

On-line haemodiafiltration – The therapy of choice

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Contents

- 1. Mortality risk for patients receiving haemodiafiltration versus haemodialysis: European results from the DOPPS**
- 2. Serum β_2 -microglobulin levels predict mortality in dialysis patients: Results of the HEMO study**
- 3. On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters**
- 4. Impact of convective flow on phosphorus removal in maintenance haemodialysis patients**

Preface

Despite significant improvements in dialysis quality and efficiency during the last years the annual mortality rate of end-stage renal disease patients treated with standard haemodialysis is still high. In the recent years several studies have shown that on-line haemodiafiltration (HDF) has multiple beneficial effects on main cardiovascular risk factors of dialysis patients and are therefore indicating its potential to significantly improve patients' outcome.

This has now been confirmed by Canaud et al. with their analysis of the DOPPS data. Patients who were treated with HDF had a significantly lower mortality risk compared to low-flux HD patients. One reason might be the higher removal of middle molecules by convective forces. The impact of β_2 -microglobulin on mortality and consequently the importance of an effective β_2 -microglobulin removal could be demonstrated in our second study by Cheung et al. The results of the two other very recent studies by Vaslaki et al. and Lornoy et al. further contribute to elucidate the superiority of HDF: improved anaemia control and phosphorus homeostasis. MB

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1. Mortality risk for patients receiving haemodiafiltration versus haemodialysis: European results from the DOPPS

The annual mortality rate of patients with end-stage renal disease treated with haemodialysis (HD) three times per week remains high. The nephrology community suggested convective based therapies as being promising modalities to improve dialysis patients' outcomes. In their prospective, observational study **Canaud et al.** compared the mortality rates of patients receiving haemodiafiltration (HDF) with those of patients receiving HD in a large cohort of European subjects from the Dialysis Outcomes and Practice Patterns Study (DOPPS).

2165 prevalent HD patients from a total of 101 facilities in France, Germany, Italy, Spain and the UK were analysed. Data collection began in 1998 and was continued at 4-month follow-up intervals through early 2001. Patients substituting 5-14.9 L of fluid per treatment were classified as receiving low-efficiency HDF, while patients substituting 15-24.9 L of fluid as high-efficiency HDF. HD patients were classified by the type of dialyser used (low-flux: UF coefficient (KUF) \leq 20 ml/h/mmHg versus high-flux: KUF > 20 ml/h/mmHg), regardless of the membrane type.

A total of 253 patients (11.7%) received HDF. These patients tended to be slightly older, have higher body weight, have more comorbid conditions - particularly cardiovascular diseases - and have longer time on dialysis compared to patients treated with HD. This indicates a preferential selection of patients with a high body weight and a poor clinical condition for HDF. In HDF patients a

trend was observed for having higher haemoglobin levels and a reduced weekly dosage of erythropoietin compared to patients treated with low-flux HD. The authors speculate that HDF may remove some specific receptor antagonists of erythropoietin and thereby increase the sensitivity of erythroblasts to the drug. The highest Kt/V value was achieved with high efficiency HDF (1.44) compared to treatment with low-flux HD (1.33, $p < 0.05$). There were no differences between HDF and HD patients regarding nutritional markers, quality of life, blood pressure and acid base status suggesting that most patients in the study received adequate renal replacement therapy.

12.8 deaths per 100 patient years occurred in the low-flux HD group, 12.7 in the high-flux group, 12.6 in the low-efficiency HDF group and 8.9 in the high-efficiency group. The relative risk (RR) of mortality after adjustments for several variables - e.g. age, comorbid conditions, haemoglobin and Kt/V - was significantly reduced by 35% for patients receiving high-efficiency HDF compared to low-flux HD ($p = 0.01$, **Fig. 1**). Since the results for low- and high-flux HD were similar, the HDF results were compared to all HD results combined. In this comparison, the RR of death for low-efficiency HDF was 0.92 ($p = 0.066$) and for high-efficiency HDF significantly lower (RR = 0.64, $p = 0.005$).

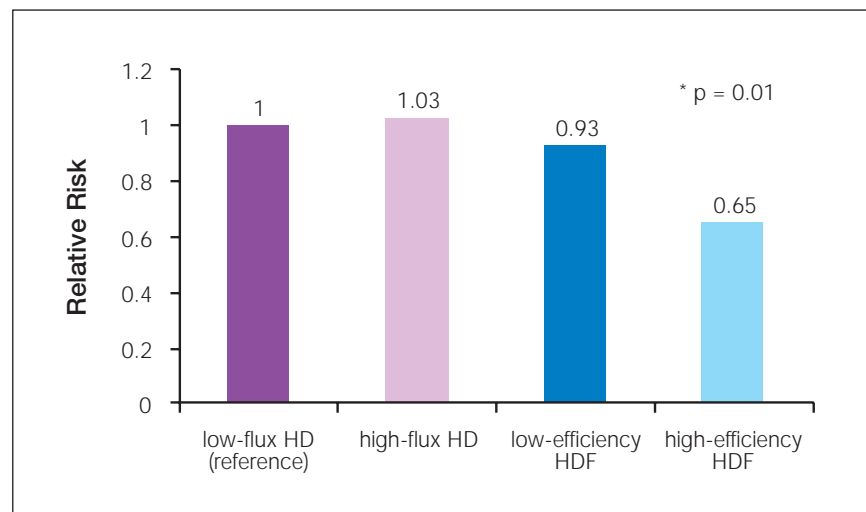


Fig. 1: Relative risk of death by dialysis modality

The authors discuss several explanations for the beneficial effect of HDF. First, HDF improves removal of small and larger molecular solutes. The latter may be even more important since the beneficial effect of HDF on reduction of mortality risk persisted after statistical adjustment for Kt/V. HDF also enhances intradialytic haemodynamic stability, and finally the prerequisites for HDF therapy (i.e. high-flux synthetic membrane and ultrapure dialysis fluid) offer a higher biocompatibility profile reducing bioactivation and a subsequent inflammation.

This is the first study in a large cohort of patients suggesting that high-efficiency HDF is associated with a reduced mortality risk compared to both, low- and high-flux HD. CL

Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK: Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS; *Kidney International* advance online publication, 26 April 2006; doi:10.1038/sj.ki.5000447

2. Serum β_2 -microglobulin levels predict mortality in dialysis patients: Results of the HEMO study

The European Best Practice Guidelines for haemodialysis recommend to maximise the removal of middle molecules and further suggest to use β_2 -microglobulin (β_2 M) as a marker for middle molecules. **Cheung et al.** examined in this secondary analysis of the HEMO (haemodialysis) study population by which factors serum β_2 M levels are determined and how serum β_2 M influences mortality.

The HEMO study was a randomised, prospective clinical trial designed primarily to examine the impact of membrane flux and dialysis dose on the clinical outcome of chronic haemodialysis patients. 1704 patients, in whom β_2 M kinetic modelling was performed at one month of follow-up, were eligible for the

investigation of Cheung et al. Blood samples for β_2 M were collected from the vascular access immediately before dialysis and 20 seconds after dialysis from the arterial blood tubing after the dialyser blood flow rate had been reduced to < 80 mL/min. Dialyser clearance of β_2 M was determined on the basis of the change in serum β_2 M concentration during the dialysis session. Mean predialysis serum β_2 M, β_2 M clearance and Kt/V for β_2 M were determined for each patient by averaging all available follow-up values.

The mean actual follow-up of the patients was 2.84 years. A total of 55.9% were female, and 62.9% were black, with a mean age of 57.8 ± 14.0 years. Long-term dialysis patients (> 3.7 years on dialysis prestudy) had significantly higher serum β_2 M values over the course of follow-up than short-term patients. The same was observed for anuric patients when compared with patients with detectable residual kidney urea clearance. The mean predialysis serum β_2 M was 41.5 ± 12.9 mg/L (n = 817) for the low-flux and 33.5 ± 9.1 mg/L (n = 887) for the high-flux group (p < 0.0001).

β_2 M is largely cleared by filtration, reabsorption, and degradation in the proximal tubule. Therefore, it was not astonishing for the authors to observe a significant correlation between serum β_2 M and residual renal function: each 1 mL/min increase in residual urea clearance, adjusted for body fluid volume, decreased the serum β_2 M level by 7.21 mg/L in a multiple regression model (p < 0.0001). Also baseline age, diabetes, body mass index (for all three parameters unexpected to the authors) and dialyser β_2 M clearance were associated with lower serum β_2 M levels (p < 0.0001). In contrast, black race and baseline duration of dialysis were associated with higher serum β_2 M (p < 0.0001).

In time-dependent Cox regression models mean predialysis serum β_2 M levels correlated significantly with mortality (RR = 1.11 per 10-mg/L increase in β_2 M

level; $p = 0.001$). This association sustained even after adjustment for the effect of residual renal function. The relative risk of death was approximately 60% higher for patients with β_2M levels of 42.5-50 mg/L compared to patients with levels below 27.5 mg/L (Fig. 2). Dialyser β_2M clearance and β_2M Kt/V were associated with lower mortality in patients who were on dialysis > 3.7 years before the study.

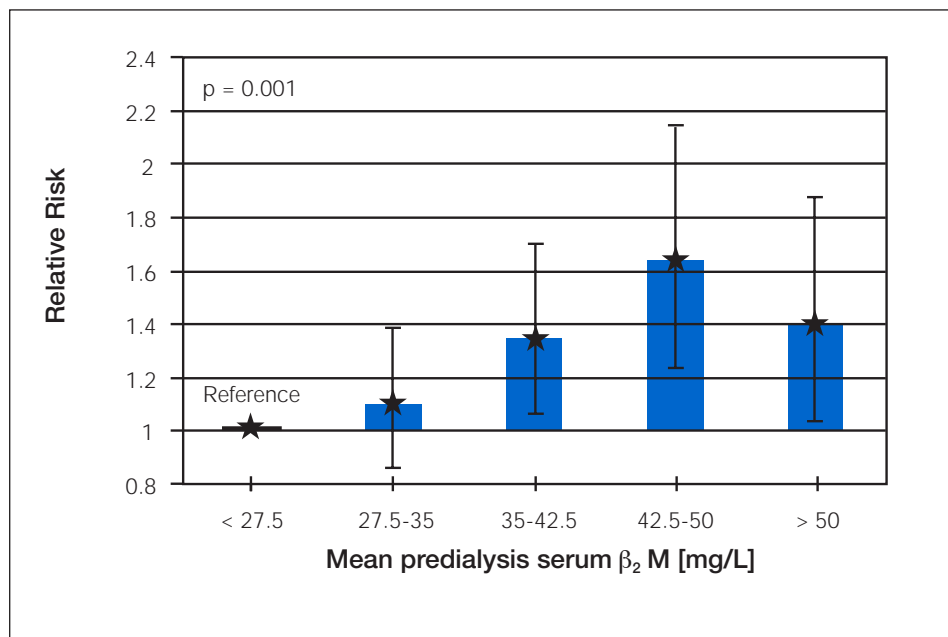


Fig. 2: Association of all-cause mortality with mean predialysis serum β_2M levels

This study revealed that predialysis serum β_2M values were significantly predictive of all-cause mortality. It further justifies the use of β_2M as a marker for middle molecules and their maximised removal recommended by the European Best Practice Guidelines. One option to reach this goal may be the routine application of on-line haemodiafiltration, which has previously been shown to reduce serum β_2M levels most probably by applying ultrapure dialysate and high convection.

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Cheung AK, Rocco MV, Yan G, Leyboldt JK, Levin NW, Greene T, Agodoa L, Bailey J, Beck GJ, Clark W, Levey AS, Ornt DB, Schulman G, Schwab S, Teehan B, Eknoyan G; for the HEMO Study Group: Serum β_2 -microglobulin levels predict mortality in dialysis patients: results of the HEMO Study; *J Am Soc Nephrol* 17, 546-555, 2006

3. On-line haemodiafiltration versus haemodialysis: Stable haematocrit with less erythropoietin and improvement of other relevant blood parameters

Vaslaki et al. addressed in this open prospective multi-centre study the effect of on-line haemodiafiltration (oHDF) in contrast to standard haemodialysis (HD) on intradialytic morbid events (IME), anaemia control and the uraemic toxicity profile in patients with end stage renal disease.

70 patients from 7 dialysis units in Hungary were treated with HD and oHDF in a cross-over design. After a pre-phase of 3 months with low-flux HD using cuprophane membranes they were randomized to group A (24 weeks on HD, then switched to oHDF for another 24 weeks) or group B (starting with oHDF and treated with HD afterwards). The HD phases were performed with low-flux polysulfone dialysers (HPS series, Fresenius Medical Care) and the oHDF phases with high-flux polysulfone dialysers (Fresenius Medical Care). To

avoid any bias by different dialysis doses in the HD and oHDF group, the treatment dose in both modes was kept sufficiently high with $eKt/V \geq 1.2$ and as close as possible to each other.

The occurrence of IME – defined as a symptom (e.g. symptomatic hypotension, muscle cramps, nausea or headache) severe enough causing the nurse to counteract – was documented for each dialysis session. In addition, the following parameters were monitored and recorded

- *weekly*: erythropoietin and iron dose,
- *monthly*: haematocrit, haemoglobin, serum ferritin, transferrin, C-reactive protein (CRP), serum calcium, and serum phosphate, and
- *at the end of each study phase (mid-week session, predialysis)*: interleukin-6 (IL-6), myeloperoxidase (MPO), fibrinogen, albumin, lipoproteins, triglycerides, pentosidines, carboxy-methyllysine (CML), advanced oxidation protein products (AOPP), homocysteine, parathyroid hormone (PTH), and β_2 -microglobulin (β_2M).

In contrast to others who found an improved cardiovascular stability of oHDF compared to HD Vaslaki et al. observed no statistically significant difference in

IMEs between HD and oHDF. However, the overall incidence of IME was low in both treatment modes (in pooled data 0.15 IME per session for HD and 0.16 IME per session for oHDF). The therapy with oHDF lead to an improved anaemia management in the patients requiring a lower erythropoietin dose during oHDF in both groups, however not statistically significant in group A (see **Fig. 3**). Nevertheless a significant increase of approx. 5% in haematocrit and haemoglobin was observed during oHDF in group A.

In addition, lower levels of free and protein bound pentosidine were measured in both groups as well as AOPP in group A. This could be a hint to reduced oxidative stress in patients on oHDF, even if CML remained unchanged. For β_2M , which was only measured in a subgroup of the study population, a significant difference was detected between oHDF and HD in group B (oHDF: 23.7 ± 11.2 mg/L; HD 42.3 ± 15.5 mg/L, $p < 0.01$), but no difference was revealed between both therapy modes in group A.

While serum albumin presented with nearly identical values, fibrinogen was statistically significantly lower in both groups during oHDF and also the other inflammatory markers IL-6 (6.1 ± 5.6 pg/mL during HD-phase in contrast to 4.0 ± 2.6 pg/mL in oHDF-phase) and CRP (from 19.6 ± 13.0 mg/L to 13.9 ± 15.3 mg/L), at least in group A. Finally, another clinically important result is the fact that the authors found a lower calcium-phosphate product due to the lower serum phosphate during oHDF in both groups (group A: -9%, $p < 0.05$; group B -14%, $p < 0.01$).

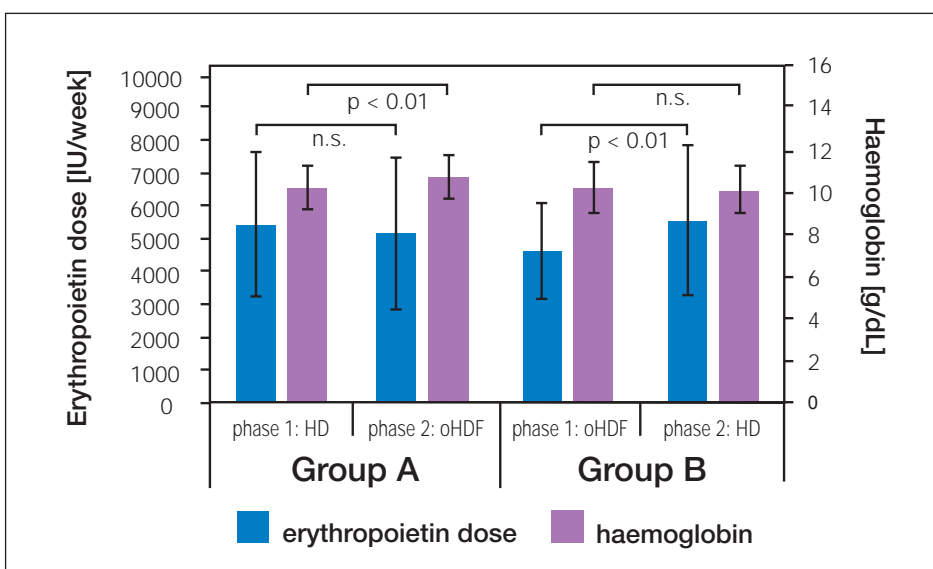


Fig. 3: Erythropoietin dose and haemoglobin levels during the study phases (mean ± SD)

In conclusion, whereas HD in none of the investigated parameters proved advantageous compared to oHDF, for many parameters oHDF was shown to be superior to HD, especially regarding parameters responsible for long-term complications. AR

Vaslaki L, Major L, Berta K, Karatson A, Misz M, Pethoe F, Ladanyi E, Fodor B, Stein G, Pischetsrieder M, Zima T, Wojke R, Gaulty A, Passlick-Deetjen J: On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters; Blood Purif 24, 163-173, 2006

4. Impact of convective flow on phosphorus removal in maintenance haemodialysis patients

The single-centre, prospective, and randomised study by **Lornoy et al.** compared the removal of inorganic phosphorus (P), the phosphorus reduction rate (PRR), and the phosphorus rebound in high-flux haemodialysis (HD) and postdilutional on-line haemodiafiltration (oHDF).

22 anuric maintenance HD patients were randomly treated with one 4-hour session of high-flux HD (800 mL/min dialysate flow rate) and one 4-hour session of postdilutional oHDF (700 mL/min dialysate flow rate and 100 mL/min substitute flow rate). Blood flow (350 mL/min) and high-flux polysulfone dialyser (F80, 1.8 m², Fresenius Medical Care) were kept identical for both dialysis modes. Before the study all patients had been stable for at least 6 months on postdilutional oHDF, three times 4 hours weekly, which has been routine therapy in the centre since 1993.

In all patients predialysis serum P and total P removal was measured. In addition, in 13 patients a postdialysis sample for serum P was drawn from the arterial needle at the end of the session to calculate the PRR, and a second serum P sample was taken 1 hour after the end of the session to calculate the P rebound percentage at 60 minutes. Total spent dialysate and ultrafiltrate volumes were collected hourly during the session. For oHDF the P concentration was measured in each sample. Besides, a mixture of the 4 hourly specimens was used to determine the total P removal per session.

As shown in **Fig. 4** the mean total P removal was 19% higher with oHDF than with the high-flux HD. The highest phosphate removal in oHDF was within the first hour of the session. In the 13 patients with additional measurement of postdialysis P and PRR values, Lornoy et al. observed a significantly higher PRR in oHDF compared to HD despite an equal predialysis mean serum P (5.3 mg/dL in oHDF vs. 5.2 mg/dL in HD; $p = \text{n.s.}$) and a high, but equal P rebound at 60 minutes (42% in oHDF vs. 39% in HD; $p = \text{n.s.}$, **Fig. 4**).

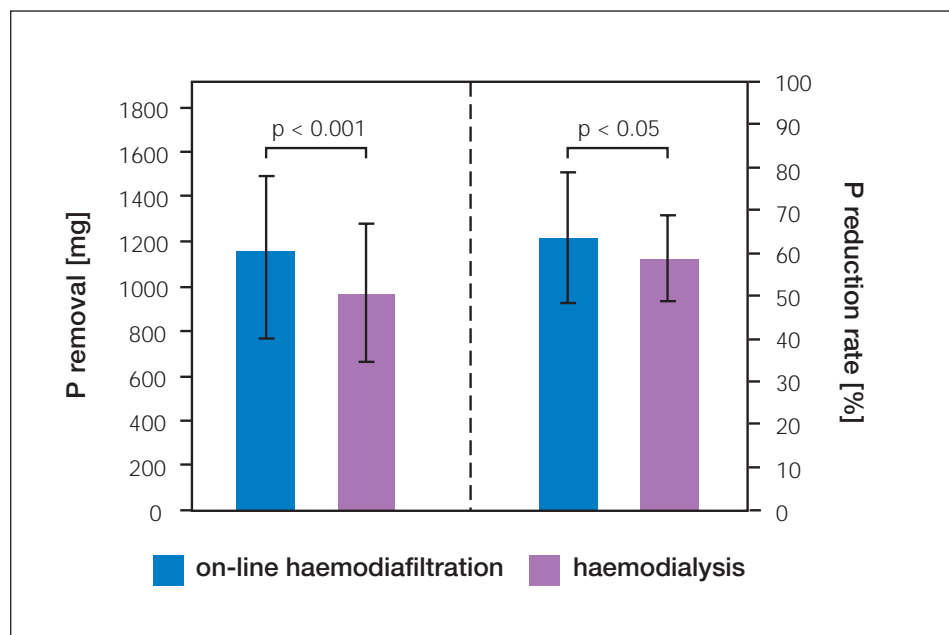



Fig. 4: Phosphorus removal in total spent dialysate and ultrafiltrate and phosphorus reduction rate in oHDF and HD



In patients with serum P levels up to 5.5 mg/dL P removal was significantly superior in oHDF. According to the authors this proves that convective flow, especially in postdilutional substitution mode, removes more P than diffusion does alone. However, with increasing serum P values the difference between the two modalities gradually decreased, reaching equal effectivity at serum P values above 7 mg/dL. This may be due to a higher contribution of diffusion to the total P removal in patients with high serum P values.

The authors discovered that in some of their patients the mean weekly amount of P removal by oHDF even equalled the weekly P intake, making P binders unnecessary. Depending on the serum P levels this could also allow dieticians to implement higher protein intakes. Lornoy et al. also found out that the weekly P removal in their study was similar to reported values with a 3-hour-weekly longer HD treatment time. Therefore they request to balance the benefits of oHDF against those with either longer sessions or daily treatments, leading to less comfort for the patients.

In summary, this study revealed a higher phosphorus removal and phosphorus reduction rate with postdilutional on-line HDF compared to high-flux HD. Long-term use of on-line HDF therefore may allow to reduce phosphate binder prescription and may have a positive impact on the cardiovascular status of the patients.

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Lornoy W, De Meester J, Becaus I, Billiouw J-M, Van Malderen PA, Van Pottelberge M: Impact of convective flow on phosphorus removal in maintenance hemodialysis patients: J Ren Nutr 16, 47-53, 2006



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