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Original article

Effect of aluminum on markers of bone formation resorption in chronic hemodialysis patients

Paweena Susantitaphong[a,b], Khajohn Tiranathanagul[a], Pisut Katavetin[a], Kearkiat Praditpornsilpa[a], Marc E. De Broe[c], Patrick C. D'Haese[c], Somchai Eiam-Ong[a]

[a]Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, [b]Extracorporeal Multiorgan Support Dialysis Center, King Chulalongkorn Memorial Hospital, Bangkok 10330, Thailand [c]Laboratory of Pathophysiology, Faculty of Pharmaceutical, Biomedical and Veterinary Sciences, University of Antwerp, Wilrijk 2610, Belgium

Background: The prevalence of aluminum (Al)-related toxicity in hemodialysis (HD) patients has declined. However, some HD patients continue to receive Al-based phosphate binders, in part because of the expense of Al-free binders.

Objective: To explore the effect of Al-based binders and their discontinuation on iron status, and markers of bone formation resorption in HD patients.

Methods: Following an initial screen of serum Al levels in 37 HD patients, a second screening was performed after discontinuation of Al-based binders in a 2-year follow-up. A desferrioxamine (DFO; 5 mg/kg) test, and assessment of iron status and bone markers were conducted in the second screening.

Results: Mean serum Al level was initially 27.8 ± 10.3 μg/L. Thirteen patients had a serum Al >30 μg/L, a level considered possibly toxic. There was a positive correlation between serum Al levels, HD duration, and cumulative dose of Al-based binder. At the second screening, the mean serum Al level decreased to 12.5 ± 7.4 μg/L. The mean serum Al level increased to 26.0 ± 14.7 μg/L post-DFO, but in none of the patients did the change in serum Al exceed the 50 μg/L threshold associated with Al-induced bone disease. The decrease in serum Al level was associated with a significant increase in intact parathyroid hormone (iPTH) whereas total alkaline phosphatase did not change.

Conclusions: We recommend that if Al-based phosphate binders are used in HD patients, serum Al level, iron, and markers of bone formation resorption be closely monitored to ensure safe use of these drugs.

Keywords: Aluminum, bone markers, DFO test, dialysis

Disturbances of calcium and phosphorus metabolism impair vitamin D function, and increase parathyroid hormone levels. These are common problems in patients with chronic kidney disease (CKD) and dialysis patients, resulting in CKD-mineral bone disorder (MBD), which includes high turnover hyperparathyroid bone disease (HPTH), low turnover osteomalacia, and adynamic bone disease (ABD) [1]. HPTH is the most common type of MBD, and can be prevented by controlling serum phosphate level. Unfortunately, conventional hemodialysis (HD) is unable to achieve adequate phosphate removal, resulting in its retention in the intracellular compartment. Dietary phosphate restriction is still the main preventive measure, but this is not easy to achieve. Therefore, most patients still require phosphate binder therapy. Calcium-based phosphate binder is generally the first choice for controlling serum phosphate although there are some limitations including hypercalcemia or high calcium and phosphate products [2, 3]. Calcium-free phosphate binders such as lanthanum or sevelamer are alternatives, but the cost of both agents is relatively high [4].

Aluminum (Al)-based phosphate binder has been previously used for controlling serum phosphate, but Al intoxication is a concerning adverse effect because Al is primarily excreted by the kidney. In addition, iron depletion results in an increased uptake of Al into

Correspondence to: Professor Somchai Eiam-Ong, MD, Division of Nephrology, Department of Medicine, Faculty of Medicine, King Chulalongkorn Memorial Hospital, Chulalongkorn University, Bangkok, 10330, Thailand.
E-mail: somchai80754@yahoo.com

the parathyroid gland [5]. The clinical consequences of Al intoxication includes neurologic syndromes, Al-induced bone disease, and anemia. Low level accumulation of Al might also cause subtle disorders of the parathyroid gland, osteoblast function, and hematopoiesis [5-8].

Al-induced bone disease comprises osteomalacia and ABD that can be diagnosed by pathological findings from bone biopsy including decrease of bone mineralization, bone formation, and bone mass [9]. Although bone biopsy with double tetracycline labeling to quantify bone formation rate is the criterion for diagnosis, noninvasive strategies such as the desferrioxamine (DFO) test [10, 11] or markers of bone formation and resorption could be effectively used to evaluate Al intoxication and Al-induced bone disease [12-20]. The present study was conducted to explore the incidence and risk factors for Al intoxication and to assess a possible correlation between the bone markers and Al-induced bone diseases in chronic HD patients.

Methods

We screened and followed a group of patients for Al intoxication at King Chulalongkorn Memorial Hospital, Bangkok, Thailand. The first screening was conducted at the beginning of 2009 to determine the baseline serum Al in 37 chronic HD patients. The second screening of the same group, conducted at the beginning of 2011 was a follow up measurement of serum Al. This was after our center had implemented an Al-based phosphate binder avoidance policy. DFO testing and bone marker assessment were also performed during the second screening to explore the association between Al level and the bone markers. Twenty-two chronic HD patients participated in the second screening. The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Chulalongkorn University and informed consent was obtained from each patient.

In the first screening, 37 serum samples and random water samples from the water treatment system were sent to the Biomedical Laboratory for Spectrometrical Analyses, University of Antwerp, Belgium, to measure Al levels. Other laboratory data such as ferritin, calcium, phosphorus, total alkaline phosphatase (TAP), and intact parathyroid hormone phosphate (iPTH) were measured at the Central Laboratory of King Chulalongkorn Memorial Hospital. The underlying kidney disease, comorbidities, HD duration, the history of aluminum exposure, and total aluminum dose were reviewed from electronic patient records. Our dialysis center had implemented an Al-based phosphate binder avoidance policy, which included increasing the use of non-Al, calcium-free phosphate binders such as sevelamer or lanthanum, and limitation in the duration of Al-based phosphate binder if such an agent was used.

During the almost 2 years after the first screening, no patients developed clinical features of Al intoxication. In the second screening, 22 chronic HD patients who agreed to continue to participated were included. The baseline and, after undergoing the pre- and post-DFO test serum samples of all patients, and random water samples from the water treatment plant, were sent for Al level measurement at the same laboratory as used for the first screening. Other laboratory data, such as ferritin, calcium, phosphorus, surrogate markers of bone formation (including TAP, total procollagen type I amino-terminal (PINP) extension peptides, and osteocalcin), and surrogate markers of bone resorption (such as iPTH and type I collagen carboxyl-telopeptide (CTx) breakdown products) were determined at King Chulalongkorn Memorial Hospital.

The DFO test protocol was used as previously described [10]. The first serum sample was taken before starting dialysis. During that session, DFO (5 mg/kg) was given intravenously during the last hour of dialysis. Forty-four hours after DFO, a second sample was taken before starting dialysis. The serum Al concentration difference between these two measurements was considered to be the aluminum accumulation in the patient.

Statistical analysis

The continuous variables are expressed as mean ± SD. Statistical analysis was performed using Student's paired *t* test for parametric data and a Wilcoxon rank sum pair test for nonparametric data. Correlations were assessed using Spearman's rho correlation. All statistical tests were determined by using the SPSS software suite (version 11.5 for Windows, SPSS Inc, Chicago, IL, USA). Statistical significance was defined as $P < 0.05$.

Results

The first screening

The Al levels in random water samples from the water treatment system were less than 2 μg/L. The

mean serum Al level in the patients was 27.8 ± 10.3 μg/L. The cumulative dose of Al-based phosphate binder varied from 180–8,550 tablets. One tablet (360 mg) contained 216 mg $Al(OH)_3$. The serum Al level was significantly correlated with total Al exposure (r = 0.6, P < 0.001) and HD duration (r = 0.6, P < 0.001). Serum Al level above 30 μg/L, a level proposed for possible Al toxicity, was observed in 13 patients (35.14%) who had slightly, but not significantly, higher mean levels of iPTH and TAP than those with serum Al level below 30 μg/L (402.2 ± 517.3 vs. 213.8 ± 214.0 pg/dL, P = 0.1 and 156.2 ± 129.4 *vs*. 94.1 ± 80.8 U/L, P = 0.08, respectively). Moreover, six patients who continually received $Al(OH)_3$ had significantly higher serum aluminum levels than those who did not receive it (39.3 ± 7.0 vs. 25.6 ± 9.4 μg/L, P = 0.003).

The second screening

The Al levels in random water samples from the water treatment system were less than 2 μg/L. The exposure dose of Al-based phosphate binder varied from 60–1,980 tablets during the 2-year follow up after the first screening. Eight patients did not receive aluminum-based phosphate binder within 2 years follow up, whereas the doses were decreased in 14 patients. All of the patients stopped Al-based phosphate binder before the pre-DFO serum samples were measured for at least 2 weeks, aiming to eliminate acute exposure effect. The mean pre-DFO serum Al levels were 12.5 ± 7.4 μg/L and the mean post-DFO serum Al levels were 26.0 ± 14.7 μg/L. There was only one patient who had a pre-DFO serum Al level above 30 μg/L and 5 patients who had post-DFO serum Al level over 30 μg/L. The maximum post-DFO level was 73 μg/L. The mean change of serum Al after the DFO test was 13.6 ± 8.9 μg/L. None of the patients had a change of Al levels >50 μg/L, a level considered to induce bone disease.

The pre-DFO serum Al level significantly correlated with the first screening serum Al level (r = 0.54, P = 0.01), 2-year Al exposure dose (r = 0.51, P = 0.015), post-DFO serum Al level (r = 0.66, P = 0.001), and serum phosphate level (r = 0.54, P = 0.009). The post-DFO serum Al level significantly correlated with the first screening serum Al level (r = 0.57, P = 0.006), 2-year Al exposure dose (r = 0.53, P = 0.012), the change of serum Al level after DFO test (r = 0.89, P < 0.001, **Figure 1A**), and serum phosphate level (r = 0.57, P = 0.006), while it was inversely correlated with serum ferritin (r = –0.59, P = 0.004).

The change of serum Al level after DFO testing significantly correlated with the first screening serum Al level (r = 0.54, P = 0.01, **Figure 1B**), 2-year Al exposure dose (r = 0.49, P = 0.022), post-DFO serum Al level (r = 0.89, P < 0.001), and serum phosphate level (r = 0.43, P = 0.047), but negatively correlated with serum ferritin (r = –0.65, P = 0.001, **Figure 1C**).

The effect of aluminum accumulation on bone markers

Because no patients in the present study developed Al-induced bone disease, the degree of change in serum Al level after the DFO test was used to represent Al accumulation in the bones of patients. The degree of change of serum Al levels correlated with the degree of the first screening serum Al levels (P < 0.05). The changes in serum Al levels after the DFO test were used to divide patients into 3 groups; 0–10 μg/L (group 1), >10–20 μg/L (group 2), and >20 μg/L (group 3).

To check for early signs of Al-induced bone disease, serum bone markers were studied (**Table 1**). The levels of surrogate markers of bone resorption, including iPTH and CTx, were slightly, but not significantly, increased along the degree of serum Al change. Although the levels of surrogate markers of bone formation, including PINP, osteocalcin, and TAP, were highest in group 2, the difference was not significant. Among three groups, group 1 had the highest serum ferritin, which was significantly higher than that in group 2 (P = 0.029).

Long-term aluminum effects on the bone markers

The change of serum Al level and the bone markers over time were studied in 22 chronic HD patients who participated in both screenings. The serum Al level decreased significantly from 28.3 ± 9.8 to 12.5 ± 7.4 μg/L (P < 0.001). The mean iPTH increased significantly from 283.5 ± 220.4 to 446.0 ± 307.9 μg/L (P = 0.05), while the mean TAP also tended to increase, but this was not significant (84.3 ± 31.8 vs. 98.5 ± 40.3. U/L, P = 0.2).

In 6 patients with a high risk of Al intoxication, defined by the first screening serum aluminum level above 30 μg/L, the serum Al level decreased significantly from 40.2 ± 7.4 to 17.7 ± 10.7 μg/L (P = 0.002). The mean iPTH increased from 388.2 ± 178.7 to 653.2 ± 289.2 pg/mL (P = 0.09) and TAP

increased from 89.2 ± 43.3 to 111.7 ± 39.3 U/L (P = 0.36) (**Figure 2**). Patients with high risk of Al intoxication had a slightly, but not significantly, higher mean increased iPTH and TAP (265.1 ± 275.5 *vs.* 124.1 ± 293.0 pg/mL, 22.5 ± 20.7 vs. 11.1 ± 46.5 U/L, respectively) (P > 0.05) than that in low risk patients, whose first screening serum aluminum level was below 30 μg/L (**Figure 3**).

Discussion

In the present study, we showed the association between total aluminum exposure dose and serum aluminum level in both screenings. Serum aluminum levels determined in the first screening were significantly associated with pre-DFO, post-DFO, and the change of serum aluminum after the DFO test, and iPTH level in the second screening. The 2-year total aluminum exposure was significantly associated with all of the surrogate markers of bone function in the second screening.

The incidence of aluminum toxicity in patients with chronic HD has diminished over the past two decades. Some experts reasoned that this may be largely attributed to the improvement in water quality [8, 21, 22]. There was still a question about the role of aluminum monitoring in patients with long-term HD [22], whereas mild to moderate aluminum exposure from aluminum-base phosphate binder was still observed [23, 24]. The present study demonstrated that most of the aluminum accumulation in patients resulted from drug ingestion, not the water. In a previous study, no correlations were found between the serum aluminum concentrations (pre-, post-, or the incremental rise after DFO testing) and the total amount of aluminum exposure [24]. Such a discrepancy might be explained by the differences in total dose exposure and the DFO test protocol. The present study showed that a single measurement of serum aluminum is not a good indicator for aluminum accumulation, as demonstrated by the insignificant difference of pre-DFO serum aluminum level between the subgroups with different levels of change after DFO aluminum levels (**Table 1**).

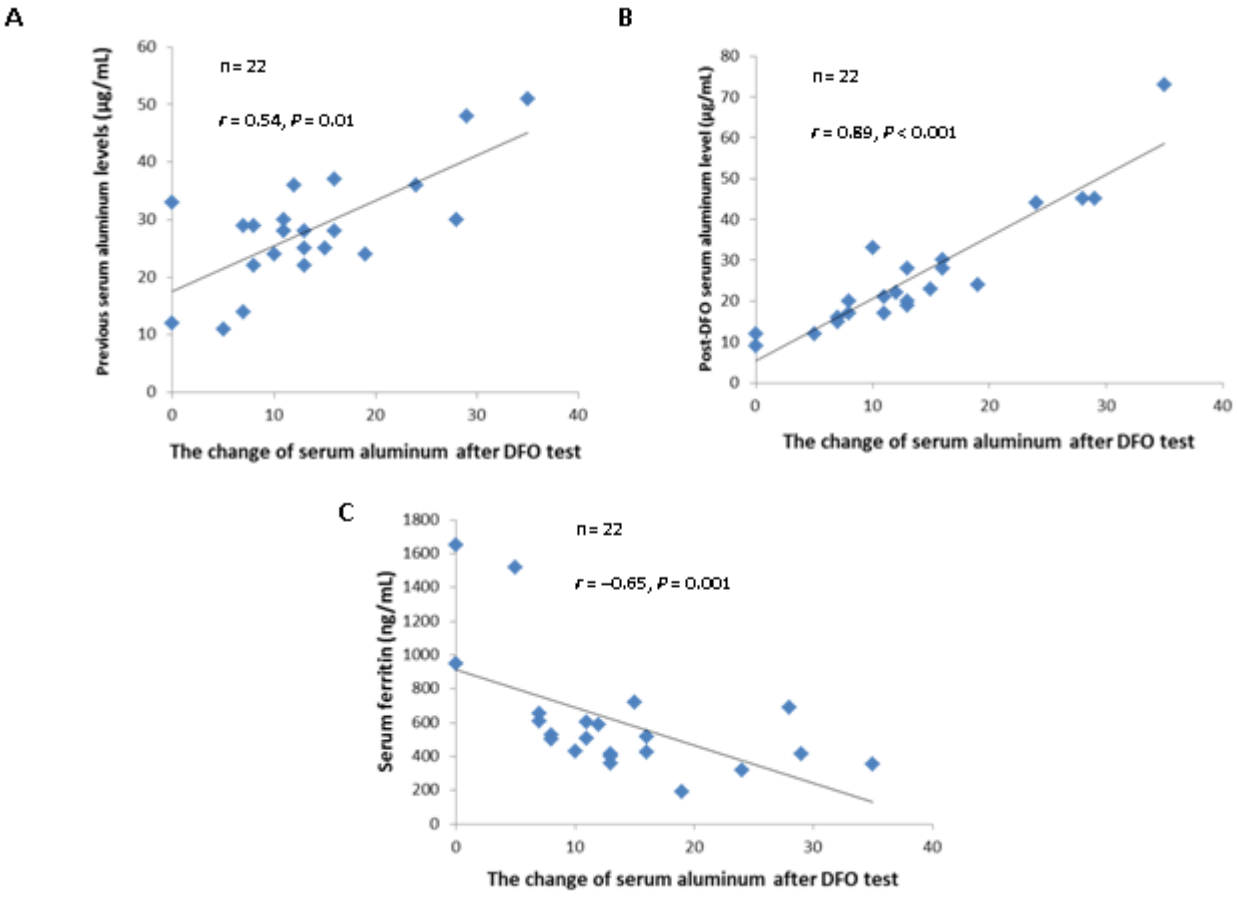


Figure 1. A: Correlation between the change of serum aluminum after the DFO test and previous-DFO serum aluminum levels,
B: Correlation between the change of serum aluminum after the DFO test and post serum aluminum levels,
C: Correlation between the change of serum aluminum after the DFO test and serum ferritin levels

Table 1. The degree change of the serum aluminum and bone markers after the DFO test

Change of serum aluminum (μg/L) (n = 22)	First screening serum aluminum level (μg/L)	Second screening		Serum ferritin (ng/mL)	TAP (U/L)	PINP (ng/mL)	Osteocalcin (ng/mL)	CTx (ng/mL)	iPTH (pg/mL)
		Pre-DFO serum aluminum level (μg/L)	Post-DFO serum aluminum level (μg/L)						
Group 1: 0–10 (n = 8)	21.8 ± 8.5[c]	11.4 ± 5.1[c]	16.8 ± 7.4[a,c]	854 ± 478[a]	84.0 ± 29.6	388.2 ± 358.3	280.3 ± 403.7	1.6 ± 1.3	295.9 ± 219.1
Group 2: 10.1–20.0 (n = 10)	28.3 ± 4.9[b]	9.3 ± 3.5[b]	23.2 ± 4.3[a,b]	472 ± 148[a]	110.8 ± 49.6	635.8 ± 584.9	327.0 ± 307.1	2.1 ± 1.3	491.2 ± 263.4
Group 3: >20.0 (n = 4)	41.3 ± 9.9[b, c]	22.8 ± 10.3[b,c]	51.8 ± 14.2[b,c]	445 ± 170	96.8 ± 29.9	436.6 ± 389.6	302.5 ± 216.5	2.7 ± 1.3	633.2 ± 479.4

[a]$P < 0.05$ when group 1 was compared with group 2, [b]$P < 0.05$ when group 2 was compared with group 3, [c]$P < 0.05$ when group 1 was compared with group 3

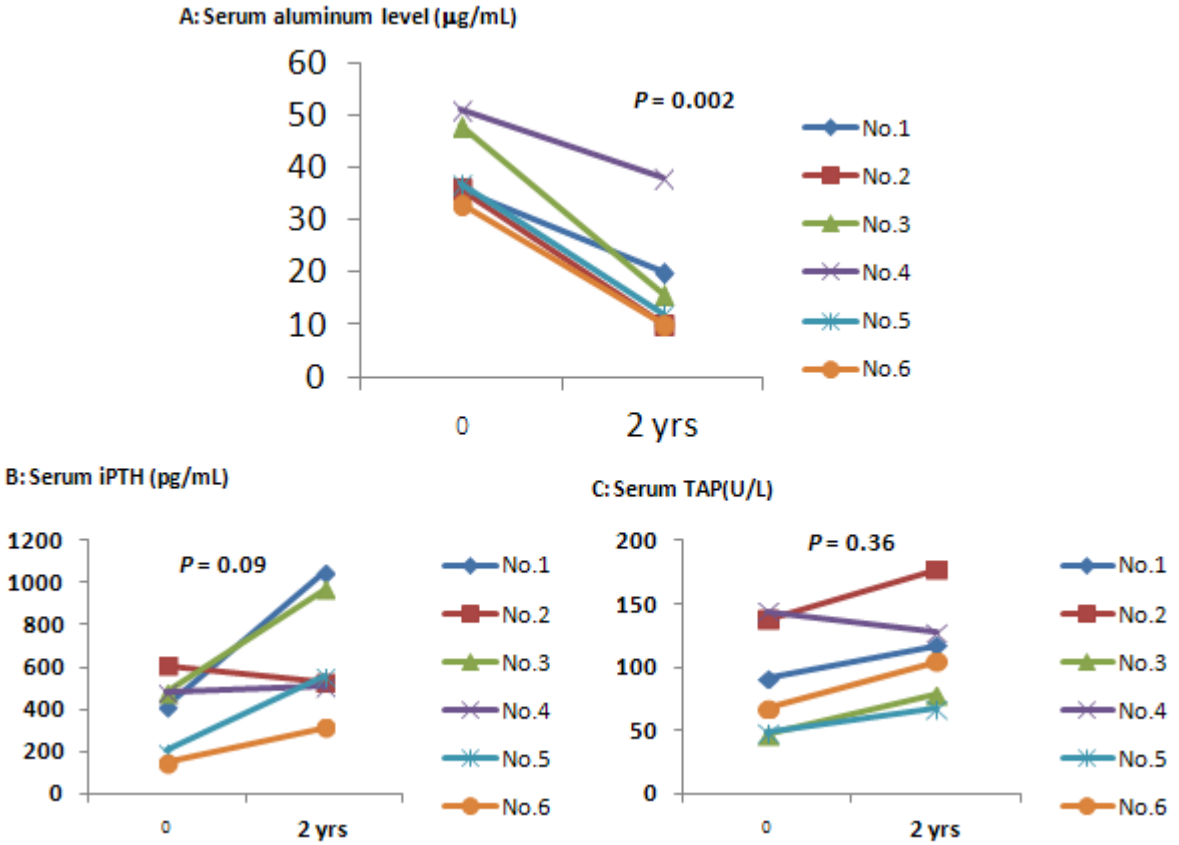
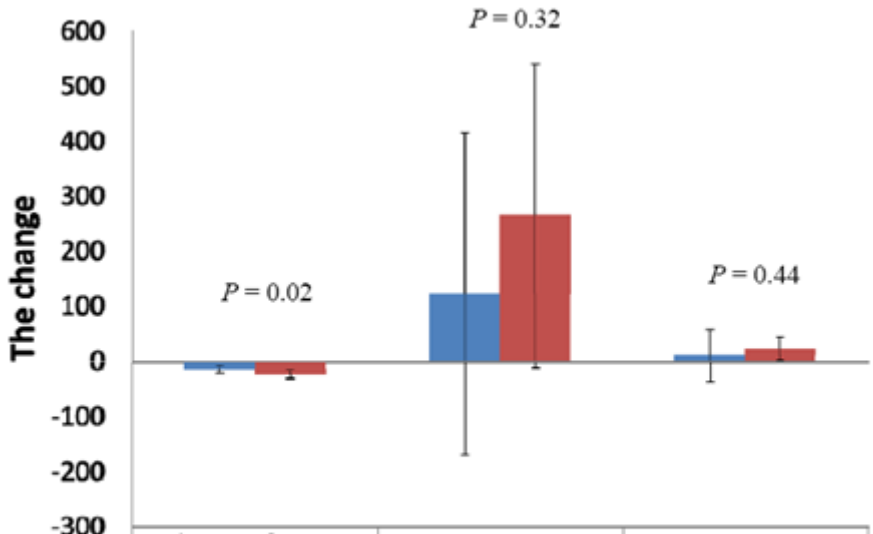


Figure 2. **A:** The change of serum aluminum level at 2 years follow-up in the group with high risk of aluminum intoxication, **B:** The change of serum iPTH level at 2 years follow-up in the group with high risk of aluminum intoxication, **C:** The change of serum TAP level at 2 years follow-up in the group with high risk of aluminum intoxication.



	Change of serum aluminum	Change of iPTH	Change of TAP
Low risk	-13.3	124.1	11.1
High risk	-22.5	265.1	22.5

Figure 3. The mean change of serum aluminum level, serum iPTH level, and serum TAP level at 2 years follow up in low risk and high risk groups.

Interestingly, we also observed that serum ferritin was significantly associated with the change of serum aluminum after the DFO test when low-dose DFO was used (**Figure 1C**). The highest serum ferritin level was observed in group 1 (**Table 1**). Different doses of DFO were explored in a previous study and revealed that low-dose (2.5 mg/kg) DFO had similar therapeutic effects to the standard-dose (5 mg/kg) on the change of serum aluminum and improvement of bone markers [25]. By contrast, we did not know about the effect of high serum ferritin on the small change of serum aluminum after the DFO test. A dose of DFO that is not adequate to chelate aluminum in bone in the presence of high serum ferritin or a protective effect serum ferritin on aluminum accumulation in bone tissue are possible reasons for these observations. Further studies are needed to clarify the reasons for this aluminum accumulation.

In the present study, earlier aluminum accumulation, as represented by the first serum aluminum level, still had a significant effect on the later aluminum accumulation as shown in the second screening (pre-, post-, and the change after the DFO test). All of the surrogate markers for bone formation and resorption, were significantly associated with aluminum exposure. These findings seem to correlate with the pathological effects of aluminum, which inhibits bone cell proliferation and decreases bone formation [9]. In an in vitro study, aluminum caused a dose-dependent increase in the number of bone nodules present at early times in cell culture, but high dose or similar concentration in long-term cultures that accelerated differentiation, seemed to be cytotoxic [26]. These effects were also observed in the present study. The TAP, PINP, and osteocalcin were highest in group 2 patients of the aluminum change after DFO test, not in group 3 patients, who had more aluminum accumulation (**Table 1**), and TAP did not significantly change after reducing serum aluminum by drug withdrawal after 2 years. The underlying mechanisms for this observation remain unknown. High dose and long-term suppression might induce unrecovered osteoblast function.

On the other hand, the levels of markers of bone resorption, such as iPTH and CTx significantly correlated with the degree of aluminum accumulation and iPTH could be significantly increased after reducing serum aluminum with the aluminum avoidance policy within 2 years (**Figure 2B**). Therefore, one might consider using surrogate markers of bone resorption for monitoring that which is associated with dose and duration of aluminum exposure and could result in early onset of aluminum-induced bone disease.

The mean value of surrogate markers of bone formation, such as TAP, PINP, and osteocalcin were highest in group 2 patients; the group with the change of serum aluminum. Whereas the mean value of surrogate markers of bone resorption, such as iPTH and CTx were highest in group 3 patients; the group with a change of serum aluminum that had the highest aluminum accumulation (**Table 1**). Therefore, the effect of aluminum on inducing surrogate markers of bone formation might have a cut-off threshold level such as found in group 2 patients and it might induce toxicity despite having higher levels as found in group 3 patients. After adhering to the aluminum avoidance policy for 2 years, the serum aluminum levels decreased and serum iPTH level was improved by aluminum suppression. Unfortunately, the markers of bone formation such as TAP did not improve because of this policy (**Figure 2**).

To our knowledge, this is the first prospective cohort study to examine the effect of Al accumulation on bone markers. We found that the surrogate markers of bone formation and resorption, seemed to be useful for the early identification of aluminum-induced bone disease. Some of the bone markers, such as iPTH, improved after adherence to the aluminum avoidance policy. Admittedly, the small sample size used in this study is an important limitation. Moreover, we did not perform bone biopsies in the present study.

In conclusion, low serum aluminum levels, resulting from mild chronic exposure of aluminum, have an effect on surrogate markers of bone formation and resorption. Withdrawal of Al-based phosphate binders can decrease the serum aluminum level and improve the levels of some of the bone markers despite long-term exposure. Therefore, to preempt permanent damage from aluminum-induced bone disease in patients who are required to take Al-based phosphate binders, we recommend the close monitoring of serum aluminum levels and markers of bone formation and resorption.

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