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The Effects of Acetate-Free Citrate-Containing Dialysate on Calcium Metabolism and Fatigue in Patients on Maintenance Hemodialysis

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Abstract: Although the significance of acetate-free citrate with 3.0 mEq/L Ca-containing-dialysate (A(−)D) has been reported, its effective Ca level and the overtreatment needed to correct metabolic acidosis on the basis of serum whole parathyroid hormone (wPTH) and arterial pH have not been evaluated in detail. Furthermore, recent reports have suggested the beneficial effect of citrate on fatigue, which is a significant risk for cardiovascular disease. Thirty-two hemodialysis patients receiving acetate with 2.75 mEq/L Ca-containing dialysate (A(+)D) participated in the present A(+)D to A(–)D one-arm switch study over 4 weeks. Predialysis wPTH increased significantly from 85.1 ± 59.0 pg/mL during hemodialysis A(+)D to 106.8 ± 78.8 pg/mL ($p = 0.0015$) after 2 weeks of A(–)D treatment. Predialysis arterial pH and bicarbonate levels significantly increased from 7.335 ± 0.037 to 7.370 ± 0.035 ($p < 0.0001$) and from 19.6 ± 2.1 mEq/L to 21.3 ± 1.7 mEq/L ($p = 0.0001$), respectively, whereas post-dialysis arterial pH and bicarbonate levels significantly increased from 7.447 ± 0.022 to 7.473 ± 0.027 ($p < 0.0001$) and from 25.2 ± 1.0 mEq/L to 28.1 ± 1.0 mEq/L ($p < 0.0001$). When all patients were divided into two equal-sized groups by fatigue score, the improvement in the fatigue score was significantly greater in the high group (Δ1.8 ± 3.7) than in the low group (Δ–0.8 ± 2.3) ($p = 0.0252$). This study demonstrated that the effective Ca level might be significantly lower in A(−)D than in A(+)D and metabolic acidosis was improved more strongly in A(–)D relative to that in A(+)D because of the higher bicarbonate concentration in A(–)D. Furthermore, A(–)D had a beneficial effect on intradialytic hemodynamics and fatigue sensation.

Keywords: Acetate-Free Citrate-Containing Dialysate, Calcium Metabolism, Fatigue, Hemodialysis

1. Introduction

Acetate, which is used to adjust pH in dialysate, is a non-physiological chemical in vivo. To avoid the harmful effects of acetate, such as headaches, fatigue, nausea, and intradialytic drop in blood pressure (BP) [1], acetate-free citrate-containing dialysate [A(–)D] (Carbostar-P®; Yoshindo Co. Ltd., Toyama, Japan) was developed in 2007 to improve various clinical conditions, including general status, hemodynamic status, metabolic acidosis, malnutrition, and erythropoiesis-stimulating agent (ESA)-refractory anemia [2, 3].

Although it has been reported that strict suppression of serum parathyroid hormone (PTH) within the target range might improve the achievement ratio in hemodialysis patients to keep serum phosphate (Pi) and calcium (Ca) within their respective target ranges by suppressing their entry into circulation from bone. Chronic over-suppression of serum PTH might induce adynamic bone disease and a risk for vascular calcification, low Ca dialysate is desired [4]. Although Carbostar-P® A(–)D contains 3 mEq/L Ca and because (i) citrate is a strong chelator of Ca and (ii) 35 mEq/L

HCO_3^-should suppress ionized Ca by inducing alkalosis, whether Carbostar-P® A(–)D or 2.75 mEq/L Ca-containing Kindaly-4E® A(+)D has a higher effective Ca concentration is an interesting question.

Furthermore, it was recently reported that patients with chronic fatigue syndrome exhibited a significant decrease in serum citrate in the first step of the tricarboxylic acid cycle compared with healthy controls [5]. We recently reported fatigue in hemodialysis patients as a significant risk for cardiovascular disease [6] and its association with erythropoietin resistance [7]. Therefore, it is possible that supplementation of citrate to hemodialysis patients might improve fatigue sensation.

This background prompted us to examine (i) whether Carbostar-P® A(–)D or the widely used 2.75 mEq/L Ca-containing A(+)D (Kindaly-4E®; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) was higher in the effective Ca concentration and (ii) the effect of A(–)D dialysate on the intra-dyalytic drop in BP fatigue score in hemodialysis patients in comparison with that of A(+)D.

2. Materials and Methods

2.1. Patients

Thirty-two hemodialysis patients [16 patients with diabetes mellitus (DM) and 16 non-DM patients] were enrolled in the study between November and December 8, 2015. All patients had been maintained on hemodialysis for >3 years at Mihama Narita Clinic (Narita City, Chiba, Japan) and maintained under stable conditions using Kindaly 4E® A(+)D. All patients enrolled had received 4-h hemodialysis sessions using A(+)D (Kindaly-4E®; Fuso Pharmaceutical Industries, Ltd., Osaka, Japan) three times a week. Patients with acute illness, malignant tumors, or severe hepatic or respiratory diseases were excluded from the study. All patients provided written informed consent before participating in this study. The study protocol was approved by the Institutional Ethics Committee at Osaka City University Graduate School of Medicine (Approval No. 3251), and the study was conducted in accordance with the principals of the Declaration of Helsinki.

2.2. Study Design

This was a single-arm study performed at a single hemodialysis center at the Narita Mihama Clinic, as shown in Table 1. After 2 weeks of hemodialysis sessions maintained on Kindaly 4E® A(+)D, the dialysate was replaced with Carbostar-P® A(–)D and then maintained for another 2 weeks thereafter without changing other dialysis conditions (dialysis membrane used, blood flow rate, dialysate flow rate, and dry weight). The components of Carbostar-P® A(–)D and Kindaly 4E® A(+)D are shown in Table 2. Blood samples were obtained just before and after the Day-1 hemodialysis session using Kindaly 4E® A(+)D, 7th hemodialysis session using the first exposure of Carbostar-P® A(–)D on Day 15 after 2 weeks of Kindaly 4E® A(+)D, and 13th hemodialysis session on Day 29 after 2 weeks of Carbostar-P® A(–)D. The hemodialysis therapy conditions other than dialysate, such as the dialysis membrane, blood flow rate, and dialysate flow rate, were kept the same during the entire study period. Furthermore, any drug administered to the enrolled patients was maintained during the study period.

Serum parameters examined were Ca, Pi, albumin, and bicarbonate performed by routine assays using standard methods. Serum-corrected Ca (cCa) levels were calculated by using Payne's formula [8]. All acid–base parameters (pH, bicarbonate) were measured on the same day by using blood gas analyzers in local laboratories. Serum whole PTH (wPTH) was measured by using a third-generation PTH chemiluminescent enzyme immunoassay (DSPB®; DS Pharma Biomedical Co. Ltd., Osaka, Japan) [9]. Serum fibroblast growth factor (FGF)-23 was measured by using a fully automated random access chemiluminescence immunoanalyzer, CL-JACK® System (Kyowa Medex Co. Ltd., Tokyo, Japan) [10].

Table 1. *Protocol during the 4-week study period.*

Week	**first**				**second**				**third**				**fourth**				**fifth**
Day	**1**	**3**	**5**	**7**	**8**	**10**	**12**	**14**	**15**	**17**	**19**	**21**	**22**	**24**	**26**	**28**	**29**
A(+)D	○	○	○		○	○	○										
A(–)D									○	○	○		○	○	○		○
Blood collection (pre- and post-dialysis)	○								○								○
Fatigue questionnaire	○																○

Table 2. *The components of acetate-containing dialysate [A(+)D] and acetate-free citrate-containing dialysate [A(–)D].*

	acetate-containing dialysate [A(+)D]	**acetate-free citrate-containing dialysate [A(–)D]**
Na (mEq/L)	140	140
K (mEq/L)	2.0	2.0
Cl (mEq/L)	112.25	111
Ca (mEq/L)	2.75	3.0
Glucose (mg/dL)	125	150
Bicarbonate (mEq/L)	27.5	35.0
Acetate (mEq/L)	8.0	–
Citrate (mEq/L)	–	2.0

2.3. Evaluation of Fatigue Levels

Fatigue levels of hemodialysis patients were evaluated by their fatigue score on the basis of a questionnaire during the hemodialysis session at the first session on A(+)D and the last session on A(–)D as described previously. The questionnaire associated with the fatigue scale consisted of eight phrases regarding fatigue (feeling so tired that I want to lie down at times, feeling tired and without energy, becoming very tired with just a small amount of exercise or work, feeling sluggish lately, recent lack of physical energy, thinking that the way I get tired recently is abnormal, general fatigue lately, even

after a night's sleep I do not feel refreshed). The patients were asked to rate how often in a recent week they experienced these symptoms by using a Likert scale (0–4), and each score was recalculated to go up to 32 points. A previous study in which a perfect score was represented by 20 points showed that patients with higher scores had higher fatigue levels [11]. In a study in which the normal fatigue score level was not used, Koyama et al. reported that the mean ± SD was 5.2 ± 4.1 in 171 healthy volunteers (age: 45.4 ± 14.0 years; male: 29.8%) [6].

2.4. Statistical Analysis

Continuous variables are expressed as means ± SDs. Unpaired samples were analyzed by Mann–Whitney U tests, whereas categorical data were analyzed by χ^2 tests. The changes in values between dialysate were analyzed statistically by using repeated-measures ANOVA and the Wilcoxon signed-rank test. Statistical analysis was performed by using the Stat View V system (Abacus Concepts, Berkeley CA) for the Apple computer. P values < 0.05 were considered as indicating statistical significance.

3. Results

3.1. Baseline Clinical Characteristics of the Enrolled Hemodialysis Patients

The clinical characteristics of the 32 patients (DM/non-DM = 16/16, age 72.0 ± 11.9 years) enrolled in this study are shown in Table 3. At the start of this study, all patients had received hemodialysis treatment using KINDALY-4E® A(+)D dialysate. Serum cCa, Pi, wPTH, and FGF-23 did not differ significantly between the DM and non-DM patients. Furthermore, neither pH nor bicarbonate in arterial blood differed significantly between the two groups of patients. The mean fatigue score, which did not differ significantly between DM and non-DM patients, was 5.7 ± 4.5 in all patients.

Table 3. *Baseline characteristics of all patients, DM patients, and non-DM patients at the start of the study.*

	All patients (n = 32)	DM patients (n = 16)	non-DM patients (n = 16)	p
Age (years)	72.0 ± 11.9	68.6 ± 12.0	75.4 ± 11.0	0.0970
Sex (male/female)	6/26	4/12	2/12	0.3726
Hemodialysis duration (years)	9.2 ± 5.1	7.8 ± 3.5	10.6 ± 6.1	0.2707
BMI (kg/m^2)	21.5 ± 4.6	22.7 ± 5.6	20.2 ± 3.0	0.1317
Systolic BP (mmHg)	155.0 ± 24.7	160.9 ± 26.7	149.1 ± 21.8	0.1868
Diastolic BP (mmHg)	76.0 ± 15.4	80.3 ± 16.2	71.8 ± 13.7	0.1515
Heart rate (per min)	66.3 ± 10.4	67.5 ± 9.6	65.2 ± 11.3	0.4730
Casual PG (mg/dL)	127.9 ± 28.3	134.3 ± 31.1	121.4 ±24.5	0.2826
cCa (mg/dL)	8.8 ± 0.6	8.8 ± 0.6	8.7± 0.6	0.9398
Pi (mg/dL)	5.9 ± 1.1	6.1. ± 1.2	5.8± 1.1	0.3956
Whole PTH (pg/mL)	85.1 ± 59.0	77.9 ± 42.8	92.3 ± 72.5	0.9399
FGF-23 (pg/mL)	6290.4 ± 7407.1	4079.2 ± 4324.0	8501.7 ± 9179.3	0.2277
pH	7.335 ± 0.037	7.328 ± 0.047	7.343 ± 0.023	0.6783
Bicarbonate (mEq/L)	19.6 ± 2.1	19.2 ± 2.4	20.1 ± 1.7	0.4064
Fatigue score	5.7 ± 4.5	5.8 ± 3.6	5.7 ± 5.5	0.6104

Data are expressed as the mean ± sd and were analyzed by the Mann–Whitney *U* test except for sex, which was analyzed by the χ^2 test. DM = diabetes mellitus, BMI = body mass index = weight (kilograms)/[height (meters)]^2, BP = blood pressure, PG = plasma glucose, cCa = corrected calcium, Pi = Phosphate, PTH = parathyroid hormone, FGF = fibroblast growth factor

3.2. Changes in Predialysis Blood Parameters During the First 2 Weeks of A(+)D and the Following 2 Weeks of A(–)D in 32 Hemodialysis Patients

Although predialysis serum levels of cCa and Pi did not change significantly during the 2 weeks of A(–)D and A(+)D hemodialysis sessions in all (A), DM (B), or non-DM (C) patients, serum wPTH significantly increased during the second 2 weeks of the A(–)D session in all and in non-DM patients (Table 4). Furthermore, predialysis pH and bicarbonate in arterial blood were significantly increased during the second 2 weeks of the A(–)D session in all, DM, and non-DM patients.

Table 4. *Changes in predialysis blood parameters at baseline, after the first 2 weeks of A(+)D, and after the following 2 weeks of A(–)D immediately before the hemodialysis session in all (A), DM (B), and non-DM (C) patients.*

(A) All patients.

	Before 1st A(+)D	After 1st 2 weeks of A(+)D	After 2nd 2 weeks of A(–)D
Whole PTH (pg/mL)	85.1 ± 59.0	92.8 ± 66.3	106.8 ± 78.8$^{*,\#}$
cCa (mg/dL)	9.1 ± 0.6	9.1 ± 0.5	9.1 ± 0.6
Pi (mg/dL)	5.9 ± 1.1	5.8 ± 1.1	5.7 ± 1.1
pH	7.335 ± 0.037	7.335 ± 0.029	7.370 ± 0.035$^{*,\#}$
Bicarbonate (mEq/L)	19.6 ± 2.1	19.4 ± 1.8	21.3 ± 1.7$^{*,\#}$

(B) DM patients

	Before 1st A(+)D	After 1st 2 weeks of A(+)D	After 2nd 2 weeks of A(–)D
Whole PTH (pg/mL)	77.9 ± 42.8	81.0 ± 40.5	91.4 ± 44.1
cCa(mg/dL)	9.1 ± 0.5	9.0 ± 0.4	9.0 ± 0.4
Pi(mg/dL)	6.1 ± 1.2	5.9 ± 1.2	5.9 ± 1.3
pH	7.328 ± 0.047	7.328 ± 0.028	7.358 ± 0.037*,#
Bicarbonate (mEq/L)	19.2 ± 2.4	18.8 ± 1.2	20.6 ± 1.4*,#

(C) non-DM patients

	Before 1st A(+)D	After 1st 2 weeks of A(+)D	After 2nd 2 weeks of A(–)D
Whole PTH (pg/mL)	92.3 ± 72.5	104.6 ± 84.5	122.2 ± 101.9*
cCa(mg/dL)	9.2 ± 0.6	9.2 ± 0.6	9.1 ± 0.7
Pi(mg/dL)	5.8 ± 1.1	5.6 ± 1.1	5.6 ± 0.9
pH	7.343 ± 0.023	7.343 ± 0.028	7.382 ± 0.029*,#
Bicarbonate (mEq/L)	20.1 ± 1.7	19.9 ± 2.1	22.0 ± 1.8*,#

Date were analyzed by repeated-measures ANOVA.
P < 0.05 * vs. Before 1st A(+)D, #vs. After 1st 2 weeks of A(+)D

3.3. Acute Change in Clinical Parameters During the 1st A(+)D, 1st A(–)D, and 7th A(–)D Hemodialysis Session in 32 Hemodialysis Patients

Serum wPTH decreased from 85.1 ± 59.0 pg/mL to 64.3 ± 51.7 pg/mL by 14.8% ± 40.9% during the 1st A(+)D hemodialysis session, from 92.8 ± 66.3 pg/mL to 64.3 ± 81.0 ± 58.7 pg/mL by 1.1% ± 48.7% during the 1st A(–)D session, and from 106.8 ± 78.8 pg/mL to 86.6 ± 57.2 pg/mL by 5.0% ± 49.4% during the 7th A(–)D session. Both the pre- and post-dialysis serum wPTH levels were significantly higher in the 7th A(–)D session than in the 1st A(+)D session (Table 5). Post-dialysis serum cCa levels were significantly greater in both the 1st and 7th A(–)D sessions than in the 1st A(+)D session, whereas post-dialysis bicarbonate was greater in the 1st A(–)D session than in the 1st A(+)D session, and both the pre- and post-dialysis pH and bicarbonate became greater in the 7th A(–)D session than in the 1st A(+)D session. Neither pre- nor post-dialysis serum levels of Pi and FGF-23 changed significantly during the entire 4-week study period.

Neither the predialysis nor post-dialysis values of systolic BP, diastolic BP, and heart rate differed significantly from the respective values among the 1st A(+)D session, 1st A(–)D session, and 7th A(–)D session. However, during the 1st A(+)D session and 1st A(–)D session, systolic BP acutely decreased significantly from 155.0 ± 24.7 mmHg to 139.0 ± 19.8 mmHg, and the heart rate tended to increase from 66.3 ± 10.4/min to 69.9 ± 12.7/min and from 152.4 ± 21.9 mmHg to 139.3 ± 1.8 mmHg with a significant increase in heart rate from 65.3 ± 11.1/min to 70.4 ± 13.2/min, respectively. However, neither systolic BP, heart rate, nor diastolic BP changed significantly during the 7th A(–)D hemodialysis session indicating the better hemodynamic stability during the hemodialysis session induced by chronic A(–)D treatment.

3.4. Change in Fatigue Score During 1st A(+)D Hemodialysis Session and 7th A(–)D Hemodialysis Session in 32 Hemodialysis Patients

All patients were divided into two equal-sized groups according to their fatigue score. The mean baseline fatigue scores were 9.3 ± 3.5 and 2.1 ± 1.6 in the highly-fatigued group (n = 16) and lightly-fatigued group (n = 16), respectively (Figure 1A). After switching the dialysate from A(+)D to A(–)D, the fatigue score in the highly-fatigued group tended to decrease to 7.6 ± 4.4 (p = 0.0734), whereas the fatigue score in lightly-fatigued patients did not change appreciable during the study period. Interestingly, the change in the fatigue score during the 2 weeks of A(–)D treatment was significantly greater in the highly-fatigued patients (Δ1.8 ± 3.7) than in the lightly-fatigued patients (Δ–0.8 ± 2.3) (p = 0.0252) (Figure 1B).

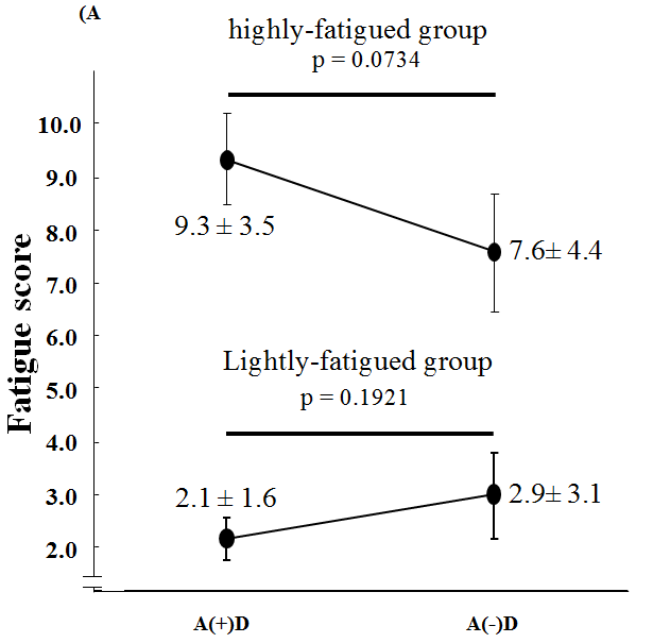

Figure 1A. *Change in fatigue score during 1st A(+)D and 7th A(–)D hemodialysis sessions in 32 hemodialysis patients.*

When the 32 patients were divided equally into two groups on the basis of fatigue score, the mean fatigue scores were 9.3 ± 3.5 in the high group (n = 16) and 2.1 ± 1.6 in the low group (n = 16). By switching dialysate from A(+)D to A(–)D, the fatigue score tended to be reduced in the high group (to 7.6 ± 4.4, p = 0.0734), but did not change in the low group (to 2.9 ± 3.1, p = 0.1921)

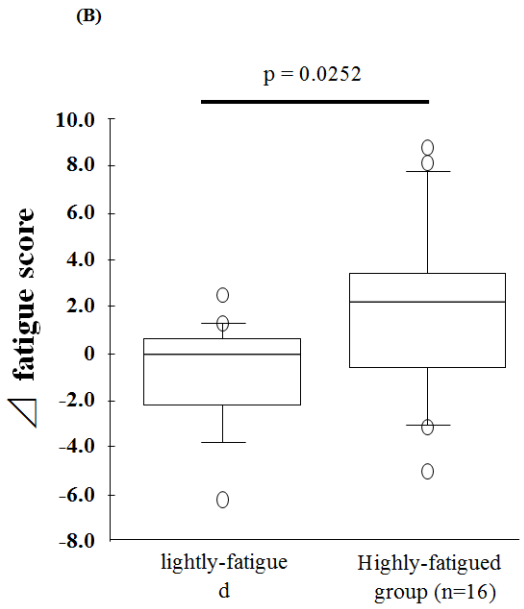

Figure 1B. *The amount of change in the fatigue score during the 1st A(+)D and 7th A(–)D hemodialysis sessions in 32 hemodialysis patients.*

The change in the fatigue score (A(+)D at the study start minus the 7th A(–)D) was significantly greater in the high group (Δ1.8 ± 3.7) than in the low group (Δ−0.8 ± 2.3) (p = 0.0252).

4. Discussion

This study demonstrated that 3.0 mEq/L Ca-containing A(–)D dialysate might have an effective Ca level significantly lower than that of 2.75 mEq/L Ca-containing A(+)D dialysate because both the pre- and post-dialysis serum wPTH levels increased significantly after switching from A(+)D to A(–)D and that although systolic BP fell significantly during the A(+)D session, it did not fall significantly during the A(–)D session. The combined findings of a significant increase in heart rate during the A(+)D session in contrast with the lack of a heart rate increase during the A(–)D session suggested that A(–)D, rather than A(+)D, could stabilize hemodynamic status during a hemodialysis session (Table 5).

Furthermore, the fatigue score tended to improve after the switch of dialysate from A(+)D to A(–)D preferentially in highly-fatigued hemodialysis patients in contrast with the insignificant change in the fatigue score in lightly-fatigued patients (Figure 1A). Together with the significantly greater improvement in fatigue score in the highly-fatigued patients relative to that in the lightly-fatigued patients (Figure 1B), the results suggested that A(–)D might be effective in improving the fatigue sensation, particularly in highly-fatigued hemodialysis patients.

Table 5. *Acute changes in various clinical parameters during 1st hemodialysis session with A(+)D, 1st A(–)D session after 2 weeks of A(+)D, and 7th A(–)D after 2 weeks of A(–)D session.*

	1st A(+)D		1st A(–)D after 2 weeks of A(+)D		7th A(–)D after 2 weeks of A(–)D	
	pre	post	pre	post	pre	post
whole PTH (pg/mL)	85.1 ± 59.0	64.3 ± 51.7	92.8 ± 66.3	81.0 ± 58.7$^{\#}$	106.8 ± 78.8* **	86.6 ± 57.2$^{\#}$
(% reduction)	14.8 ± 40.9		1.1 ± 48.7$^{\#}$		5.0 ± 49.4	
cCa (mg/dL)	9.1 ± 0.6	9.4 ± 0.2	9.1 ± 0.5	9.6 ± 0.2$^{\#}$	9.1 ± 0.6	9.6 ± 0.3$^{\#}$
phosphate (mg/dL)	5.9 ± 1.1	2.2 ± 0.5	5.7 ± 1.1	2.1 ± 0.5	5.7 ± 1.1	2.1 ± 0.5
FGF-23(pg/mL)	6290.4 ± 7407.1	3488.4 ± 4092.3	6295.3 ± 7119.1	3464.2 ± 3818.8	7340.6 ± 8905.7	3986.4 ± 4506.1
pH	7.335 ± 0.037	7.447 ± 0.022	7.335 ± 0.029	7.457 ± 0.030	7.370 ± 0.035* **	7.473 ± 0.027$^{\#\,\#\#}$
bicarbonate (mEq/L)	19.6 ± 2.1	25.2 ± 1.0	19.4 ± 1.8	26.7 ± 1.1$^{\#}$	21.3 ± 1.7* **	28.1 ± 1.0$^{\#\,\#\#}$
systolic BP (mmHg)	155.0 ± 24.7	139.0 ± 19.8‡‡	152.4 ± 21.9	139.3 ± 1.8‡‡	156.0 ± 24.6	146.2 ± 24.0‡
diastolic BP (mmHg)	76.0 ± 15.4	70.8 ± 11.1‡	75.3 ± 13.3	73.4 ± 12.5	79.5 ± 14.9	76.2 ± 14.4
heart Rate (/min)	66.3 ± 10.4	69.9 ± 12.7‡	65.3 ± 11.1	70.4 ± 13.2‡‡	67.6 ± 12.5	66.9 ± 14.2

Date were analyzed by repeated-measures ANOVA.
P < 0.05 * vs. pre 1st A(+)D, ** vs. pre 1st A(–)D after 2 weeks of A(+)D
P < 0.05 $^{\#}$ vs. post 1st A(+)D, $^{\#\#}$ vs. post 1st A(–)D after 2 weeks of A(+)D
Data were analyzed by Wilcoxon signed-rank test
P < 0.1 ‡vs. pre hemodialysis, p < 0.05 ‡‡ vs. pre-hemodialysis

The lower effective Ca level in the 3.0 mEq/L Carbostar-P® A(–)D dialysate than that in the 2.5 mEq/L Kinadaly 4E® A(+)D dialysate might be explained by at least two mechanisms. First, a higher 35 mEq/L bicarbonate level would decrease the ionized fraction of Ca by shifting the dialysate toward an alkaline pH. Second, citrate binds Ca strongly, which would decrease the effective Ca level. Bone biopsy data of hemodialysis patients have revealed a recent trend toward increased development of adynamic bone disease [12], which is now widely recognized as a cardiovascular risk in hemodialysis patients by attenuating the buffering action of bone to absorb surplus Ca and Pi in circulation [13]. It has been reported that Ca overload might induce adynamic bone disease either by inhibiting the bone turnover rate through suppression of PTH [14] or by increasing the rate of bone calcification through an increase in serum Ca × Pi product [15]. With increasing use of calcimimetics, the set-point of serum Ca levels for half-maximal secretion of PTH has decreased with suppression of baseline PTH levels [16]. In Japan, the target range of serum PTH defined by the Japanese Society of Dialysis Therapy is 60–240 pg/mL, which is significantly lower than those in other countries [17]. Therefore, recognition of the importance of a low Ca dialysate to avoid the suppressive effect of Ca overload on serum PTH and the resultant development of a dynamic bone disease has

increased [18].

As already reported [2], metabolic acidosis was improved more strongly in A(–)D relative to that in A(+)D hemodialysis in this study because of the higher bicarbonate concentration in A(–)D (Tables 2 and 4). It has been reported that overcorrection of metabolic acidosis might increase all-cause mortality and cardiovascular mortality in hemodialysis patients. The previous result based on data form the renal registry of the Japanese Society of Dialysis (2008–2009), including 15,132 hemodialysis patients ≥16 years demonstrated that (i) those with predialysis pH ≥ 7.40 exhibited significantly higher risk of all-cause mortality [hazard ratio (HR): 1.36; 95% CI, 1.13–1.65] and cardiovascular mortality (HR, 1.34; 95% CI, 1.01–1.79) and (ii) those with post-dialysis pH < 7.40 exhibited a significantly higher risk of all-cause mortality (HR, 1.22; 95% CI, 1.00–1.49), and (iii) pre- and post-dialysis bicarbonate levels were not associated with all-cause and CV mortality, which suggested predialysis pH might be the most appropriate reference for acute correction of metabolic acidosis in hemodialysis patients [19]. As shown in Table 5, even with 2 weeks of A(–)D, including 35 mEq/L bicarbonate, the mean predialysis pH was 7.370, which did not exceed a pH of 7.40, and the mean post-dialysis pH was 7.470, which is >7.40 and clearly suggested that A(+)D is safe from the standpoint of mortality on the basis of the relationship between pH and mortality data in Japanese hemodialysis patients. Those treated with (A+)D also exhibited predialysis and post-dialysis pH values of <7.40 and ≥7.40, respectively, which suggested that both A(+)D and A(–)D are safe in terms of the relationship between pH and mortality in hemodialysis patients.

Because acetate contained in dialysate might increase the fatigue sensation [20], it has been suggested that the main factor related to fatigue reduction was the stability of hemodynamics in an hemodialysis session by using A(–)D instead of A(+)D (Table 5). Furthermore, it is possible that citrate contained in A(–)D contributed to fatigue reduction because citrate is recognized widely as a nutrient with anti-fatigue effects. Sugino et al. reported that an oral citric acid supplement (2,700 mg/day) reduced physiological stress and attenuated physical fatigue in 18 healthy volunteers [21]. Carbostar-P® contains 2 mEq/L citrate, and it is known that the serum citrate concentration is significantly elevated after hemodialysis treatment. Indeed, Michael et al. reported that citrate-containing A(–)D also might contribute to improving fatigue in hemodialysis patients [22]. Comprehensive metabolomic analyses of plasma from chronic fatigue syndrome have demonstrated that citrate was preferentially decreased, which suggested deficiencies in adenosine triphosphate production secondary to dysregulation of the flow from pyruvate to citrate via acetyl CoA and that dysfunctional energy metabolism through the citric acid cycle is a fatigue phenotype [23]. We previously reported that fatigue can be an important predictor for cardiovascular events in hemodialysis patients independent of their nutritional or inflammatory status [6]. It is important that patients are given hemodialysis treatment in consideration of the fatigue accumulated in daily life.

The limitations of our study were as follows. First, the sample size was small and the observation period was short. We guessed that A(–)D was more useful in DM hemodialysis patients in particular. However, because the sample size was small and most of the parameter levels did not differ significantly between the patients with and without DM, we were not able to evaluate this speculation. Second, the clinical study was conducted in a single clinic. Third, because we told the patients before starting this study that the dialysate would be changed and here may have been a psychological factor that we did not investigate. Fourth, because the condition of most of the patients who participated was very stable and only a few patients needed treatment by A(–)D, we might not have sufficiently evaluated the effect of A(–)D. The strength of the present study is that we did not change the treatments other than the dialysate, such as the dialysis conditions and type of drug, during the study period.

In summary, the present study observed effects of A(–)D for improvement of Ca overload and fatigue reduction in hemodialysis patients. We suggest that A(–)D is worth using in hemodialysis patients who have a tendency toward adynamic bone disease because of Ca overload or exhaustion in their daily lives.

Conflict of Interest Statement

The authors have no conflicts of interest directly relevant to the content of this article.

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The authors have no financial relationships to disclose.

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