Nephrol Dial Transplant (2009) 24: 1574–1579
doi: 10.1093/ndt/gfn707
Advance Access publication 7 January 2009

The mortality risk of overhydration in haemodialysis patients

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Abstract

Background. While cardiovascular events remain the primary form of mortality in haemodialysis (HD) patients, few centres are aware of the impact of the hydration status (HS). The aim of this study was to investigate how the magnitude of the prevailing overhydration influences long-term survival.

Methods. We measured the hydration status in 269 prevalent HD patients (28% diabetics, dialysis vintage = 41.2 ± 70 months) in three European centres with a body composition monitor (BCM) that enables quantitative assessment of hydration status and body composition. The survival of these patients was ascertained after a follow-up period of 3.5 years. The cut off threshold for the definition of hyperhydration was set to 15% relative to the extracellular water (ECW), which represents an excess of ECW of ∼2.5 l. Cox-proportional hazard models were used to compare survival according to the baseline hydration status for a set of demographic data, comorbid conditions and other predictors.

Results. The median hydration state (HS) before the HD treatment (ΔHS_{pre}) for all patients was 8.6 ± 8.9%. The unadjusted gross annual mortality of all patients was 8.5%. The hyperhydrated subgroup ($n = 58$) presented ΔHS_{pre} = 19.9 ± 5.3% and a gross mortality of 14.7%. The Cox adjusted hazard ratios (HRs) revealed that age (HR_{age} = 1.05, 1/year; $P < 0.001$), systolic blood pressure (BP_{sys}) ($HR_{BPsys} = 0.986$ 1/mmHg; $P = 0.014$), diabetes (HR_{Dia} = 2.766; $P < 0.001$), peripheral vascular disease (PVD) ($HR_{PVD} = 1.68$; $P = 0.045$) and relative hydration status (ΔHS_{pre}) ($HR_{\Delta HSpre} = 2.102$ $P = 0.003$) were the only significant predictors of mortality in our patient population.

Conclusion. The results of our study indicate that the hydration state is an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes. We believe that it is essential to measure the hydration status objectively and quantitatively in order to obtain a more clearly defined assessment of the prognosis of haemodialysis patients.

Keywords: bioimpedance; fluid status; haemodialysis; mortality; overhydration

Introduction

The achievement of a normal hydration state (HS) is one of the major targets of haemodialysis (HD) therapy. The concept of 'dry weight' is clinically undisputed and an integral part of the routine dialysis practice [1,2]. The abnormal hydration state has been related to arterial hypertension, dialysis-associated hypotension and other symptoms and signs including pulmonary and peripheral oedema, heart failure, left ventricular hypertrophy and other adverse cardiovascular sequelae [3–5]. To determine the hydration state, clinical surrogate parameters are used such as interdialytic weight gain, ultrafiltration rate or blood pressure [6,7]. In several observational studies, registry data and uncontrolled single-centre studies, the association between hydration state and outcome has been described [8–13]. However, clinical findings are not always conclusive and often contradictory as demonstrated for interdialytic weight gain and hydration state [14,15].

Traditionally, concepts to define a normal hydration state in anuric dialysis patients have aimed mainly for the achievement of clinically tolerable dialysis sessions (e.g. the absence of hypotensive episodes) [16] or a clinically desirable interdialytic period (e.g. the absence of interdialytic hypertension).

One major cause for the dichotomy of findings and paradoxical observations is the lack of a reliable method for the assessment of individual euvolaemia, for the detection of small changes in fluid volumes and even more importantly for the prediction of a target endpoint such as an individual normal hydration state in kilograms. Only such a method would avoid the reliance on subjective changes in hydration state and would allow a reliable quantification of a deviation from euvolaemia. In the present study, we used a bioimpedance spectroscopy method that defines objectively the individual hydration state on the basis of an individual's normal extracellular volume, taking into account the individual's body composition. The bioimpedance spectroscopy method applied was validated by isotope dilution methods [17], by accepted reference body composition methods [18,19], by techniques that measure relative changes in fluid volumes [20] and by extensive clinical assessment of the hydration state [21–24] in more than 1000 healthy subjects and patients. The relationship between the change in hydration state caused by ultrafiltration and the withdrawn ultrafiltration volume (UFV) was

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0.015 ± 0.8 l [24]. The aim of this study was to investigate and quantify a possible link between hydration state and risk of death in chronic HD patients.

Methods

Patients, HD treatment

All patients that received HD treatment in the three study centres in 2003 and fulfilled the inclusion criteria were included in the study, in total 269 prevalent patients (dialysis vintage $= 41.2 \pm 70$ months). The patients with pacemakers/implanted defibrillators or amputation of a major limb were excluded. The patients were measured once with the body composition monitor (BCM), and all other clinical data were collected simultaneously. The physicians and the nurses were blinded from the hydration status (HS) results. The survival of patients until 1 January 2007 (3.5 years follow-up) was documented. Death was counted as the outcome event, whilst patients who had received a transplant ($n = 29$) or left the centre ($n = 10$) were censored at the time of the event. Details of the patient population are presented in Table 1. HD therapy was performed three times per week for 4–5 h with a mean blood flow of 420 ml/min. A majority of patients were treated using 4008 series Fresenius Medical Care dialysis systems. Dialysis membranes were primarily polysulphone and high-flux membranes. Intradialytic weight loss (IDWL) was calculated as the difference between the pre- and post-weight normalized to the post-weight of the patient. Ultrafiltration volume (UFV) was expressed as the effective volume removal.

Assessment of body composition and hydration state

Body composition and hydration state were assessed with a portable whole body bioimpedance spectroscopy device (BCM—Fresenius Medical Care D GmbH). The BCM measures the impedance spectroscopy at 50 frequencies. Measurements were performed before the start of the HD treatment with the patient sitting relaxed in the dialysis chair. Electrodes were attached to one hand and one foot on the same side of the body. All measurements were performed by one trained nurse—no failure of measurement especially due to possible electrical interference was recorded. The fluid volumes extracellular (ECW), intracellular (ICW) and total body water (TBW) were determined using the approach described by Moissl [17]. The hydration status, lean tissue mass (LTM) and fat mass were calculated based on a physiologic tissue model described by Chamney [25]. To facilitate the comparison between patients, the hydration state was normalized to the ECW ($\Delta HS = HS/ECW$). The patient population was divided into a hyperhydrated and a normohydrated groups using a cutoff of 15% for the relative hydration status ($\Delta HS > 15\%$). The definition of hyperhydration for $\Delta HS > 15\%$ is based on the work described by Wabel *et al*. [26]. The boundary of $\Delta HS > 15\%$ represents the highest quartile of the measured population. The normohydrated group also included patients with mild overhydration ($6{,}8\% < \Delta HS \leq 15\%$), and these patient groups were not separated for further analysis. LTM and Fat were normalized to the body surface area to obtain lean tissue index ($LTI = LTM/height^2$) and fat tissue index ($FTI = Fat/height^2$). The values for LTI and FTI were compared to an age- and gender-matched reference population ($n = 1248$) [27]. Values below the 10th percentile of the reference population were regarded as clinically significant. It has been demonstrated in studies in HD patients that the reproducibility of the used BIS device [coefficient of variation ($CV_{ECW} = 2.6\%$; $CV_{TBW} = 2.6\%$)] is far superior to the reproducibility of clinical measurements like the blood pressure ($CV_{BPsyspre} = 8.5\%$; $CV_{BPsyspost} = 15.7\%$) [28]. Therefore, only one BCM measurement was performed, while the blood pressure was averaged for six consecutive dialysis treatments as described by Agarwal [29].

The hydration status at the end of the treatments (HS_{post}) was calculated by subtracting the UFV from the hydration status at the start of the treatment (HS_{pre}).

Lab tests, antihypertensive medication and instrumental tests

The last monthly lab data before the treatment involving the BCM measurement were recorded with regard to serum albumin, haematocrit, urea, serum creatinine and serum inorganic phosphates. Additionally, the number of antihypertensive medications (AHT) was recorded—diuretics and drugs administered for cardioprotective reasons were included in the analysis.

No chest x-rays are routinely performed in the centres involved in the study. Therefore, no cardiothoracic ratio was available for the patients.

Symptoms

The symptoms were assessed with an advanced clinical score [5]. To simplify the analysis, the signs and symptoms were grouped into three classes: those of dehydration (interdialytic weakness and dizziness, thirst after HD), those of overhydration (dyspnoea, oedema, raised jugular venous pressure, cough caused by fluid overload) and those of vascular intolerance (cramps, hypotension, vomiting). The last six treatments before the treatment involving the BCM measurement were analysed for the occurrence of the respective symptoms. Additionally, the average appearance of intradialytic adverse events per HD treatment was calculated.

Comorbidities

The comorbidities recorded included diabetes, cardiovascular problems (cardiac insufficiency, atrial fibrillation, ischaemic heart disease, coronary artery disease) and peripheral vascular disease (PVD).

Statistics/analysis

Mean values and frequencies of the parameters were compared by ANOVA or chi square test, as appropriate. The level of significance was set to $P < 0.05$. Survival functions according to the baseline hydration status were described using the Kaplan–Meier technique. The log-rank test was

Table 1. Patient characteristics of all patients and the subgroup of all hyperhydrated and all normohydrated patients

	Hyperhydrated	Normohydrated	All
Number of patients	58	211	269
	2 Transplanted	27 Transplanted	29 Transplanted
	2 Centre change	8 Centre change	10 Centre change
Age (years)	65 ± 14.8	66 ± 15.2	65 ± 15
Weight (kg)	66.6 ± 14.1	72.9 ± 13.7	71.3 ± 14
BMI (kg/m^2)	23.9 ± 3.8[a,b]	25.8 ± 4.8[a]	25.6 ± 4.7[b]
Diabetics (y/n)	15%	32%	28%
Cardiovascular problems (y/n)	32%	35%	35%
Peripheral vascular disease (y/n)	18.9%	12%	13%
Intradialytic adverse events (1/treatment)	2.9%	7.3%	6.5%
Albumin (g/l)	40 ± 4	41 ± 3.2	40.8 ± 3.4
Haematocrit (%)	31.1 ± 4.9	33 ± 4.3	33 ± 4.5
Urea removal rate (%)	72.4 ± 9.8	73.6 ± 11.7	73.3 ± 11.4
Phosphate (mmol/l)	2.0 ± 5.7	1.9 ± 1.4	1.9 ± 3.0
Creatinine (mg/dl)	6.6 ± 2.3	6.6 ± 2.4	6.5 ± 2.4
Dialysis vintage (months)	57.3 ± 88.8[a]	37.6 ± 62[a]	41.2 ± 70
Intradialytic weight loss (%)	3.7 ± 1.1	3.09 ± 1.1	3.29 ± 1.2
Ultrafiltration volume (l)	2.28 ± 0.76	2.25 ± 0.86	2.26 ± 0.84
Equilibrated (kT/V)	1.3 ± 0.3	1.36 ± 0.3	1.34 ± 0.3
Preblood pressure$_{sys/dia}$ (mmHg)	142 ± 17/77 ± 11	135 ± 22/74 ± 12	136 ± 21/75 ± 12
Postblood pressure$_{sys/dia}$ (mmHg)	143 ± 17[a,b]	128 ± 19[a]	133 ± 20[b]
	78 ± 9	74 ± 10	75 ± 10
Number of antihypertensive medication	1.5 ± 1.5	1 ± 1.2	1 ± 1.3
Extracellular water (l)	17.6 ± 3.3	16.1 ± 3.0	16.5 ± 3.2
Total body water (l)	34.5 ± 7.3	33.3 ± 7.1	33.5 ± 7.1
Hydration status$_{pre}$ (l)	3.5 ± 1.2[c]	0.9 ± 1.1[c]	1.4 ± 1.6[c]
Hydration status$_{post}$ (l)	1.3 ± 1.5[c]	−1.25 ± 1.4[c]	−0.7 ± 1.8[c]
Relative hydration status$_{pre}$ (%)	19.9 ± 5.3[c]	5.7 ± 6.4%[c]	8.6 ± 8.9%[c]
Relative hydration status$_{post}$ (%)	8.2 ± 8.2[c]	−8.9 ± 11.4[c]	−5.6 ± 13.5[c]
Lean tissue index (kg/m^2)	12.6 ± 3.2	12.8 ± 3.0[b]	12.7 ± 3[b]
Fat tissue index (kg/m^2)	6.4 ± 3.5[c]	8.8 ± 4.2[c]	8.2 ± 4.2[c]
Relative fat (%)	29.3 ± 11.1[a,b]	33.8 ± 10.6[a]	32.5 ± 10.8[b]
Mortality in 3.5 years	41%	30%	32%

[a]Significantly different between the group 'hyperhydrated' and group 'normohydrated'.
[b]Significantly different between the group 'all' and group 'hyperhydrated'.
[c]Significantly different between all groups.

used for univariable comparisons. Cox-proportional hazard models were used to compare survival according to the baseline hydration status adjusting for demographic data (age, gender), comorbid conditions (diabetes, cardiovascular problems and PVD) and other predictors (anthropometric indexes as LTI and FTI, dialysis vintage, blood pressure, IDWL, lab data as albumin, haematocrit, intact PTH, pre-dialysis phosphate, pre-dialysis creatinine and a dialysis dose as expressed by equilibrated Kt/V). Both Kaplan–Meier curves and Cox model used the same endpoint (time of death), and patients were censored when they were transferred to another dialysis unit, received a kidney graft or were still on extra-corporeal treatment on the final observation date (1 July 2007). When Cox-proportional hazard regression was applied, stepwise methods were used to obtain the best multivariate model. Estimated relative risks (hazard ratios) and their 90% confidence intervals were calculated with the use of the estimated regression coefficients and their standard errors. The contribution of covariates to explain the dependent variable was assessed by means of a two-tailed Wald test, with $P < 0.05$ considered significant. The proportion hazard assumption was checked for each model by inspection of the complementary log minus log plots. All statistical analyses were performed using the SPSS software, version 15 (SPSS Inc., Chicago, IL, USA).

The Cox-proportional hazard regression was applied for the highest tertile (ΔHS > 12%) and the highest quartile (ΔHS > 15%) of the population. In the further analysis, the quartile analysis (ΔHS > 15%) was preferred over the tertile analysis because this analysis demonstrated a higher independent risk factor.

Results

The patient characteristics and the differences between all patients, the hyperhydrated and the normohydrated patients are recorded in Table 1. The dialysis vintage was highest in the hyperhydrated group (57.3 months). The hyperhydrated patients were found to have a lower body mass index (BMI_{HyH} = 23.9 kg/m^2; BMI_{NHy} = 25.8 kg/m^2; BMI_{all} = 25.6 kg/m^2) and a lower relative fat mass ($relFat_{HyH}$ = 29.3%; $relFat_{NHy}$ = 33.8%; $relFat_{all}$ = 32.5 kg) than the normohydrated group and all patients. The systolic blood pressure after the treatment was significantly higher in the hyperhydrated patient group ($postBP_{sys\_HyH}$ = 143 mmHg; $postBP_{sys\_NHy}$ = 128 mmHg; $postBP_{sys\_all}$ = 133 mmHg), while there was no difference in the blood pressures before the treatment. The hydration status before and after the treatment was significantly different between all groups.

The hyperhydrated patients presented the highest hydration status ($HS_{pre\_HyH} = 3.5$ l; $HS_{pre\_NHy} = 0.9$ l; $HS_{pre\_all} = 1.4$ l/$HS_{post\_HyH} = 1.3$ l; $HS_{post\_NHy} = -1.25$ l; $HS_{post\_all} = -0.7$ l).

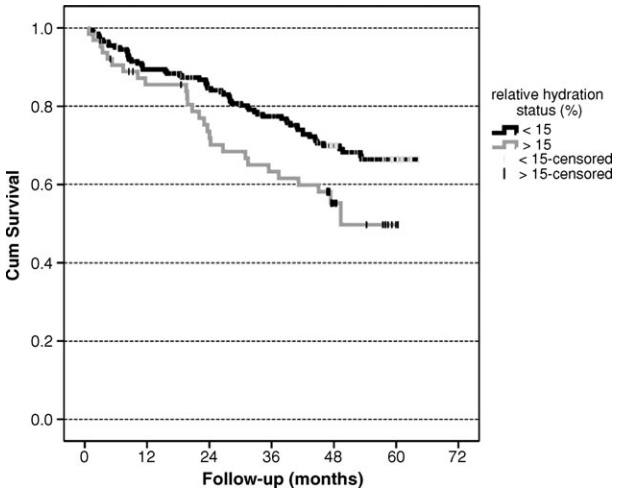

Fig. 1. Kaplan–Meier curve separating the patients for the relative hydration status (ΔHS >15%).

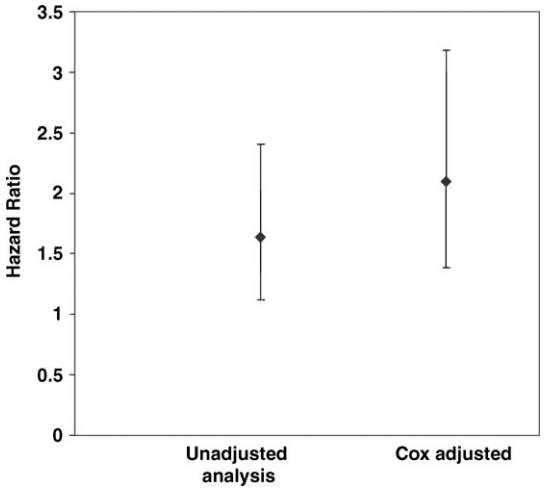

Fig. 2. Hazard ratio of the relative hydration status (ΔHS >15%) for the unadjusted analysis and the Cox adjusted model (together with the upper and lower limits for the 90% confidence interval).

Table 2. Cox adjusted hazard ratios

		90% confidence interval		
	Hazard ratio	Lower	Upper	Significance
Age (/year)	1.047	1.029	1.066	<0.001
BP_{sys} (/mmHg)	0.986	0.979	0.995	0.014
Diabetes (y/n)	2.766	1.879	4.073	<0.001
Peripheral vascular disease (y/n)	1.683	1.097	2.582	0.045
ΔHS_{pre} (>15%)	2.102	1.389	3.179	0.003

The cumulative survival factored for the relative hydration status (ΔHS) is shown in a Kaplan–Meier analysis in Figure 1.

Figure 2 shows the unadjusted and Cox adjusted hazard ratios for the relative hydration status (unadjusted $HR_{HS} = 1.64$, $P = 0.033$). The Cox adjusted hazard ratios (see Table 2) reveal that age, systolic blood pressure, diabetes, PVDs and relative hydration status are the only significant predictors of mortality ($HR_{age} = 1.05$, $P < 0.001$; $HR_{BPsys} = 0.986$, $P = 0.014$; $HR_{Dia} = 2.766$, $P < 0.001$; $HR_{PVD} = 1.68$, $P = 0.045$; $HR_{HS} = 2.102$, $P = 0.003$).

Discussion

The results of our study indicate that the hydration state is an important and independent predictor of mortality in chronic HD patients secondary only to the presence of diabetes. Our patient mix is comparable to other published European HD populations [30] although the mortality rate of 8.5% is significantly lower than that reported in comparable studies [30–32], but in the range of studies involving patients under strict volume control [10]. These findings are consistent with uncontrolled single-centre studies that have demonstrated an association between excellent control of hypertension and low mortality [10,13,33].

Our low mortality indicates that a healthier group of patients was investigated in the current study. This notion is supported by a comparably high mean serum albumin level as compared to DOPPS data of the HD populations [34]. Serum albumin in dialysis patients is associated with nutritional state [35], inflammation [36], MIA syndrome [37], atherosclerosis [38,39] and concentration of free toxins such as p-cresol [40]. The low overall mortality rate and normal serum albumin concentrations in our study population, which was treated with ultrapure dialysate, high-flux membranes, high urea removal rates and low ultrafiltration rates, may also account for the failure of albumin (<40 g/l) as a predictor of outcome both in the unadjusted and adjusted Cox model. The only selection bias that might have been introduced could have resulted from the exclusion of patients with pacemakers and defibrillators from BCM measurements. Though small, this group of patients is probably at high risk.

Interestingly, the dialysis vintage was significantly higher in the hyperhydrated group. To be sure that this was not the reason for the increased survival in the hyperhydrated group, we set up an additional Cox model forcing dialysis vintage into the model with the result that the hazard ratio and the significance of the relative hydration status increased even further. Additionally, the dialysis vintage showed a negative hazard ratio. With each additional month on dialysis, the risk was decreased by 0.3%. Thus, the higher dialysis vintage in the hyperhydrated group was not the cause of the increased mortality risk.

Of major interest is that diabetic patients have a significantly lower LTI and an increased FTI. In the unadjusted analysis, LTI showed a clearly increased hazard ratio, but as most patients in this category were diabetic the impact of diabetes on mortality effectively takes into account the influence of LTI. Thus, LTI was no longer

significant in the Cox adjusted analysis. This finding is also confirmed by a paper of Kakiya [41] who did not find any predictive value of lean mass index after adjustment with a multivariate model. Kakiya *et al.* used DEXA to assess body composition, but as DEXA was not able to differentiate between hyperhydration and muscle mass they had no possibility to assess the hydration status [42].

In our survival analysis, the threshold for the relative hydration status was set to $\Delta HS > 15\%$ that is comparable with a hyperhydration of $\sim$2.5 l [26]. This threshold might appear to be low when compared to UFVs arising in many dialysis centres. However, in our population we observed a low average hyperhydration before the treatment ($\Delta HS_{all} = 8.6 \pm 8.9\%$; $HS_{all} = 1.4 \pm 1.6$ l). In many of our patients, the IDWL was lower than that in other studies [11], which is likely to be the consequence of a low dietary salt intake. This may have been one factor contributing to the long-term survival of the study population.

With regard to other possible study limitations, CRP (which is known to be a factor influencing mortality) was not measured at the time of the BCM measurement in 2003.

Due to the inability to quantify the individual hydration state, previous studies assessing the outcome have used surrogate parameters such as IDWL [43], inter-dialysis weight gain and ultrafiltration rate [44]. However, those measurements are also surrogates for patients' compliance [45], nutritional behaviour and even the ultrafiltration/dialysis duration policy in the respective dialysis centre, which may not always be linked to the baseline hydration state. A patient can very well remain hyperhydrated despite the low interdialytic weight gain. The causes of death could not be separated into cardiovascular and noncardiovascular events since the majority of patients died at home. The death certification is not reliable enough for specifying correctly the cause of death. Therefore, no differentiation between cardiovascular and non-cardiovascular events was included.

In retrospective [43] and prospective cohort studies [45,46], the association between such subjective measures of hydration state and mortality is present only for subgroups of HD patients such as diabetics [43] or incident patients [45] but can be absent or even reversed in young and well-nourished patients [46]. The complex relationship between fluctuations in hydration state in HD patients and outcome clearly underlines the importance of an objective target for normohydration. The advantage of our method is that the individual body composition is taken into account when calculating the overall hydration state. Thus, the confounding influence of the body composition assessed by crude measures such as body mass index (BMI) is largely eliminated.

In our study, we found a clear impact of the relative hydration state on mortality, defined as $>15\%$ expansion of ECW. A recent study has shown that 25% of patients suffer from hyperhydration of >2.5 l [26], which is consistent with the current study.

This study confirmed the association between hyperhydration and higher mortality on the basis of a quantitative method to estimate the hydration status. This association does not necessarily imply a causal relationship: formal clinical trials will be required to confirm the improvement in survival once the dry body weight has been adjusted according to the BCM's indications. The reliability and simplicity of using the device will facilitate this. The results will support its routine use in the follow-up of dialysis patients.

Acknowledgements. The authors would like to thank E. Dorhout-Mess and F. Woods for their ideas and feedback.

Conflict of interest statement. P.W., P.C., U.M. and D.M. are employees of Fresenius Medical Care.

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Received for publication: 25.7.08
Accepted in revised form: 24.11.08