Title

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Fluid Retention is Associated with Cardiovascular Mortality in Chronic Hemodialysis Patients

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Abstract

Background—Patients with chronic kidney disease (CKD) stage 5 who undergo hemodialysis (HD) treatment have similarities to heart failure patients, in that both populations retain fluid frequently and have excessively high mortality. Volume overload in heart failure is associated with worse outcomes. We hypothesized that in HD patients greater interdialytic fluid gain is associated with poor all-cause and cardiovascular survival.

Methods and Results—We examined the 2-year (7/2001-6/2003) mortality in 34,107 HD patients across the United States, who had an average weight gain of at least 0.5 kg above their end-dialysis dry weight by the time the subsequent HD treatment started. The 3-month averaged interdialytic weight gain was divided into 8 categories of 0.5 kg increments (up to >=4.0 kg). Over 85% of patients gained >1.5 kg between dialysis sessions. In unadjusted analyses, higher weight gains was associated with better nutritional status (higher protein intake, serum albumin and body mass index) and tended to be linked to greater survival. However after multivariate adjustment for demographics (case-mix) and surrogates of malnutrition-inflammation complex, higher weight gain increments were associated with increased all-cause and cardiovascular death risk. Cardiovascular death hazard ratio (and 95% confidence interval) of weight gain <1.0 kg and >=4.0 kg (compared to 1.5 to 2.0 kg as the reference) were 0.67 (0.58-0.76) and 1.25 (1.12-1.39), respectively.

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Conclusions—In HD patients greater fluid retention between two subsequent HD treatment sessions is associated with higher all-cause and cardiovascular death risk. The mechanisms by which fluid retention influences cardiovascular survival in HD may be similar to HF patients and warrants further research.

Keywords

Hemodialysis population; heart failure; interdialytic fluid gain; ultrafiltration; cardiovascular death; malnutrition-inflammation-complex

Introduction

Fluid retention is a major clinical problem in individuals with advanced chronic kidney disease (CKD), also known as stage 5 CKD or end-stage renal disease, and is associated with morbid conditions such as lower extremity edema, anasarca, ascities, pulmonary vascular congestion or edema, hypertension and worsening heart failure.[1-3] Not infrequently dialysis treatment needs to be initiated to prevent or treat complications related to fluid retention, especially when diuretic therapy fails. Hence, removal of fluid during the dialysis treatment, also known as *ultrafiltration*, is the cornerstone of volume management in advanced-stage CKD. Ultrafiltration is also used occasionally in heart failure patients resistant to medical treatment.[4] A main challenge related to ultrafiltration interventions is the assessment of the required magnitude and frequency of fluid removal. However, it is not clear whether fluid removal can improve clinical outcomes in CKD or heart failure patients.

In addition to a tendency to retain fluid, chronic dialysis patients have also other similarities to heart failure patients; they both have excessively high mortality (currently 20% to 25% per year in the USA) mostly attributed to cardiovascular causes.[5] Furthermore, both dialysis and heart failure patients suffer from chronic wasting syndrome [6-8] and both exhibit survival paradoxes such as the obesity or cholesterol paradox.[9-11] Hence, studying the risk factors of poor survival in dialysis patient population may help advance strategies to mitigate high mortality in both dialysis and heart failure patients. Since fluid retention is a major morbid condition in both populations, we hypothesized that in chronic dialysis patients, greater interdialytic (between two consecutive dialysis treatment sessions) fluid gain is associated with poor all-cause and cardiovascular survival. In the current study, we examined a 2-year cohort of over 34,000 chronic hemodialysis (HD) outpatients across the nation, as currently over 90% of individuals who need dialysis therapy undergo thrice-weekly HD treatment in outpatient dialysis clinics in the United States and many other countries. We also hypothesized that the association between greater fluid retention and poor survival persists in diverse subgroups of HD patients. In particular, since the interdialytic weight gain is a function of oral fluid intake that includes routine food ingestion, we hypothesized that the mortality-predictability of higher fluid gain holds independent of other outcome predictors such as nutritional status.

Methods

Patients

This study examined data from all individuals with CKD stage 5, who underwent chronic HD treatment from July 1, 2001, to June 30, 2003, in one of the 580 outpatient dialysis clinics of a large dialysis organization in the United States (DaVita, Inc., El Segundo, CA). The study was approved by the Institutional Review Committees of both Los Angeles Biomedical Research Institute at Harbor-UCLA and DaVita Clinical Research.

Clinical and Demographic Measures and Comorbid States

The creation of the 2-year cohort has been described previously.[12-15] To minimize measurement variability, all repeated measures for each patient during any given calendar quarter, i.e., over a 13-week interval, were averaged and the summary estimate was used in all models. Averaged values were obtained for up to 8 calendar quarters (q1 through q8) for each laboratory and clinical measure for each patient over the 2-year cohort period. Dialysis treatment vintage was defined as the duration of time between the first day of dialysis treatment and the first day that the patient entered the cohort. The first (baseline) studied quarter for each patient was the calendar quarter, in which patient's dialysis treatment vintage was >90 days during at least half of the time of that given quarter.

In addition to the presence or absence of diabetes mellitus, histories of tobacco smoking and preexisting comorbid conditions were obtained by linking the DaVita database to the Medical Evidence Form 2728 of the United States Renal Data System (USRDS) [16] and categorized into 11 comorbid conditions: (1) ischemic heart disease, (2) congestive heart failure, (3) post cardiac arrest, (4) post myocardial infarction, (5) pericarditis, (6) cardiac dysrhythmia, (7) peripheral vascular disease (8) chronic obstructive pulmonary disease, (9) HIV/AIDS status, (10) ambulatory status, and (11) cancer. Computerized causes of death were obtained, and cardiovascular death was defined as death due to myocardial infarction, cardiac arrest, heart failure, cerebrovascular accident, and other cardiac causes.

Interdialytic Fluid Gain Measurement

Since HD patients usually undergo thrice weekly (Monday-Wednesday-Friday or Tuesday-Thursday-Saturday) dialysis treatment for 3 to 5 hrs, during the time between the two consecutive dialysis treatments they usually gain weight, which is almost entirely due to fluid retention. Hence, the amount of fluid that is ultrafiltrated during the subsequent HD treatment, i.e., the difference between the pre-HD (wet) and post-HD (dry) weight, is equivalent to the magnitude of weight gain immediately prior to the treatment as shown in Figure 1. To mitigate the inter-person variability over short periods, we calculated the 13-week averaged pre- and post-HD weights for each patient during each of the 8 calendar quarters of the 2-year cohort, i.e., up to 39 dialysis treatments per calendar quarter. The averaged amount of fluid gain or ultrafiltration for each patient was the difference between pre- and post-HD weight (Figure 1). Hence, a surviving patient could have up to 8 quarterly ultrafiltration or fluid retention values over the 2 years of follow-up. In this manuscript we chose to use "kg" instead of "liter" as the unit of fluid gain measurement. The body mass index (BMI) was calculated using the post-HD (dry) weight divided by height squared.

Laboratory Measures

Blood samples were drawn using uniform techniques in all of the DaVita dialysis clinics and were transported to the DaVita Laboratory in Deland, Florida, typically within 24 hrs. All laboratory values were measured by automated and standardized methods in the DaVita Laboratory. Most laboratory values, including complete blood cell counts and serum levels of urea nitrogen, creatinine, albumin, calcium, phosphorus, bicarbonate, and total iron binding capacity (TIBC), were measured monthly. Serum ferritin and intact PTH were measured at least quarterly. Hemoglobin was measured at least bi-weekly to monthly. Kt/V was used to estimate dialysis dose and normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR),[15] an estimation of daily protein intake, were measured monthly as a measure of protein intake. Most blood samples were collected pre-dialysis with the exception of the post-dialysis serum urea nitrogen that was obtained to calculate urea kinetics (Kt/V and nPNA).

Epidemiologic and Statistical Methods

We used logistic regression models to calculate the multivariate adjusted odds ratio of interdialytic weight gain ≥1.5 kg (as compared to <1.5 kg). We chose the 1.5 kg cutoff level, since targeting an interdialytic fluid gain below 1.5 to 2.0 kg is suggested as the optimal traget.[17] In survival analyses, patients with the fluid retention between 1.5 to 2.0 kg were the reference group as the immediately adjacent category to this cutoff level. Survival analyses were carried out using time-dependent (quarterly varying) Cox models that included all repeated measures that were averaged over each 13-week calendar quarter. In particular, we examined the association between quarterly averaged ultrafiltration volume and all-cause and cardiovascular mortality during each calendar quarter. For each analysis, three levels of multivariate adjustment were examined:

I. Minimally adjusted (here referred to as "unadjusted) model that included mortality data, ultrafiltration volume categories, baseline height and weight and the entry calendar quarter (q1 through q8);

II. Case-mix adjusted models that included all of the above plus age, sex, race and ethnicity (African Americans and other self-categorized Blacks, Non-Hispanic Caucasians, Asians, Hispanics and others), diabetes mellitus and 11 pre-existing comorbid states, history of tobacco smoking, categories of dialysis vintage (<6 mos, 6 mos to 2 yrs, 2-5 yrs and ≥5 yrs), primary insurance (Medicare, Medicaid, private and others), marital status (married, single, divorced, widowed and other or unknown), the standardized mortality ratio of the dialysis clinic during entry quarter, dialysis dose as indicated by Kt/V (single pool), presence or absence of a dialysis catheter, and residual renal function during the entry quarter, i.e. urinary urea clearance; and

III. Malnutrition-inflammation-cachexia syndrome (MICS) adjusted models which included all of the covariates in the case-mix model, BMI and 12 laboratory variables as surrogates of the nutritional state or inflammation with known association with clinical outcomes in HD patients: (1) nPNA as an indicator of daily protein intake, (2) serum albumin, (3) serum TIBC, (4) serum ferritin; (5) serum creatinine, (6) serum phosphorus, (7) serum calcium, (8) intact PTH, (9) serum bicarbonate, (10) peripheral white blood cell count (WBC), (11) lymphocyte percentage, and (12) hemoglobin.

Missing covariate data (under 2% for most laboratory and demographic variables and under 18% for any of the 10 comorbid conditions) were imputed by the mean or median of the existing values, whichever most appropriate. All descriptive and multivariate statistics were carried out with the SAS, version 9.1, SAS Institute, Inc., Cary, North Carolina, and Stata version 9.0, Stata Corporation, College Station, Texas. The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

Results

A total of 69,819 HD patients underwent chronic HD treatment over 500 DaVita dialysis clinics across the nation during the 2-year (7/2001-6/2003) study interval. After excluding patients who did not remain in DaVita beyond 3 months of HD, i.e., 5,600 patients from the first 7 calendar quarters and 5,870 patients from the last quarter, 58,058 HD patients remained, of whom 42,996 HD patients had all the required pre-HD and post-HD weight data documented electronically during every single HD treatment. After averaging weight values of up to 39 thrice-weekly HD treatment per each calendar and obtaining the averaged fluid retention per quarter, patients with a mean interdialytic weight gain below 0.5 kg in any of the 8 cohort quarters (n=8,889) were excluded, since they likely had either significant residual renal function or other unusual or acute conditions (such as diarrhea, vomiting, starvation, blood

loss, etc) which could confound the analyses. Hence, the study cohort comprised of 34,107 HD patients including 21,828 patients (64%) from the first calendar quarter dataset (summer 2001) and 12,279 from the subsequent 7 calendar quarters (q2 through q8).

Table 1 compares 4,900 HD patients whose interdialytic fluid gain was between 0.5 and 1.5 kg to 29,207 HD patients who gained >1.5 kg fluid. The greater fluid retainers were younger, included more men and diabetics, and had higher BMI and dietary protein intake (estimated by nPNA) and higher serum levels of albumin, creatinine, phosphorus and TIBC concentrations. In order to examine the correlates of interdialytic fluid gain ≥1.5 kg, we calculated odds ratios using logistic regression models as shown in Table 2. Older age and female sex was associated with lower likelihood of fluid retention. Diabetic status and longer dialysis vintage over 5 years were associated with 94% and 67% higher risk of greater fluid retention, respectively. Higher dietary protein intake (nPNA) and higher serum creatinine, phosphorus and TIBC concentrations and lower blood lymphocyte count, all known as surrogates of better nutritional status, were associated with increased risk of fluid retention.

In order to examine the incremental effect of interdialytic weight gain on survival, we created eight *a priori* defined increments of fluid retention including seven 0.5 kg increments between 0.5 and 4.0 kg and the group ≥4.0 kg interdialytic weight gain, as shown in Table 3. Patient weight and BMI were higher across the increments of fluid retention categories, and so were serum albumin and estimated protein intake via nPNA. Crude (unadjusted) mortality appeared lower across higher increments of fluid gain.

To study the independent mortality trends across fluid retention categories, we calculated death hazard ratios using time-dependent survival models at three levels of multivariate adjustment as shown in Figure 2. Using the 1.5 to 2.0 kg as the reference group, death hazard ratios appeared counter-intuitively lower across greater fluid retention volumes, but after controlling for demographics and other case-mix covariates, a higher interdialytic weight gain especially above 3.0 kg was associated with increased death risk. Additional adjustment for measures of nutritional status did not change the death risks considerably. In fully adjusted models, compared to the 1.5 to 2.0 kg interdialytic fluid gain, a weight gain above 4.0 kg during over two consecutive dialysis sessions was associated with 28% death risk, whereas with the minimal fluid retention between 0.5 and 1.0 kg, there was 26% higher survival chance. A very similar trend was found with cardiovascular mortality as shown in Figure 3, with 25% increased and 23% decreased cardiovascular death risk for the above-mentioned fluid gain groups, respectively.

To examine whether greater fluid retention is associated with poor survival across different groups of HD patients, the mortality predictability of interdialytic weight gain ≥1.5 kg was studied within diverse patient subgroups as shown in Figure 4, and the death risk of high interdialytic weight gain was found to be consistently increased across most of these groups. The death risk due to greater fluid retention was significant among Black or non-diabetic HD patients, those with higher serum albumin levels, and those who have undergone dialysis treatment for less than 2 years. Patients with no history of CV disease also exhibited stronger death predictability of fluid gain (data not shown).

Discussion

We found that in 34,107 chronic HD patients from a large dialysis organization in the 21st century, over 85% gained >1.5 kg body fluid between two consecutive dialysis treatment sessions. Younger, male and diabetic patients and those with higher protein intake and better nutritional status were greater fluid retainers. After controlling for these confounders, higher interdialytic weight gain was incrementally associated with increased death risk over 2 years

of observation. The incremental death predictability of fluid retention was robust for both all-cause and cardiovascular mortality. The mortality association of the interdialytic weight gain above 1.5 kg appeared somewhat consistent across different subgroups of HD patients. Patients with the lowest interdialytic fluid retention (<1.0 k) had a robust survival advantage and lowest cardiovascular death risk irrespective of confounders. These data suggest that in individuals with advanced CKD who require maintenance dialysis treatment, higher amounts of fluid gain are associated with poor survival and increased cardiovascular death.

Fluid retention is the main clinical feature in several pathologic conditions including in a number of renal and cardiovascular disorders. Fluid overload is usually the main manifestation of decompensated heart and kidney failure, so that not infrequently these two conditions cannot be distinguished from each other solely based on clinical signs or symptoms.[18] In advanced heart failure, compensatory mechanisms may lead to maladaptive consequences.[19] Increased sympathetic nervous system, renin-angiotensin-aldosterone system, and antidiuretic hormone release can lead to a vicious cycle, in that augmenting pre-load, contractility and after-load via these mechanisms may worsen fluid overload.[20-22] Even though diuretics remain the main medical therapy in both heart failure and CKD, administration of albumin, neurohormonal antagonists such as vasopressin receptors antagonists, aldosterone antagonists, or nesiritide, may help restoring plasma volume and osmolality.[23] In refractory fluid retention cases, however, fluid removal via dialysis treatment, i.e., the so-called ultrafiltration, offers a fast and effective alternative to medical therapy.[24]

Thrice weekly hemodialysis treatment is currently offered to some 400,000 Americans with CKD stage 5 to remove uremic toxins and to restore electrolyte balance. Concurrent fluid removal via ultrafiltration, however, is also performed during virtually each hemodialysis treatment. This intermittent ultrafiltration leads to non-physiologic fluctuations in body fluid as shown in Figure 1. More frequent (e.g. daily) hemodialysis or peritoneal dialysis that appear more consistent with the physiologic fluid alterations are currently administered in only less than 10% of all adult dialysis patients in the USA. Hence, gaining weight due to fluid retention between 2 consecutive HD sessions, usually 2 to 3 days apart, is commonplace. Adhering to fluid restrictions represents one of the most difficult aspects of the hemodialysis treatment regimen.[25, 26] We found that 86% of the 34,107 dialysis patients in our study retain at least 1.5 liters of fluid during two consecutive dialysis sessions. In addition to younger age, male sex, longer dialysis vintage, diabetic status, and larger body size, having a better nutritional status including a higher dietary protein intake was also associated with higher likelihood of excessive fluid retention. Most of the foregoing associations are biologically and clinically plausible, given the assumption that greater appetite and food intake is also associated with higher amount of fluid intake with resultant fluid overload. Nevertheless, nutritional status per se is a strong and robust predictor of greater survival in both dialysis and heart failure patients. Hence, the association between increased interdialytic weight gain and mortality may be confounded and overshadowed by the nutritional link with survival. Consistent with the latter expectation, our analyses showed that crude mortality appeared paradoxically lower in individuals with higher fluid retention (Table 3). However, after multivariate adjustment, an opposite association was disclosed (Supplemental Table and Figures 2 and 3). Among the case-mix variables, age was the most influential confounder in reversing the associations, followed by gender and race. Younger patients, who are usually healthier and who have greater appetite, have greater food and fluid intake, leading to the spurious association in unadjusted models. Hence, all things equal, restriction of fluid gain appears associated with greater survival.

In this study, we found that higher interdialytic weight gain was also associated with incrementally higher risk of cardiovascular mortality. Similarly, in heart failure patients volume overload, as indexed by pulmonary capillary wedge pressure, is associated with worse outcomes.[27] In dialysis patients almost half of the causes of dialysis patients mortality,

currently above 20% per year, is attributed to cardiovascular diseases.[28] Traditional cardiovascular risk factors such as hypercholesterolemia, hypertension or obesity are not associated with this excessive cardiovascular death risk in dialysis patients, an unresolved survival paradox that is also observed in chronic heart failure.[5, 9, 29-32] Instead, malnutrition, inflammation and wasting are strong correlates of cardiovascular mortality in dialysis patients.[33] Although a diagnosis of heart failure per se is associated with higher risk of death in dialysis patients,[34] the association we found between higher fluid retention and mortality independent of comorbid conditions is reported for the first time to the best of our knowledge. Intermittent fluid retention may imitate intermittent episodes of acute decompensated heart failure, leading to fluctuations in compensatory mechanisms including catecholamine release to increase sympathetic activity,[35] as well as changes in renin-angiotensin-aldosterone system and antidiuretic hormone,[19] which alone or together may increase the risk of cardiovascular events and death.[18]

Another interesting finding was that African Americans, who comprise almost one third of all dialysis patients in the USA, showed the strongest association between fluid retention and mortality in our study (Figures 3 and 4). Whereas in the US general population African Americans have a lower life expectancy than Whites, they have far greater survival chances once on dialysis, a phenomenon also known as African American paradox.[10] The fluid retention-survival association was also stronger in non-diabetic dialysis patients, and those who have been on dialysis for less than 2 years or those with better nutritional status (reflected by serum albumin >3.8 g/L). Nevertheless, we found no group of dialysis patients in whom fluid retention conferred survival advantages.

Our study should be qualified for its observational-epidemiological nature, its retrospective nature, and the lack of more elaborate and precise measures of fluid retention such as bioelectrical impendence analyses or radioactive tagged molecules. [36, 37] Furthermore, the target “dry weight” that is usually determined by the nephrologist based on his/her clinical judgment may not necessarily reflect the optimal edema-free status of the patient. However, in thrice weekly hemodialyzed patients it is highly unlikely that weight gain between two consecutive hemodialysis sessions be due to reasons other than interdialytic fluid gain. Another limitation was lack of data on measuring dietary fluid intake, especially since interdialytic weight gain correlated with surrogates of nutritional status. However, we did examine and controlled for biochemical measures of nutritional status including nPNA (nPCR) and serum albumin, transferrin, creatinine and phosphorus, Furthermore, even though we did not have explicit markers of inflammation(themselves strong mortality predictors in dialysis and heart failure patients[7, 38]), we controlled for blood WBC and administered erythropoietin dose, which have significant associations with inflammation in HD patients.[39, 40] Another limitation of our analysis is that it is based on 2-year period of the cohort, rather than a longitudinal follow-up of many years. Nonetheless, HD is a state with high mortality, since on average over one-third of dialysis patients in the USA die within 2 years of commencing HD treatment.[28] Hence, any insight into the short-term survival of dialysis patients is of major clinical relevance. The strengths of our study include: (1) Its contemporary nature, since all patient data were obtained from the 21st century (2001-2003); (2) uniform laboratory measurements with all laboratory data obtained from one single facility, (3) large sample size; (4) 3-month averaged laboratory and pre- and post-dialysis weight data from virtually every single dialysis session, and use of the means of several measurements to minimize measurement variability; (5) large proportion of incident MHD patients, who are less amenable to survivor bias; and (6) use of time-dependent survival models and sensitivity analyses.

Conclusions

In chronic HD patients, higher interdialytic weight gain is associated with poor survival and increased cardiovascular death. Patients with the lowest interdialytic fluid retention have the greatest survival. The mortality predictability of higher interdialytic weight gain is observed across most subgroups of HD patients. Given the striking similarities between individuals with chronic heart failure and those with advanced CKD undergoing chronic dialysis treatment, the mechanisms by which fluid retention influences survival in dialysis patients may be similar to those occuring in heart failure patients. Hence, examining pathophysiologic mechanisms that link fluid retention to increased cardiovascular death and effective strategies that can mitigate fluid retention may lead to improved outcome in dialysis patients, and warrant further research.

Short Commentary

Management of fluid status is a significant clinical challenge in both persons with heart failure and those with chronic kidney disease who undergo hemodialysis treatment. Volume overload may be associated with poor clinical outcomes, but it is not clear whether higher amounts of fluid retention are associated with increased mortality. In this 2-year cohort of 34,107 chronic hemodialysis patients across the United States, patients with an average weight gain of at least 0.5 kg between two consecutive (thrice weekly) hemodialysis treatments were studied. The authors found that over 85% of patients gained 1.5 kg or more between two hemodialysis sessions, probably due to fluid retention. After controlling for demographics and measures of nutritional status, higher weight gains were incrementally associated with higher all-cause and cardiovascular mortality. These associations remained consistent across different subgroups of hemodialysis patients. Although the mechanisms by which fluid retention influences cardiovascular survival in hemodialysis patients remains unknown, these associations may better justify ongoing efforts to restrict fluid retention in these patients. Given the striking similarities between hemodialysis and heart failure patients and the recently heightened enthusiasm about ultrafiltration treatment in heart failure patients, these findings may have clinical implications to current management of patients with edematous states.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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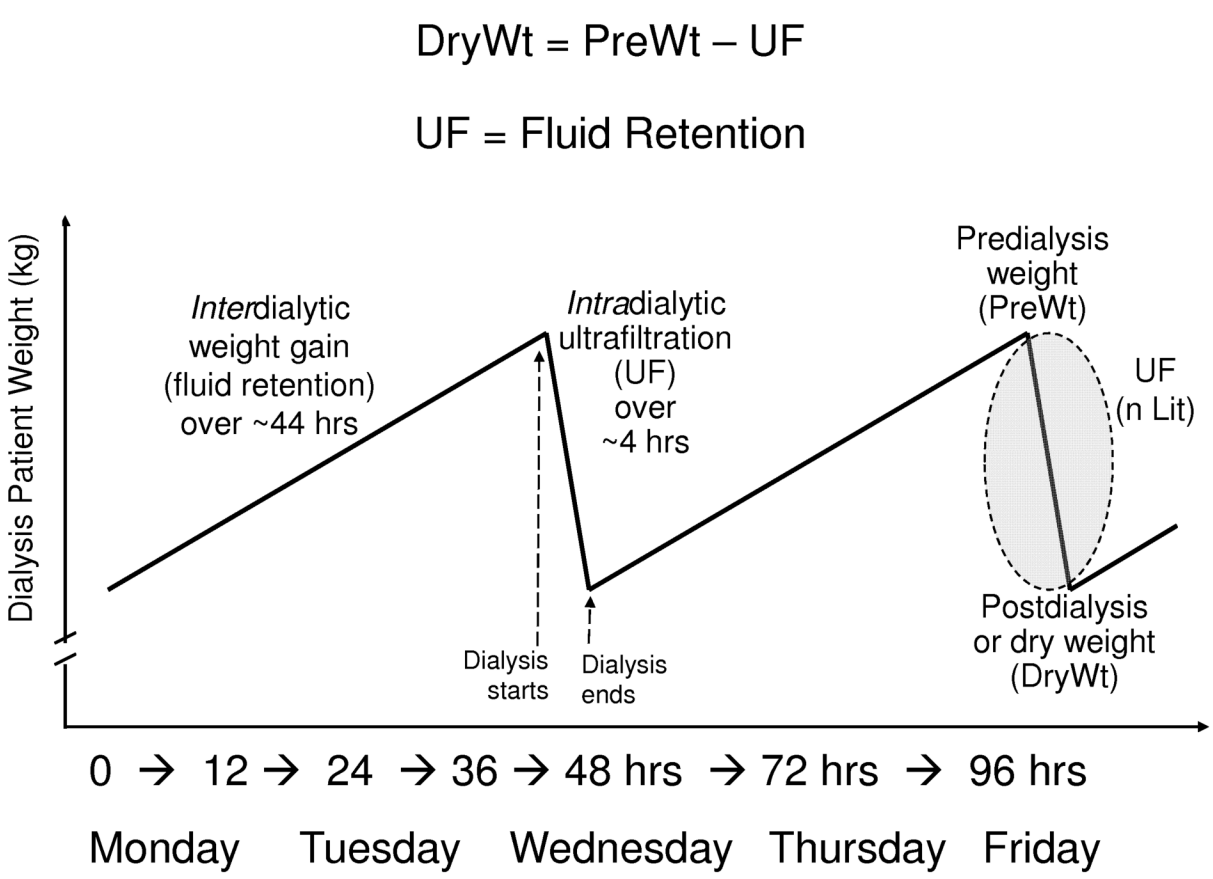

Figure 1.
Schematic representation of the bi-diurnal variation of fluid status in chronic hemodialysis patients. Between the two subsequent dialysis treatment sessions, usually 44 hrs apart, patient's interdialytic weight gain to reflect fluid retention between two consecutive hemodialysis treatments, which will then be removed rather quickly via dialysis ultrafiltration (UF) during a 4-hr dialysis treatment.

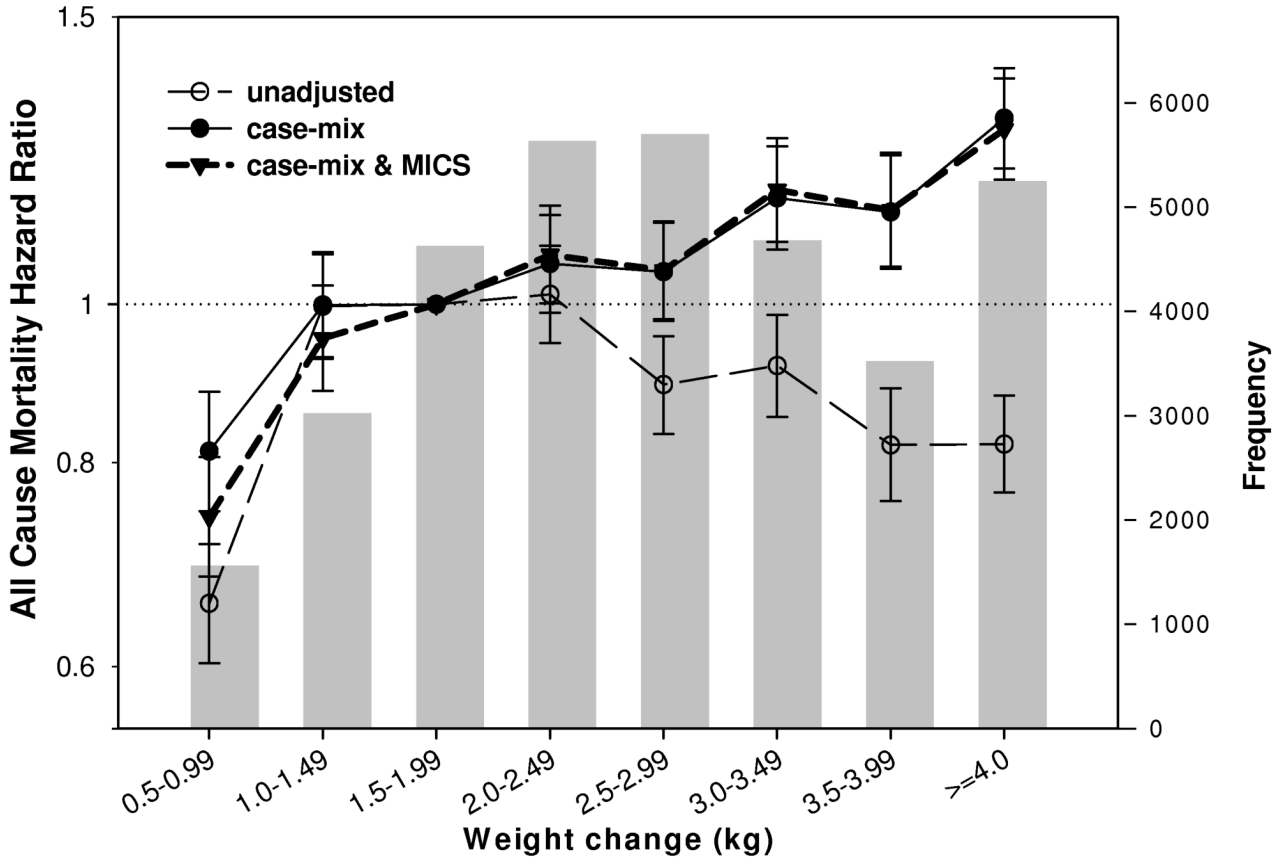

Figure 2.

All-cause death hazard ratios (and 95% confidence interval error bars) for the entire range of interdialytic fluid gain categories in 34,107 HD patients over 2 years (7/2001-6/2003). Hazard ratios are calculated via time-dependent Cox regression with 3 levels of multivariate adjustment, i.e., minimally adjusted (herewith referred to as “unadjusted” including adjustment for baseline height and weight and calendar quarter), adjusted for “case-mix” (including additional adjustment for age, gender, race/ethnicity, diabetes mellitus and other comorbid states, dialysis vintage, tobacco smoking, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function); and “malnutrition-inflammation-cachexia syndrome” (MICS) surrogates (including 10 laboratory markers, see text). Note that patient population frequency in each group is demonstrated via background bar diagrams in grey.

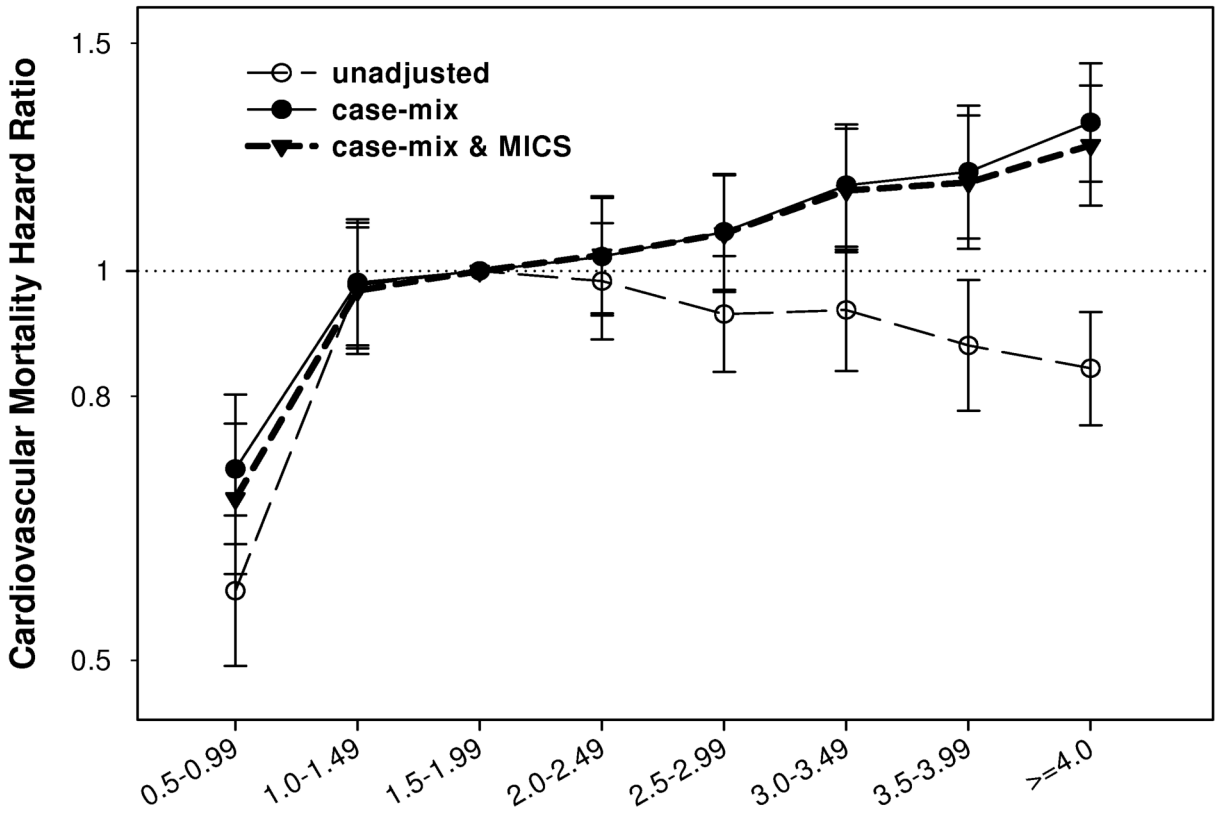

Figure 3.

Cardiovascular death hazard ratios (and 95% confidence interval error bars) for the entire range of interdialytic fluid gain categories in 34,107 HD patients over 2 years (7/2001-6/2003). Hazard ratios are calculated via time-dependent Cox regression with 3 levels of multivariate adjustment, i.e., minimally adjusted (herewith referred to as "unadjusted" including adjustment for baseline height and weight and calendar quarter), adjusted for "case-mix" (including additional adjustment for age, gender, race/ethnicity, diabetes mellitus and other comorbid states, dialysis vintage, tobacco smoking, primary insurance, marital status, standardized mortality ratio, dialysis dose, dialysis catheter, and residual renal function); and "malnutrition-inflammation-cachexia syndrome" (MICS) surrogates (including 10 laboratory markers, see text).

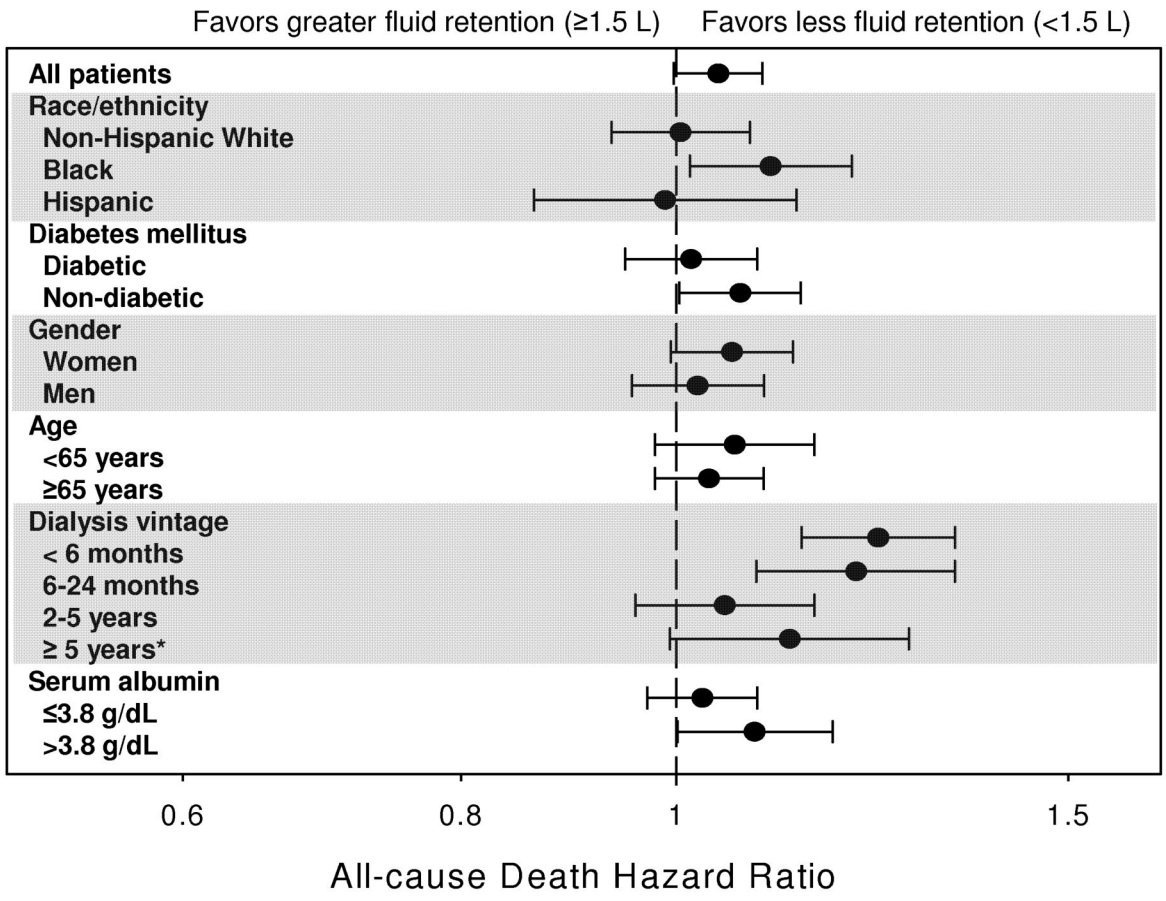

Figure 4.

Hazard ratio of all-cause mortality for interdialytic weight gain greater than 1.5 kilograms or liters (vs. <1.5 kilograms or liters) between two subsequent dialysis sessions in 34,107 HD patients adjusted for case-mix and laboratory surrogates of malnutrition and inflammation (time-dependent regression model over 2 year). Error bars indicate 95% confidence intervals. * Dialysis patients with vintage >10 years (<5% of the entire cohort) are excluded to mitigate confounding by number of years of functioning kidney transplant (usually part of the vintage).

Table 1

Baseline (first calendar quarter) data of 34,107 HD patients (July 2001 to June 2004), including 21,828 patients from the first calendar quarter (q1) and 12,279 patients From subsequent calendar quarters (q2 to q8)

Variable	Interdialytic weight gain	
	0.5 – 1.5 kg (n=4,900)	**> 1.5kg (n=29,207)**
Age (years)	63.7±16.0	59.1±15.2
Gender (% women)	58	44
Diabetes mellitus (%)	35	47
Race and ethnicity:		
Caucasians (%)	39	35
Blacks (%)	30	32
Asians (%)[a]	4.0	3.2
Hispanics (%)	14	16
Vintage (time on dialysis):		
3-6 months (%)	66	56
6-24 months (%)	13	16
2-5 years (%)	13	18
>5 years (%)	9	11
Primary insurance		
Medicare[c] (%)	65	66
Known causes of death:		
Cardiovascular[c] (% of all-cause)	47	49
Infectious[c] (% of all-cause)	14	12
Standardized mortality ratio[b]	0.81±0.24	0.80±0.26
Body mass index (kg/m^2)	24.3±5.3	26.9±6.5
Kt/V (single pool)	1.55±0.34	1.53±0.32
nPNA (nPCR) (g/kg/day)	0.90±0.24	1.02±0.25
Serum albumin (g/dL)	3.67±0.50	3.76±0.40
creatinine (mg/dL)	7.5±3.0	9.1±.3.4
ferritin (ng/mL) [c ¥]	417 (281)	433 (278)
Phosphorus	5.3±1.4	5.8±1.5
Calcium	9.3±0.7	9.2±0.7
Bicarbonate	22.1±3.0	21.6±2.8
TIBC (mg/dL)	200±47	206±42
Blood hemoglobin[c] (g/dL)	12.1±1.4	12.1±1.3
WBC [c] (per fl)	7.4±2.5	7.3±2.3
lymphocyte [c] (% of total WBC)	21.1±8.0	21.2±7.9
EPO dose[c¥]	15,556 (9,117)	15,567 (9,089)

p-value <0.001 unless otherwise specified

[a] 0.001 < p < 0.01

[b] 0.01 < p < 0.05

[c] p >0.05

¥ median (IQR)

Table 2

Odds ratio of substantial interdialytic weight gain (>1.5 kg vs. 0.5 to 1.5 kg) during the first calendar quarter in 34,107 HD patients (July 2001 to June 2003)

Variable	Unadjusted	Case-mix Adjusted	Case-mix and MICS adjusted
Age (each 10 year increase)	0.83 (0.82 - 0.85)	0.86 (0.84 – 0.88)	0.96 (0.94 – 0.98)
Gender (women vs. men)	0.56 (0.52 - 0.59)	0.49 (0.45 – 0.52)	0.55 (0.51 – 0.59)
Diabetes mellitus (yes vs. no)	1.73 (1.62 - 1.85)	1.72 (1.61 – 1.84)	1.94 (1.80 – 2.08)
Race and ethnicity: (reference: non-Hispanic Caucasians)			
Blacks	1.09 (1.01 - 1.18)	0.96 (0.89 – 1.04)	0.90 (0.83 – 0.98)
Asians	0.80 (0.68 - 0.94)	0.93 (0.78 -1.10)	0.79 (0.67 – 0.94)
Hispanics	1.17 (1.07 - 1.29)	0.98 (0.88 -1.08)	0.92 (0.83 – 1.02)
Vintage (time on dialysis): (reference: 6-24 months)			
3-6 months	0.91 (0.81 - 1.02)	0.95 (0.85 -1.06)	0.99 (0.88 – 1.11)
2-5 years	1.27 (1.13 - 1.43)	1.29 (1.15 – 1.46)	1.22 (1.08 – 1.38)
>5 years	1.56 (1.35 - 1.82)	1.76 (1.51 -2.05)	1.67 (1.43 – 1.96)
Primary insurance (reference: Medicare)			
Medicaid	1.13 (0.99 - 1.29)	1.04 (0.91 – 1.20)	1.05 (0.91 – 1.21)
Private	1.06 (0.98 - 1.14)	0.97 (0.90 – 1.05)	0.96 (0.89 – 1.04)
BMI (each 1 kg/m^2 increase)	1.08 (1.07 - 1.09)	1.08 (1.07 – 1.08)	1.07 (1.06 – 1.08)
Kt/V dialysis dose (1 unit increase)	0.74 (0.68 - 0.82)	1.46 (1.31 – 1.63)	1.77 (1.59 – 1.98)
nPNA (nPCR) (0.1 g/kg/d increase)	1.23 (1.21-1.25)	1.23 (1.21-1.25)	1.19 (1.17-1.21)
Serum albumin (0.1 g/dL increase)	1.03 (1.03 - 1.04)	1.01 (1.01 – 1.02)	1.00 (0.99 – 1.01)
creatinine (1 mg/dL increase)	1.15 (1.14 - 1.16)	1.14 (1.13 – 1.16)	1.12 (1.10 – 1.14)
ferritin (100 ng/mL increase)	0.98 (0.98 - 0.99)	0.99 (0.98 – 1.00)	1.00 (0.99 – 1.00)
Phosphorus (1 mg/dL increase)	1.29 (1.26 - 1.32)	1.25 (1.22 – 1.28)	1.13 (1.10 – 1.16)
calcium (1 mg/dL increase)	0.84 (0.80 - 0.87)	0.84 (0.80 – 0.88)	0.81 (0.77 – 0.85)
Bicarbonate (1 mEq/L increase)	0.94 (0.93 - 0.95)	0.94 (0.93 – 0.95)	0.99 (0.97 – 1.00)
TIBC (10 mg/dL increase)	1.04 (1.03 -1.04)	1.02 (1.01 – 1.03)	1.02 (1.01 – 1.03)
Blood hemoglobin (1 g/dL increase)	1.01 (0.99 - 1.04)	1.02 (0.99 – 1.04)	1.03 (1.00 – 1.06)
WBC [c] (1 unit per fl)	1.01 (0.99 - 1.02)	1.00 (0.99 – 1.01)	1.00 (0.99 – 1.01)
lymphocyte [c] (each 10 % increase)	0.97 (0.94 - 1.01)	0.93 (0.89 – 0.97)	0.92 (0.88 – 0.96)
EPO dose[c]¥ (each 1,000 unit increase)	1.00 (1.00 - 1.01)	1.00 (1.00 - 1.01)	1.00 (1.00 – 1.01)

Footnote: The unadjusted models are separate univariate models. In case-mix adjusted models all case-mix variables are included and the MICS variables are added separately one at a time. In the full (case-mix plus MICS) adjusted model, one single multivariate model has been created.

Table 3

Categories of interdialytic weight gain (fluid retention) and mortality and other relevant characteristics in 34,107 HD patients

Fluid retention categories (kg)	n (%)	All cause death n[%]	Albumin mg/dL Mean (SD)	Weight kg Mean (SD)	BMI kg/m^2 Mean (SD)	Protein intake g/kg/day Mean (SD)	patient age Mean (SD)	Women (%)
0.5 – 1.0	1,561 (5)	457 [29]	3.65 (0.53)	65.4 (16.7)	23.9 (5.32)	0.88 (0.24)	63.5 (16.3)	57
1.0 – 1.5	3,025 (9)	785 [26]	3.68 (0.48)	66.7 (16.7)	24.4 (5.3)	0.90 (0.23)	63.8 (15.7)	58
1.5- 2.0 (ref.)	4,630 (14)	1,103 [24]	3.73 (0.43)	67.9 (16.4)	24.9 (5.4)	0.95 (0.25)	63.1 (15.7)	56
2.0 – 2.5	5,636 (17)	1,231 [22]	3.75 (0.41)	70.7 (17.3)	25.5 (5.7)	0.99 (0.24)	61.6 (15.5)	51
2.5 – 3.0	5,700 (17)	1,181 [21]	3.76 (0.39)	73.6 (17.8)	26.3 (5.8)	1.02 (0.25)	60.6 (15.1)	47
3.0 – 3.5	4,679 (14)	936 [20]	3.78 (0.38)	76.8 (18.4)	27.0 (6.1)	1.03 (0.24)	58.5 (15.0)	42
3.5 – 4.0	3,522 (10)	710 [20]	3.77 (0.39)	80.8 (19.6)	27.9 (6.6)	1.05 (0.25)	57.0 (14.3)	37
≥4.0	5,354 (16)	1,025 [20]	3.78 (0.38)	89.6 (24.4)	29.9 (7.6)	1.07 (0.25)	53.5 (13.6)	28

Values in parentheses represent the proportion of the MHD patients in each weight change category. Values in brackets indicate the crude death rate in the indicated group during the 3 years of observation.