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ORIGINAL RESEARCH

Association of low serum aluminum level with mortality in hemodialysis patients

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Background: The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative recommends that the serum aluminum level (SAL) should be below 20 µg/L for patients with maintenance hemodialysis (MHD). However, serum aluminum may have toxic effects on MHD patients even when it is in the apparently acceptable range (below 20 µg/L).

Methods: The Medical Ethics Committee approved this study. Initially, 954 MHD patients in dialysis centers were recruited. A total of 901 patients met the inclusion criteria and were followed-up for 1 year. Patients were stratified by SAL into four equal-sized groups: first quartile (<6 µg/L), second quartile (6–9 µg/L), third quartile (9–13 µg/L), and fourth quartile (>13 µg/L). Demographic, biochemical, and dialysis-related data were obtained for analyses. A linear regression model was applied to identify factors associated with SAL. Cox proportional hazard model was used to determine the significance of variables in prediction of mortality.

Results: Only 9.3% of MHD patients had SALs of 20 µg/L or more. At the end of the follow-up, 54 patients (6%) died, and the main cause of death was cardiovascular disease. Kaplan–Meier survival analysis showed that patients in the fourth SAL quartile had higher mortality than those in the first SAL quartile (log rank test, χ^2=13.47, P=0.004). Using the first quartile as reference, Cox multivariate analysis indicated that patients in the third quartile (hazard ratio =1.31, 95% confidence interval =1.12–1.53, P=0.038) and the fourth quartile (hazard ratio =3.19, 95% confidence interval =1.08–8.62, P=0.048) had increased risk of all-cause mortality.

Conclusion: This study demonstrates that SAL, even when in an apparently acceptable range (below 20 µg/L), is associated with increased mortality in MHD patients. The findings suggest that avoiding exposure of aluminum as much as possible is warranted for MHD patients.

Keywords: aluminum, mortality, hemodialysis

Introduction

Aluminum (Al) is a toxicant that is especially harmful to patients with chronic kidney disease (CKD).[1] An elevated Al level can lead to dialysis encephalopathy,[2] bone disorders,[3] and anemia[4] in patients with end-stage renal disease (ESRD). In dialysis settings, Al is eliminated from the dialysate by reverse osmosis and deionization since the early 1980s.[5] The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (KDOQI) recommends measurement of SAL at least once per year to assess Al levels and risk for Al toxicity.[6] These guidelines also recommend measurement of SAL every 3 months for patients who take Al-containing medications.[6]

Previous studies have documented an association between overt Al toxicity and mortality in hemodialysis (HD) patients. For example, Chazan et al[7] demonstrated that moderately elevated SAL was associated with mortality in a large population of maintenance HD (MHD) patients and that SAL-dependent mortality was evident when the level was above 59.8 µg/L. Salahudeen et al[8] reported that Whites with MHD had

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higher SALs than Blacks with MHD (20±2.3 vs 14±0.6 μg/L) and suggested this might contribute to the higher mortality of Whites. However, the association between SAL in the apparently acceptable range (below 20 μg/L) and mortality in MHD patients is uncertain.

The KDOQI guidelines recommend that the baseline SAL should be below 20 μg/L,[6] but the basis for this cutoff value is unclear. One report[5] demonstrated that an abnormal SAL (>40 μg/L) was present in only 2.1% of the 1,410 measurements of 207 dialysis patients and was present in only 2.5% of more than 43,000 patients in a nationwide survey. Another study[9] revealed that the mean SAL was 12.7 μg/L in MHD patients from the UK and suggested reevaluation of the use of Al monitoring.[10] Moreover, even though recent studies reported low SALs in MHD patients,[5,9] the clinical significance of SAL when it is in the apparently acceptable range in these patients is unknown.

This observational study was conducted to evaluate the relationship between SAL and 1-year mortality in MHD patients.

Methods

Ethics statement

This retrospective observational study complied with the guidelines of the Declaration of Helsinki, and was approved by the Medical Ethics Committee of Chang Gung Memorial Hospital, a tertiary referral center in the northern part of Taiwan. As this study involved a retrospective review of existing data as well as medical records, and all individual information was securely protected by delinking identifying information from main data set and was only available to investigators, the Institutional Review Board of Chang Gung Memorial Hospital approved this study and specifically waived the need for written informed consents. Moreover, all of the data were analyzed anonymously.

Patients

Study patients were recruited from three HD centers in Chang Gung Memorial Hospital (Taipei, Linkou, and Taoyuan). Initially, all 954 MHD patients in the HD centers were included in this study. Only MHD patients who were older than 18 years and received HD for 6 months were enrolled. Patients with histories of occupational exposure to Al and previous Al intoxication, or who used Al-containing medications within 6 months before the study or during the 12-month study period were excluded. Patients with malignancies, obvious infectious diseases, or who were hospitalized or underwent surgery in the 3 months before enrollment were also excluded. Finally, a total of 901 MHD patients entered this study.

Most patients underwent 4 hours of HD three times per week. HD was conducted using single-use hollow-fiber dialyzers that were equipped with modified cellulose, polyamide, or polysulfone membranes. In all study patients, the dialysate had a standard ion composition and was in a bicarbonate-based buffer.

The incidence of cardiovascular diseases (CVDs), including cerebrovascular disease, coronary arterial disease, congestive heart failure, and peripheral vascular disease, was recorded in all patients. Their smoking behavior was also recorded. Hypertension was defined as blood pressure ≥140/90 mmHg based on at least two measurements or the regular use of antihypertensive medications. Diabetes mellitus (DM) was diagnosed by a physician or by the presence of two measurements of fasting glucose above 126 mg/dL.

Measurement of SAL

To ensure that patients were not exposed to water or dialysate that was contaminated with Al during HD, two samples of dialysate were collected at least from the outlets and inlets of the dialysate portion of the dialyzers at each HD center by using Al-free plastic bottles. The blood samples for Al measurement were centrifuged for serum separation. All samples were deproteinized using trichloroacetic acid and microwave irradiation before measurement, and all sample preparation procedures were conducted under a laminar flow hood. Al was measured by graphite furnace atomic absorption spectrometry using a Perkin-Elmer 5100 (Norwalk, CT, USA) atomic absorption spectrometer with Zeeman background correction and an L'vov platform, equipped with a graphite furnace and an auto sampler. Distilled and deionized water was used for all procedures. A solution that contained 1,000 mg/L Al (Merck, Darmstadt, Germany) was used to prepare working standard solutions. Nitric acid (HNO_3, 65% m/m, 1.17 g/mL; Merck) was further purified by subboiling distillation. Only plastic materials were used to avoid contamination. All laboratory ware (pipette tips, volumetric flasks, etc) were immersed for at least 48 hours in a 10% (v/v) HNO_3/ethanol solution and washed with purified water shortly before use. To avoid contamination from the air, all steps of the sample and reagent preparation were performed on a clean bench. Besides, internal and external quality control procedures were applied and achieved satisfactory results consistently. A certified commercially prepared product (Seronorm Trace Elements; Sero AS, Billingstads, Norway)

was employed to determine intrabatch accuracy and to ensure interbatch standardization. The intra- and interbatch coefficient of variation for Al measurements was 5.0% or less, and the detection limit was 0.1 μg/L. External quality control was maintained via participation in the National Quality Control Program conducted by the government of Taiwan.

Based on the mean of two measurements of SAL with a 6-month interval, all enrolled patients were stratified into four equal-sized groups for statistical analysis.

Laboratory parameters

All blood samples were drawn from the arterial end of the vascular access immediately before initiating the midweek HD session and were then centrifuged and stored at −80°C until analysis. The biochemical parameters which might influence the mortality of MHD patients were examined using an automatic chemistry analyzer, including hemoglobin, albumin, creatinine, ferritin, calcium, phosphate, intact parathyroid hormone (iPTH), and cholesterol. Serum high-sensitivity C-reactive protein (hsCRP) concentrations were measured by immunonephelometry (Nanopia CRP; Daiichi Inc., Tokyo, Japan), with a detection limit of 0.15 mg/L. The normalized protein catabolic rate was calculated using validated equations and normalized to actual body weight.[11] The dialysis clearance of urea was expressed as Kt/V urea as described by Daugirdas et al.[10] Serum calcium levels were corrected using the serum albumin levels and the following formula: corrected calcium (mg/dL) = serum calcium (mg/dL) +0.8× (4.0 − serum albumin [g/dL]).

Follow-up

All patients were followed up for at least 1 year after the initial assessment. All deaths during the follow-up period were reviewed. Physicians who were not involved in this study assigned the underlying causes of death. The outcomes were categorized as cardiovascular-related death, infection-related death, or other-cause death. Cardiovascular death was defined as an event of arrhythmia, acute or subacute ischemic heart disease, congestive heart failure, intracerebral hemorrhage, occlusion of cerebral arteries, or sudden death. For patients who died in the hospital, cardiovascular events or infections that occurred during the follow-up were obtained from the discharge diagnosis and death certificates in the charts. For patients who died outside the hospital, family members were interviewed by telephone to ascertain the circumstances. All other patients were classified as transferred to long-term peritoneal dialysis, recipient of renal transplant, or transferred to another facility while remaining on MHD.

Statistical analysis

The Kolmogorov–Smirnov test was used to determine the distribution of the continuous variables. Unless otherwise stated, continuous variables were expressed as means ± standard deviations or medians (minimum, maximum), and categorical variables were expressed as numbers and percentages. Comparisons of the four study groups were analyzed with trend tests. The following variables had nonnormal distributions and were subjected to logarithmic transformation before analysis: SAL, iPTH, ferritin, and hsCRP.

In this study, a linear regression model was used to identify factors associated with SAL. All potential variables ($P<0.05$) from a simple linear regression analysis were entered into a multiple linear regression model using backward stepwise procedures. The Cox proportional hazard model was used to measure all potential variables and determine their significance in prediction of mortality. The hazard ratios (HRs) and 95% confidence intervals (CIs) for death were obtained by this model. All potential variables ($P<0.05$) from a univariate Cox analysis were entered into a multivariate Cox model using forward stepwise procedures. In addition, Kaplan–Meier survival analysis was performed to compare the survival rates of the different groups.

For all statistical tests, a variable with P-value less than 0.05 was considered significant. All data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 18.0 for Windows XP (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Initially, all 954 MHD patients in the three HD centers were included in this study. However, 53 patients were excluded because of their histories of Al exposure or the lack of complete data collection resulting from malignancies, obvious infectious diseases, hospitalization or surgery within 3 months before this study. A total of 901 MHD patients (465 men and 436 women) entered this study (Figure 1). The mean age was 56.2±13.6 years, and the mean HD duration was 6.6±5.3 years. Among them, 350 patients (38.8%) had hypertension, 199 (22.1%) had DM, and 43 (4.77%) had previous CVD. All study patients were stratified into four equal-sized groups based on SAL: the first quartile (<6 μg/L, n=222), the second quartile (6–9 μg/L, n=229), the third quartile (9–13 μg/L, n=230), and the fourth quartile (>13 μg/L, n=220).

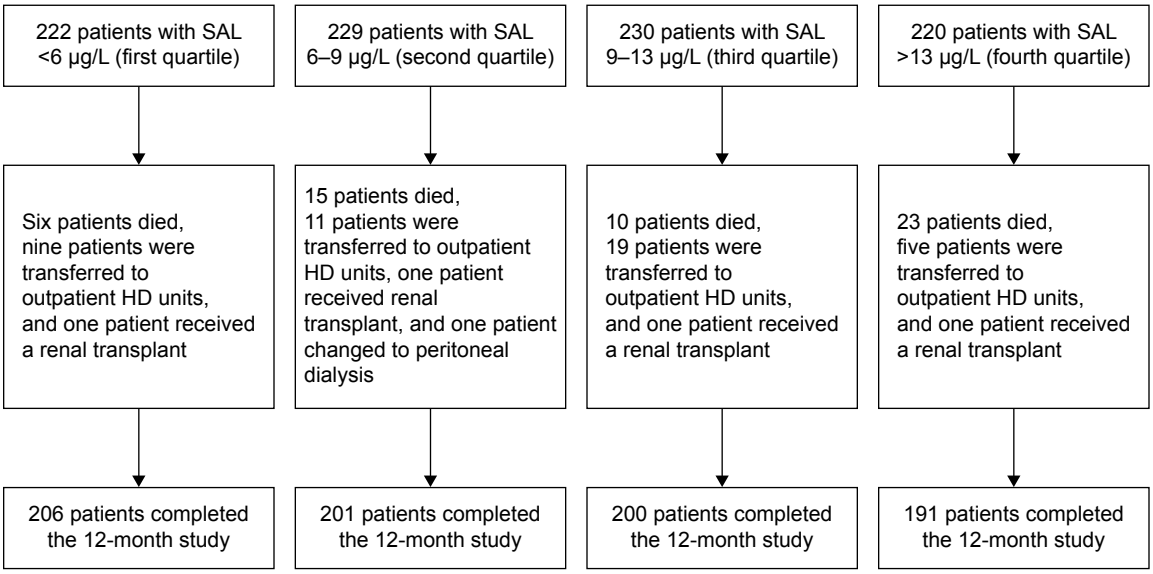

Figure 1 Enrollment and status of all study patients.
Abbreviations: SAL, serum aluminum level; HD, hemodialysis.

Table 1 shows the demographic and clinical characteristics of these four groups. Patients in the fourth quartile had a longer HD duration and a higher prevalence of calcitriol use, but lower serum levels of albumin, creatinine, and phosphate. The groups neither significantly differ in age, sex, body mass index, smoking status, presence of hypertension, DM, or previous CVD, use of an arteriovenous fistula or a biocompatible membrane dialyzer, nor in erythropoietin, *Kt*/*V* (Daugirdas), normalized protein catabolic rate, or prevalence of residual daily urine less than 100 mL. Moreover, the groups were not statistically different in serum hemoglobin, transferrin saturation, ferritin, corrected calcium, iPTH, high-density lipoprotein, low-density lipoprotein, hsCRP, and cardiothoracic ratio.

Al levels in water and dialysate and SAL of MHD patients

Al levels in all water and dialysate samples (n=12) were less than 8 μg/L, which was below the standard (10 μg/L) of the American Association for Advancement of Medical Instrumentation. Among all study patients, the mean SAL was 10.1±6.6 μg/L and the median SAL was 9.0 μg/L (1.0 μg/L, 38.0 μg/L).

Determinants of SAL in MHD patients

The multiple linear regression analysis with backward stepwise procedures demonstrated that SAL had a significantly positive association with HD duration and use of calcitriol, but a significantly negative association with serum phosphate level (Table 2).

Analysis of 1-year mortality and Kaplan–Meier survival analysis

At the end of the 1-year observational period, 54 of 901 patients (6.0%) died, including 31 (57.4%) from CVD, 21 (38.9%) from infections, and two (3.7%) from malignancy and liver cirrhosis. Analysis of the SAL in these 54 patients indicated that six (6/222, 2.7%) were in the first quartile, 15 (15/229, 6.5%) were in the second quartile, ten (10/230, 4.3%) were in the third quartile, and 23 (23/220, 10.5%) were in the fourth quartile. The Kaplan–Meier survival analysis showed that the cumulative mortality of the fourth quartile was significantly greater than that of the first quartile (log rank test, χ^2=13.47, P=0.004) (Figure 2). A total of 798 patients (88.6%) completed the 1-year follow-up (Figure 1). During this period, 44 were transferred to other outpatient HD units, four underwent renal transplantations, and one switched to continuous ambulatory peritoneal dialysis.

Multivariate Cox proportional hazards model for 1-year mortality

All of the potential variables (P<0.05) from the univariate Cox analysis were further analyzed by use of the multivariate Cox analysis with forward stepwise procedures. Using the first quartile as the reference (HR =1), the analytic results indicated that patients in the third quartile (HR =1.31, 95% CI =1.12–1.53, P=0.038) and the fourth quartile (HR =3.19, 95% CI =1.08–8.62, P=0.048) had increased risk of all-cause mortality (Table 3).

Table 1 Baseline characteristics of study patients who had different serum aluminum levels (n=901)

Characteristics	First quartile (SAL <6 μg/L) (n=222)	Second quartile (SAL: 6–9 μg/L) (n=229)	Third quartile (SAL: 9–13 μg/L) (n=230)	Fourth quartile (SAL >13 μg/L) (n=220)	*P*-value
Demographics					
Age (years)	56.0±13.6	55.3±13.9	55.3±13.6	58.4±13.1	0.080
Gender (female)	94 (41.8)	109 (50.4)	119 (52.8)	114 (51.4)	0.058
Body mass index (kg/m^2)	22.1±3.3	22.0±2.8	22.2±3.3	22.3±3.3	0.377
Smoking	45 (20.9)	32 (14.6)	41 (17.4)	38 (17.9)	0.623
Comorbidities					
Previous CVDs	12 (5.3)	14 (6.2)	11 (4.7)	6 (2.8)	0.111
Hypertension	86 (38.7)	89 (40.3)	78 (33.6)	97 (44.5)	0.539
Diabetes mellitus	52 (23.1)	44 (19.9)	47 (20.4)	56 (24.8)	0.621
Dialysis-related data					
HD duration (years)	5.7±4.8	6.4±5.2	6.9±5.3	7.4±5.6	0.001
Use of fistula	182 (82.2)	174 (79.2)	187 (81.7)	170 (77.5)	0.313
Use of BCM dialyzers	169 (76.0)	154 (70.8)	170 (74.0)	162 (73.9)	0.769
Erythropoietin use	210 (94.7)	199 (91.2)	213 (92.8)	200 (89.9)	0.243
Calcitriol use	13 (6.2)	17 (8.0)	38 (17.0)	50 (22.9)	<0.001
Erythropoietin (U/kg/wk)	76.7±44.7	71.3±49.2	73.2±46.4	76.7±45.4	0.909
Kt/V (Daugirdas) urea	1.75±0.33	1.81±0.31	1.83±0.32	1.81±0.33	0.143
nPCR (g/kg/d)	1.16±0.26	1.17±0.26	1.19±0.26	1.19±0.28	0.231
Residual daily urine >100 mL/d	55 (25.3)	40 (17.7)	52 (23.0)	45 (20.6)	0.542
Biochemical data					
Hemoglobin (g/dL)	10.5±1.1	10.7±1.5	10.5±1.4	10.4±1.3	0.159
Albumin (g/dL)	4.11±0.33	4.07±0.35	4.08±0.35	4.02±0.37	0.021
Creatinine (mg/dL)	11.1±2.4	11.0±2.4	10.9±2.4	10.4±2.2	0.008
Transferrin saturation (%)	29.7±11.0	30.2±13.7	28.5±12.1	29.5±11.2	0.540
Ferritin (μg/L)	318.4 (8.7–1,454.6)	300.0 (10.9–3,571.2)	299.1 (9.3–4,658.8)	323.5 (6.6–1,641.8)	0.467
Corrected-calcium (mg/dL)	9.7±0.8	9.9±0.9	9.8±0.9	9.9±1.0	0.263
Phosphate (mg/dL)	4.8±1.4	4.8±1.3	4.8±1.4	4.5±1.3	0.020
iPTH (pg/mL)	138.4 (0.20–1,473.7)	109.4 (0.20–1,754.0)	105.1 (0.3–1,655.4)	127.0 (0.7–1,574.2)	0.858
Cardiovascular risks					
HDL-C (mg/dL)	43.6±14.3	46.0±13.6	45.0±14.3	45.5±16.4	0.285
LDL-C (mg/dL)	93.5±29.7	98.7±29.6	95.2±29.9	92.4±31.5	0.458
hsCRP (mg/L)	2.62 (0.20–63.45)	3.01 (0.32–70.88)	2.70 (0.20–49.40)	3.13 (0.21–73.21)	0.668
Cardiothoracic ratio (%)	49.8±6.9	49.6±6.7	49.6±7.4	50.1±6.8	0.626

Notes: Data are presented as means ± SDs, numbers (percentages), or medians (minimum, maximum). Significance was assessed by ANOVA test or Chi-square test. A *P*-value of <0.05 was considered statistically significant. Previous CVD includes cerebrovascular disease, coronary arterial disease, congestive heart failure, or peripheral vascular disease. Hypertension was defined as; blood pressure ≥140/90 mmHg based on at least two measurements or regular use of an antihypertensive drug. Diabetes mellitus was diagnosed by a physician previously or by two measurements of fasting glucose of 126 mg/dL or more.

Abbreviations: BCM, biocompatible membrane; CVD, cardiovascular disease; HD, hemodialysis; HDL, high-density lipoprotein; hsCRP, high sensitivity C-reactive protein; iPTH, intact parathyroid hormone; LDL, low-density lipoprotein; nPCR, normalized protein catabolic rate; SAL, serum aluminum level; SD, standard deviation.

Discussion

Al accumulation can induce dialysis dementia,[2] osteomalacia,[3] and anemia[4] in ESRD patients. Al-contaminated dialysate has not been a major issue for MHD patients as the use of reverse osmosis and deionization techniques in the early 1980s.[5] However, Al-based phosphate binders are still used for short-term treatment of dialysis patients with severe hyperphosphatemia.[6] Moreover, use of Al-containing antacids for treatment of peptic ulcers or gastroesophageal reflux may increase the SAL in CKD patients. In this study, subjects with histories of Al poisoning, occupational Al exposure, and use of Al-containing medications were excluded. The results revealed that patients in the third and fourth SAL quartiles had greater risk of all-cause mortality than those in the first SAL quartile. Using the first quartile as reference (HR =1), the HR of all-cause mortality was 3.19 in the fourth quartile and 1.31 in the third quartile. This is the first study to show that serum Al, even when it is in the apparently acceptable range (below 20 μg/L), increases the risk of 1-year mortality in MHD patients.

The current study, which adjusted for potential confounders by multiple linear regression analysis, demonstrated that SAL was positively associated with HD duration and use of calcitriol, but negatively associated with serum phosphate level.

Table 2 Factors associated with $\log_{10}$ (SAL) in study patients (n=901)

Variable	Simple linear regression analysis (β coefficient ± SE)	*P*-value	Multiple linear regression analysis (β coefficient ± SE)	*P*-value
HD duration (years)	0.006±0.002	0.002	0.004±0.002	0.033
Hypertension (Yes =1)	0.082±0.029	0.005	–	–
Calcitriol use (Yes =1)	0.160±0.032	<0.001	0.154±0.032	<0.001
Kt/V (Daugirdas)	0.077±0.034	0.023	–	–
Albumin (g/dL)	–0.072±0.031	0.021	–	–
Creatinine (mg/dL)	–0.01±0.005	0.017	–	–
Phosphate (mg/dL)	–0.023±0.008	0.004	–0.026±0.008	–

Abbreviations: Log, logarithmic transformation; SAL, serum aluminum level; SE, standard error; HD, hemodialysis.

The kidney is the major organ for Al excretion, and it is difficult to remove Al by dialysis in clinical settings, so Al may progressively accumulate in patients with CKD or ESRD. Hence, MHD patients may have higher SALs than healthy persons, and an association between SAL and dialysis duration may be expected. In addition, although a positive correlation between Al and use of calcitriol was observed in this study, a recent study[12] demonstrated that calcitriol may lead to a decline in serum Al levels in CKD patients. Then, the definite effect of calcitriol on SAL in dialysis population still needs further evaluation. Moreover, a study[13] of HD patients revealed that Al accumulates in the parathyroid glands and leads to reductions of serum iPTH, which may disrupt the uptake of phosphate from the intestine and bones into the blood. This previous report was consistent with the observation of an inverse correlation between SAL and serum phosphate level in this study. However, more studies are needed to explore the pathogenic effects of SAL, calcitriol, and serum phosphate in MHD patients.

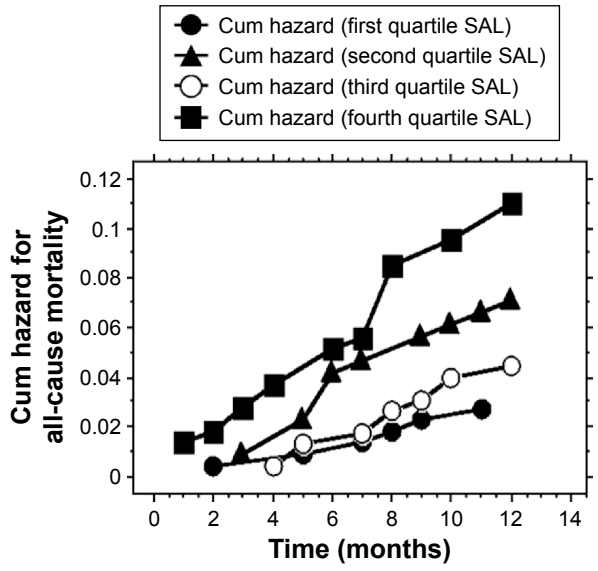

Figure 2 Kaplan–Meier survival curves of the different SAL quartiles.
Abbreviations: Cum, cumulative; SAL, serum aluminum level.

At the end of the 1-year observation period, 54 patients (54/891, 6.1%) had died, 31 from CVD, 21 from infections and 2 from other causes. The Kaplan–Meier survival analysis demonstrated that the cumulative survival rate was significantly lower for the fourth SAL quartile than for the first SAL quartile. After adjustment for potentially confounding variables, including HD duration, this study revealed that individuals in the fourth SAL quartile had a 3.19-fold increased risk of all-cause mortality and those in the third SAL quartile had a 1.31-fold increased risk of all-cause mortality. Thus, the study results indicated that MHD patients with SALs of 9 μg/L or more had increased risk of mortality. In the present study, the mean SAL was 10.1±6.6 μg/L and the median of SAL was 9.0 μg/L, slightly higher than previously reported for CKD patients not undergoing dialysis (8.2±5.6 μg/L).[6] The mean SAL in the study patients was lower than that of MHD patients of another recent study[8] (Whites: 20±2.3 μg/L, Blacks: 14±0.6 μg/L) in the United States, but similar to that of 1,626 patients in a study[9] (12.7 μg/L) from the United Kingdom. The KDOQI guidelines recommend that the baseline SAL should be

Table 3 Multivariate Cox regression analysis of 12-month mortality in study patients (n=901) according to baseline quartile of SAL and variables with *P*-values less than 0.05 in univariate Cox analysis

Variable	Multivariate HR (95% CI)	*P*-value
Age (years) (increment of 1 year)	1.05 (1.02–1.08)	0.003
Hemoglobin (g/dL) (increment of 1 g/dL)	0.74 (0.58–0.94)	0.012
Log hsCRP (mg/L) (increment of 10 mg/mL)	2.51 (1.34–4.70)	0.004
First quartile SAL as reference (HR =1)		
Second quartile SAL	2.46 (0.45–13.33)	0.462
Third quartile SAL	1.31 (1.12–1.53)	0.038
Fourth quartile SAL	3.19 (1.08–8.62)	0.048

Abbreviations: HR, hazard ratio; CI, confidence interval; hsCRP, high sensitivity C-reactive protein; SAL, serum aluminum levels.

below 20 μg/L, and only 9.3% of the study patients had SALs of 20 μg/L or more. Moreover, Al levels in all of the water and dialysate samples were below 8 μg/L. The study findings suggest that serum Al has toxic effects on MHD patients even when it is in the apparently acceptable range (below 20 μg/L). Further studies are required to explore the underlying pathogenesis of SAL-related mortality.

The mechanism underlying the association between low SAL and mortality in MHD patients remains unknown. However, some previous studies and the present study provide insight into this mechanism. A previous in vitro study indicated that Al inhibits the regeneration of reduced glutathione from the oxidized form through inhibition of the nicotinamide adenine dinucleotide phosphate hydrogen supply in the mitochondria, thereby leading to oxidative damage.[14] In other words, a decline in cellular glutathione enhances the production of reactive oxygen species. In humans, the overproduction of reactive oxygen species may induce anemia and atherosclerosis,[15] and these contribute to the increased mortality of dialysis patients.[16] Moreover, this study also demonstrated that even when the SAL is apparently acceptable (below 20 μg/L), it can impact the nutritional status of dialysis patients. Although a direct relationship between SAL and malnutrition has not been established, some reports provided indirect evidences for this finding. For example, a study[17] showed that Al sulfate could enhance proinflammatory and proapoptotic gene expression in human brain cells. A clinical study[18] also revealed an association between inflammatory markers (tumor necrosis factor-alpha and interleukin-4) with plasma Al levels in asthmatics. These findings suggested that Al may potentiate inflammatory events in humans. Moreover, inflammation clinically may further predispose ESRD individuals to malnutrition.[19] Hence, it may be expected that there are more malnourished patients in the highest SAL group in this study. Furthermore, inflammation and malnutrition may each increase the risk of mortality in patients with ESRD.[19] In addition, a study[20] also reported that the accumulation of Al taken up from the environment might be a potential cause of protein-energy wasting, which is also a strong predictor of mortality in the CKD population.[21] Taken together with the current study findings, these results may explain how SAL increased the mortality of MHD patients. However, further studies are needed to explore the underlying mechanism.

The study findings support the view that it is important for MHD patients to reduce their exposure to Al. For example, cooking with Al utensils may be a major source of exposure in patients with CKD.[1,20] Al-containing food ingredients, such as preservatives, coloring agents, leavening agents, and anticaking agents, may be another major source of Al exposure in humans.[22] In addition, even short-term or intermittent use of Al-containing pharmaceuticals may increase the SAL and have long-term detrimental effects in patients with ESRD.[23] Thus, individuals with MHD should avoid all of these possible sources of Al. Moreover, although the reverse osmosis and deionization techniques used to prepare dialysate are used widely, dialysis facilities should continue to perform routine testing of dialysate for Al.[5]

There are several limitations to this study. First, this was an observational study, so the reported associations do not indicate causality. Further studies are required to determine whether the removal of environmental Al exposure would improve the survival of MHD patients. Second, patients with different HD durations were enrolled in this study, which might have caused a bias. However, after adjusting for HD duration in the multivariate Cox analysis model, the relationship between SAL and HR for mortality remained significant. Third, patients might obtain Al from the diet, but the lack of detailed diet histories was a limitation of this study. However, physicians in our hospital educated MHD patients to avoid consuming Al-containing food ingredients as much as possible, and diet might only have little effect on SALs. Finally, Al accumulates in the bone, but bone biopsies were not performed, and so the Al burden in the study patients could not be estimated. However, it is very difficult or impossible to perform bone biopsies in such a large number of patients. Although the desferrioxamine test is a noninvasive alternative to bone biopsy, it does not allow a definite diagnosis due to a substantial percentage of false-negative results.[3] Moreover, by excluding patients with known Al exposure and using the means of two measurements of SAL, this analysis may have minimized possible bias.

Conclusion

This is the first study to demonstrate that SAL, even when in an apparently acceptable range (below 20 μg/L), is associated with increased mortality in MHD patients. The study results suggest that avoiding exposure of Al as much as possible is warranted for this population. Further studies are required to confirm these observations and to elucidate the pathogenic effects of Al in MHD patients.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Cannata-Andia JB, Fernandez-Martin JL. The clinical impact of aluminium overload in renal failure. *Nephrol Dial Transplant*. 2002;17(Suppl 2):9–12.
2. Rob PM, Niederstadt C, Reusche E. Dementia in patients undergoing long-term dialysis: aetiology, differential diagnoses, epidemiology and management. *CNS Drugs*. 2001;15:691–699.
3. Malluche HH. Aluminium and bone disease in chronic renal failure. *Nephrol Dial Transplant*. 2002;17(Suppl 2):21–24.
4. Agarwal AK. Practical approach to the diagnosis and treatment of anemia associated with CKD in elderly. *J Am Med Dir Assoc*. 2006;7:S7–S12; quiz S7–S21.
5. Jaffe JA, Liftman C, Glickman JD. Frequency of elevated serum aluminum levels in adult dialysis patients. *Am J Kidney Dis*. 2005;46:316–319.
6. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis*. 2003;42:S1–S201.
7. Chazan JA, Lew NL, Lowrie EG. Increased serum aluminum. An independent risk factor for mortality in patients undergoing long-term hemodialysis. *Arch Intern Med*. 1991;151:319–322.
8. Salahudeen AK, Deogaygay B, Fleischmann E, Bower JD. Race-dependent survival disparity on hemodialysis: higher serum aluminum as an independent risk factor for higher mortality in whites. *Am J Kidney Dis*. 2000;36:1147–1154.
9. Gault PM, Allen KR, Newton KE. Plasma aluminium: a redundant test for patients on dialysis? *Ann Clin Biochem*. 2005;42:51–54.
10. Daugirdas JT, Depner TA, Greene T, Levin NW, Chertow GM, Rocco MV. Standard Kt/Vurea: a method of calculation that includes effects of fluid removal and residual kidney clearance. *Kidney Int*. 2010;77:637–644.
11. Huang WH, Hsu CW, Weng CH, Yen TH, Lin JH, Lee M. Association of a high normalized protein catabolic rate and low serum albumin level with carpal tunnel syndrome in hemodialysis patients. *Medicine*. 2016;95:e4050.
12. Azik FM, Ekim M, Sakallioglu O, Aydin A. A different interaction between parathyroid hormone, calcitriol and serum aluminum in chronic kidney disease; a pilot study. *Int Urol Nephrol*. 2011;43:467–470.
13. Berland Y, Charbit M, Henry JF, Toga M, Cano JP, Olmer M. Aluminium overload of parathyroid glands in haemodialysed patients with hyperparathyroidism: effect on bone remodelling. *Nephrol Dial Transplant*. 1988;3:417–422.
14. Murakami K, Yoshino M. Aluminum decreases the glutathione regeneration by the inhibition of NADP-isocitrate dehydrogenase in mitochondria. *J Cell Biochem*. 2004;93:1267–1271.
15. Morena M, Delbosc S, Dupuy AM, Canaud B, Cristol JP. Overproduction of reactive oxygen species in end-stage renal disease patients: a potential component of hemodialysis-associated inflammation. *Hemodial Int*. 2005;9:37–46.
16. Stenvinkel P. The role of inflammation in the anaemia of end-stage renal disease. *Nephrol Dial Transplant*. 2001;16(Suppl 7):36–40.
17. Lukiw WJ, Percy ME, Kruck TP. Nanomolar aluminum induces pro-inflammatory and pro-apoptotic gene expression in human brain cells in primary culture. *J Inorg Biochem*. 2005;99:1895–1898.
18. Guo CH, Chen PC, Hsia S, Hsu GS, Liu PJ. The relationship of plasma aluminum to oxidant-antioxidant and inflammation status in asthma patients. *Environ Toxicol Pharmacol*. 2013;35:30–38.
19. Kalantar-Zadeh K, Ikizler TA, Block G, Avram MM, Kopple JD. Malnutrition-inflammation complex syndrome in dialysis patients: causes and consequences. *Am J Kidney Dis*. 2003;42:864–881.
20. Krewski D, Yokel RA, Nieboer E, et al. Human health risk assessment for aluminium, aluminium oxide, and aluminium hydroxide. *J Toxicol Environ Health B Crit Rev*. 2007;10(Suppl 1):1–269.
21. Jadeja YP, Kher V. Protein energy wasting in chronic kidney disease: an update with focus on nutritional interventions to improve outcomes. *Indian J Endocrinol Metab*. 2012;16:246–251.
22. Soni MG, White SM, Flamm WG, Burdock GA. Safety evaluation of dietary aluminum. *Regul Toxicol Pharmacol*. 2001;33:66–79.
23. Bohrer D, Bertagnolli DC, de Oliveira SM, et al. Role of medication in the level of aluminium in the blood of chronic haemodialysis patients. *Nephrol Dial Transplant*. 2009;24:1277–1281.