DIALYSIS update

The importance of strict volume control in HD patients

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Contents

Preface

The abnormal hydration state in HD patients has been related to arterial hypertension, intradialytic dialysis hypotension and other symptoms and morbid conditions. including pulmonary and peripheral oedema, heart failure, and left ventricular hypertrophy. Consequently, targeting at a normal hydration state in HD patients is an integral part of the routine dialysis practice. To assess the hydration state, usually clinical surrogate parameters, e.g. the patient's dry weight, are used. However, when using such a parameter as indicator, the nephrologist has to consider that midterm changes in dry body weight can occur due to changes in both, body water and lean or fat tissue mass. Therefore, ideally a tool measuring patient hydration state and composition should be able to evaluate parameters of lean and fat tissue. Multifrequency bioimpedance offers the possibility of evaluating in a simple way at bedside the body composition ***and*** hydration state of the patient. The Body Composition Monitor (BCM) has been validated and successfully introduced for use in a number of clinical trials and in everyday clinical practice.

This *Dialysis Update* deals with publications stressing the importance of normalizing hydration state in HD patients and summarizes the clinical benefits of optimal fluid management, ranging from improvement in cognitive function, through better control of blood pressure up to survival advantages.

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DIALYSIS update

1. Determinants of left ventricular mass and hypertrophy in haemodialysis patients assessed by cardiac magnetic resonance imaging

Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular (CV) mortality in HD patients. **RK Patel et al.** aimed to assess the determinants of LV mass index (LVMI, corrected for body surface area) and LVH in HD patients by cardiac magnetic resonance imaging (CMRI). CMRI provides a more detailed, volume-independent measurement of cardiac structure and has been established as the most accurate noninvasive method for assessing ventricular dimensions in patients, including those with stage 5 chronic kidney disease.

A total of 246 HD patients with a mean age of 51.4 ± 12.1 years and a mean duration on HD of 3.0 ± 3.0 years were assessed between 2002 and 2008. CMRIs were performed 24 h after the end of the last dialysis session. LVM was analyzed by two experts, who were blinded to patient clinical characteristics. LVH was defined as LVMI (LVM/BSA) >84.1 g/m² (male) or >76.4 g/m² (female), and LV systolic dysfunction was defined as LV ejection fraction (LVEF) <55%. LV dilation was defined as EDV (end-diastolic volume)/BSA >111.7 ml/m² (male) or 99.3 ml/m² (female) or ESV (end-systolic volume)/BSA >92.8 ml/m² (male) or 70.3 ml/m² (female). HD information, including pre-HD and post-HD systolic and diastolic blood pressure (BP), dosage of ultrafiltration, dialysis adequacy, and biochemical and haematologic blood results was collected retrospectively at 30 d intervals up to 180 d before CMRI and mean results were calculated.

LVH was found in 63.8% of patients. **Table 1** shows parameters that were statistically significantly different in patients with LVH and no LVH.

There were no significant differences between both groups regarding age, gender, body mass index, CV history, duration on HD, post-HD systolic and diastolic BP, and pre-HD diastolic BP and urea reduction ratio, haemoglobin, albumin, adjusted serum calcium, or PTH, and in drug use.

Parameter	No LVH	LVH	p-value
Pre-HD systolic BP (mmHg)	138.1±24.3	144.6±20.0	0.02
Pre-HD pulse pressure (mmHg)	59.1±17.6	64.4±16.5	0.02
Ca x PO_4	2.72±0.90	3.05±1.00	0.03
Ejection fraction (%)	68.5±7.9	62.6±15.1	0.001
LVMI (g/m²)	67.2±10.8	116.9±31.3	0.001
End-diastolic volume/BSA (ml/m²)	58.2±18.3	88.7±34.7	0.001
End-systolic volume/BSA (ml/m²)	19.7±10.8	36.5±27.5	0.001
LV systolic dysfunction (ml/m²)	6 (6.7%)	39 (24.8%)	0.001
LV dilatation (n)	2 (2.2%)	37 (23.6%)	0.001

Table 1

Multivariate logistic regression analysis identified EDV/BSA (OR 1.06, 95% CI 1.04 to 1.08, p<0.001), pre-HD systolic BP (OR 1.02, 95% CI 1.01 to 1.04, p=0.01), and Ca x PO_4 (OR 1.74, 95% CI 1.17 to 2.57, p=0.006) as the strongest independent predictors of LVH. The authors discuss that development of LVH in dialysis patients is partly due to the adaptive response of the LV to long-term volume overload. On the other hand, elevated Ca x PO_4 is a risk factor for arterial calcification and, as a consequence, contributes to BP and the development of LVH.

In conclusion, determination of the factors that are linked to LVH may lead to new treatment strategies to address CV risk in dialysis patients. The authors identified the main determinants of LVH being EDV/BSA (a preload factor) and pre-HD BP and Ca x PO_4 (afterload factors). Improved BP, fluid volume and mineral control offer interventions with potential to prevent or regress LVH. *CL*

Patel RK, Oliver S, Mark PB, Powell JR, McQuarrie EP, Traynor JP, Dargie HJ, Jardine AG: Determinants of left ventricular mass and hypertrophy in hemodialysis patients assessed by cardiac magnetic resonance imaging; Clin J Am Soc Nephrol 4, 1477 – 1483, 2009

2. The effect of strict volume control on cognitive functions in chronic haemodialysis patients

Apart from the higher risk of cardiovascular diseases in HD patients in comparison to the general population, cognitive dysfunction is also a well-known complication that is evident in 30% of the HD population. However, the pathogenesis is unknown. **A Dogukan et al.** investigated in this cross-sectional study the effect of strict volume control (strict salt restriction and increased ultrafiltration) on cognitive function in HD patients.

22 HD patients from one Turkish centre who were normotensive by applying a strict volume control, and 24 HD patients from another Turkish centre who were normotensive by receiving anti-hypertensive drugs and 20 healthy subjects (controls) were investigated. "Normotensive" was defined as pre-dialysis BP < 140/90 mmHg. Auditory event-related potentials (P300) were recorded electroencephalographically with electrodes at the scalp when blood pressures were reached at target level at the end of six-month follow-up period. Prolongation of P300 latency was shown to be the earliest sign of cognitive dysfunction in metabolic encephalopathies, including uraemic encephalopathies.

P300 amplitudes were significantly lower in patients on antihypertensive drugs than in the controls or in patients applying strict volume control. P300 latency was longer in patients on antihypertensive drugs than in the controls or in patients applying strict volume control (see **Table 2**).

The study results suggest that strict volume control may have beneficial effects on cognitive function in HD patients. *KB*

A Dogukan, M Guler, MF Yavuzkir, A Tekatas, OK Poyrazoglu, B Aygen, AI Gunal, TK Yoldas: The effect of strict volume control on cognitive functions in chronic hemodialysis patients; Renal Failure 31: 641 – 646, 2009

Electrophysiological studies in control and patient groups

	Control (n=20)	Pat. applying strict volume control (n=22)	Pat. on antihypertensive drugs (n=24)	p-value
Age (year)	43.7 ± 8.0	42.0 ± 15.1	42.7 ± 12.9	
P300 latency (ms)	321.6 ± 28.3	345.6 ± 36.7	359.9 ± 39.6	<0.005*§,<0.001&
P300 amplitude (µV)	12.4 ± 5.3	11.3 ± 5.4	9.5 ± 5.1	<0.05§&

Tab. 2: ** Control vs. patients applying strict volume control.*
§ Patients applying strict volume control vs. patients on antihypertensive drugs.
& Control vs. patients on antihypertensive drugs.

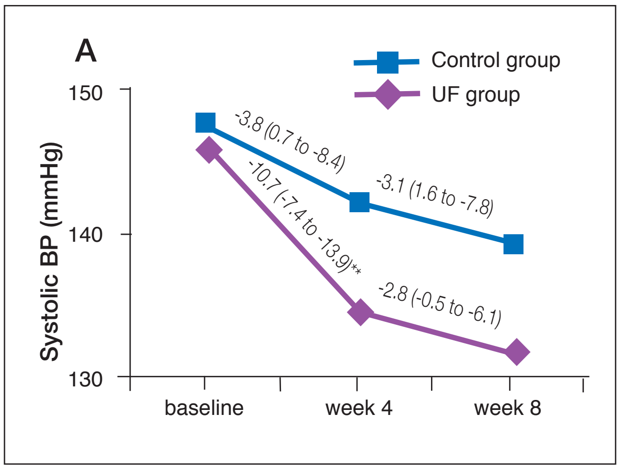
3. Dry-weight reduction in hypertensive haemodialysis patients (DRIP): - A randomized, controlled trial

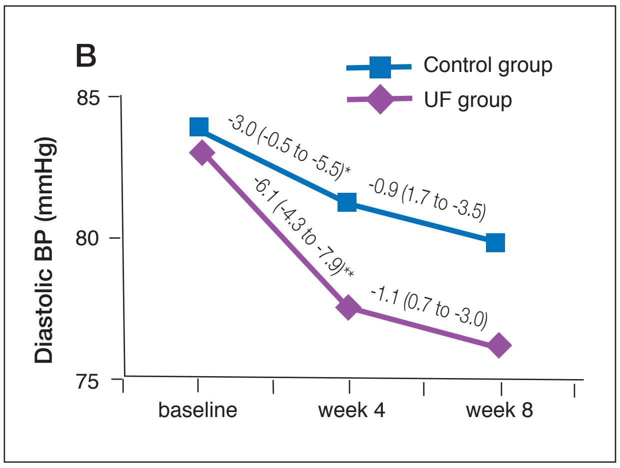
The majority of HD patients is hypertensive. Among the causative factors in this patient population, excess volume is thought to be of prior importance. **R Agarwal et al.** aimed at determining whether additional volume reduction will result in better blood pressure (BP) control among hypertensive HD patients.

The hypothesis was tested in a 8-week, prospective, randomized trial in prevalent HD patients from 4 dialysis units and who were categorised hypertensive based on a mean interdialytic BP ≥135/85 mmHg. Patients with stroke, myocardial infarction, limb ischaemia in the previous 6 months, ambulatory BP of >170/100 mmHg, who missed >1 dialysis in the previous month, had chronic atrial fibrillation or morbid obesity were excluded. Patients were randomised 1:2 to a control group (n=50, 92% blacks, 38% diabetics) and an ultrafiltration (UF) group (n=100, 85% blacks, 40% diabetics). In the UF group, an initial additional weight loss of 0.1 kg/10-kg body weight was prescribed per dialysis without increasing the time or frequency of dialysis. This additional weight loss was combined with the UF volume required to remove interdialytic weight gain to achieve the desired reduction in dry weight. If UF was not tolerated, the additional prescribed weight loss was continuously reduced until even a 0.2-kg incremental weight loss per dialysis was not tolerated. At this point, the patient was said to be at his or her dry weight. No changes in antihypertensive medication were allowed during the study. Ambulatory BP monitoring was performed after the midweek session for 44 hours.

There was no significant difference between the two groups with respect to baseline characteristics. All of the patients were haemodialyzed 3 times per week (w) for an average of 235 minutes, at a blood flow rate of 400 ± 34 mL/min and dialysate flow rate of 765 ± 77 mL/min. Baseline postdialysis weight in the UF group was 81.3 ± 19.6 kg and 82.0 ± 19.2 kg in the control group (p = 0.73). In the UF group the change from baseline postdialysis weight was -0.9 kg (p<0.001) at 4 w and -1.0 kg at 8 w (p<0.001). In the control group the change from baseline was 0.0 kg at 4 weeks and at 8 weeks. Baseline ambulatory BP was 146.4 ± 10.6 / 83.4 ± 10.9 mmHg in the control group and 145.8 ± 10.2 / 82.9 ± 10.0 mmHg in the UF group (p=ns). **Figures 1a and 1b** depict the effect of dry weight reduction on systolic and diastolic BP in hypertensive HD patients. Compared to baseline the UF-attributable change in systolic BP was -6.9 mmHg at 4 w (p=0.016) and -6.6 mmHg at 8 w (p=0.021); and for the diastolic BP it was -3.1 mmHg at 4 w (p=0.048) and

Fig. 1a and 1b: *Effect of dry-weight reduction on interdialytic ambulatory systolic and diastolic BP. Mean systolic and diastolic BP values and the mean changes in BP (95%CI) at week 4 and 8 are depicted (*p<0.05, **p<0.001).*





-3.3 mm Hg at 8 w (p=0.037). The authors see the change in BP in the control group likely to be a result of participation in the study and numerous physician visits, which may have had a placebo effect. Interdialytic weight gain averaged 2.9 kg in the UF group and 2.8 kg in the control group at baseline and did not change significantly within or between groups over time. Cramps, dizziness, intradialytic hypotension, need for saline, or reduction in UF rates were more commonly seen among patients in the UF group. Despite more intradialytic symptoms, the Kidney Disease Quality of Life-Short Form questionnaire including domains on energy, symptoms related to kidney disease, and physical functioning, was unchanged from baseline to week 8.

In conclusion, the data provide support for the hypothesis that extracellular volume expansion, even if clinical signs of volume overload are lacking, may mediate hypertension. Challenging dry weight in long-term HD patients as first line therapy appears a reasonable strategy for controlling hypertension. However, close clinical supervision is required owing to the potential risks of hypotension-related symptoms. CL

Agarwal R, Alborzi P, Satyan S, Light RP: Dry-weight reduction in hypertensive hemodialysis patients (DRIP): - A randomized, controlled trial; Hypertension 53, 500 – 507, 2009

4. The mortality risk of overhydration in haemodialysis patients

V Wizemann et al. have published a study referring to the hydration status in HD patients. They investigated if there is a link between hydration state and risk of death in chronic HD patients.

A total of 269 prevalent HD patients (dialysis vintage: 41.2 ± 70 months) fulfilled the inclusion criteria in three European dialysis centres in 2003. The patients were measured once at baseline pre-dialysis with the body composition monitor (BCM, Fresenius Medical Care) to assess the hydration status. The survival of patients until 2007 (3.5 years follow-up) was documented. HD treatment was performed three times per week for 4 – 5 h with a mean blood flow of 420 ml/min, and primarily polysulphone high-flux membranes were used. The patient population was divided into a hyperhydrated (n = 58) and a normohydrated group (n = 211).The threshold for hyperhydration was set to a relative excess of extracellular water (ECW) > 15% that is comparable with a expansion of ECW of ~ 2.5 L.

The median relative hydration status (HS) was for all patients 8.6 ± 8.9% before the HD treatment, for the hyperhydrated subgroup it was 19.9% ± 5.3%. The cumulative survival factored for the relative HS is shown in a Kaplan-Meier analysis in **Figure 2**.

The unadjusted gross annual mortality of all patients was 8.5%, however, for the hyperhydrated subgroup it was 14.7%.

The Cox adjusted hazard ratios (HR) revealed that the following parameters are significant predictors for mortality:

- age (HR: 1.05/year; p < 0.001),
- diabetes (y/n) (HR: 2.8; p < 0.001),
- peripheral vascular disease (y/n) (HR: 1.68; p = 0.045),
- relative HS pre-dialysis (> 15%) (HR: 2.1; p = 0.003).

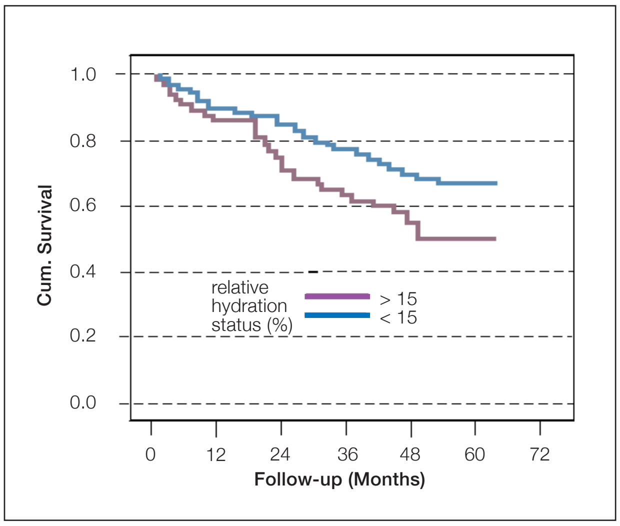


Fig. 2: *Kaplan-Meier curve separating the patients for the relative hydration status (HS > 15%).*

The results of the study confirm the association between hyperhydration and higher mortality in HD patients on the basis of a quantitative method (BCM) to estimate the hydration status. *KB*

V Wizemann, P Wabel, P Chamney , W Zaluska, U Moissl, C Rode, T Malecka-Masalska, D Marcelli: The mortality risk of overhydration in haemodialysis patients; Nephrol Dial Transplant 24: 1574 – 1579, 2009

5. Guided optimization of fluid status in haemodialysis patients

The achievement of a normal hydration state is one of the major targets of HD therapy. Both fluid overload and dehydration are linked to an increased morbidity in HD patients. In this study a bioimpedance spectroscopy device for body composition measurement was used to determine the normohydration weight. The body composition monitor (BCM, Fresenius Medical Care) provides an objective target for the normal volume status in an individual patient without the need for a reference population. **P Machek et al.** performed the study to reduce fluid overload in hyperhydrated patients whilst minimizing the frequency of intradialytic adverse events.

The hydration status was monitored and targeted at least monthly with the BCM over the course of appr. 1 year (2006 – 2007) in the available patient population of one dialysis centre in the Czech Republic. The 52 patients were divided into three groups: the hyperhydrated group (relative fluid overload > 15% of extracellular water (ECW) (n = 13, group A), the adverse event group (patients with more than two adverse events, e.g. symptomatic hypotension, cramps in the last 4 weeks (n = 12, group B)) and the remaining patients (n = 27, group C).

In group A, the fluid overload was reduced significantly during the study period ($p < 0.001$), see **Figure 3 and 4**. A significant reduction in the systolic ($p = 0.029$) and diastolic ($p = 0.042$) blood pressure before and after the treatment could be observed in group A together with a reduction of the antihypertensive medication ($p = 0.031$). The patients in group A exhibited an increase in the left ventricular ejection fraction from 51.8 ± 9.8% to 58.4 ± 8% ($p = 0.021$).

Group B showed an increase in fluid status ($p < 0.001$). The recorded adverse events reduced significantly from 25.7% ± 10% to 6.9% ± 7.8% ($p < 0.001$), while all other clinical parameters including the blood pressure and the ejection fraction did not change.

The number of patients achieving the defined target for the pre-and post-dialysis fluid overload increased by 66%.

The results of the study show that with the help of the BCM, it was possible to modify the fluid status in incident and prevalent dialysis patients towards normohydration without causing additional intra- or interdialytic adverse events. Furthermore, the reduction in fluid overload made a significant reduction in the antihypertensive medication possible. *KB*

P Machek, T Jirka, U Moissl, P Chamney, P Wabel: Guided optimization of fluid status in haemodialysis patients; Nephrol Dial Transplant 25: 538 – 544, 2010

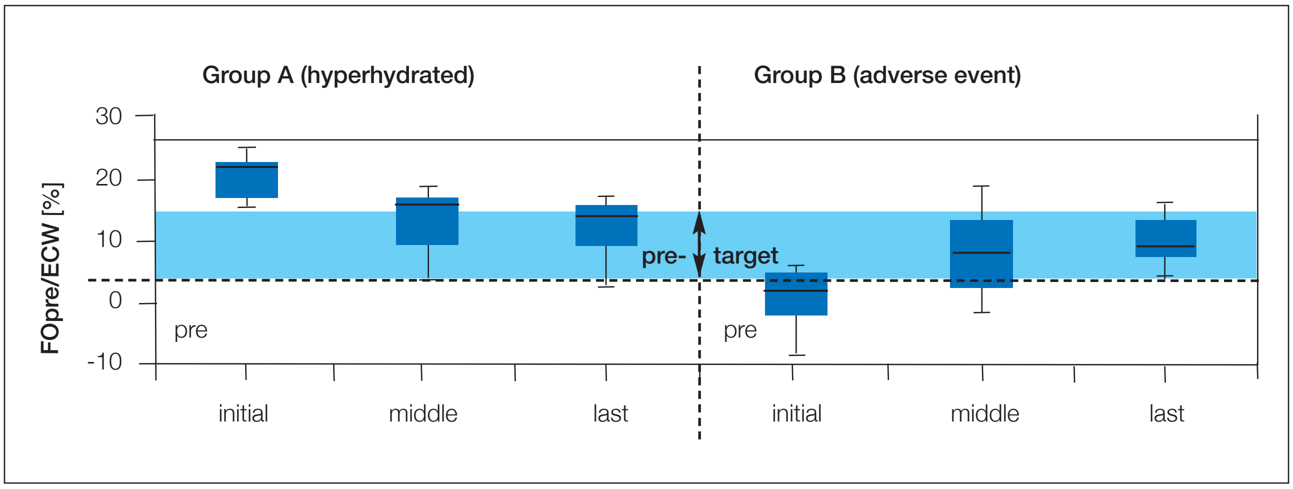


Fig. 3: *Fluid status changes in group A and group B before dialysis treatment. In these groups, the relative fluid status before dialysis treatment is shown. Each box summarizes the results of the initial, the middle and the last measurements. Additionally, the target range for the relative fluid overload before dialysis treatment (between 6% and 15%) is indicated. The boundaries of the boxes are the 25th and the 75th percentile. The whiskers show the 10th and the 90th percentile.*

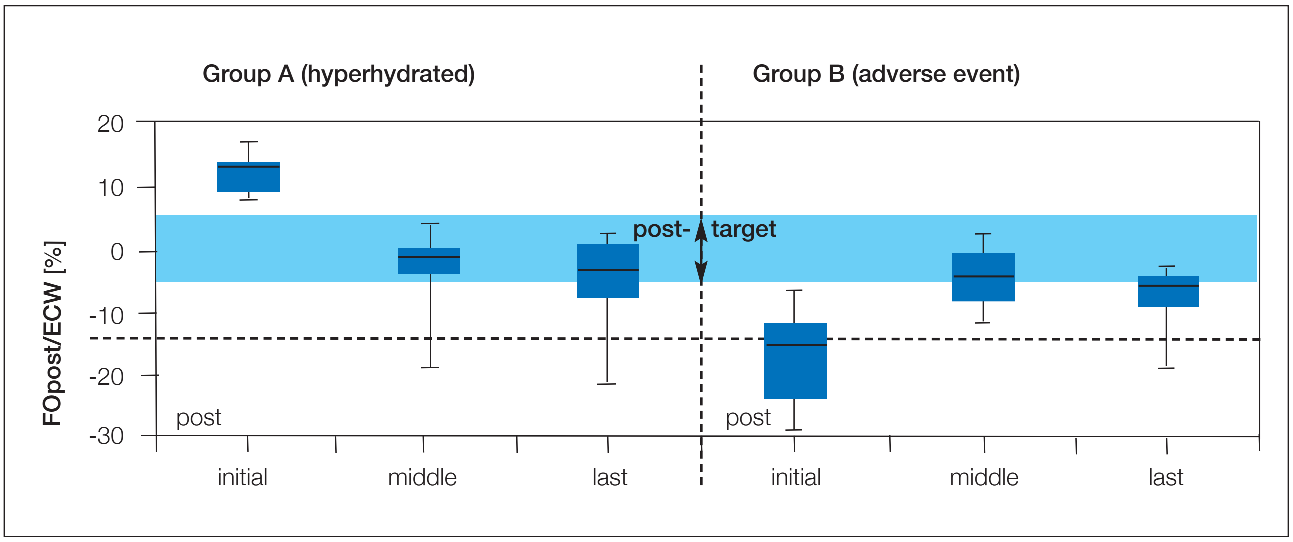


Fig. 4: *Fluid status change in group A and group B after dialysis treatment including the target range for the relative fluid overload after treatment (-6% to +6%). The boxes show the results of the initial, the middle and the last measurements.*

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