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The first year on haemodialysis: a critical transition

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Abstract

The first year following the start of haemodialysis (HD) is associated with increased mortality, especially during the first 90–120 days after the start of dialysis. Whereas the start of dialysis has important effects on the internal environment of the patient, there are relatively few studies assessing changes in phenotype and underlying mechanisms during the transition period following pre-dialysis to dialysis care, although more insight into these parameters is of importance in unravelling the causes of this increased early mortality. In this review, changes in cardiovascular, nutritional and inflammatory parameters during the first year of HD, as well as changes in physical and functional performance are discussed. Treatment-related factors that might contribute to these changes include vascular access and pre-dialysis care, dialysate prescription and the insufficient correction of the internal environment by current dialysis techniques. Patient-related factors include the ongoing loss of residual renal function and the progression of comorbid disease. Identifying phenotypic changes and targeting risk patterns might improve outcome during the transition period. Given the scarcity of data on this subject, more research is needed.

Keywords: arterial stiffness; fluid overload; haemodialysis; pre-dialysis; vascular calcification

Introduction

One of the most critical periods in the life of an end stage renal disease (ESRD) patient is the start of dialysis [1, 2]. During this period, the patient becomes dependent upon medical technology, which can have critical pathophysiological and psychological consequences. Although the start of haemodialysis (HD) has pronounced effects on the physiology of the patient, relatively few studies have looked into detailed phenotypic changes following the start of dialysis. It is the aim of this review, which will be limited to HD patients, to discuss the time course of various clinically relevant parameters early after start of HD, attempting to provide a better understanding of the risk associated with the early transition period following initiation of dialysis. Given their relation with outcome, the main emphasis will lie on changes in cardiovascular, nutritional and inflammatory parameters, followed by a short discussion on physical and functional performance.

Early mortality after dialysis and its predictors

Several large-scale observational studies have shown that the first months on dialysis can be considered as a critical period. Especially the first 90–120 days are associated with an increased risk of mortality [3–5]. Previous registry data from Europe and North America showed that ~35% of the mortality during the first year after start of dialysis occurred in the first 90 days [3]. In addition, despite regional differences, recent data from the Dialysis Outcomes and Practice Patterns Study (DOPPS) in 86 886 patients showed that the increased risk of death early after the start of dialysis can be considered as a global phenomenon [4].

Two large studies have looked into the detailed causes of death in the early period following the start of dialysis. In a DOPPS study in incident US patients, causes of mortality after the start of dialysis were predominantly classified as cardiovascular, followed by withdrawal, with a relatively low percentage of infection-related mortality [6]. In the European Dialysis and Transplant Association registry, the relative contribution of non-cardiovascular death to early mortality was higher, specifically infectious-related disease (14% of all deaths) [5].

Given the strong mortality risk associated with central venous catheters (CVC) in this and other studies, the relatively low contribution of infection to early death in the US DOPPS cohort appears surprising, given the large percentage of patients treated with catheters in USA [4]. However, part of this discrepancy might be explained by the observation that cardiovascular mortality was greatly increased following infection-related hospitalization in dialysis patients [7].

With regard to cardiovascular mortality, both a high incidence of cardiac as well as vascular-related mortality was observed in the early period following the start of dialysis [6]. Few studies looked into overall or specific morbidity or mortality during the transition period of starting dialysis, with inclusion of the pre-dialysis period. A recent study in elderly patients showed a high incidence of stroke following the start of dialysis with a peak in the first month of dialysis, although the incidence started to increase from 2 months before the start of dialysis [8]. The risk of stroke was increased by the presence of hypertension, atherosclerotic disease and diabetes.

Both patient- and treatment-related factors (especially the use of CVC and the quality of pre-dialysis care) are important risk factors for early mortality. Important treatment-related risk factors in the transition period include the use of CVC and the quality of pre-dialysis care [4, 9, 10]. Consistent care in the transition period [defined as visits in 3 or more of the 6 months prior to renal replacement therapy (RRT) start] was received by only a minority (29.1%) of patients in a large cohort study (12 143 patients), and even in only 38.1% of patients which were known at the outpatient nephrology clinic for more than 6 months [11]. These are important modifiable factors, as several observational studies found an increase in modality selection and timely creation of a permanent access, and even an improvement in short-term mortality by adequate pre-dialysis care and education [12]. Patient-related risk factors include age, factors related to cardiovascular disease (such as congestive heart failure) as well as to malnutrition (low serum phosphorus) and/or inflammation (decreased serum albumin) and haemoglobin [6, 13, 14]. Other studies also showed an important mortality risk associated with frailty at the start of dialysis [15]. Notably, in a recent report from Taiwan, dialysis was even associated with an increased mortality risk when compared with conservative care in patients above 70 years of age [14], although this finding, which is in contrast to previous literature [16], needs to be confirmed. Also, it is likely that many other (potentially modifiable) factors are predictive of outcome after dialysis. However, at present, there are only a limited amount of studies covering the transition period of the pre-dialysis to the dialysis period.

Cardiovascular parameters

Fluid overload

Fluid overload (FO) is an important risk factor for hypertension, left ventricular hypertrophy (LVH) and mortality in dialysis patients [17, 18]. Limited evidence is available on the changes in fluid state after the start of RRT, or regarding comparisons between incident and prevalent dialysis patients. Given the removal of salt and water by dialysis, fluid state can be expected to improve, but this effect might be offset by the continuing loss of residual renal function [19]. Most of the evidence on fluid state in chronic kidney disease (CKD) patients has been obtained using bioimpedance methodology. One observational study in 269 prevalent HD patients, using bioimpedance spectroscopy (Body Composition Monitor®) showed that ∼25% of prevalent HD patients were classified as severely overhydrated, defined as an FO relative to 15% of extracellular volume (∼2.5 L), which was an independent risk factor for mortality [18]. In a multicentre study in prevalent dialysis patients, the mean level of FO in HD patients, assessed by the same methodology, was

1.7 L [20]. A smaller study of Yilmaz *et al.* has also shown that abnormalities in indicators of FO already are observed before the start of dialysis, which appears to be related to the severity of the CKD stage [21]. This study of Yilmaz *et al.* observed a mean level of FO, assessed by the same methodology, of 3.9 L in 68 non-dialysed CKD stage 5 patients [mean estimated glomerular filtration rate (eGFR) 8.8 mL/min/1.73 m^2], when compared with 2.3 L in 62 CKD stage 3–4 (mean GFR 28.9 mL/min/1.73 m^2) [21], both higher when compared with the levels in the dialysis population studied by van Biesen *et al.* [20]. Other markers related to FO, such as N-terminal prohormone brain natriuretic peptide (NT-pro-BNP) and vena cava diameter, were higher in CKD stage 5 when compared with CKD stage 3–4 patients [17]. These findings corroborate earlier studies showing evidence of FO in patients with mild-to-moderate CKD [22, 23]. Hung *et al.* observed a high prevalence (52%) of FO (defined as FO above 1.1 L, i.e. above the 90th percentile of a matched population) in patients with stages 3–5 CKD, 52% were hypervolaemic. Strikingly, whereas FO was strongly associated with all of the components of malnutrition–inflammation–atherosclerosis syndrome, measures of kidney function (estimated GFR) and proteinuria were not [24].

However, these findings were not confirmed in a recent single-centre study in 175 patients with a mean eGFR of 15.6 mL/min/1.73 m^2, given the fact that the mean level of FO in these patients was only 0.21 L [25]. No studies directly compared FO between pre-dialysis and dialysis patients. However, in the single prospective study which has, to the best of our knowledge, been published on this subject, the extracellular water:total body water (ECW:TBW) ratio, assessed by multi-frequency bioimpedance, declined from 53 to 42%. The study cohort included 46 patients [65% HD and 35% peritoneal dialysis (PD)], no significant differences in the ECW:TBW trends were observed between PD and HD patients [26]. Regardless of the dialysis vintage, interventions based on the Body Composition Monitor aiming for normovolaemia have resulted in an improvement in blood pressure (BP) regulation, arterial stiffness, LVH and even a reduction in all-cause mortality [27, 28].

Summarizing, FO appears to be already present before the start of dialysis, at least according to several studies, and appears to increase in relation to the severity of the CKD. Scarce available data suggests that FO improves after the start of dialysis therapy. However, more detailed studies are needed to assess the determinants and effects of different treatment policies on changes in fluid state following the start of dialysis.

Hypertension

There have been few studies assessing BP trends after the start of dialysis. A single-centre study from Tassin in France in 308 incident patients showed that BP in general decreased after the start of dialysis [29]. In this cohort, mean systolic BP decreased from 142 to 131 mmHg, and mean diastolic BP from 75 to 69 mmHg in the first year of dialysis. However, this centre is unique, especially in terms of dialysis duration, and it is therefore not known to what extent these data can be extrapolated to the general dialysis population. Low BP at the start of dialysis was associated with a higher mortality, in agreement with the 'reversed epidemiology concept' which is in line with previous studies [30, 31]. However, BP at 3, 6 and 12 months was not associated with adverse outcome. In contrast, the tertile of patients which experienced the largest decline in BP during the first year on dialysis had better

outcomes when compared with the other tertiles. Thus, in combination with the excellent survival reported in this centre, the decline in BP after the start of dialysis was interpreted as beneficial [29].

In contrast, a study comprising 3446 incident dialysis patients of a US provider [32] showed an initial decrease in systolic BP within the first week after the start of dialysis, followed by a steady increase and a plateau phase after 12 weeks. No major differences in mean pre-dialytic systolic BP levels in the overall cohort were observed between the start of dialysis and a 1-year follow-up period [32]. Also in this study, low pre-dialytic BP (defined as systolic BP <120 mmHg) at the start of dialysis was associated with increased early (6–12 weeks) mortality. In addition, the authors identified different BP slopes. Intriguingly, in contrast to the Tassin study, patients with a declining BP during the first year of dialysis had higher mortality when comparing with an increasing BP slope during dialysis. As will be discussed later, body weight initially declined in the first 12 weeks of dialysis, followed by an increase during the remainder of the first year period. Although data on treatment policies in the study by Sipahioglu *et al.* are not available, the differences between both studies might among others be due to differences in dialysis prescription (minimum 5 h in Tassin; dialysate sodium 138 mmol/L), diet (strict sodium restriction in Tassin) and case-mix. Whereas an improvement in BP control achieved by gradual reduction in dry weight and a salt-restricted diet may be beneficial, a decline in systolic BP due to deterioration in cardiac function is associated with an adverse prognosis.

Therefore, changes in BP during the first year on dialysis are quite variable between patients. The complex relation between BP trends and outcome is likely dependent on the context.

Cardiac structure and function

Patients with CKD stage 5 often already have many abnormalities in cardiac structure and function before they start on dialysis, which carry important prognostic significance. The prevalence of LVH is high. One report in 213 non-dialysis CKD patients showed a prevalence of LVH of 76% in patients with CKD stage 5 when compared with 52% in patients with CKD stage 3 [33]. Hypertension is an important risk factor for progression of LVH in pre-dialysis CKD [34]. In a study of 433 incident dialysis patients, 15% had systolic dysfunction, 32% left ventricular dilatation and 74% LVH at the start of dialysis, all associated with an adverse prognosis [35]. In another study by the same group, 31% had congestive heart failure at the start of dialysis, whereas 25% of patients without signs of congestive heart failure at the start of dialysis developed this complication during a mean follow-up period of 42 months. Important risk factors for the development of congestive heart failure were hypoalbuminaemia, anaemia and hypertension [36]. In a smaller study in 30 non-diabetic dialysis patients, mean left ventricular mass (LVM) did not change significantly from baseline (the start of dialysis) in 12 and 24 months after the start of dialysis, although changes in LVM in individual patients were related to changes in BP and inversely to haemoglobin [37].

Indeed, changes in cardiac function after the start of dialysis appear to be quite variable between patients. In a multicentre incident cohort of 227 dialysis patients (54% HD), 30% had a history of cardiac failure before the start of dialysis, whereas 6% developed new-onset cardiac failure during the first year after the start of dialysis and 15% developed cardiac failure after the first year on dialysis. On the other hand, systolic function and LVM improved in respectively 48 and 46% of patients [38].

The question is how these differences in changes in cardiac structure and/or function following the start of dialysis can be explained. It is not unreasonable to assume that an improvement in fluid status could be involved in the improved cardiac function observed in a subgroup of patients, although no data on this subject are available. On the other hand, both patient- and treatment-related factors could play a role in the deterioration in cardiac function after the start of HD treatment. With regard to patient-related factors, LVM index at baseline was related to the emergence of cardiac failure following the start of dialysis [38]. A study in prevalent dialysis patients showed an inverse relation between LVM and residual renal function [39]. With regard to treatment-related factors, several studies have shown disturbances in regional wall contractility during the dialysis procedure, attributed to cardiac stunning (impaired but reversible myocardial contractility due to ischaemia) [40], which were not present before dialysis [41, 42]. Reversible intra-dialytic changes in regional LV wall contractility were predictive of persistently impaired systolic function during later follow-up, as well as for increased mortality [43, 44]. Given these data, it is suggestive that the dialysis procedure itself plays a role in the loss of myocardial contractile tissue, although patient susceptibility also plays a role, given the fact that intra-dialytic regional wall abnormalities followed by a persistent loss of systolic function are primarily observed in a subset of dialysis patients, notably in those with pre-existent higher LVM and higher interleukin-6 (IL-6) levels [43, 45].

Summarizing, the effect of starting dialysis on cardiac function appears to be variable, with a subgroup showing an improvement, and the other subgroup showing deterioration. To what degree underlying cardiac pathology, or the effects of dialysis treatment are responsible for the changes observed in the latter group, further research is needed.

Arterial stiffness and vascular calcification

An increase in vascular stiffness increases the systolic burden to the heart and is an important risk factor for mortality both in dialysis patients as well as in patients with CKD. Various studies have shown that arterial stiffness, assessed by different parameters, is increased in both CKD as well as dialysis patients when compared with controls [46–50]. The processes leading to arterial stiffness likely start early in the course of renal failure [46, 50]. Also, the age-related progression in arterial stiffness may be more rapid in patients with ESRD when compared with subjects without renal impairment. In a study in 80 prevalent dialysis patients and 60 controls, the mean change in pulse-wave velocity (PWV), as a marker of arterial stiffness over a 3-year time period was larger in dialysis patients (64 cm/s) when compared with the 27 cm/s observed in controls [51]. However, in a sub-study of the Convective Transport Study, no change in PWV was observed in 189 prevalent patients during a maximal follow-up period of 3 years [52]. One cross-sectional study found an increase in vascular stiffness in both pre-dialysis patients as well as maintenance dialysis patients when compared with controls, without significant differences between both patient groups [49]. To the best of our knowledge, longitudinal studies following changes in arterial stiffness from the

transition phase of pre-dialysis ESRD to the dialysis period are yet lacking.

With regard to vascular calcifications, there is ample evidence that these progress during time on dialysis [53]. However, as holds true for arterial stiffness, vascular calcification is also prevalent in earlier stages of CKD [54]. Whereas pharmacological treatment can, to some degree, influence the calcification process, this is not yet clear for dialysis therapy, as no long-term studies concerning the effect of different dialysate calcium levels on vascular calcification are available. Thus, until now, the question whether the progression in vascular calcification observed during dialysis treatment is (partly) due to a detrimental effect of the dialysis treatment itself or only to insufficient correction of the abnormalities in mineral metabolism remains to be answered.

Summarizing, available evidence suggests that arterial wall parameters, both with regard to stiffness as well as calcifications, deteriorate during dialysis, but also show a high prevalence of arterial disease before the start of dialysis. The extent to which dialysis treatment itself can influence arterial wall properties in the long term needs further study.

Nutritional state and body composition

Protein-energy wasting is an important risk factor for mortality in dialysis patients, certainly when accompanied by inflammation [55]. Abnormalities in nutritional state already occur in the pre-dialysis stage, associated with a spontaneous decline in protein intake [56]. Both in prevalent dialysis patients but also at the onset of dialysis, malnutrition is an important risk factor for mortality [57, 58].

The start of dialysis could theoretically have both positive and negative effects on nutritional state [58, 59]. Positive effects include the increased removal of uraemic toxins, which might be involved in anorexia, the correction of acidosis and the possibility for a more liberal diet when compared with the pre-dialysis stage. Negative effects include the loss of (micro)nutrients, as well as the inflammatory process which may accompany dialysis treatment [58–61]. Whereas studies in prevalent patients suggest a decline in nutritional parameters over time [62, 63], studies in incident patients suggested an improvement in (especially biochemical) parameters reflecting malnutrition, such as pre-albumin and albumin, as well as an increase in protein intake (reflected by protein nitrogen appearance) in the first year following the start of dialysis [64, 65]. These findings were confirmed by later studies [66]. However, it is uncertain whether these biochemical changes are also reflected in improvements in body composition.

The least specific parameter reflecting body composition is body weight. Changes in body weight after the start of dialysis can either reflect changes in hydration, lean tissue mass (LTM) or fat mass. A single-centre study from Tassin in 363 incident dialysis patients showed that mean target (dry) body weight decreased by 6.5% in the first 8 weeks after the start of dialysis, followed by an increase of 1.9% during Week 8–52 [66]. Changes in target body weight after 8 weeks were positively related to protein intake (reflected by protein nitrogen appearance) and serum albumin, but inversely to C-reactive protein (CRP) at 12 weeks after the start of dialysis. Moreover, an increase in body weight between Week 8 and 52 after the start of dialysis was predictive of survival. However, this subsequent increase in body weight occurred only in 60% of patients. After 1 year of treatment, mean target body weight in the cohort was still ~4 kg lower than the weight at the start of dialysis. The initial decline in body weight is suggested to reflect a decrease in extracellular volume due to the removal of excess fluid by ultrafiltration, whereas the later increase is suggested to reflect an improvement in nutritional state, which would be supported by the relation between changes in body weight and biochemical nutritional parameters. In the earlier mentioned study of Sipahioglu *et al.*, mean pre-dialytic body weight decreased from 80.7 kg at baseline to 79.4 kg after 3 months, followed by a gradual increase to 80.7 kg at the end of the first year [32]. In contrast, a study, in 142 incident HD patients (34 diabetics), which assessed body composition in more detail by dual-energy X-ray absorptiometry (DEXA) showed a decline in lean body mass of 1.1 kg in non-diabetic patients and of 3.4 kg in diabetic patients in the first year of dialysis [67]. Still, studies in which body composition is assessed by DEXA or bioimpedance using a two-compartment model likely cannot differentiate well between ECW and LTM in patients with FO [68].

In a study using both DEXA as well as neutron activation analysis, Pellicano *et al.* did not observe significant changes in total protein stores as well as lean body mass in a combined cohort of 46 HD and PD patients which was followed for 12 months from the start of dialysis [26].

Summarizing, although there is evidence for a beneficial effect of starting dialysis regarding protein intake and laboratory parameters, the relation between the start of dialysis and changes in body composition deserve further study. Changes in nutritional state appear to have prognostic significance.

Systemic inflammation

The presence of systemic inflammation is an important characteristic of CKD. Also in non-dialysed CKD patients, inflammation likely plays a very important role in the pathogenesis of various systemic complications associated with ESRD such as cardiovascular disease and malnutrition [69], whereas markers of systemic inflammation, such as CRP, are consistently related to mortality [55, 69, 70]. The pathogenesis of systemic inflammation in patients with ESRD is multifactorial. Next to the uraemic state itself, systemic inflammation can also occur as a result of comorbidity related to CKD, such as e.g. systemic atherosclerosis, heart failure or (occult) infections [69, 71–73]. Dialysis-related factors, such as bioincompatible membranes may play a role in its pathogenesis [74] although, also with the use of synthetic membranes was an inflammatory response observed during dialysis [75, 76]. Also dialysate impurity may play a role, given the fact that markers of inflammation and oxidative stress were significantly lower in patients treated with ultrapure versus standard dialysate [77].

Moreover, also the vascular access is likely involved in the pathogenesis of systemic inflammation. Recently, in a study in 583 incident HD patients, the use of CVC and arterio-venous (AV) grafts was associated with a respectively 62 and 30% higher increase in CRP levels during a follow-up period of 3 years when compared with patients with AV fistula [78]. Given the multifactorial pathogenesis of inflammation in ESRD patients, the uraemia- or dialysis-specific role in the pathogenesis of systemic inflammation may be difficult to unravel from those of comorbid factors in clinical research, although in patients with an unexplained increase in CRP levels, a search for underlying pathology is warranted [72, 73].

Few other studies assessed the effects of starting dialysis on inflammatory parameters. McIntyre *et al.* found in a cross-sectional analysis higher endotoxin levels endotoxin levels in patients on dialysis when compared with patients with pre-dialysis CKD, which was associated with systemic inflammation. Endotoxin levels in HD patients were related to intra-dialytic haemodynamic stress, which led to authors to suggest that recurrent gut ischaemia due to intra-dialytic hypotension may play a role in its pathogenesis [79]. In contrast, despite the fact that in a study in prevalent dialysis patients IL-6 levels increased during a 3-year follow-up period [62], Pupim *et al.* did not observe a change in inflammatory parameters or parameters related to oxidative stress in the year following the start of dialysis [80]. Summarizing, despite evidence for an acute effect of dialysis treatment on the inflammatory response, it is uncertain whether HD treatment itself, when performed with biocompatible membranes and ultrapure dialysate, is an important contributor to chronic systemic inflammation. However, HD access may be an important determinant for systemic inflammation. Still, the relative effects of treatment-related factors, the uraemic state and comorbidity are likely complex and not easy to unravel.

Physical activity and functional performance

It is well known that both physical activity and performance in dialysis patients is low. Many HD patients lead a sedentary lifestyle [81, 82]. In a recent international survey, physical activity was classified as low (defined by a number of steps <7500/day) in 64% of 134 dialysis patients with a mean age of 54.9 years [82]. The mean number of steps in their population was 5660. Both a sedentary lifestyle and low physical performance important risk factors for mortality [83, 84]. Physical activity was related to serum albumin, lean body mass and haemoglobin levels showing an important correlate between potentially reversible factors [85]. Some reports suggest that physical activity is also already low in the pre-dialysis phase, possibly due to the fatigue associated with advanced renal failure and the presence of comorbid disease, but possibly also to pre-existent lifestyle factors [86]. However, using the same methodology (Sensewear®) as in the Avesani study [82], in a study of 24 patients with CKD stage 4–5 not on dialysis (mean age 60.9 years), a mean daily physical activity duration of 74 min and a mean number of steps of 10423/day was observed, which lead the authors to conclude that physical activity was generally satisfactory in their cohort [87].

To the best of our knowledge, there are no prospective studies looking at the effects of starting dialysis. However, two studies showed that physical activity was lower on dialysis when compared with non-dialysis days [82, 88].

With regard to the effects of the start of dialysis on functional performance, especially in relation to activities of daily living (ADL), recent studies have shown concerning results. In a study in nursing home patients on dialysis, Kurella Tamura *et al.* not only observed an excess mortality early after the start of dialysis, but also a significant decline in ADL functional capacity in survivors [89]. To the best of our knowledge, no studies have been performed on functional performance in younger patients starting dialysis. Summarizing, there is limited evidence on the relation between the start of dialysis and changes in physical performance. Observational studies in elderly and frail patients showed a sharp decline in functional status following dialysis. Given the observational nature of these data, it is difficult to distinguish between cause and effect. Possibly, the additional stressor of starting dialysis put further stress in these very frail patients at high risk of homeostatic breakdown. Alternatively, dialysis may have been started within a course of an already irreversible decline in physical functioning [90, 91].

Conclusion

The start of dialysis is associated with pronounced phenotypic and pathophysiologic changes. Causes of these changes are multifactorial and may include the dialysis treatment itself, the progressive loss of renal function, next to the insufficient correction of the internal milieu by current dialysis modalities, as well as ongoing and progressive comorbid disease. The relative role of these different mechanisms is not easy to unravel in clinical studies, and clinical studies performed during the transition period from pre-dialysis ESRD to the dialysis period are surprisingly scarce. Although the focus of this review is not on therapeutic implications, the positive effects of early intervention programmes suggest that multidimensional approach might improve outcome in the transition period of the start of dialysis [92]. Next to adequate preparation of the patient for dialysis therapy including access care, individualized and targeted prescription of dialysis treatment, attention for diet and physical rehabilitation, 'just in time' starting of dialysis and adequate treatment of comorbid disease are all likely important in improving outcome during this critical period [59, 93, 94].

Conflict of interest statement. The authors declare that they have no conflict of interest.

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