# Introduction

Hyperphosphatemia is highly prevalent in hemodialysis (HD) and peritoneal dialysis (PD) patients and is a major risk factor for cardiovascular mortality ***(Kuhlmann, 2010).***

Elimination of inorganic phosphate by dialysis is a cornerstone of the management of hyperphosphatemia in chronic hemodialysis patients. Phosphate clearance during HD is affected by various factors of dialysis prescription, such as blood and dialysate flow rate, dialyzer membrane surface area and ultrafiltration volume ***(Kuhlmann, 2010).***

Also phosphate removal during dialysis is influenced by Plasma phosphate levels and the volume of blood that passed the dialyzer ***(Gallar et al., 2007)***.

It has been recently suggested that the major barrier to phosphate removal is limited transfer of phosphate between the intracellular and extracellular compartments, although other complex factors also play important roles. Theoretical predictions suggest that increasing either treatment frequency or treatment duration can increase phosphate removal ***(Leypoldt, 2005).***

That use of high-flux dialyzer can be an efficient alternative in terms of controlling the clearance of β2-microglobulin and impaired Calcium and Phosphorous metabolism. These beneficial effects of high-flux dialyzers are

probably mediated by the improved clearance of middle and high molecular weight toxins ***(Meltem, 2005).***

Enhanced phosphate removal by HD must not be dismissed and quantification of phosphate removed by dialysis is mandatory to analyse phosphate balance ***(Gutzwiller,2002)***.

The total amount of phosphate removed can be estimated from two samples and treatment time.

$$M_{PO4pred} = 0.1t - 17 + 50c_{ds60} + 11c_{b60}$$

Most importantly, samples are taken early in dialysis, soon enough to predict removal as a function of treatment time and to allow for the adjustment of dialysis prescription. The inclusion of phosphate concentration in plasma and dialysate measured at the same time is an indirect measure of dialyser clearance. The plasma value at 60 min ($c_{b60}$) is a good measure of apparent mean phosphate concentration during the entire treatment ***(Gutzwiller et al., 2002).***

# Aim of the work

Study the effect of dialyzer flux on phosphorous clearance by comparing high flux and low flux dialyzer in chronic hemodialysis patients using mass phosphate clearance as a parameter of dialysis dose.

# Dialyzer membranes

Dialyzer membranes can be divided according to their permeability to water into low-flux and high-flux membranes. The permeability of a membrane to water is indicated by its ultrafiltration coefficient ($K_{Uf}$). $K_{Uf}$ is defined as the number of milliliters of fluid per hour that will be transferred across the membrane per mm Hg pressure gradient across the membrane ***(Leypoldt et al., 2004).***

High-flux membranes have high water permeability, with $K_{Uf}$ values > 10 mL per hour per mm Hg, and mostly > 20 mL per hour per mm Hg ***(Misra, 2005).*** Large molecules, such as $\beta_2$ microglobulin, cannot get through the pores of standard (low-flux) dialysis membranes at all. However, high-flux membranes have pores of sufficient size to pass this molecule ***(Leypoldt et al., 2004).*** Removal of middle molecules (MMs) also occurs to a variable extent by adsorption onto the dialyzer membrane ***(Penne et al., 2005).***

In high-flux HD, solutes are cleared by both diffusion and convection. Total ultrafiltration usually exceeds the required weight loss due to internal filtration; this increases convective transport up to 8-10 L per session ***(Ronco et al., 2000).***

HD is divided into low-flux and high-flux HD. During low-flux HD, small MW substances are cleared by diffusion,

driven by the concentration gradient between the blood and dialysate. In contrast, large MW substances are largely cleared by convection, occurring passively with the flux of water through the dialyzer membrane. During low-flux HD, convective transport is minimal, since UF is restricted to the required fluid removal and the membrane limits the sieving of larger solutes ***(Ronco et al., 2000).***

## Clinical benefits of dialysis membranes

The uremic retention solutes, accounting for at least 90 described compounds, can be divided into three categories; first, the small water-soluble compounds with a MW less than 500 dalton (Da), which oppose to the larger "MMs" with a MW of more than 500 Da, and finally the protein-bound compounds ***(Laecke et al., 2006).***

Some of the morbidity associated with chronic HD is thought to result from retention of large MW solutes that are poorly removed by diffusion in conventional HD ***(Ward et al., 2000).***

Some authors demonstrated that an increased MM removal in chronic HD patients correlates with a better survival after adjustment for comorbidities and small solute clearance (urea Kt/V) ***(Laecke et al., 2006).***

Published data on the magnitude of the impact of high-flux membranes on decreasing patients' mortality are

controversial, although all of them support favourable effects ***(Locatelli, 2003).***

A decreased RR of mortality was reported by Hornberger et al. for patients treated with high-flux membranes compared with standard HD ***(Hornberger et al., 1992).***

In another retrospective analysis, Woods et al. demonstrated lower mortality and increased 5-year survival among patients treated with high-flux polysulfone versus patients treated with low-flux polysulfone ***(Woods et al., 2000).***

In addition, in a large retrospective study of almost 13000 patients, Port et al. reported an 18% reduction in mortality for patients treated with high- versus low-flux membranes ***(Port et al., 2001).***

Also of note, in addition to a 38 % decrease in the ACM rate, Koda et al. observed that high-flux dialysis was associated with 26 and 29 % decreases in cardiac and infectious mortality rates, respectively, compared with low-flux dialysis ***(Koda et al., 1997).***

The HEMO study was a randomized controlled trial (RCT) in 1846 patients ***(Levin et al., 2003)*** conducted between 1995 and 2001 in the US. The aim of the study was to evaluate morbidity and mortality of patients randomized to standard- or high-dose dialysis and to low- or high-flux membranes, respectively, using a two-by-two factorial design ***(Locatelli, 2003).***

The primary analysis of the HEMO Study demonstrated that randomization to high-flux dialysis thrice-weekly did not significantly alter the primary outcome of ACM and the four main secondary outcomes (the composite of first cardiac hospitalization or ACM, the composite of first infectious hospitalization or ACM, the first decrease in serum albumin levels of ≥ 15 % or ACM, and non-vascular access-related hospitalizations) ***(Cheung et al., 2003).***

However, the risk reductions associated with the high-flux arm, compared with the low-flux arm, reached statistical significance for two outcomes involving cardiac death. Specifically, high-flux dialysis was associated with a 20 % decrease in cardiac deaths and a 13 % decrease in the composite of first cardiac hospitalization or cardiac death ***(Cheung et al., 2003).***

In contrast, the likelihood of infection-related death which is the second most common cause of death (after cardiovascular disease), did not differ between patients randomized to high-flux or low-flux membranes. Observational studies have suggested that the use of a high-flux membrane may decrease the likelihood of infectious events, but these potential benefits have not been evaluated in randomized studies ***(Allon et al., 2003).***

Randomization to the high-flux arm in the HEMO Study was not associated with an improvement in infectious outcomes. Several proteins that inhibit granulocyte functions in

vitro were previously isolated from the serum of patients with renal failure. Those proteins are substantially larger than $\beta_2$-microglobulin and therefore might not have been removed by the high-flux membranes used in the HEMO Study ***(Cheung et al., 2003).***

The study showed 8 % reduction in the RR of death in the high-flux group ***(Locatelli, 2003).*** Lower risks were also observed in the high-flux arm, compared with the low-flux arm, for most of the secondary outcomes. None of these effects reached the criterion for statistical significance. The overall pattern, however, is consistent with the possibility of a benefit of high-flux dialysis that was too small to be detected, given the power of the study. For example, detection of an 8 % reduction in risk for high-flux dialysis with 80 % power would have required randomization of approximately 10,000 patients, instead of 1846 patients, under the conditions of the HEMO Study ***(Cheung et al., 2003).*** So the lack of a statistically significant difference does not imply equivalence; rather, there was not enough evidence to conclude for high-flux superiority ***(Locatelli, 2003).***

According to a secondary analysis, the support of the HEMO Study data for a benefit of high-flux dialysis is strongest for patients with several years of prior dialysis. In this context, the patients were stratified into a short-duration group and a long-duration group, on the basis of the mean duration of dialysis of 3.7 years before randomization. The

trends favoring high-flux dialysis were generally larger in the subgroup with > 3.7 years of dialysis before the study than in the entire cohort, with risk reductions for high-flux dialysis ranging from 8 to 37 % for the same nine outcomes of the HEMO study ***(Cheung et al., 2003).***

It is tempting to speculate that the favourable impact on this group, who would have had very little residual renal function, reflected the accumulation of toxins over a long period, which may have had higher clearance on high flux ***(Levin et al., 2003).***

In the subgroup that had been on dialysis for > 3.7 years, randomization to high-flux dialysis was associated with significant lower risks of ACM, the composite of first albumin level decrease or ACM, and cardiac deaths, compared with low-flux dialysis. No significant differences were observed in outcomes related to infection for either duration subgroup. For the subgroup of patients with < 3.7 years of dialysis before the study, assignment to high-flux dialysis had no significant effect on any of the examined clinical outcomes ***(Cheung et al., 2003).***

Serum albumin levels represent one of the strongest predictors of clinical outcomes among patients undergoing maintenance hemodialysis. In this study, randomization to high-flux dialysis had no significant effect on the main secondary composite outcome of serum albumin level

decrease or ACM. For patients with > 3.7 years of dialysis before the study, however, there was a 26 % decrease in the risk of this outcome. If the increase in serum albumin levels was indeed the result of improved dietary intake, then a potential explanation could have involved the removal of plasma substances that inhibit appetite, such as the putative factor in uremic plasma (1 to 5 kD), leptin (16 kD), and other peptides ***(Cheung et al., 2003).***

However, high-flux dialysis could also remove more plasma amino acids and proteins than low-flux dialysis, which would result in lower serum albumin levels. The loss of amino acids into the dialysate was not examined in the HEMO Study. However, the loss of albumin through the dialyzers was observed to be quite modest for a subset of HEMO Study patients examined. The average loss among six patients for whom albumin was detectable in the dialysate was only 0.5 g/session ***(Cheung et al., 2003).***

Hypoalbuminemia could also result from the suppression of hepatic albumin synthesis as a result of inflammation. A potential stimulus of systemic inflammatory responses during high-flux dialysis is the back-transfer of cytokine-inducing substances from contaminated dialysate through the dialyzer membrane. Despite the greater potential for albumin leakage into the dialysate and back-transfer of cytokine-inducing substances, randomization to high-flux dialysis was associated with a lower, rather than a higher,

incidence of the decreased serum albumin level composite outcome in the HEMO Study ***(Cheung et al., 2003).***

Assuming that the interaction between dialysis years and flux was real, we considered possible mechanisms. The case mixture of the subgroup with > 3.7 years of dialysis before the study was substantially different from that of the subgroup with < 3.7 years of dialysis. The long-duration group was younger, was more likely to be male and black, was less likely to be diabetic, and exhibited a lower postdialysis body weight. Age, gender, race, diabetic status, and body weight were not noted to interact with the flux interventions, however. Therefore, these factors could not individually explain the potential differences in the responses to high-flux dialysis between the long-duration and short-duration groups, although it is conceivable that a combination of these factors and/or other factors could account for the differences ***(Cheung et al., 2003).***

Another potential explanation is that patients who had been on long-term dialysis had accumulated more toxic MMs and lacked the residual kidney function to remove them; therefore, these patients would benefit more from the removal of MMs with high-flux dialysis during the follow-up period than would patients on short-term dialysis. As expected, there were fourfold more patients in the long-duration group who were anuric, compared with the short-duration group. Furthermore, patients on long-term dialysis who had been

using low-flux dialyzers before the study demonstrated a 41% decrease in ACM rate when randomized to the high-flux arm, compared with the low-flux arm, which is consistent with the idea that more toxic MMs had accumulated in this subpopulation. Patients with lower residual kidney function, however, responded to high-flux dialysis similarly to those with greater residual kidney function, and anuric patients responded to high-flux dialysis similarly to those without anuria. Therefore, these observations did not seem to explain the flux-dialysis year interaction ***(Cheung et al., 2003).***

These data are interesting and worthy of further investigation but insufficient to allow us to definitively conclude at this time that the effect of flux depends on years of dialysis ***(Cheung et al., 2003).***

Another sub-analysis of the HEMO study suggested a decreased risk of death from cerebrovascular disease (CBVD) for patients on high-flux HD, without baseline evidence of CBVD, or with a duration of HD therapy longer than 3.7 years ***(van der Weerd et al., 2008).***

The main results of the HEMO Study were published in December 2002. Since the publication of this report, several articles have appeared which discuss the implications of the HEMO Study results for clinical practice, including generalizability, statistical power and design ***(Rocco et al., 2005).***

In an interpretation of the HEMO study by Locatelli, study sample selection bias was revealed. Participants in the HEMO study were not fully representative of the US composite HD population. In fact, in the HEMO study sample, mean age was lower (57.6 ± 14.0 years) and percentage of blacks was much higher (63% of study participants) than in the US HD population at large. Due to the study exclusion criteria, very heavy weight patients (97% of patients who underwent randomization weighed less than 100 Kg) and severely malnourished patients were excluded (mean serum albumin 3.6 ± 0.4 g/dl) ***(Locatelli, 2003).***

In addition, subgroup analyses examining the effect of the flux intervention in relation to the number of prior years of dialysis indicated that there was a potential benefit of high-flux dialysis for patients with > 3.7 years of prior dialysis, but no benefit of high flux in patients with fewer years on dialysis. Thus, it is unlikely that a beneficial effect of high-flux dialysis would have been detected if the study had been restricted to incident patients ***(Rocco et al., 2005).***

Also of note, as indicated in our primary outcomes report, there was no significant interaction between the dose and flux interventions for the primary outcome of mortality, which indicates that there is no evidence that the effect of either the dose or flux interventions varied depending on the level of the other intervention. Thus, in accordance with the study's analysis plan and standard practice for the analysis of factorial

designs, the primary analysis considered the effect of the dose intervention, combining patients in both flux groups, and, similarly, the effect of the flux intervention, combining patients in both dose groups. Figure 4 shows the post-hoc comparisons of the four individual dose–flux combinations in the study design on mortality. None of the six possible pair-wise comparisons of these four treatment groups approached statistical significance ***(Rocco et al., 2005).***

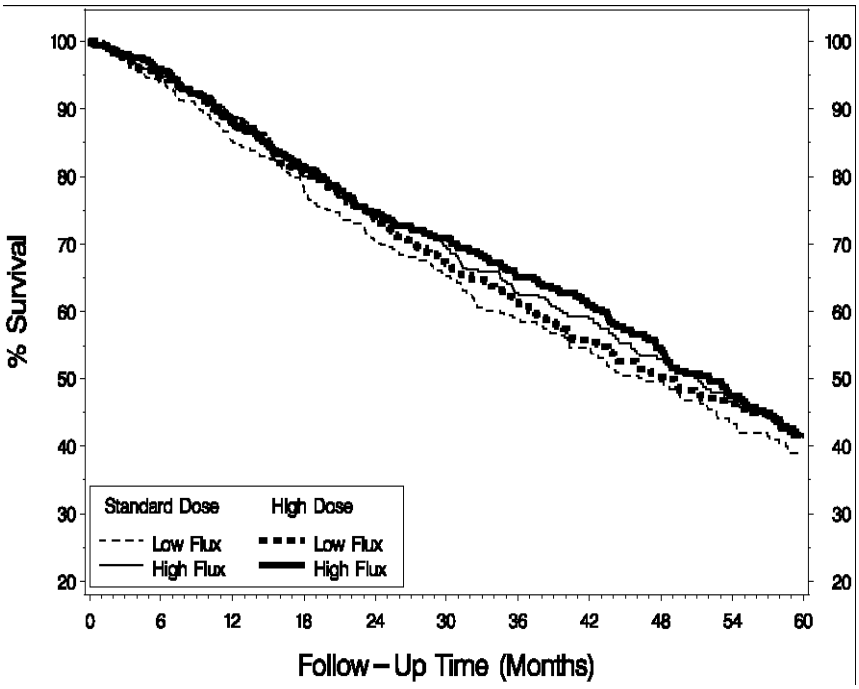


**Figure (1):** Patient survival curves for the dose-flux combinations in the HEMO study ***(Rocco et al., 2005).***

Very recently, the results of another randomized clinical trial in this domain was presented, which is the European Membrane Permeability and ESRD Patient Outcome (MPO) study ***(van der Weerd et al., 2008).***

This RCT has been designed to evaluate prospectively the long-term effect of membrane permeability on clinical outcomes including mortality and morbidity ***(Locatelli, 2003).***

The MPO study is a European study with some striking points of difference with the HEMO study. The MPO study was relatively well powered, with a targeted sample of 660 patients. In the MPO study, the threshold pore size defining high-flux membranes was larger than in the HEMO study, with a markedly higher ultrafiltration coefficient and β2-microglobulin clearance ***(Vanholder et al., 2008a),*** as only a single use of filters was allowed ***(Ledebo et al., 2008).***

The length of the follow-up was considerably longer than that in the HEMO study, with focus on incident patients starting with dialysis under a poorer clinical condition upon enrolment (serum albumin ≤4.0 g/dL for the large majority of patients). Although the study was originally designed only for such hypoalbuminaemic patients, the protocol was amended after 11 months due to too slow patient inclusion into the study, and from then on normoalbuminaemic patients were also enrolled. At the end of the study, however, 76.2% of patients under evaluation appeared to have been still hypoalbuminaemic, according to the study definitions ***(Vanholder et al., 2008a).***

Many studies have shown a mortality risk inversely proportional to serum albumin levels, thereby supporting the rationale of the initial study design to enroll a sicker patient