be representative in this respect, EDTA registry data show that having diabetes is equivalent to adding at least a decade to the chronological age of the patient on RRT. Data from the US also show the detrimental effect of diabetes. In the study of Byrne *et al.* [31], only 18.1% of diabetic patients who were 55–64 years of age at the start of treatment were alive after 5 years.

Atheromatous renovascular disease is an increasingly recognized, if not always precisely documented, cause of ESRF in the elderly [32]. Occurring as part of generalized atheroma, it invariably is associated with vascular disease elsewhere, and the death rate from cardiovascular causes is high and inevitable. For the small percentage of patients on RRT as a result of aggressive glomerulonephritis or of vasculitis, there appears to be little risk of the underlying disease progressing systematically and causing death.

Although the condition causing ESRF may also determine the outcome on RRT, co-morbid illness, broadly defined as concomitant vascular (cardiac, cerebral, peripheral [33], disabling respiratory or active hepatic) disease, is frequently the determining factor. It would be prudent to include also disabling psychosocial problems, but these have been assessed systematically in only a few studies.

Co-morbidity is common in ESRF. In a survey of the RRT population of Australia and New Zealand, it was found that overall <30% of patients were free of any co-morbid condition if diabetes was included either as a cause of ESRF or as an associated illness. Even in the non-diabetic patients aged 55–74, coronary artery disease was reported in 47% and peripheral vascular disease in 25%.

In a recent analysis of 115 consecutive patients accepted for HD, Patel and the author [35] found that 58% of the study population had at least two co-morbid conditions. This was skewed to the older age group and was found in 90% of patients over 65 compared with only 30% of patients under 35. In all groups, cardiovascular disease predominated. Patients who died had the highest number and greatest severity of medical conditions.

Recent studies [36,37, D. Eadington, personal communication] have documented how, provided that co-morbidity is taken account of when RRT is contemplated, properly selected patients even at advanced age can survive and benefit. Patients up to the eighth decade who are free of significant co-morbidity have survival rates on RRT which compare with those of a patient aged 40 with insulin-dependent diabetes mellitus (IDDM) and ischaemic heart disease. In a Portuguese study of 50 patients entering RRT aged >80, there was cardiovascular disease in 74%, and <29% were free of any co-morbid factors. Nevertheless, 48% were alive after 3 years [38].

Great caution is needed in weighting the presence of co-morbid factors; in the study quoted above, an increasing number and severity of co-morbid conditions was found to be an important determinant of the objective quality of life indicators (physical functioning
and mobility) but did not affect subjective indicators of quality of life (emotional and social well being). Cambi and the author have piloted a study in Northern Italy in which the importance of clinical, nutritional and metabolic patient management might be assessed in relation to ‘adequate’ dialysis. The weekly hours of dialysis and type of dialyser membrane are controlled for. Certainly, professionally encouraged attention to the diet and to the individualized management of cardiovascular and metabolic complications must contribute to the perceived benefit of treatment and may also prove to have an objectively measurable benefit.

Quality of life as an outcome measure

In any case, for the patient, it is the quality of life that RRT makes possible that is the central consideration. Thus, for a patient, ‘adequate’ treatment may be perceived more as the confidence the patient has that the treatment will reliably maintain well being and independence than as survival alone. Patel and the author [35] showed recently that, despite having a higher co-morbidity score, older patients (particularly those >65) did significantly better on the emotional and social subscales of the instruments used [Nottingham Health Profile (NHP) and SF36] and perceived fewer aspects of dialysis therapy as stressful. No significant associations were found between the quality of life parameters and the medical indicators of outcome.

The management of the complications of renal failure and of coincident (co-morbid) illness, whether physical, psychosocial or a combination of both, plus the provision of adequate nutrition and a stable home environment, all contribute to the well being of the patient and, as is increasingly recognized, to survival itself.

Neither a strictly biochemical approach to the provision of dialysis, nor consideration of the age of a patient, nor of the primary renal disease, nor even of patients.

References

34. Disney APS. *Australia and New Zealand Dialysis and Transplant Report Registry*, 1995. p. 135