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INVITED COMMENTARY

Improving outcomes after renal transplantation starts well before surgery – the role of renal replacement modality

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More efficient immunosuppressive medication has markedly improved both graft and patient survival after renal transplantation. However, more potent immunosuppressants also have detrimental effects, such as increasing the risk of infection and cancer. Emphasis should therefore be placed on interventions that reduce the risk of rejection, graft dysfunction, and patient death without increasing the immunosuppressive load. This has been clearly validated for better HLA matching between the donor and recipient, shorter cold ischemia times and improving organ preservation by machine perfusion [1].

The article by Balzer *et al.* [2] in this issue of Transplant International provides evidence that the method of renal replacement therapy is another important factor associated with both patient and graft survival after renal transplantation. These findings should remind clinicians that the choice of dialysis modality has important long-term implications beyond the actual period of dialysis therapy.

In their single-center retrospective cohort study of 2277 kidney transplantations performed between 2000 and 2014, the authors first confirm that pre-emptive transplantation provides the best results both in terms of patient and in terms of graft survival. This is in line with available evidence and has led the Descartes working group and the ERBP Advisory Board to recommend pre-emptive transplantation in order to avoid the initiation of maintenance dialysis therapy [3]. Unfortunately, the scarcity of donor organs implies that pre-emptive transplantation with deceased donor kidneys remains the exception and that most candidates without a living donor must receive renal replacement therapy while waiting for an organ.

The potential impact of the method of renal replacement therapy on post-transplant outcomes is therefore highly relevant for patients who are to be waitlisted for transplantation. Although the available evidence clearly documents that peritoneal dialysis (PD) is associated with a reduced incidence of delayed graft function

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[4–7], contradictory results have been reported on the effect on acute rejection, as well as graft and patient survival. In addition, most of the available evidence has been generated using large registries, which do not record long-term data on graft function. The study by Balzer *et al.* [2] used a large single-center database with a comprehensive set of outcome data and long follow-up to address these shortcomings of previous studies.

The study shows that, as compared to haemodialysis (HD), PD was associated with a 45% reduction in the risk of delayed graft function (DGF) requiring dialysis after transplantation and a 30% reduction in the hazard of acute rejection. In the long term, PD prior to kidney transplantation was associated with a 35% lower all-cause mortality after multivariate adjustment for confounders and a trend to fewer death-censored graft losses. Patients previously treated with PD also experienced a 35% reduction in the slope of eGFR loss over time, although this observation did not attain statistical significance.

How do these impressive results relate to the available evidence? In spite of the marked reduction in the risk of DGF, older registry studies of cohorts transplanted mostly during the last century reported long-term patient and death-censored graft survival that was similar for patients on HD and PD [8,9]. More recently, the same conclusion has been drawn in an analysis of the ANZDATA registry [5], whereas two large cohorts from the Collaborative Transplant Study (CTS) registry and the US Scientific Registry of Transplant Recipients (SRTR) reported significantly better unadjusted patient and graft survival in patients treated with PD as compared to HD [7,10]. Contrary to previous studies, an important reduction in long-term post-transplant mortality persisted for patients previously treated with PD even after multivariate adjustment for potential confounders. Both studies linked the lower mortality to a significantly reduced risk of death from cardiovascular causes [7,10]. On the contrary, and in accordance with data by Balzer *et al.* [2], multivariate analysis reduced the benefit in terms of death-censored graft survival, which was no longer statistically significant.

The clear-cut benefit associated with PD at the univariate level and conflicting results after multivariate adjustment in retrospective cohort studies reflect the difficulty to separate the effect of dialysis modality from confounding by the markedly different background characteristics of these two populations. In the study by Balzer *et al.* [2], PD was associated with many characteristics associated with better post-transplant patient and graft outcomes such as younger age, better HLA matching, shorter cold ischemia times, and more frequent living donor transplantation. Although the authors have invested considerable effort to correctly adjust for these differences, residual confounding cannot be completely excluded. This has also been illustrated by a recent ERA-EDTA registry analysis which showed significant benefits in terms of patient and death-censored graft survival in patients previously treated with PD in multivariate Cox models but not after using the case-mixed adjusted center percentage of PD patients in instrumental variable analysis [11].

The Dutch NECOSAD study has attempted to prospectively compare HD and PD in a randomized study [12]. It showed a significant survival advantage for patients on PD but the study was limited by the fact that only 38 out of 773 patients fulfilling the inclusion criteria consented to random allocation of the modality of renal replacement therapy [12]. In the absence of correctly powered prospective and controlled studies, retrospective data, although imperfect, are the only available evidence to inform the choice of dialysis modality. In this respect, it is also reassuring that in recent USRDS data and European studies the survival of dialysis patients over time has improved more rapidly for patients on PD, which now have lower mortality rates for prolonged periods after dialysis initiation as compared to HD patients [13,14].

The study of Balzer *et al.* [2] provides additional retrospective data to a growing body of evidence suggesting that peritoneal dialysis provides equivalent or even improved survival before transplantation, the known advantages of home dialysis and potentially improved post-transplant outcomes in the form of significantly lower risk of delayed graft function and patient death. This evidence should probably lead renal units to orient larger numbers of patients without the possibility for pre-emptive transplantation to PD as dialysis modality, while waiting for a suitable organ.

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Conflicts of interest

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