

Congress Service

43rd Annual Meeting of the
American Society of Nephrology

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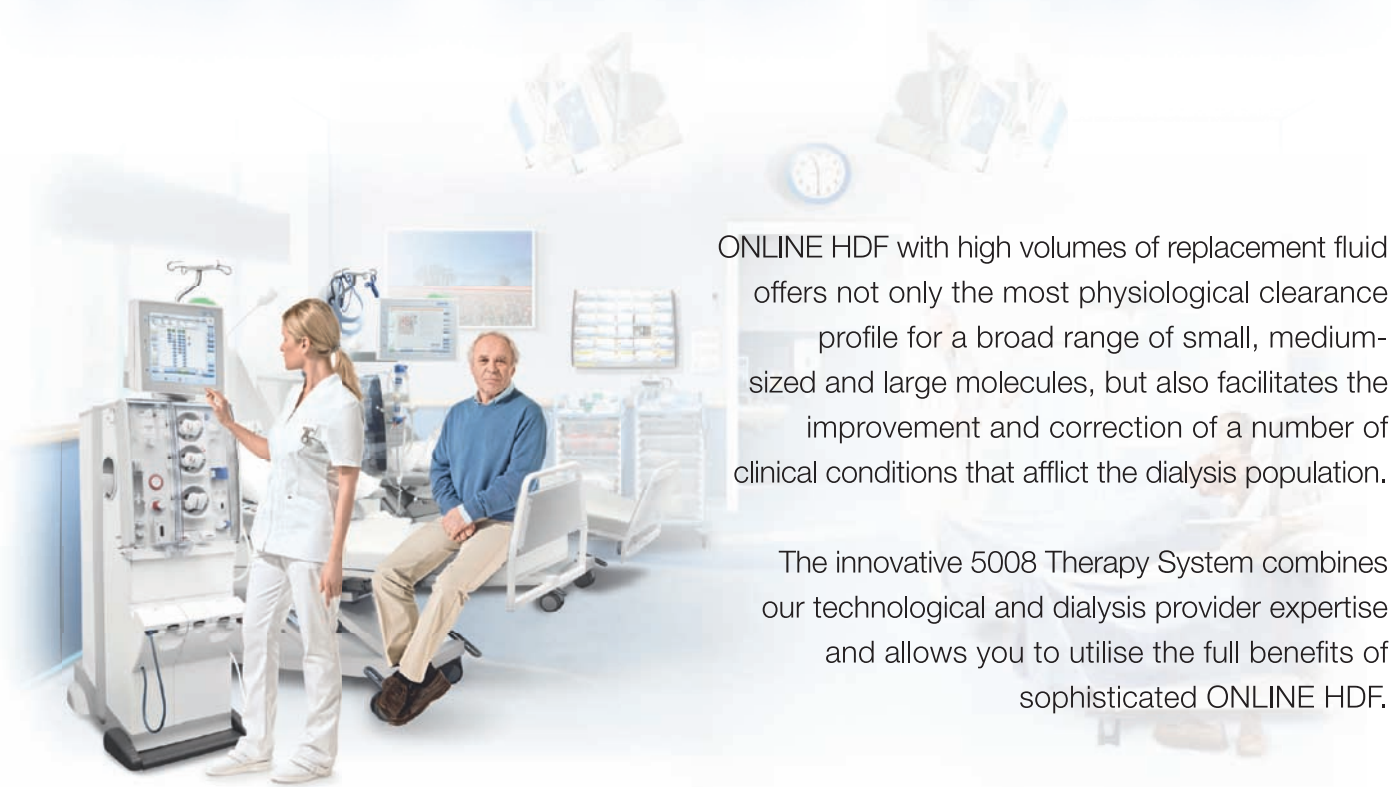


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Selected Abstracts of the
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1. Anaemia Therapy

Effect of Intravenous and Oral Ascorbic Acid in Hemodialysis Patients with Anemia and Hyperferritinemia

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Hemodialysis patients with anemia and hyperferritinemia often develop resistance to recombinant human erythropoietin (EPO). Ascorbic acid is believed to improve anemia in hemodialysis patients.

We evaluated the efficacy of intravenous and oral ascorbic acid on Epo-hyporesponsive anemia in hemodialysis patients with hyperferritinemia. Fortyseven of 156 hemodialysis patients with Hb < 11g/dL and ferritin levels greater than 300 ng/ml were prospectively followed up. Patients were randomly divided into three groups. 16 patients had received standard care (group 1), 17 patients had received standard care and daily oral ascorbic acid at a dose of 500 mg/day (group 2) and 14 patients had received standard care and 300 mg of intravenous vitamin C with each dialysis session (group 3). Each group was similar in clinical characteristics. Blood samples for measurement of hemoglobin, hematocrit, serum iron, ferritin, transferrin saturation and EPO dose

were obtained at baseline and after three months of treatment.

After 3 months, hemoglobin and hematocrit and transferrin saturation levels significantly increased in group 2 and 3 ($p < 0.05$) but did not change in group 1. EPO dosage and ferritin levels decreased in group 2 and 3 ($p < 0.05$).

There was no difference in group 2 and 3.

In conclusion, our study has demonstrated that intravenous or oral ascorbic acid therapy can improve anemia, hyperferritinemia and EPO resistance in hemodialysis patients. The effects of intravenous and oral ascorbic acid are similar. Further studies are needed to determine ascorbic acid dosing optimization.

Baseline and 3 Month Data Summary

	Group 1		Group 2		Group 3	
	baseline	after 3 months	baseline	after 3 months	baseline	after 3 months
Hb (g/dL)	8.9 ±1.4	8.8±1.3	8.8±1.3	9.5±1.1*	9.0±1.2	9.6±1.2*
Fe (µ/L)	55.84±23	58.6±19	58.57±25	63.7±22*	61.12±21	67.29±19*
EPO dose (unit/week)	14729	14538	15584	12369*	14986	11345*
Ferritin (µg/L)	764±217	781±192	783±191	646±189*	754±220	634±231*
T sat (%)	18±6.4	18.2±5.8	20.6±5.5	26.4±4.1*	19.8±4.9	24.5±3.2*

* <0.05

EPO Treatment at the Start of Hemodialysis is More Beneficial than at the End of Hemodialysis

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Background and Aims: Although erythroid progenitors require iron for their maturation after EPO stimulation, EPO is usually injected at the end of hemodialysis (HD) for renal anemia treatment as clinical guidelines suggest, because EPO given at the start HD is supposed to be absorbed in the HD circuit decreasing its efficacy.

Previously, we have shown that EPO treatment at the start of HD could improve iron utilization and reduce EPO dose, while hemoglobin (Hb) level and iron treatment frequency were unaffected in a short pilot study. Here, we performed a longer study to confirm the beneficial impact of EPO treatment at the start of HD.

Method: Thirty six HD patients providing written informed consent were enrolled. At the beginning, EPO treatment was changed from the end of HD (Period I) to the start (Period II). Anemia treatment was carried out as usual. EPO dose was altered biweekly to maintain a target Hb level of 11-12 g/dL. After 12 and 25 weeks, average EPO dose, clinical parameters and rate of operational incidents were examined.

Results: At the start of the study, mean Hb level was 10.99 ± 0.85 g/dL and was unchanged at week 12 and 25 (11.22 ± 0.83 g/dL and 11.05 ± 0.83 , $p=0.16$ and $p=0.89$). Frequency of iron treatment (28%, 33% and 17%, $p=0.69$ and $p=0.40$) and serum ferritin were

also unchanged (174 ± 113 ng/mL, 190 ± 130 ng/mL and 176 ± 109 , $p=0.46$ and $p=0.76$). Average EPO dose in 2 weeks was significantly reduced from $4,771 \pm 2,528$ IU/week in Period I to $3,949 \pm 2,140$ IU/week at week 12 ($p=0.048$). At week 25, EPO dose remained reduced at 4412 ± 2583 IU/week, but not significantly ($p=0.34$). There were no operational incidents such as neglecting EPO injection in Period II.

Conclusions: Results indicate EPO treatment at the start of HD was more beneficial and effective than EPO treatment at the end of HD. It was suggested that improved iron utilization reduces EPO dose, although Hb level and iron treatment were unaffected. Moreover, more reliable EPO injection can be achieved because incidents at the start of HD were rare. Further study should provide information to establish an efficient EPO treatment.

Evaluating the Impact of Change in Pre-Dialysis Weight on a Change in Measured Hemoglobin

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The literature has shown an association between low hemoglobin (Hb), higher ESA doses and increased morbidity and mortality in dialysis patients, but many have questioned the role of confounding factors. Interdialytic weight gain is associated with increased morbidity and mortality. Increased volume status could produce spuriously low Hb measures via simple dilution, triggering ESA dose increases and confounding associations between both variables and outcomes. We examined the association between interdialytic weight gain, measured Hb, and ESA dose.

Methods: Retrospective analysis of 164,866 hemodialysis patients dialyzed between January 1 and December 31 of 2009 at a large dialysis organization. Sequentially paired Hb values were created within a 30 day period. For each treatment corresponding to those dates, change in ESA and Hb were recorded and categorized by change in pre dialysis weight. Mul-

tiple observations per patient were used.

Results: Prior mean Hb ranged from 11.2 to 11.7 g/dL and prior mean weekly ESA dose from 20 k to 26 k Units. Table shows change in Hb and ESA dose by interdialytic weight gain category. To control for multiple measurements on many patients, the weighted Pearson product moment correlation was calculated on mean scores. The correlation was $r = -0.17$ between change in pre-dialytic weight and change in Hb, and $r = 0.03$ between change in pre-dialytic weight and change in ESA dose.

Conclusions: Changes in pre-dialysis weight were associated with reciprocal changes in both Hb and, in sequence, ESA dose. Given the magnitude of these effects, changes in pre-dialysis weight may be a clinically meaningful confounder of the relationship between Hb, ESA dose and morbidity & mortality in dialysis patients.

Changes in Hb and ESA Dose by Weight Category

Change in Pre-Dialytic Weight	Matched Hb Draws	Change in Hb (g/dl) Mean±SD	Change in Weekly ESA Units from Prior Draw
>2.0 to 10.0 kg	422,528	-0.29±0.86	6.8%
0.5 to ≤2.0 kg	1,467,172	-0.09±0.73	1.0%
>-0.5 to <0.5 kg	1,544,905	+0.07±0.70	-1.3%
-0.5 to ≤-2.0 kg	1,473,124	+0.23±0.74	-2.5%
<-2.0 to -10.0 kg	478,550	+0.39±0.91	0.4%

Dissociation of Relative Thrombocytosis Associated with Higher ESA Dose vs. Hemoglobin Levels in Hemodialysis Patients

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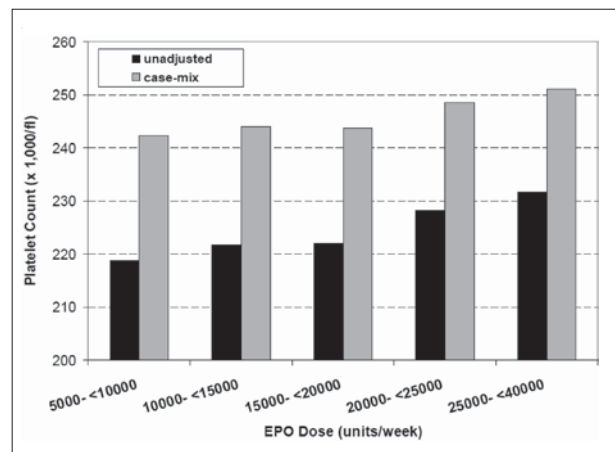
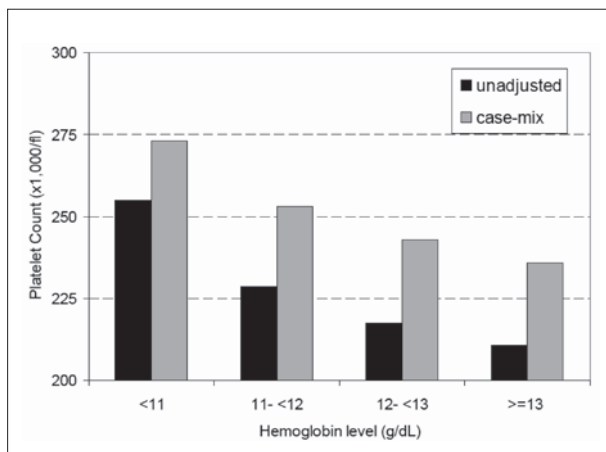
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Background: Recent randomized controlled trials indicated increased thromboembolic events and mortality upon targeting higher hemoglobin levels using higher doses of erythropoietin stimulating agents (ESA). It is not clear whether the high mortality is as a result of high ESA per se or high hemoglobin level. We, hence, examined the association of the latter 2 factors with relative thrombocytosis (increased platelet count), which is a predictor of increased thromboembolic events and death.

Methods: Using linear regression models, we separately examined the associations between ESA dose and hemoglobin levels with 13-week (calendar quarter) averaged platelet count during July to Dec 2001 in a cohort of 40,697 maintenance hemodialysis (MHD) patients from in all DaVita clinics. Models were adjusted for case-mix.

Results: MHD patients were 47% women; 46% diabetics; 34% African Americans, respectively. The 13-week averaged platelet count was $229 \times 10^3/\mu\text{l}$. In unadjusted, and case-mix adjusted models, incrementally higher hemoglobin levels were associated with lower platelet count, whereas incrementally higher ESA doses were associated with higher platelet count (see Figures).

Conclusions: Observed higher hemoglobin levels is not per se associated with thrombocytosis, but only if associated with higher ESA dose or conditions that require higher ESA dose.



2. Cardiovascular Diseases

Predictors of Survival in Dialysis Patients with Acute Myocardial Infarction: Findings from the USRDS AMI Special Study

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Background: Acute myocardial infarction (AMI) in dialysis patients is associated with poor survival. This study aims to identify predictors of survival in dialysis patients prior to AMI and to examine the association between survival and different revascularization techniques.

Methods and Results: 3049 US prevalent dialysis patients hospitalized for AMI 4/1/1998-6/30/2000 were identified by cross-matching United States Renal Data System (USRDS) database and the Third National Registry of Myocardial Infarction (NRFMI 3). Of the 3011 data abstraction forms sent to the 18 renal networks, 1696 were sufficiently complete for analysis. Average age was 66.4 years old and average years on dialysis 2.7 years. 69% were white and 47% were females. Diabetes (DM) and dysrhythmia were prevalent in 72.5% and 65.5% respectively. At 1 yr post-AMI, 62% of the cohort had died. The impact of independent predictors on survival was examined in a Cox Proportional Hazards model. Beta Blocker (BB) use was associated with a favorable 1-yr all-cause mortality (hazard ratio (HR) of 0.8, $p=0.003$). As compared to patients who dialyzed via catheter, fistula use was associated

with favorable outcome (HR=0.76, $p=0.008$), as was graft use (HR=0.82, $p=0.016$). Compared to pre-dialysis systolic blood pressure (PDSBP) between 120-179 mmHg, PDSBP < 120 mmHg was more hazardous (HR=1.46, $p \leq 0.0001$) while PDSBP ≥ 180 mmHg (HR=0.7, $p=0.004$) had better survival. Coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI) within 30 days of AMI were examined in time-independent and time-dependent Cox models. In the time-independent model, PCI and CABG were similarly associated with favorable outcome. However, in all time-dependent models, CABG lost its significance (HR = 0.86, $P = 0.35$), while PCI maintained its protective association (HR=0.67, $p=0.0005$).

Conclusion: BB use prior to AMI, and PCI within 30 days of AMI are associated with favorable one year survival in dialysis patients. Validation of these observational findings by randomized clinical trials is needed.

Intravenous Erythropoetin does not Influence Intradialytic Hypertension

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Intradialytic hypertension [IDH] confers a 22% increased risk of hospitalization or death per 10 mm Hg postdialysis increase in systolic blood pressure [BP]. Intravenous [IV] and not subcutaneous erythropoetin [EPO] elevates endothelin-1 levels and mean arterial pressure 30 minutes after administration and has been hypothesized to contribute to IDH. However there are no large studies on this in clinical practice.

In this retrospective cohort study of 166 patients established [>90 d] on hemodialysis [HD] and receiving protocolised care at 1 dialysis unit at our center Jan-Dec 2009, EPO [darbepoetin] was given IV 1 hour into dialysis weekly and adjusted to target hemoglobin [Hb] 10.5-12.5g/dL. The dialysis prescription was tailored to target postdialysis BP \leq 130/80mmHg with ultrafiltration [UF] to euvolemia and subsequent antihypertensive use. IDH was defined with precedent as ± 15 mmHg increase in postdialysis MAP from predialysis levels.

We examined 20,407 sessions in all patients [mean age 66.4 \pm 14.0 yrs, 57% male, 42% diabetic, 57% hypertensive] using mixed effects models to account for repeat

measures. Mean pre & postdialysis BP was 140 \pm 24/78 \pm 14 mm Hg & 136 \pm 24/75 \pm 14 mmHg respectively. 6,800 EPO doses were given [mean 0.60 \pm 0.35 μ g/kg] with mean predialysis Hb 12.2 \pm 1.0 g/dL, ferritin 278 \pm 112 ng/mL. Overall IDH occurred in 13.7% sessions and clustered with $\pm 20\%$ prevalence in 21% of the cohort.

IV EPO was not associated with absolute changes in MAP [p=0.2] or odds of IDH [OR 0.9, p=0.3]. UF volume reduced MAP by 1.6 mm Hg/liter UF [p<0.001] and odds of IDH by 14% per liter. Older age associated with intradialytic rise in MAP [1.4 mmHg/10 yrs age, p=0.002] and increased odds of IDH by 10% per decade [p=0.03]. Patient ethnicity, major comorbid diagnoses, dry weight and Hb had no significant effect on intradialytic change of MAP or IDH.

This large comprehensive study demonstrates no association of IV EPO use with IDH and MAP changes which are predominantly associated with UF volume and patient age.

Troponin I as a Cardiac Biomarker for Cardiovascular Mortality in Patients on Chronic Haemodialysis

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Background: The high prevalence of cardiovascular mortality in patients on chronic haemodialysis is well established. Biomarkers like BNP and Troponin T are correlated with cardiovascular (CV) mortality, but this relationship is much less clear for troponin I (TnI). With a more sensitive test for TnI we found a strong correlation between

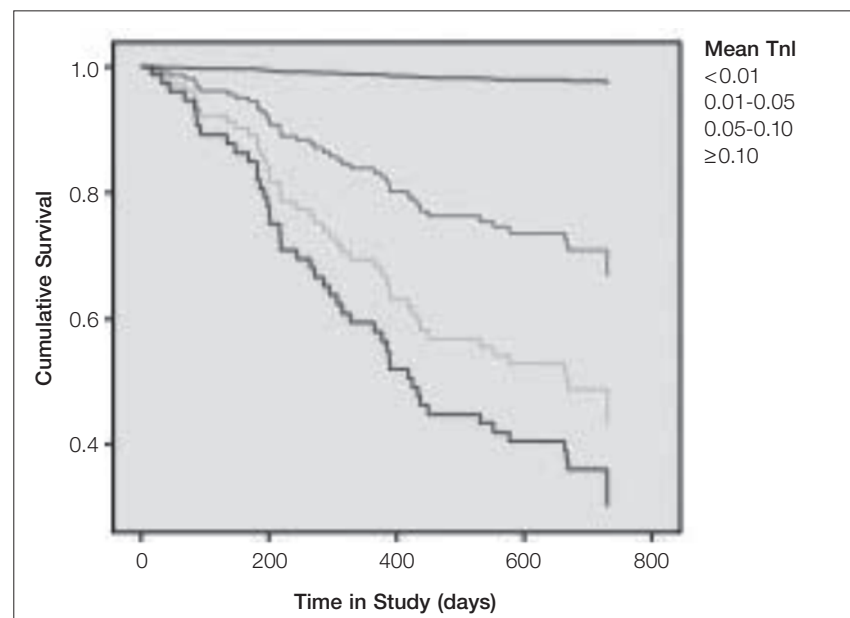
TnI and cardiovascular mortality.

Materials and methods: Plasma TnI levels of 206 chronic haemodialysis patients in our centre were measured every 3 months for a period of 24 months. We used a TnI-ultra assay on an Advia Centaur analyzer. Cardiovascular morbidity and mortality were assessed over a period of 30 months.

Results: 206 patients were divided in 4 groups by their mean TnI according to the reference values of TnI used in our hospital. Group 1 (n=59) had a TnI level $<0.01\mu\text{g/l}$; group 2 (n=94) had TnI levels of $0.01\text{-}0.05\mu\text{g/l}$; group 3 (n=29) $0.05\text{-}0.10\mu\text{g/l}$ and group 4 (n=24) had a TnI level $\geq 0.10\mu\text{g/l}$. Forty-nine patients (23.8%) died; 31 (63.3%) due to CV disease. In group 1 one patient (1.7%) died of

a CV cause. Group 2 had 21 deaths (22.3%); 11 (52.4%) of a CV cause. In group 3 13 patients (44.8%) died; 8 (61.5%) due to CV causes. Fourteen patients (58.3%) in group 4 died. Eleven of them (78.6%) died of a CV event. Twenty patients had a heart attack; per subgroup: n=2 (3.4%), n=9 (9.6%), n=3 (10.3%) and n=6 (25.0%) respectively. In a univariate analysis a high TnI was related with a significant higher risk for myocardial infarction ($p=0.007$) and cardiovascular death ($p=0.001$). In a multivariate analysis TnI remained a strong independent risk factor.

Conclusion: TnI can be a prognostic biomarker for (cardiovascular) mortality in patients on chronic haemodialysis.



Rosuvastatin and LDL-Cholesterol in Diabetic Patients Receiving Hemodialysis – A Post Hoc Analysis of the AURORA Trial

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Background: Patients with chronic kidney disease and renal transplant recipients are at high risk for cardiovascular events. Use of statins reduces cardiovascular risk in these populations. Two randomized controlled trials in hemodialysis populations (4D, AURORA) showed no benefit of statin treatment.

Methods: We performed a post hoc-analysis of the pre-specified subgroup of diabetes patients in the AURORA trial. Of the 2776 patients recruited to the AURORA trial, 731 patients had a diagnosis of diabetes mellitus at inclusion. We examined whether the effect of rosuvastatin treatment on clinical outcome was dependent on LDL cholesterol at baseline.

Results: Patients randomized to rosuvastatin in the highest quartile of LDL cholesterol (greater than 3.04 mmol/L) had a 37% reduced risk of the primary combined endpoint; death from cardiovascular causes, or nonfatal myocardial in-

farction, or nonfatal stroke (hazard ratio [HR] 0.63, confidence interval [CI] 0.40 – 0.99, $p = 0.045$). There was also a 46% risk reduction in the secondary cardiac event; cardiac death or nonfatal myocardial infarction (HR 0.54, CI 0.31 – 0.93, $p = 0.026$). No such decreases were observed in any of the other quartiles of LDL cholesterol at baseline.

The clinical events for total mortality and stroke did not differ significantly in any quartile of LDL cholesterol.

Conclusion: Use of rosuvastatin reduced the risk of death from cardiovascular causes, nonfatal myocardial infarction and nonfatal stroke in diabetic hemodialysis patients with LDL cholesterol > 3.04 mmol/L. Rosuvastatin also reduced the risk of the secondary cardiac endpoint. Diabetic patients undergoing hemodialysis with elevated LDL cholesterol may be considered for lipid lowering therapy.

Lowering Dialysate Calcium Concentration from 3.0 mEq/L to 2.5 mEq/L Attenuates the Progression of Abdominal Aortic Calcification in Patients on Chronic Hemodialysis

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Background: Vascular calcification is an independent determinant of cardiovascular events in patients on chronic hemodialysis (HD). However, the relation between dialysate Ca concentration and vascular calcification has not been clarified. This study was planned to clarify the effect of lowering dialysate Ca concentration from 3.0 mEq/L to 2.5 mEq/L on the progression of abdominal aortic calcification in HD patients.

Methods: We enrolled 44 HD patients with dialysate containing 3.0 mEq/L of Ca, and randomly 26 HD patients (lowering group) lowered their dialysate Ca concentration from 3.0 mEq/L to 2.5 mEq/L after about three years. Eighteen patients (control group) continued HD with dialysate containing 3.0 mEq/L of Ca. All patients underwent abdominal computed tomography (CT) three times at an interval of approximately three years. The aortic calcification index (ACI) was quantified morphometrically using abdominal CT films (range of ACI, 0–240). The progression rate of aortic calcification was calculated as Δ ACI/year.

Results: The first ACI and Δ ACI/year was no significant difference in lowering and control group (first ACI: 42.7 ± 42.8 vs 57.4 ± 38.1 , first Δ ACI/year: 6.7 ± 6.4 vs 8.5 ± 6.4). In lowering group, the second Δ ACI/year, after lowering dialysate Ca concentration, was significantly decreased compared with the first Δ ACI/year (6.7 ± 4.3 vs 4.9 ± 5.1 , $p < 0.0263$, Wilcoxon signed rank test). On the other hand, in control group the second Δ ACI/year was significantly increased compared with the first Δ ACI/year (8.5 ± 6.4 vs 12.1 ± 7.2 , $p < 0.0249$). In stepwise multivariate analysis the progression of ACI after lowering dialysate Ca concentration was negatively and independently associated with lowering dialysate Ca concentration, age and serum Ca concentration just after HD, and positively associated with serum phosphate.

Conclusion: Lowering dialysate Ca concentration from 3.0 mEq/L to 2.5 mEq/L attenuated the progression of abdominal aortic calcification in HD patients.

Accelerated Coronary Artery Calcification and Hyperparathyroidism in Hemodialysis Patients Receiving Low Calcium Dialysate

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Background: Coronary artery calcification (CAC) has been shown to be a significant predictor of cardiovascular mortality and morbidity in hemodialysis (HD) patients. Some concern regarding the calcium loading is raised as an inducer of CAC. We hypothesized that lowering of dialysate calcium levels would result in decreased the progression rate of CAC compared to that of standard calcium dialysate.

Methods: Seventy-six HD patients were randomized to receive low calcium dialysate (LCD; 1.25 mmol/L, n=36) or continue on standard calcium dialysate (SCD; 1.5 mmol/L, n=40) for 12 months. The 64-slice multidetector computed tomography was performed at entry into the study and again at 12 months to calculate coronary artery calcium scores (CACS). Biochemical data were evaluated every 3 months.

Results: Baseline demographic or clinical characteristics were not different between the two groups. Serum calcium, phosphorus and calcium x phosphorus product at baseline, 3, 6, 9, 12 months were similar in both groups. However,

intact-PTH levels of LCD group showed an increase at 3 months and maintained higher thereafter. At 12 months, the CACS significantly increased in LCD group and not at all in SCD group (LCD: median 64.1 at baseline vs 328.9 at 12 months, $P=0.001$, SCD: median 40.1 vs 199.7, $P=0.9$, between group $P=0.03$). There was no difference in doses of a calcium-based phosphate binder and the frequency of intradialytic hypotension between the two treatments.

Conclusions: Use of LCD appears to be associated with more progression of CAC than use of SCD. While the exact mechanisms accounting for this result cannot be ascertained, increased serum PTH levels in LCD group might have influenced on the progression of CAC. However, a larger study should be undertaken to confirm these results.

Sudden Cardiac Arrest Risk Associated with Low Calcium Dialysate in Hemodialysis Patients

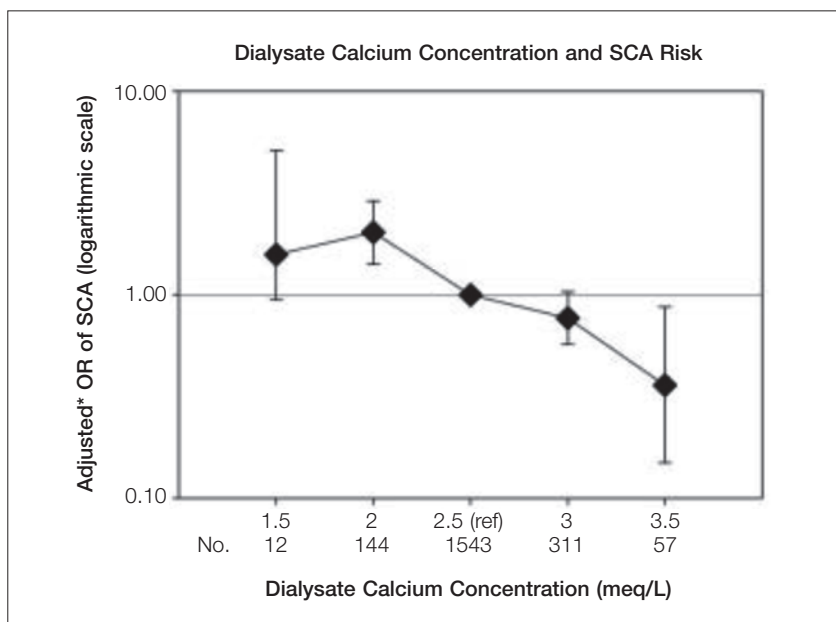
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The optimal dialysate calcium (Ca) concentration to maintain normal mineralization and reduce risk of cardiovascular events is in debate. KDOQI guidelines suggest that the dialysate Ca concentration should be lowered to 2.5 mEq/L among patients receiving oral Ca to avoid potential risks of vascular and soft tissue calcification. However, arrhythmias may be more likely to occur with lower dialysate Ca secondary to worsening of QT prolongation. We sought to examine the influence of low dialysate Ca on the risk of witnessed sudden cardiac arrest (SCA) within dialysis clinics.

We previously designed a case control study from among 43,200 US Davita hemodialysis patients between 2002-2005. 502 patients who experienced a witnessed SCA were compared with 1,632 randomly selected age and dialysis-vintage-matched controls. We examined baseline clinical and dialysis characteristics including last prescribed dialysate Ca concentration and concurrent prescription of medications associated with QT prolongation. Adjusted risk of SCA was modeled using logistic regression techniques. 82% (N=1699) of patients received dialysate Ca ≤ 2.5 meq/L at the time of event (cases) or index date (controls). After adjusting for differences in demographics, comorbidity, serum Ca levels and other baseline differences, use of dialy-

sate Ca ≤ 2.5 meq/L was independently associated with risk of SCA (adjusted OR 1.5, CI 1.1-2.1). Concurrent exposure to QT prolonging medications (OR 2.23, 95% CI 1.42-3.49) and low potassium dialysate (OR 2.9, 95% CI 1.9-4.3) conferred additional risk. Lowering of dialysate Ca concentration is associated with an increased risk of SCA. Our study suggests that inherent or acquired cardiac conduction disturbances and coincident medication exposures should be considered in addition to Ca absorption and bone turnover in determining the optimal dialysate Ca prescription.



3. Mineral Metabolism and Bone Disease

Has the Control of Mineral Metabolism Disorders Improved in the Past Three Years? Data Analysis of the OSERCE I and OSERCE II Studies

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Objective: To analyze the degree of compliance with the K/DOQI guidelines in chronic kidney disease (CKD) patients with GFR < 60 mL/min/1.73 m² (stages 3, 4, and 5 not on dialysis) by comparing the results of the OSERCE I and OSERCE II studies.

Patients and methods: The OSERCE I study is a multicenter, cross-sectional study that collected consecutive data in April and May 2006 in 634 patients from the outpatient clinics of 32 sites. The OSERCE II study also intends to analyze the degree of compliance in mineral and bone disorders in CKD patients, in addition to other primary objectives including 742

patients from 39 sites, with the same inclusion criteria (April and May 2009). The degree of compliance with the K/DOQI guidelines parameters is shown in the table.

Conclusions: It is still very difficult to achieve the objectives established by the K/DOQI guidelines for mineral and bone metabolism disorders in stage 3, 4, and 5 CKD patients not on dialysis; no improvement was seen in the past three years. The main compliance difficulty is with the iPTH goals. The levels of 25-(OH) Vit. D are inadequate in a high percentage of patients in both studies.

Degree of Compliance with the K/DOQI Guidelines

Compliance with K/DOQI guidelines	inadequate (%)	higher (%)	lower (%)
iPTH (pg/mL) OSERCE I	68.4	50.7	17.7
iPTH (pg/mL) OSERCE II	70.0	50.2	19.8
Corrected calcium (mg/dL) OSERCE I	44.0	40.0	4.4
Corrected Ca (mg/dL) OSERCE II	64.4	61.0	4.4
Phosphorus (mg/dL) OSERCE I	25.1	18.8	6.3
Phosphorus (mg/dL) OSERCE II	23.5	5.7	17.7
Ca x P (mg ² /dL ²) OSERCE I	3.0	3.0	–
Ca x P (mg ² /dL ²) OSERCE II	1.0	1.0	–
25-(OH)Vit. D (ng/mL) OSERCE I	81.5	–	81.5
25-(OH)Vit. D (ng/mL) OSERCE II	84.0	–	84.4

iPTH was measured with Immulite 2000 (chemiluminescence)

Genetic Variants that Modify the Association of Vitamin D Deficiency with Clinical Outcomes: A Candidate Gene Study

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Consistent data from prospective health studies link lower serum 25-hydroxyvitamin D concentrations with incident cardiovascular disease, fracture, cancer, and premature death. 25-hydroxyvitamin D represents available vitamin D substrate, which requires a series of metabolic steps for activation.

In this study, we investigated whether variation within 6 genes involved in 25-hydroxyvitamin D metabolism modifies the association of 25-hydroxyvitamin D deficiency with the composite outcome of myocardial infarction, hip fracture, cancer, or death (gene x environment interaction). Our cohort consisted of 1,509 Caucasian participants (mean age 74 years) from the Cardiovascular Health Study. We tested 141 single nucleotide polymorphisms (SNPs) genotyped by the Illumina 370CNV BeadChip platform from genes encoding the vitamin D receptor (VDR), cubilin (CUBN), 1-alpha hydroxylase (CYP27B1), 24-alpha hydroxylase (CYP24A1), megalin (LRP2), and the vitamin D-binding protein (GC). We used Cox proportional hazards models to test for multiplicative interactions of 25-hydroxyvitamin D and SNP on the risk of composite outcome, using a false discovery rate threshold of 0.25 to account for multiple testing (no more than 25% of our reported discoveries are expected to be false positives).

There were a total of 944 events during 14 years of follow-up (median 11 years). We found 6 SNPs located within CYP27B1, CUBN, and VDR that significantly modified the association of 25-hydroxyvitamin D with the combined endpoint. Each additional copy of the minor allele in these 6 SNPs was associated with an estimated 30-40% difference in the hazard ratio (all q-values <0.25, p-values between 0.002 and 0.009).

These findings suggest that known associations of vitamin D deficiency with clinical outcomes vary according to genetic differences in 25-hydroxyvitamin D metabolism. If confirmed, specific genetic variants may identify individuals for whom vitamin D deficiency is associated with greatest risk of adverse events.

Restoration of Physiological Concentrations of 25-OH-Vitamin D (25-OH-D) Enables Calcitriol (1,25-[OH]₂-D) Production in Hemodialysis (HD) Patients: Evidence from a Multicentre Randomized Controlled Trial

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Aim of the study: To investigate the impact of correcting cholecalciferol deficiency on mineral and bone disorder (MBD) parameters in HD patients.

Methods: Adult HD patients with 25-OH-D level <30 ng/ml from 2 Belgian centres were included. Participants were randomly allocated 1:1 in double-blinded manner to receive an oral dose of 25,000 IU 25-OH-D or placebo once a week for 13 weeks. Based on preliminary data, we estimated that 15 case subjects and 15 controls would provide >95% power to detect a standardized difference of 15 ng/ml in 25-OH-D levels, assuming a two-sided type 1 error rate of 5%.

Results: 54 patients were randomized and data were analysed according to intention to treat. Baseline serum 25-OH-D and 1,25-(OH)₂-D levels were similar in both groups (13.8 ± 5.51 vs 16.1 ± 7.96 ng/ml and 18 ± 9.8 vs 16.1 ± 7.14 pg/ml, respectively p=NS).

After 13 weeks, serum 25-OH-D, 1,25-(OH)₂-D and calcium levels significantly increased in the treated group compared to the placebo group (31.3±12.6 vs 15.7±8.13 ng/ml, p <.0001; 26.1±12.2 vs 12.4±5.36, p<.0001 and 8.80±0.57 vs 8.26±1.20 mg/dl, p=.029). No statistical difference was found for serum intact parathormone (376±278 vs 463±288 pg/ml), phosphorus (4.56±1.60 vs 5.02±1.82), C-telopeptide (2,257±1,261 vs 2,393 ±1,085.4), and bone specific alkaline phosphatase (34.4±25.3 vs 31.6±31.9) levels.

Conclusion: Weekly oral administration of 25.000 IU cholecalciferol for 3 months is safe and efficient to correct 25-OH-D as well as 1,25-(OH)₂-D deficiencies in HD patients.

Long term studies are required to hypothesize the impact of cholecalciferol therapy on MBD.

4. Vascular Access

Catheter (CVC) Related Septicemia: Associations with Seasons from the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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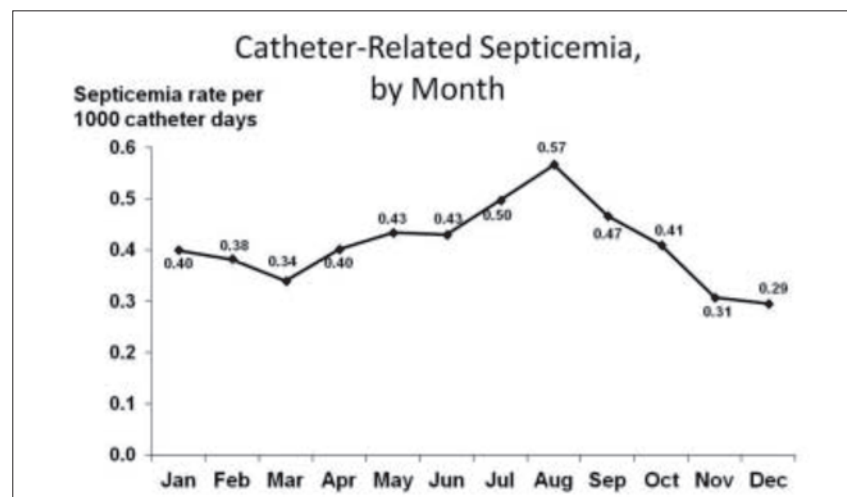
While CVC-related sepsis (CRS) contributes to adverse health outcomes in hemodialysis patients, unexplored risk factors remain, such as season of year and CVC dressing protocols.

8,412 hemodialysis patients in 12 countries from DOPPS I and II (1996-2004) were analyzed. CRS was defined as septicemia during or within 15 days after hemodialysis CVC use. Catheter time at risk (n=1,754,293 days) and CRS were assigned to 1 of 4 seasons in each country. CRS rates by season and the association of facility vascular access dressing protocols with hazard ratio (HR) of CRS were determined by Poisson and Cox regression, respectively.

Overall CRS rate was 1.2/month or 0.41/1000 CVC days. In North America, CRS was 0.47/CVC 1000 days. CRS varied by month (Figure) with an adjusted RR for "summer" of 1.42 (95% CI 1.09-1.87) compared to "winter".

CRS was lower with use of betadine [adjusted HR=0.81, 95% CI (0.65,0.996)], or chlorhexidine [HR=0.81 (0.59,1.11)] vs. alcohol, with attenuated HRs (0.87-1.06) for combined cleansing agents. Vascular access infection rates varied by personnel type who typically inspects CVC site /changes dressings: nephrologist [HR=0.64 (0.45,0.92)], technician [HR=1.47, 95% CI (0.98,2.2)] compared with nurse.

The higher CRS rate in summer may be due to higher heat, humidity, and perspiration, potentially facilitating bacterial growth and compromising protective measures. Extra vigilance by staff may reduce CRS in this high risk season. Betadine and chlorhexidine may be more effective than other cleansing agents.



Bacterial Biofilm in Non-Infected Tunneled Hemodialysis Catheters

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Background: Biofilm forms on the surface of tunneled hemodialysis catheter and is often associated with bacteremia. Knowledge about biofilm thickness and location is important, especially in the subset of patients without clinical evidence of infection, to plan preventive anti-biofilm strategies.

Methods: We identified patients in whom tunneled HD catheter was removed for non-infective etiologies and who did not have current clinical evidence of infection. The sterile catheter segment immediately distal to cuff and the double-barreled distal tip were defined as “extravascular” and “intravascular” segments respectively. Outer and luminal surfaces of both catheter segments were analyzed separately. Paired Student’s t-test was used.

Results: We examined 22 catheters with a confocal laser scanning microscope. Median duration of catheter was 101 days. Biofilm was seen in 17 of them (77%). As shown in the table, biofilm was

significantly thicker on the outer surface compared to luminal surface for both extravascular and intravascular segments. Overall, extravascular segments had thicker biofilm compared to intravascular segments on both outer and luminal surfaces.

Despite absence of clinical infection, 3 catheters grew an organism (14%). All the three patients had significant growth from outer surface of extravascular segment. One patient had growth from outer surface of both extra and intravascular segments. *S. epidermidis* was the commonest organism (3/3) and one patient had *S. aureus* (1/3).

Conclusions: Biofilm is present on the surface of tunneled HD catheter even in the absence of clinical infection. Outer surface of extravascular catheter segment has the thickest biofilm and harbors bacteria in few patients. It is possible that exit site may be the primary port of entry for bacteria.

Biofilm Thickness on Tunneled Catheters

	Outer surface	Luminal surface	p-value
Extravascular	3.1 μ	2.4 μ	<0.001
Intravascular	2.4 μ	1.5 μ	<0.0001
p-value	0.001	0.001	-

Long Term Vascular Access Survival and Complications with Daily Dialysis

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Background: A potential complication of daily hemodialysis is repeated access cannulation (six times per week). There are no studies that examined long term effects of frequent hemodialysis (FHD) on vascular access patency.

Methods: We conducted a non-randomized, controlled trial of the effect of daily (six sessions/week of three hours each) or conventional (three sessions/week of four hours each) hemodialysis on hemodialysis access outcomes. We enrolled 26 short daily hemodialysis and 51 matched conventional hemodialysis patients and collected vascular access procedures and treatment attendance. Baseline characteristics were similar between groups in terms of age, diabetes status and baseline vascular access.

Results: At 48-month follow-up, there were no significant differences between the two groups in the numbers of access procedure (thrombectomy or revision); 320.7/1000 person/year in the daily dial-

ysis group versus 433.3/person/year in the conventional dialysis group ($P = 0.4$). At 4 year follow-up, there were 7 access revisions in the daily dialysis group and one access revision in the conventional dialysis group. The numbers of treatments per month was significantly higher in the daily dialysis group compared with the conventional dialysis group (25 [24, 25] versus 14 [13, 22] $P = 0.008$).

Conclusion: At four years of follow-up, 3 hour daily (six times a week) hemodialysis does not lead to increased vascular access complications and is associated with good long term fistula and graft survival.

Increased Hemoglobin Variability as a Risk Factor for Vascular Access Dysfunction in Chronic Hemodialysis Patients

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Objective: Increased hemoglobin level leads to the occurrences of vascular access thrombosis in hemodialysis patients. Recently, increased variability of hemoglobin has been highlighted as a risk of mortality of hemodialysis patients. However, the influences of hemoglobin variability (HbV) on vascular access have not yet been explored. In the present study, therefore, the associations of HbV with occurrences of vascular access dysfunction (VAD) were evaluated in HD patients.

Design and Methods: In 70 chronic hemodialysis patients, HbV was estimated at the prospective follow-up of 1 year by 4 parameters including standard deviation (SD) of hemoglobin, residual SD (RSD) of hemoglobin, and numbers of hemoglobin cycling defined by cycles which amplitude > 1.5 g/dL and duration > 8 weeks, and numbers of excursion defined by half of one cycle. The parameters of HbV and the other factors affecting VAD were compared between 29 patients complicated with VAD defined by venous stenosis or thrombosis (D group) and the remainders without VAD (N group).

Results: SD and RSD of hemoglobin were significantly elevated in D group compared with N group (0.86 ± 0.09 g/dL, 0.70 ± 0.06 g/dL

vs 0.67 ± 0.03 , 0.54 ± 0.01). The numbers of hemoglobin cycling and excursion were also increased in D group than in N group (0.74 ± 0.20 per patient/year, 1.84 ± 0.21 per patient/year vs 0.31 ± 0.02 , 1.31 ± 0.14). However, averaged levels of hemoglobin, weekly erythropoiesis stimulating agent (ESA) doses and responsiveness to ESA defined by the weekly ESA doses divided by hemoglobin, did not differ between the two groups. There was no difference in calcium x phosphate product, C-reactive protein, interdialytic weight gain and blood pressure during hemodialysis between both groups. In multiple logistic regression analysis, SD of hemoglobin and weekly ESA doses were independent determinant factors for VAD, as shown by odds ratio of 12.01 (95% CI 1.38-209.49) and 0.997 (95% CI 0.993-0.999), respectively.

Conclusions: In chronic hemodialysis patients, the occurrences of VAD might be associated with HbV in addition to the used dosage of ESA.

5. Dialysis Therapy

Fibroblast Growth Factor 23 is Effectively Removed by Online Hemodiafiltration, but not by Low-Flux Hemodialysis

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Background. Fibroblast Growth Factor 23 (FGF-23, ± 27 kDa) is strongly associated with increased mortality in dialysis patients. If causality exists, methods to lower FGF23 can have beneficial effects on outcome.

Purpose. To investigate whether FGF-23 is more effectively removed by online hemodiafiltration (HDF) than by low-flux hemodialysis (HD).

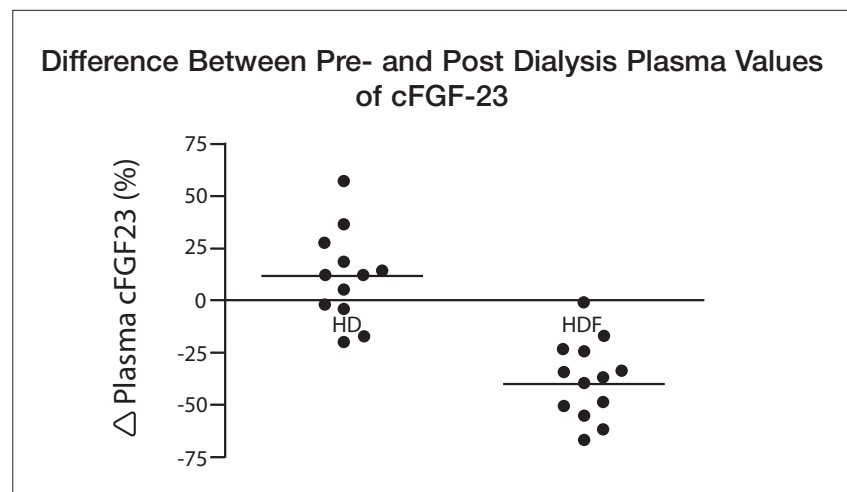
Methods. Blood samples were obtained at the beginning and end of 1 dialysis session in 12 HDF and 12 HD patients. Both full-length FGF-23 (iFGF-23) and C-terminal FGF-23 (cFGF-23, ± 12 kDa) were measured. FGF-23 levels are depicted as medians (total ranges). Differences were analyzed by Mann-Whitney tests.

Results. cFGF-23 changed from 5,030 RefU/mL (531-42,319) to 4,549 RefU/mL (678-47,268) in HD patients and from 8,449 RefU/mL (717-2,2018) to 4,540 RefU/mL (378-13,635) in HDF. Pre dialysis levels did not differ between the two groups ($p=0.5$). During HD, cFGF-23 did not change (+12% (-19 to +57)), whereas it decreased during HDF (-37% (-65 to -15)) ($p<0.001$, for difference in Δ change see figure).

iFGF-23 remained stable during HD (+11%) and decreased significantly during HDF (-28%) ($p<0.001$). Residual kidney function, weight- and calcium change were the same in the two groups. Phosphate and PTH levels decreased significantly more in HDF, but did not explain the change in FGF-23.

Conclusions. FGF-23 is effectively removed by HDF but not by low flux HD. In view of the possible adverse actions of FGF-23 in the development of cardiovascular disease, removal by HDF may be beneficial.

Further studies are needed to elucidate the long-term effects of increased FGF removal.



Sodium Gradient & Hospitalization for Fluid Overload in Hemodialysis Patients

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Introduction: Sodium load is associated with fluid retention in hemodialysis patients. We hypothesized that the sodium gradient (between serum vs. dialysate) may impact salt/fluid retention and hospitalization risk for fluid overload.

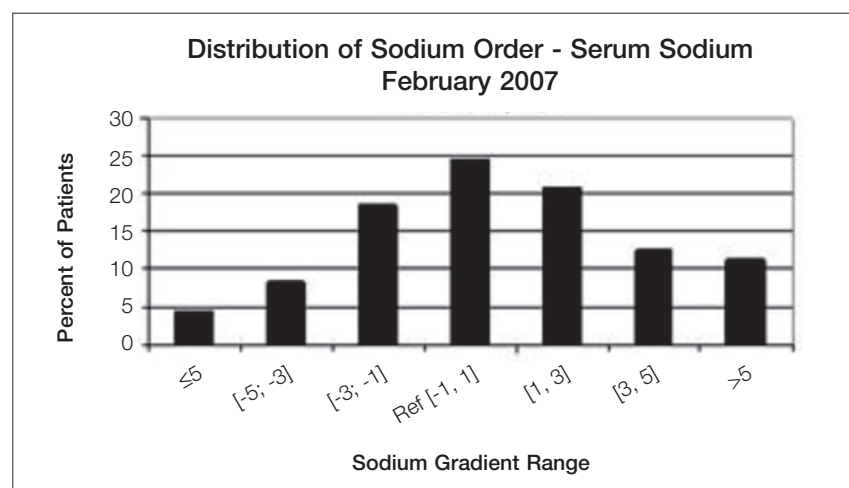
Methods: All chronic HD patients treated from January 1 to March 31, 2007 at legacy Fresenius Medical Care North America facilities with serum sodium data (~89%) were included. The weighted mean of the prescribed dialysate

sodium was computed monthly and the gradient determined. Inter-dialytic weight gain (IDWG) was recorded. Case-mix (age, gender, race, DM, BSA, and vintage) and vascular access were identified as of 1/1/07 and hospitalizations (± 1 day) primarily due to fluid overload (including heart failure and acute pulmonary edema) were tracked. Cox models were constructed based on the sodium gradient for each of the three study months.

Results: Mean age (N=71,767) was 61.3 ± 14.9 years, with 54.3% males, 49.9% white, 41.3% black and 52.5% diabetic, with vintage of 3.6 ± 3.7 years and 44% had fistulas, with 28% grafts, and 28% catheters. The distribution of sodium gradient was similar from month to month (February shown below):

The monthly hazard ratios for hospitalization due to fluid overload for Jan/Feb/Mar was consistently high at 1.54/2.17/1.92 for gradient >5 meq/L and after case-mix adjustment were 1.48/2.08/1.86, respectively (all $p < 0.003$). A gradient >5 meq/L was also associated with +0.4 kg higher IDWG each month ($p < 0.0001$).

Conclusion: A positive sodium gradient >5 meq/L, seen in 11%-14% of patients, was consistently associated with greater IDWG and a 50-100% increased hazard rate for hospitalization due to fluid overload. Physicians need to pay more attention to the sodium component of dialysate prescriptions. Minimizing the sodium gradient could potentially decrease hospitalizations for fluid overload.



Negative Sodium Gradients are Associated with Greater Sodium Removal without Adversely Affecting Inter-Dialytic Weight Gain: Support for an Individualisation of Dialysate Sodium

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Background: Larger inter-dialytic weight gains (IDWG) and higher ultrafiltration volumes and rates are associated with cardiac morbidity and mortality. Control of IDWG is a key therapeutic aim. The sodium set-point hypothesis predicts that the gradient between serum sodium (SNa) and dialysate sodium (DNa) is a major driver of thirst and IDWG. A positive sodium gradient ($GNa = DNa - SNa$), results in sodium loading and increased IDWG, but the effects of a negative gradient have been subjected to only limited study.

Methods: 19 chronic HD patients were studied over four weeks, dialysed against a constant 136 mmol/l dialysate Na concentration. 15 were anuric and 4 had urine output <150 ml/day. We used continuous on-line conductivity monitoring, ion-specific electrodes and a validated sodium kinetic model to calculate sodium gradients and related this to both ionic mass balance (IMB), IDWG, and blood pressure.

Results: A full dataset was available for 214 treatment sessions. The mean±SD are presented. GNa was -6.1 ± 3.8 mmol/l, IMB 347 ± 146 mmol, UF volume 1.9 ± 0.9 l, IDWG $2.7 \pm 1.4\%$, pre-HD systolic BP 142 ± 25 and diastolic

BP 83 ± 17 mmHg. Inter-patient variation in IMB was much greater than intra-patient variation. There was a reasonable correlation of negative gradients with higher ionic mass balance ($r = 0.59$, $p < 0.01$). There was no detectable effect on IDWG or BP.

Conclusion: Negative sodium gradients enhance sodium removal without increasing intra-dialytic hypotension. There was no detectable effect on IDWG.

Relevance. This study needs to be confirmed in a larger population but suggests that having dialysate sodium set lower than plasma sodium may enhance diffusive removal of sodium without adverse effects. Use of on-line conductivity monitoring makes this operationally feasible.

A Randomized Controlled Trial of Low Dialysate and Dietary Sodium on Blood Pressure in Hemodialysis

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Up to 85% hemodialysis patients need antihypertensives as well as ultrafiltration for blood pressure control. Dietary sodium [Na] restriction with aggressive ultrafiltration and lowered dialysate Na can reduce interdialytic weight gain [IDWG] and antihypertensive use. We studied the combined effect of these measures which has not been prospectively examined to date.

Fifty stable maintenance hemodialysis patients entered an open-label prospective trial Aug 2008-Dec 2009 with a 12week run-in [dialysate Na 140mM, unrestricted diet] and a 36week intervention phase. Sodium gradient [NaG] is defined by the difference dialysate - serum Na. Groups consisted of controls, low dialysate Na alone [target 3mM below patient's mean serum level by graded reduction: 1mM / 2 weeks], low dietary Na alone [2.3g/d with dietetic input], low dialysate and dietary Na. Blood pressure was recorded on hemodialysis and 24hr ambulatory records taken 6 weekly [midpoint of dialysis week]. Antihypertensive dose was recorded as defined daily dose [WHO]. A 22-point version of the Dialysis Symptom Index was completed 6 weekly.

Patients reaching the treatment phase were analysed [n=31, mean age 65.1±12.4yrs, 84% male, 40% diabetic]. Na restriction did not significantly alter predialysis Na. Low dialysate Na alone led to significant changes in NaG [+1.3 → -1.0mM, p<0.05]. Combined restriction led to reductions in NaG [+0.3 → -2.6mM, p<0.05] as well as IDWG [1.9 → 1.5kg, p<0.001] & improved intradialytic BP stability [p<0.05].

Any form of Na restriction caused more frequent but not severe cramps [+21%, p=0.04] vs controls. Isolated low dialysate Na reduced symptomatic intradialytic hypotension [27% → 4%, p=0.002]. Significant reductions in IDWG and antihypertensives require combined Na restriction which improves intradialytic hemodynamic stability. Na restriction (dialytic + dietary) leads to more muscle cramps but not of a degree to force treatment change.

Findings from this small but prospective study need larger numbers and longer follow up to determine any long term impact on cardiovascular outcomes.

Relation between Intradialytic Changes in Systolic Blood Pressure and Sodium Gradient in Chronic Hemodialysis Patients

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Intradialytic hypertension has been associated with increased hospitalization and mortality rates in chronic hemodialysis (HD) patients. Intradialytic sodium loading has been proposed as a contributor of intradialytic hypertension. The aim of the present analysis was to evaluate the relation between intradialytic blood pressure changes and sodium gradient (grNa^+), defined as the difference between the dialysate sodium and the serum sodium concentration ($\text{grNa}^+ = \text{dNa}^+ - \text{sNa}^+$).

Chronic hemodialysis patients from nine Renal Research Institute clinics that did not use dialysate sodium profiling between Sep 1 2009 and Dec 31 2009 were included. The relation between the average grNa^+ and intradialytic changes in SBP (ΔSBP) during this period were analyzed with linear regression models, adjusting for patient characteristics (sex, age, race, diabetes, dialysis vintage) and ultrafiltration rate (UFR). In addition, odds ratios (OR) for an increase in SBP ($\Delta\text{SBP} > 0$ mmHg) during treatment were estimated. We studied 560 patients (age

61 ± 15 [$\pm\text{SD}$] yr, 53% males and 49% blacks). Mean pre- and post-dialysis blood pressures were $149 \pm 19/77 \pm 12$ and $139 \pm 18/72 \pm 10$ mmHg, respectively. The mean grNa^+ was -2.2 ± 2.7 mEq/L ($\text{grNa}^+ > 0$ mEq/L in 19% of the patients). The adjusted grNa^+ was positively related to ΔSBP ($B=0.5$; 95% CI 0.1 to 1.0, $P=0.02$). Dialysis vintage ($P=0.02$), diabetes ($P=0.004$) and UFR ($P=0.001$) were inversely related to ΔSBP . SBP increased in 126 patients (23%). Increases in SBP were more often observed in patients with a positive gradient (OR = 2.1; 95% CI 1.3 to 3.3).

These data identify a positive sodium gradient as a contributing and potentially modifiable factor for intradialytic hypertension, which can probably be explained by intradialytic sodium loading. Whether intradialytic hypertension can be treated by lowering the dialysate sodium concentration in these patients needs further study.

Study of the Relationship between Fluid Overload and Autonomic Response during Hemodialysis

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 Dinna N. Cruz, Flavio Basso,
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Background: Fluid overload (FO) is an important and independent predictor of mortality in chronic hemodialysis (HD) patients [Wizemann V. et al., 2009]. The aim of this study was to investigate the relationship between FO and the autonomic response to the HD, estimated from Heart rate variability (HRV).

Methods: 80 patients were recruited from the dialysis unit of San Bortolo Hospital, Vicenza, Italy. 24 hr ECG Holter recordings were performed once for each patient starting before the HD treatment, immediately after fluid overload (FO_{pre}) was assessed with a whole body bioimpedance spectroscopy device (BCM, Fresenius Medical Care, Germany). Heart rate variability (HRV) was analyzed with time domain parameters and frequency domain indices [Task Force, Circulation, 1996]. Mean values of time and frequency domain indices of HRV were calculated for the first 30 minutes and last 30 minutes of HD, and for the entire HD session [Task Force, Circulation, 1996].

Results: SDANN* estimated over the entire HD was significantly different between overhydrated ($FO > 2.5l$) and non-overhydrated patients ($FO \leq 2.5l$) both for D and ND patients (T-test p-value < 0.05) (see table).

Conclusion: These results for the first time demonstrate that there is a link between fluid status and autonomic function. Heart rate variability as a marker of autonomic function significantly changes with rising fluid overload. Diabetic and non-diabetic patients present different correlations between FO and HRV indices.

* (Standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording)

Pearson Coefficients (HRV indices vs $FO_{pre}/ECW\%$)

	All patients	Diabetic patients	Non-diabetic patients
SDANN*	$\rho = -0.40$ $P = 0.002$	$\rho = -0.16$ $P = 0.552$	$\rho = -0.51$ $P = 0.001$
VLF (ms^2)	$\rho = -0.31$ $P = 0.020$	$\rho = -0.28$ $P = 0.302$	$\rho = -0.39$, $P = 0.015$
HF%	$\rho = +0.33$ $P = 0.012$	$\rho = +0.56$ $P = 0.024$	$\rho = +0.30$, $P = 0.062$

VLF = very low frequency; HF = high frequency; HRV = heart rate variability

Comparison of Body Composition Determined by Multifrequency Bioelectrical Impedance and Dual Energy X-Ray Absorptiometry in Stable Peritoneal Dialysis Outpatients

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Medical School, Royal Free Campus, London, United Kingdom

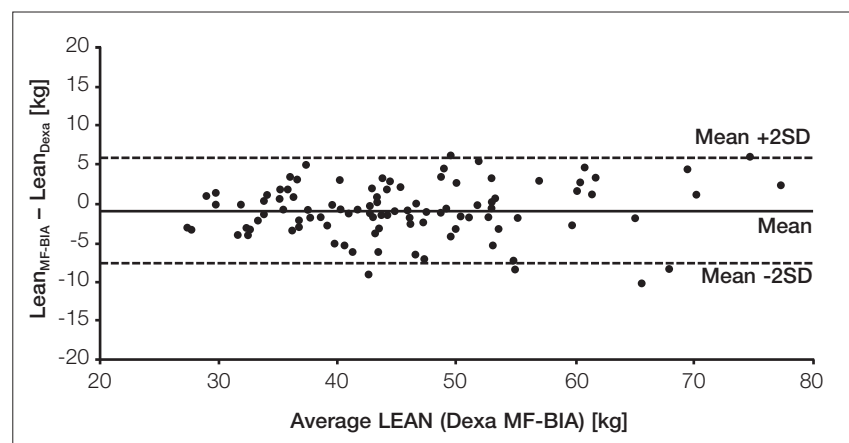
Introduction: Malnutrition is common in peritoneal dialysis patients and associated with poor outcome. Therefore, simple, reliable and easily available methods to determine nutritional status and to recognise short-term changes in body composition are desirable. The accuracy of multifrequency bioelectrical impedance analysis (MF-BIA) as a tool to assess body composition is unknown in this population.

Methods: We compared whole body and segmental composition determined by MF-BIA with that obtained using dual energy x-ray absorptiometry (DEXA) in 104 outpatient adult peritoneal dialysis patients.

Results: Assessment of whole body composition showed that lean body mass (LBM) measured by the two techniques was highly correlated with good method agreement (Figure) using DEXA as the

reference test ($r=0.95$, $p<0.0001$; BIAS -0.88 kg; 95% CI -1.53 to 0.23 kg). Similarly, high correlation and good method agreement were found for fat mass (FM) ($r=0.93$, $p<0.0001$; bias 0.69 kg; 95% CI 0.03 kg to 1.6 kg). Segmental analysis of the lean body mass revealed strong correlations between lean body mass of trunk, left and right arms and legs ($r= 0.90, 0.86, 0.84, 0.89$ and 0.90 respectively, $p<0.0001$). Bone mineral content (BMC) derived by MF-BIA overestimated that measured by DEXA (bias 0.740 kg; 95% CI 0.66 to 0.82 kg).

Conclusion: MF-BIA appears to be a robust tool for measuring and monitoring body composition in peritoneal dialysis patients.



Adapted APD, Varying Sequentially Dwell-Time Exchanges Short and Thereafter Longer, and Fill Volume Exchanges Small and Thereafter Larger: Impact on Dialysis Efficacy

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Varying the duration of dwell-time or fill volume could modify peritoneal dialysis efficiency. Nevertheless APD is classically given as a recurrent repetition of exchanges each of them having the same dwell-time and the same fill volume, that is conventional APD (APD-C). We propose a new, adapted APD (APD-A) by first using a short dwell time with a small fill volume to favour ultrafiltration (UF) and subsequently using a longer dwell time and a larger fill volume, to promote blood purification. The study was a prospective, cross over, multicenter trial to investigate the impact on overnight UF and weekly peritoneal Kt/V_{urea} , weekly peritoneal creatinine clearance per 1.73 m^2 BSA (K_{creat}), phosphate/sodium dialytic removal (PDR, SDR: mmol/session). Normalization to the absorbed glucose estimated the metabolic cost. Blood pressures were recorded. 25 patients were selected in the study, 6 with drew, 2 at enrolment, 1 at day 75 (transplantation), 2 at day 30 (catheter dysfunction), 1 for drainage alarms.

The same amount of dialysate (same cost), balance lactate 1.5% glucose, and the same duration of overnight APD were prescribed.

Tolerance was good. APD-A compared to APD-C realized a significant enhancement of Kt/V_{urea} , of K_{creat} , and of PDR. The glucose metabolic cost for urea, creatinine and PDR was significantly lower in APD-A compared to APD-C. The UF increased during APD-A versus APD-C. The SDR was significantly higher with APD-A compared to APD-C, 35.23 ± 52.00 mmol/session and 18.35 ± 48.68 mmol/session ($p < 0.01$). The mean BP (day 45) was significantly lower for the APD-A periods compared to the APD-C periods.

Our study supported that varying the dwell-times short and thereafter longer, and the fill volumes small and thereafter larger as described (APD-A) could improve dialysis efficiency for UF, Kt/V_{urea} , K_{creat} , phosphate dialytic removal and sodium dialytic removal.

These results were achieved without more costs, even with reduced glucose metabolic cost.

Quality of Life (QoL) in the Oldest Dialysis Patients – Important Differences between Hemodialysis and Peritoneal Dialysis?

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The elderly dialysis population is increasing, little is known about their QoL, and very few choose peritoneal dialysis.

Aims: was to describe and compare the QoL of the older Norwegian hemodialysis and peritoneal dialysis population, and to explore whether the starting point of peritoneal dialysis and hemodialysis differ (early vs late start).

Method: All patients > 75 years (n = 320) who according to the Norwegian Renal Registry (NRR) were on dialysis by 01.01.2009 and alive by Sept 2009 were asked to participate and mailed the QoL questionnaire SF 36. Medical data were collected from the NNR.

Results. In total, 230 patients (72%) responded, 152 (66%) men and 78 (34%) women, 189 patients (82%) were on hemodialysis, 41 patients (18%) on peritoneal dialysis. Mean age hemodialysis: 80.5 years, peritoneal dialysis: 80.0 years. At start of dialysis, there was no significant difference in the distribution of comorbidities (diabetes mellitus type II, coronary

and cerebrovascular diseases and malignancies), estimated glomerular filtration rate (eGFR, ml/min) (HD: 8.7; PD: 8.1) or the proportion of early start (eGFR > 10 ml/min), 27% in both groups. Pre-planned start was more frequent among peritoneal dialysis patients (86% vs 73%) and duration of treatment was shorter (27 vs 38 months).

Peritoneal dialysis patients had lower blood pressure (mean 131/72 mm/Hg vs 143/71, annual report NNR 2008). S-Albumin g/l (HD: 38.1, PD: 36.2) and BMI (kg/m²) (HD: 24.0, PD: 25.9) were comparable.

Overall, the QoL scores were low, and there was no statistical or clinically significant difference between the two groups.

In conclusion there are little differences between hemodialysis and peritoneal dialysis patients in terms of QoL scores and basic characteristic. The findings may encourage a higher peritoneal dialysis proportion in the elderly dialysis population.

SF 36 Scores

Mean	HD	PD
Physical Function	42.0	38.3*
Role Physical	19.1	11.4*
Bodily Pain	56.7	60.6*
General Health	46.2	44.7*
Vitality	40.2	35.4*
Social Function	61.4	69.7*
Role Emotional	43.5	39.0*
Mental Health	73.9	72.2*

* p > 0.05 (Mann-Whitney U test)

6. Miscellaneous

Oral Anticoagulants (OAC): Prescription Patterns and Outcomes in the Dialysis Outcomes and Practice Patterns Study (DOPPS)

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Indications for OAC use in hemodialysis remain controversial. We report OAC prescription and clinical events in the international DOPPS cohort.

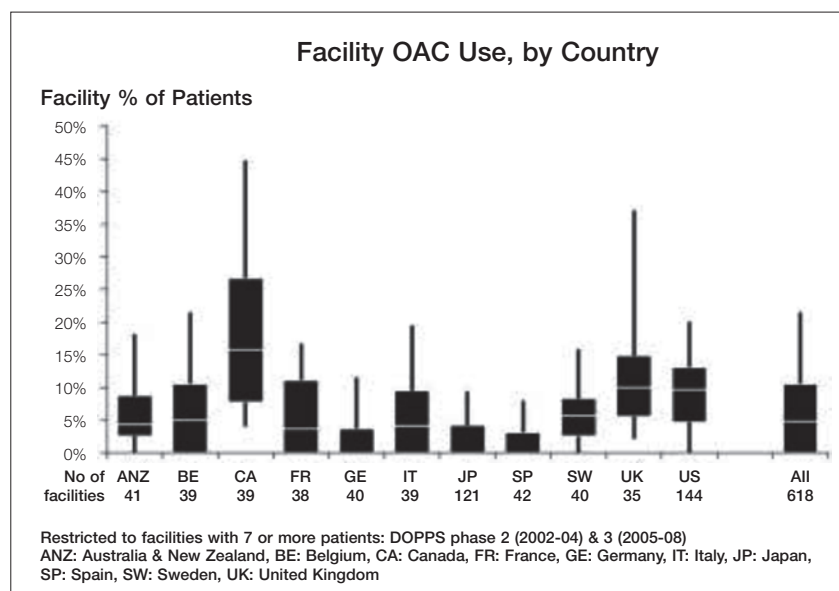
The study sample comprised 37,863 hemodialysis patients with no mechanical heart valves from 925 facilities in the US, Canada (CA), Japan (JP), Europe and Australia and New Zealand [Eur/ANZ] in 1996-2008. Associations between baseline OAC prescription and bleeding events, stroke, and mortality were assessed in fully adjusted Cox models.

OAC prescription was 18% in CA, 10% in the US, 5% in Eur/ANZ, and 3% in JP. OACs were more commonly used in patients with atrial fibrillation (40% in CA, 34% in the US, 20% in Eur/ANZ and 13% in JP); OAC use in patients using a catheter was more common in CA (22%) vs. the US (8%) and Eur/ANZ (6%). Among patients on

OACs, low dose warfarin (<10.5 mg/week) was prescribed to a minority of patients (31% in CA; 29% in JP; 17% in Eur/ANZ and the US). The % of facility patients on OACs varied in each country.

Older age, low serum albumin, cardiovascular and lung disease were associated with OAC use. Compared those not on OAC, OAC patients had a higher risk of bleeding events (hazard ratio: 1.19 [95% confidence interval: 1.04-1.37]; $p=0.01$), all-cause (1.16 [1.08-1.25]; $p<.0001$) and cardiovascular mortality (1.13 [1.01-1.26]; $p=0.03$) and stroke (1.13 [0.92-1.38]; $p=0.25$).

OAC use varies internationally and is associated with poor clinical outcomes, despite extensive case-mix adjustment. Health care providers should consider the potential harms of OAC therapy in HD patients.



Survival Advantage of Excess Fat Relative to Lean Body Mass in Long-Term Hemodialysis Patients

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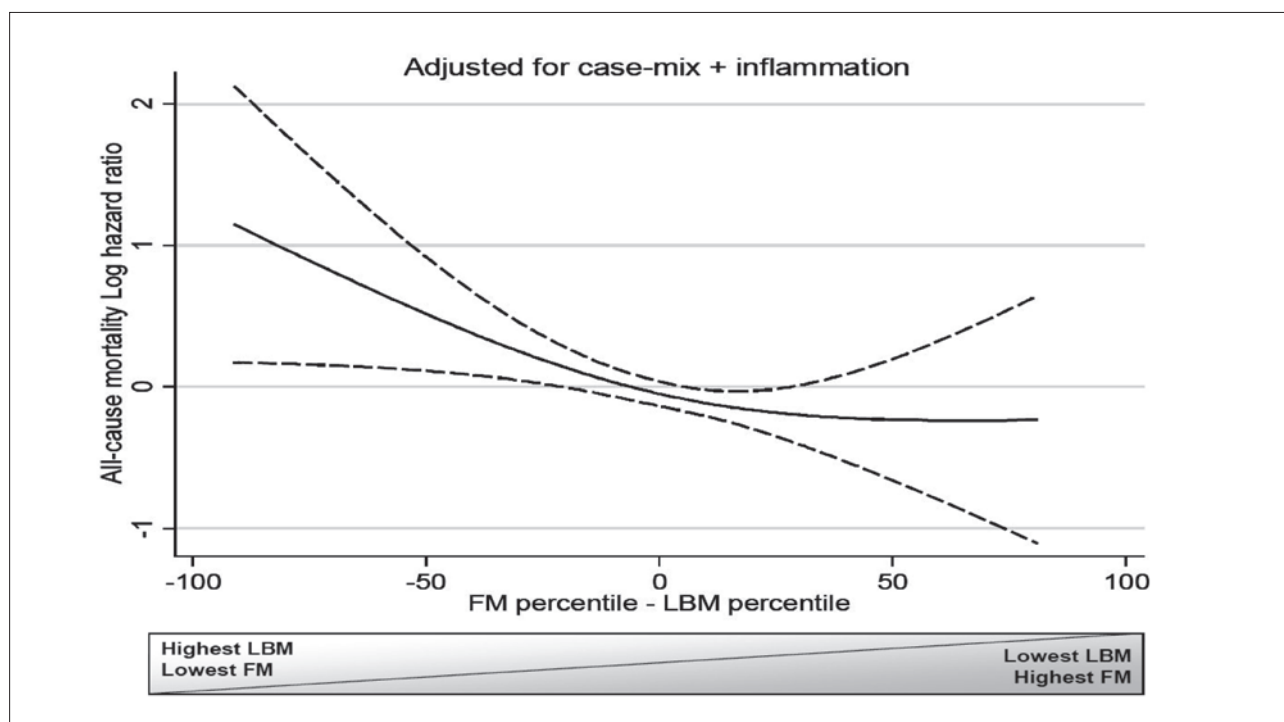
Background: Several studies have suggested that maintenance hemodialysis patients (MHD) with higher body mass index (BMI) enjoy a survival advantage. It is not clear whether lean body mass (LBM) or fat mass (FM) confers this survival benefit.

Methods: Using near infrared (NIR) technology we measured body compositions in 732 MHD patients and ranked them twice, once according to their absolute FM or then LBM (in kg) and assigned a percentile score to each patient within each gender group, i.e., a number between 0 (lowest) and 100 (highest FM or LBM). The difference between the two percentile scores (FM percentile minus LBM percentile) in each patient yielded a number

between -100 (indicating a patient with lowest FM but highest LBM) and +100 (indicating a patient with highest FM and lowest LBM). The Cox survival regression was modeled using cubic spline for the “FM minus LBM percentiles” after adjustment for case-mix and inflammatory markers.

Results: A relatively linear and downgoing trend towards greater survival was observed with higher excess fat relative to lean mass (Figure).

Conclusions: In MHD patients the excess fat relative to lean mass appears associated with greater survival. Clinical trials to examine the outcomes of interventions that modify body composition in MHD patients are indicated.



Obesity is a Risk Factor for Mortality, Especially among Younger Dialysis Patients

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Obesity is an important risk factor for cardiovascular disease and mortality in dialysis patients. However, differences in mortality between young and elderly dialysis patients have not been well addressed. Therefore, our aim was to investigate whether the association of BMI and mortality differs between younger (<65 y) and older (≥ 65 y) dialysis patients.

In a prospective multi-centre cohort study, all dialysis patients (>18 y) starting with their first dialysis treatment were included and followed until death, transplantation or a maximum of 7 years (NECOSAD). We divided patients into eight categories based on their baseline BMI and age: <20 (7.5%), 20 to 25 (47%), 25 to 30 (34.5%) and ≥ 30 (11%) kg/m². Cox regression analysis was performed to calculate hazard ratios (HR) associated with BMI groups, using a normal BMI (20-25 kg/m²) in the younger patients as the reference category. Analyses were adjusted for age, sex, treatment modality and smoking.

In total, 1749 patients were included (age (mean (SD)) younger patients: 49 y (11), older patients: 73 y (5) years, BMI: 25 (4) kg/m², 62% male, 62% HD). Overall, the 7-year mortality was 67%. Compared to a normal BMI and <65 y at baseline, the adjusted HRs (95%-CI) by BMI category were for the younger patients: 2.16 (1.37-3.40), 1 (reference), 0.89 (0.65-1.23), 1.60 (1.11-2.30), and for the elderly 1.64 (1.03-2.63), 1.18 (0.84-1.66), 1.18 (0.84-1.65), 1.06 (0.71-1.59).

We conclude that both young and elderly dialysis patients with underweight have an about 2-fold increased risk factor for mortality, although this may be due to reverse causality. However, obesity is about 1.5-fold stronger risk factor for mortality in young compared to elderly dialysis patients.

Circulating Cell Free DNA (CFD) in Hemodialysis Patients is Associated with Risk Factors and Mortality

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Circulating cell-free DNA (CFD) is present in healthy individuals and increases in hemodialysis and in various disorders including inflammation and diabetes, which are important risk factors in hemodialysis patients. We hypothesized that CFD is an integrative marker of damage and thus has prognostic value.

Therefore, we assessed CFD in hemodialysis patients and its relation to clinical/laboratory parameters and prognosis. In a prospective study, 31 chronic hemodialysis patients with no acute disease were evaluated for serum CFD levels before and after hemodialysis, using the reported rapid non-cumbersome inexpensive fluorometric assay developed in our laboratory. Follow-up CFD levels were assessed at 18 months in 20 patients. Pre-HD-CFD levels were higher than in healthy subjects (582 ± 305 vs 431 ± 221 ng/ml, $p < 0.05$) and increased after hemodialysis (832 ± 296 ng/ml, $p < 0.01$). Post-HD CFD were high (> 850 ng/ml) in 35% of patients and at 18 months in 80%, with 47% increase in levels ($p < 0.0001$). Post-HD-CFD was higher in the diabetes subgroup (1004 ± 278 vs 737 ± 268 ng/ml in non-DM, $p < 0.05$), correlated positively to post-HD inter-

leukin-6 (IL-6) levels ($p < 0.05$, $r = 0.51$) and negatively to creatinine ($p < 0.01$, $r = -0.54$). No correlation was found with serum albumin, urea, glucose, hemoglobin, leukocyte count and dialysis-related parameters. Pre-HD-CFD levels correlated with neutrophil number ($p < 0.05$, $r = 0.36$), but showed less prominent correlation than post-HD-CFD for other parameters. Post-HD-CFD was positively correlated with death at one year ($p < 0.01$, $r = 0.46$) and 5/6 patients who died within one year had elevated CFD levels.

Conclusions: CFD in hemodialysis patients is associated with diabetes, inflammation, low muscle mass reflected by serum creatinine and mortality. The increase after hemodialysis and the stronger associations with post-HD levels suggest combined effect of patients' state and the dialysis process.

We suggest that CFD is an integrative marker of pathologic processes and a correlate of outcome. Its' detection is a cheap applicable tool for identifying patients at risk and follow up.

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