How to Cite this article: Ali Gardezi, Fahad Aziz, and Sandesh Parajuli, The role of Peritoneal Dialysis in different phases of Kidney Transplantation, Kidney360, Publish Ahead of Print, 10.34067/KID.0000482022

Article Type: Review Article

The role of Peritoneal Dialysis in different phases of Kidney Transplantation

DOI: 10.34067/KID.0000482022

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Key Points:

Abstract:
The utilization of Peritoneal Dialysis (PD) has been increasing in the past decade owing to various government initiatives and recognition of benefits like better preservation of residual renal function, quality of life, and lower cost. The Advancing American Kidney Health initiative aims to increase the utilization of home therapies like PD and kidney transplantation to treat end-stage kidney disease (ESKD). A natural consequence of this development is that more patients will do PD, and many will eventually undergo kidney transplantation. Therefore, it is important to understand the effect of pre-transplant PD on post-transplant outcomes like delayed graft function (DGF), rejection, thrombosis, graft, and patient survival. Furthermore, some of these patients may develop DGF, which raises the question of the utility of PD during DGF and its risks. While transplant is the best renal replacement therapy option, it is not everlasting, and many transplant recipients must go on dialysis after allograft failure. Can PD be a good option for these patients? This is another critical question. Furthermore, a significant proportion of non-renal solid organ transplant recipients develop ESKD. Is PD feasible in this group? In this review, we try to address all of these questions in the light of available evidence.

Disclosures: S. Parajuli reports the following: Research Funding: Veloxis. The remaining authors have nothing to disclose.

Funding:

Author Contributions: Ali Gardezi: Conceptualization; Data curation; Formal analysis; Writing - original draft Fahad Aziz: Writing - review and editing Sandesh Parajuli: Supervision; Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:
The role of Peritoneal Dialysis in different phases of Kidney Transplantation

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The utilization of Peritoneal Dialysis (PD) has been increasing in the past decade owing to various government initiatives and recognition of benefits like better preservation of residual renal function, quality of life, and lower cost. The Advancing American Kidney Health initiative aims to increase the utilization of home therapies like PD and kidney transplantation to treat end-stage kidney disease (ESKD). A natural consequence of this development is that more patients will do PD, and many will eventually undergo kidney transplantation. Therefore, it is important to understand the effect of pre-transplant PD on post-transplant outcomes like delayed graft function (DGF), rejection, thrombosis, graft, and patient survival. Furthermore, some of these patients may develop DGF, which raises the question of the utility of PD during DGF and its risks. While transplant is the best renal replacement therapy option, it is not everlasting, and many transplant recipients must go on dialysis after allograft failure. Can PD be a good option for these patients? This is another critical question. Furthermore, a significant proportion of non-renal solid organ transplant recipients develop ESKD. Is PD feasible in this group? In this review, we try to address all of these questions in the light of available evidence.
Introduction:

Peritoneal dialysis (PD), ever since its conceptualization as a potential method of uremic toxins removal, has endured a turbulent course.\(^1\)\(^-\)\(^3\) After the initial success in treating acute kidney failure in the 1940s\(^4\), the use of PD gained traction in the treatment of End-Stage Kidney Disease (ESKD) in the 1960s.\(^5\)\(^-\)\(^7\) But the concerns about the high incidence of peritonitis, technique failure, and higher mortality compared to hemodialysis (HD) led to a steady decline in the prevalence of PD after peaking in mid 1990s.\(^8\)\(^-\)\(^10\)

In the past decade, there has been a resurgence in the utilization of PD.\(^11\) With the improvements in our understanding of peritoneal physiology, reduction in peritonitis rates, and overall improvements in the care of ESKD patients, the mortality of patients on PD has improved dramatically.\(^11\) Additionally, multiple studies have shown benefits like better preservation of residual renal function,\(^12\)\(^,\)\(^13\) better quality of life,\(^14\)\(^,\)\(^15\) and lower cost\(^16\) compared to HD. An impetus to increase the use of PD was provided by the introduction of a new expanded prospective payment model by the Center of Medicare and Medicaid (CMS) in 2011, which incentivizes dialysis units to put more patients on home dialysis therapies.\(^17\)

Furthermore, a key component of the “Advancing American Kidney Health” initiative, launched in 2019, is to have 80 percent of new ESKD patients either receiving dialysis at home or kidney transplantation.\(^18\)

If the goals of this initiative are to come to fruition, we could see more patients doing PD and many of these getting kidney transplants. Therefore, it is imperative to understand how pre-transplant PD can affect transplant outcomes, what the role of PD is in the immediate post-transplant period, and where it stands as a renal replacement therapy option for those with failing kidney allograft. This review tries to answer these questions in the light of available literature.
The effect of pre-transplant PD on transplant outcomes

The effect of pre-transplant dialysis modality on post-transplant outcomes has been the subject of multiple studies done across different eras, locations, and methodologies. \(^{19,20}\) A recurring theme in most research on this topic is the inherent differences between pre-transplant HD and PD patients. \(^{21-23}\) Most studies have attempted to reduce this selection bias by using models adjusting for some of these differences. (Table 1)

*Probability of getting a kidney transplant*

Snyder et al. \(^{24}\) used the CMS data to compare the post-transplant outcomes of patients who were initiated on either PD or HD from 1995 to 1998 and underwent kidney transplantation before November 30th, 2000. The relative likelihood of receiving a kidney transplant was 1.39 times higher in patients on PD than HD even after adjusting for the variables. Another study utilizing United Kingdom Renal Registry data showed a significantly higher percentage of PD patients on transplant waitlist than age-matched in-center HD patients. \(^{25}\) Other studies have shown similar results with transplant rates 30-60% higher in PD patients. \(^{26,27}\) As mentioned earlier, selection bias may be an important factor in these results. The same qualities that make one a better PD candidate might also positively affect the probability of getting a kidney transplant. Additionally, it is possible that PD was selected more often in those patients who were more likely to receive a kidney transplant in the near future.

*Delayed Graft Function (DGF)*

DGF is defined as the need for dialysis within one week of a kidney transplant. \(^{28}\) It has been associated with the increased risk of poor outcomes like rejection, graft failure, and mortality. \(^{29-31}\) Most of the
smaller single-center studies have shown a lower incidence of DGF with pre-transplant PD,\textsuperscript{32-39} while some have shown no difference.\textsuperscript{40-43} Among the larger studies utilizing national databases, Snyder et al.\textsuperscript{24} showed a lower incidence of DGF in the pre-transplant PD group than pre-transplant HD. Molnar et al.\textsuperscript{44} linked data from the Scientific Registry of Transplant Recipients (SRTR) to patients who underwent PD or HD through a large dialysis organization between 2001 to 2006. Furthermore, they adjusted the outcomes based on three additional models, including case mixed adjusted model, the malnutrition inflammation complex syndrome (MICS) adjusted model, and transplant data adjusted model. They noted that pre-transplant PD was associated with a 36\% lower risk of DGF in the unadjusted model, but after applying the models mentioned above, this result no longer remained statistically significant. This further reiterates that reduced risk of DGF with pre-transplant PD could be due to other favorable factors. The most important among these is the likelihood of higher residual renal function in patients on PD.\textsuperscript{12,13} Furthermore, it has been postulated that pre-transplant PD patients may have higher volume going into the transplant surgery than HD patients which may offer protection against DGF.\textsuperscript{45,46} Van Biesen et al.\textsuperscript{47} looked at this theory in a small study including 40 pre-transplant PD and 79 HD patients. Even after adjusting for variables like higher central venous pressure and weight gain before transplant, pre-transplant PD was still associated with a shorter time required to attain more than 50\% decrease in serum creatinine. Another proposed mechanism is lower inflammation and oxidative stress due to biocompatibility of peritoneal membrane compared to dialyzer membranes.\textsuperscript{19,20}

\textit{Acute rejection}

Acute allograft rejection can have deleterious effects on long-term allograft survival.\textsuperscript{48} However, the incidence has diminished significantly in the past 30 years owing to the introduction of robust immunosuppression regimens.\textsuperscript{49,50} Van Holder et al.\textsuperscript{35} noticed a higher incidence of rejection in patients
on PD before transplant. They attributed this observation to a possibility of better immunity in PD patients compared to those on HD.\textsuperscript{51} Other studies have not shown any difference in the incidence of rejection between these two groups.\textsuperscript{36,39,40,52} Tang et al.\textsuperscript{20} studied this outcome in a meta-analysis of six studies with 3,283 patients and did not find any difference between the two groups.

\textit{Graft thrombosis}

Vascular thrombosis of the kidney allograft is a feared complication resulting in immediate graft loss. Reported incidence is 0.1-8.2\%.\textsuperscript{53} Several studies have found pre-transplant PD to be an independent risk factor for renal allograft thrombosis.\textsuperscript{24,54-56} Murphy et al.\textsuperscript{54} were the first to report this risk. Ojo et al.\textsuperscript{56} examined the United States Network for Organ Sharing (UNOS) data from 1990-1996. The incidence of graft thrombosis was 0.89\%. Repeat transplantation and pre-dialysis PD were the strongest predictors of graft thrombosis. Snyder et al.\textsuperscript{24} looked at the causes of graft failure in pre-transplant HD and PD patients. Of all the causes, graft thrombosis was the only one found to be more common in PD patients. Higher plasma fibrinogen, apolipoprotein A and higher pro-coagulant activity in PD patients have been proposed as the underlying mechanisms.\textsuperscript{57,58} It is also possible that some of the patients had to choose PD because of difficulty maintaining vascular access for HD due to underlying pro-thrombotic conditions and, therefore, had a higher inherent risk of thrombotic events. Concurrently, using heparin during pre-operative HD may protect against thrombosis. The studies mentioned above were done on patients who received a transplant in the UK or USA in the late 80s to mid-90s. Thereafter, more studies done in other parts of the world showed no significant difference in the incidence of graft thrombosis between the two groups.\textsuperscript{59,60} Most recently, Lin et al.\textsuperscript{61} utilizing Taiwan national transplant registry, also found no significant difference. It is possible that more widespread use of anticoagulation during the
perioperative period in this era may have conferred a protective effect on the risk of graft thrombosis with pre-transplant PD.

**Graft survival**

Death censored graft failure (DCGF) is one of the most important outcomes reported by the studies comparing the effect of pre-transplant dialysis modality on post-transplant outcomes. Two large studies utilizing national databases done before the turn of century yielded opposite results.\textsuperscript{24,62} Snyder et al.\textsuperscript{24} showed a higher rate of DCGF in pre-transplant PD patients, mainly in the first three months. This was found to be due to a higher risk of graft thrombosis in this group. On the contrary, Goldfarb et al.\textsuperscript{62} looked at 92,844 patients from USRDS data who received kidney transplants from January 1991 to December 1999 and found a 3\% lower risk of DCGF in pre-transplant PD group. Considering these conflicting results, Molnar et al.\textsuperscript{44} looked at this outcome in patients transplanted in the 21\textsuperscript{st} century between July 2001 and June 2006 using SRTR data. This population was more representative of patients who got a transplant in the era of improved immunosuppression regimens. They made further adjustments based on case mix, MICS, and transplant-related variables. Pre-transplant PD was associated with a lower DCGF in the unadjusted analysis but not in the analysis adjusting for above mentioned variables. Similar results were shown in two other large, registry-based studies.\textsuperscript{63,64} Schwenger et al.\textsuperscript{63} analyzed data from 60,008 patients from North America, Europe, Australia, and New Zealand. While Kramer et al.\textsuperscript{64} utilized European Renal Association–European Dialysis and Transplant Association (ERA–EDTA) Registry to analyze 29,088 patients. In both of the studies, pre-transplant PD was associated with better graft survival in the unadjusted analysis but did not show any advantage when multivariable cox regression analysis and instrumental variable method were applied. The results indicated that the advantage of PD shown in previous studies might have resulted from inherent
differences between the two groups. The dialysis modality, by itself, may not influence graft survival. This notion is further strengthened by various single-center studies done in the past decade that have shown similar graft survival between the two groups.\(^{42,52,65}\)

**Patient survival**

While most large studies utilizing registry data have shown mortality benefit with pre-transplant PD compared to HD,\(^{44,62,63,65}\) some have shown no difference.\(^{24,61,64}\) Interestingly, the mortality of non-transplanted patients on PD has improved in the past two decades and is now better than those on HD.\(^{11,26}\) Being on pre-transplant PD may confer benefits that continue after renal transplantation and contribute to better survival. Lesser fluctuation in volume status and blood pressure, no risk of myocardial stunning as opposed to HD and better residual renal function may contribute to better cardiovascular (CV) outcomes in PD, although, the results of studies are conflicting.\(^{66,67}\) The first large-scale study to show post-transplant mortality benefit with pre-transplant PD was done by Goldfarb et al.\(^{62}\), which showed 6% lower mortality in this group compared to pre-transplant HD. However, the study done by Snyder et al.\(^{24}\) using a similar population in the same era did not show any difference. As mentioned above, Molnar et al.\(^{44}\) re-examined the difference in post-transplant outcomes according to pre-transplant modality after the turn of the century. They utilized multiple models to adjust for the inherent differences between the two groups. After adjusting for the variables, pre-transplant PD patients had 43% lower mortality than pre-transplant HD patients. Most of this benefit was due to 66% lower CV mortality in pre-transplant PD patients. Similar results were noticed by Schwenger et al.\(^{63}\), showing lower all-cause and CV mortality in patients on pre-transplant PD. Around the same time, Kramer et al.\(^{64}\) analyzed 10,135 PD and 18,953 HD patients who underwent kidney transplantation in Europe. In addition to applying multivariable regression analysis, they also used the instrumental variable method to address confounding by indication. After applying the latter, there was no difference
in mortality between the patients treated with PD and HD before transplant. The authors concluded that the selection of patients to do PD as opposed to HD might be based on factors that have positive effects on mortality after transplant. Two meta-analyses were published in 2016, which combined data from most of the major studies done in the past two decades. Both showed better survival in pre-transplant PD patients. It is safe to conclude that patients on pre-transplant PD have better survival after transplant owing to lower cardiovascular mortality, which, in turn, could be due to better overall health and other factors like residual renal functions.

**The role of PD immediately after kidney transplant**

*PD during DGF*

Whether PD can be continued during DGF safely has been examined in several different retrospective studies. (Table 2) Thomson et al. showed a shorter duration of DGF and length of hospital stay but a higher incidence of infections and fluid leak in patients who did PD during DGF than those who did HD. On the other hand, Yan et al. found higher rates of peritonitis and longer DGF duration in patients who did PD during DGF. Our group established a low volume, supine PD protocol for patients who were on PD before transplant and developed DGF. (Figure 1) We found a lower risk of peritonitis than previous studies, no fluid leak or wound infection, and no difference in duration of DGF between those doing PD or HD during DGF. In all three studies mentioned above, there was no difference in other outcomes like acute rejection and graft or patient survival. Other studies have shown a higher risk of peritonitis, wound infection, and fluid leak with PD use during DGF. If PD is not employed in DGF, most of these patients would require a central venous catheter which subsequently increases the risk of central line bloodstream infections and central venous stenosis. Considering these risks, if a pre-transplant PD
patient develops DGF, PD could be done using low fill volumes, strictly supine position with close monitoring for side effects like peritonitis, fluid leak, and wound infection.

**Timing of PD catheter removal**

There has been no consensus on the timing of PD catheter removal after a successful kidney transplant in pre-transplant PD patients. European best practice guidelines recommend that earlier removal is advisable, but it can be left in the body for up to 3 months. Some have advocated removal at the time of transplant to prevent catheter-related complications. Others have suggested that it can be kept for up to 6 weeks. It is reasonable to remove the PD catheter at the time of transplantation in patients with very low pre-transplant risk of developing DGF like living donor kidney recipients. In others, it should be removed as soon as there is enough graft function to ensure no need for dialysis. Some centers have developed calculators to determine the risk of DGF, which could be used to decide on the timing of catheter removal.

**PD after kidney transplant failure**

Despite improved graft survival, the number of transplant recipients initiating dialysis due to allograft failure is rising. A large majority of these patients do HD, with PD utilization rates as low as 5-16%. It is pertinent to note that history of an abdominal surgery like kidney transplantation is not a contraindication to PD. Multiple studies have compared the outcomes of patients initiating PD after failed kidney transplant to incident ESRD patients doing PD. While some small studies have shown poor outcomes in failed transplant patients, larger studies and a meta-analysis have demonstrated similar outcomes, including peritonitis rates, technique, and patient survival. One study compared the
outcomes of patients who initiated PD after allograft failure to those who initiated HD. There was no difference in adjusted survival at short and long-term follow-up. Stopping or continuing the immunosuppression is a critical decision in patients starting PD after renal transplant failure. On one hand, immunosuppression may increase the risk of peritonitis, but on the other hand, it may help conserve residual kidney functions, which may improve outcomes. Studies have shown a faster decline in residual kidney functions in patients on PD after failed kidney transplant than those without a transplant; but none have compared these outcomes between patients doing PD or HD after a failed transplant. Nonetheless, patients with a failing kidney allograft must be given opportunities to explore different dialysis modalities and choose the one most suitable for their lifestyle. This is particularly important in younger patients with longer life expectancy who may require multiple renal replacement therapy modalities throughout their life. Starting with PD would provide them more flexibility in their daily life and preserve their vasculature for future HD access should PD fail. This aligns to formulate an “ESKD Life plan” for each patient according to the recently published KDOQI vascular access guidelines.

**PD in ESKD associated with non-renal solid organ transplantation**

Patients with non-renal solid organ transplant (NRSOT) like liver, heart and lung have high risk of developing ESKD due to factors like long term use of Calcineurin inhibitors (CNI). Studies have shown an ESKD incidence of 1.0-1.5% per year in NRSOT. Concerns regarding the increase risk of peritonitis with immunosuppression use and resulting poor survival have limited the use of PD in this population. Several studies have compared the infection and survival outcomes of NRSOT patients on PD with non-transplant PD patients and have shown no difference between these groups. It is suspected that CNI may also increase the risk of encapsulating peritoneal fibrosis. Furthermore, exposure of peritoneum to high glucose in the presence of steroids and CNI may also increase the risk of
post-transplant Diabetes Mellitus. However, these outcomes have not been studied in patients with NRSOT who have PD for ESKD. Even though the authors of above mentioned studies have concluded that PD is a safe option for these patients, studies with larger number of patients are required to substantiate these findings.

**Conclusion:**

Thanks to various initiatives, PD is now well placed to be more prevalent in the future. Owing to its better preservation of residual renal functions, pre-transplant PD may offer benefits like a lower incidence of DGF and better patient survival after kidney transplant. While most of the benefits may be due to patient selection for PD and may no longer be significant once more patients are placed on this modality regardless of their health status; the available literature still does not show any major disadvantage of PD compared to HD when it comes to transplant. With more patients doing PD and eventually getting a transplant, it is important to understand the relationship of PD with various stages of a kidney transplant. It is equally important to present PD as a therapeutic option to those whose kidney allograft is failing so that they have more understanding and knowledge of all the available options for renal replacement therapy.

**Disclosures:** S. Parajuli reports the following: Research Funding: Veloxis. The remaining authors have nothing to disclose.

**Funding:** None

**Author Contributions:** Ali Gardezi: Conceptualization; Data curation; Formal analysis; Writing - original draft. Fahad Aziz: Writing - review and editing. Sandesh Parajuli: Supervision; Writing - review and editing.
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Table 1: Major Studies comparing post-transplant outcomes between pre-transplant PD and HD patients.

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<th>Study Characteristics</th>
<th>Outcomes</th>
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<td>Goldfarb et al.</td>
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<td>Kramer et al.</td>
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HD=Hemodialysis, PD=Peritoneal Dialysis, USRDS= United States Renal Data System, SRTR=Scientific Registry of Transplant Recipients, ERA-EDTA= European Ren Association- European Dialysis and Transplant Association
Table 2: Studies comparing outcomes of PD versus HD during delayed graft function.

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<th>Author</th>
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<td>Patient Survival</td>
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DGF=Delayed Graft Function, HD=Hemodialysis, PD=Peritoneal Dialysis, PD-DGF=PD during DGF, HD-DGF=HD during DGF
Figure 1: Guidelines for doing peritoneal dialysis during delayed graft function in post-transplant patients.

Initiate peritoneal dialysis in patient with delayed graft function only after consultation with the transplant surgeon.

Confirm that none of the following contraindications are present
- Any peritoneal breach during the transplant surgery
- Abdominal distention due to ileus
- Any active intra-abdominal pathology like infection or bleeding
- Life threatening hyperkalemia
- Severe hypervolemia causing pulmonary edema and hypoxia

Only do Continuous Cycler PD. Avoid Continuous Ambulatory PD
- Prior to starting the treatment, do a test dwell with 500 ml of 1.5% dextrose peritoneal fluid.
- Look for any pain or fluid leak
- If no symptoms occur, start cycler PD with 1 liter fill volume, dwell time of 90 minutes and 6 exchanges.
- Instruct the patient to stay supine during the treatment.
- Gradually increase the fill volume to meet the dialysis needs but never exceed two thirds of patient’s home prescription
- Monitor for pain, cloudy fluid and fluid leak through the wound
- Do not instill heparin in the PD fluid