Calcif Tissue Int (2014) 94:301–310
DOI 10.1007/s00223-013-9811-x

ORIGINAL RESEARCH

Is the Dialysate Calcium Concentration of 1.75 mmol/L Suitable for Chinese Patients on Maintenance Hemodialysis?

Dong-liang Zhang · Li-yan Wang · Fang Sun · Yi-lun Zhou · Xiao-feng Duan · Sha Liu · Yi Sun · Tai-gen Cui · Wen-hu Liu

Received: 25 July 2013 / Accepted: 16 October 2013 / Published online: 6 November 2013
© Springer Science+Business Media New York 2013

Abstract We studied the effects of increasing the dialysate calcium concentration (DCa) to 1.75 mmol/L on controlling chronic kidney disease–mineral and bone disorder in Chinese patients on maintenance hemodialysis (MHD). We reviewed the data of MHD patients in one center (cohort 1) during prior 10 years and analyzed the risk factors of mortality and transference calcification (TC) in120 MHD patients surviving in 2003 (cohort 2). A multicenter, prospective, parallel-group, controlled trial (cohort 3) was also conducted from January 2011 to December 2012. The DCa at one center was increased from 1.5 to 1.75 mmol/L but was not changed at the other two centers. The clinical outcomes, biochemical parameters, medicine treatments, and TC markers [aortic arch calcification score (AoACS)] were compared between groups. In cohort 1, the annual mean serum iPTH increased significantly over 10 years. In cohort 1, 72 patients survived for 10 years, whose doses of calcium salts and active vitamin D_3 and AoACs increased progressively. In cohort 2, the main cause of death was cardiocerebrovascular disease (CCVD) ($n = 18$, 48.6 %). Male sex and lower serum calcium concentrations were independent risk factors for CCVD mortality. In cohort 3, serum phosphorus, iPTH, and 25(OH)D decreased and serum calcium increased significantly; also, the doses of calcium and vitamin D_3 decreased from 2011 to 2012 in the DCa 1.75 group. There were no significant differences in clinical outcomes either between groups or between the two calendar years. Our results indicate that increasing DCa to 1.75 mmol/L can decrease the elevated levels of serum iPTH and phosphorus, reduce the doses of calcium and vitamin D_3, and be safe for short periods of time.

Keywords Dialysate · Calcium · Maintenance hemodialysis

Introduction

Chronic kidney disease–mineral and bone disorders (CKD–MBD) are common complications in maintenance hemodialysis (MHD) patients. These disorders not only contribute to the development of bone disease [1, 2] but also increase the risk for cardiovascular and all-cause mortality (ACM) [2–5], events that are potentially mediated by vascular calcification [6, 7]. Many national [8, 9] and international [10] guidelines advocate tighter control of the biochemical parameters associated with CKD–MBD within specific target ranges, particularly of serum calcium (Ca), phosphorus (P), and intact parathyroid hormone (iPTH) levels.

Small changes in dialysate calcium concentrations (DCa) may have much larger effects on biochemical parameters. Therefore, appropriate selection of the DCa is

The authors have stated that they have no conflict of interest.

Electronic supplementary material The online version of this article (doi:10.1007/s00223-013-9811-x) contains supplementary material, which is available to authorized users.

D. Zhang · L. Wang · S. Liu · W. Liu (✉)
Nephrology Faculty, Beijing Friendship Hospital, Capital Medical University, No. 95 Yong-An Street, Xi-Cheng District, Beijing 100050, China
e-mail: nephro@ccmu.edu.cn

F. Sun · Y. Zhou · T. Cui
Nephrology Faculty, Beijing ChaoYang Hospital, Capital Medical University, Beijing, China

X. Duan · Y. Sun
Nephrology Faculty, Beijing FuXing Hospital, Capital Medical University, Beijing, China

very important for MHD patients. Of note, low DCa (e.g., 1.25 mmol/L) increases circulating PTH and bone-specific alkaline phosphatase (BAP) concentrations [11, 12]. Although secondary hyperparathyroidism (SHPT) can be effectively controlled using a high DCa (e.g., 1.75 mmol/L), dialysis patients may be at increased risk of oversuppression of PTH, adynamic bone disease, hypercalcemia, and soft-tissue calcification [13].

In China, the DCa of 1.5 mmol/L has been used in clinical practice since 2004, following the introduction of the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for the management of SHPT in MHD patients. However, we noticed that the prevalence of SHPT in Beijing has increased greatly in recent years. Of note, in Beijing in 2011, only 8.8 % of cases had levels of three blood parameters (serum Ca, P, and iPTH) within the target ranges [14]. This raises the question of which DCa (1.5 or 1.75 mmol/L) is more appropriate for Chinese MHD patients.

Methods

Study Design

There were three cohorts in the present study. Cohort 1 enrolled most of the MHD patients treated at the Beijing Friendship Hospital (BFH), who were followed up from January 2003 to December 2012. Cohort 1 was a dynamic population which included new patients, transferred patients, and patients who died during every calendar year. The data of cohort 1 gave the background information of CKD–MBD in BFH for the long term when the DCa decreased from 1.75 to 1.5 mmol/L in January 2004 and was returned to 1.75 mmol/L in January 2012. We calculated the changes in blood parameters associated with CKD–MBD and analyzed clinical outcomes over 10 years retrospectively. Furthermore, the MHD patients who survived for the 10-year period were designated as a subgroup to analyze their CKD–MBD treatments and transference calcification (TC) outcomes in details.

Cohort 2 was a fixed cohort. There were 139 MHD patients in 2003 at the BFH. We identified 120 (86.3 %) MHD patients from this cohort whose iPTH was measured 10 years ago and whose records were complete for 10 years. This cohort of patients was used to analyze the correlations between blood parameters associated with CKD–MBD and clinical outcomes.

Cohort 3 was designed to conduct a prospective, parallel-group, controlled trial which involved three dialysis centers (BFH, Beijing Chao-Yang Hospital, and Beijing Fu-Xing Hospital). Only patients on dialysis for >3 months and whose life expectancy was >2 years were enrolled. Considering the risk of TC, patients with high serum calcium (>9.5 mg/dL) and low iPTH (<100 pg/mL) were excluded. Patients were followed up for 2 years since January 2011. Dialysates were prepared using a concentrated liquid supply system in each center. The dialysate consisted of 35 mmol/L bicarbonate, 135 mmol/L sodium, 2.0 mmol/L magnesium, and 2.5 mmol/L potassium. The DCa of the three centers was 1.5 mmol/L during 2011. The DCa used at BFH was increased to 1.75 mmol/L in January 2012 but was not changed at the other two centers. For this part of the study, patients in BFH are referred to as the "DCa 1.75 group," while patients in other centers are referred to as the "DCa 1.5 group." We measured biochemical parameters (serum Ca, P, iPTH, 25-hydroxyvitamin D [$25(OH)D_3$], and BAP), as well as TC markers (aortic arch calcification score [AoACS], aorta abdominalis calcification [AAC], and cardiac valve calcification [CVC]). Clinical outcomes and medicines were also recorded.

The study protocol was approved by central ethical review boards. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Data Collection and Measurements

In the retrospective cohort study, the following data were recorded: age, sex, cause of end-stage renal disease (ESRD), duration of dialysis, dialysis adequacy (Kt/V; dialyzer clearance of urea × dialysis time/volume of distribution of urea), medicine treatments (calcium salts and active vitamin D [$VitD_3$]), laboratory data, radiographic data, and outcomes. Because the serum parameters were measured several times per calendar year in an individual patient, we calculated the mean value over each year. The mean daily doses of medicines were also calculated. The proportions of patients achieving KDOQI targets for serum Ca (8.4–9.5 mg/dL), P (3.5–5.5 mg/dL), Ca × P (<55 mg^2/dL^2), and iPTH (150–300 pg/mL) in calendar years were calculated, as well as the Kidney Disease: Improving Global Outcomes (KDIGO) guideline [10] targets for serum Ca (8.0–10.0 mg/dL), P (3.0–5.0 mg/dL), and iPTH (125–560 pg/mL).

In the prospective study, laboratory data measured in local laboratories were collected for 2 years. Serum Ca, P, iPTH, hemoglobin (Hb), albumin, $25(OH)D_3$, and alkaline phosphatase (ALP) were measured using standard methods. These parameters were measured every 3 months or according to KDOQI guidelines. Serum iPTH was detected by an electrochemiluminescence immunoassay (ECLIA) using third-generation PTH assays (Siemens Healthcare, Glyn Rhonwy, UK; ADVIA Centaur Immunoassay system). The reference range of serum iPTH was 10–62 pg/mL at BFH. Serum $25(OH)D_3$ levels were measured every

6 months using the Elecsys Vitamin D total assay by ECLIA (Roche Diagnostics, Mannheim, Germany; Cobas® e 601 analyzer series). Serum BAP levels were measured every 6 months using an enzyme immunoassay (Osteolinks BAP; Quidel, San Diego, CA, USA).

AoACS, AAC, and CVC were determined twice per year regularly. AoACS was semiquantitatively assessed using plain chest radiographs, as previously described [15]. AAC and CVC were qualitatively assessed using lateral abdominal plain films and echocardiograms, respectively. The radiographs were collected and assessed again by two radiologists. The mean values of both AoACS and AAC were calculated according to the values given by the radiologists. The assessments of CVC were in accordance with the records. Any positive result of AoAC, AAC, and CVC would be defined as TC.

Clinical outcomes include ACM, cardiocerebrovascular mortality (CCVM), serious cardiocerebrovascular diseases (CCVD), and TC.

Statistical Methods

Continuous variables are expressed as mean ± standard deviation and were compared with independent *t* tests or one-way analysis of variance, as appropriate. Categorical variables are expressed as proportions and were compared using χ^2 tests.

Biochemical parameters in the surviving patients from cohort 1 were compared before and after changing the DCa at BFH. Logistic regression analysis was used to identify factors associated with TC in the surviving patients in cohort 1. Risk factors for clinical outcomes in cohort 2 were determined using Cox regression and Kaplan–Meier analyses.

For the DCa 1.75 and DCa 1.5 groups in cohort 3, we compared the clinical factors at baseline and at 2 years between the two groups using independent *t* tests or χ^2 tests, respectively, and within each group using paired samples *t* tests or χ^2 tests.

For all tests, significant differences were accepted at $p < 0.05$. All data were analyzed using SPSS software (version 13.0 for Windows; SPSS, Inc., Chicago, IL, USA).

Results

Annual Distribution of CKD–MBD Factors According to DCa

The mean age was 63.4 ± 14.1 years, and the mean duration of dialysis was 56.0 ± 54.9 months in cohort 1. The annual mean serum iPTH concentration increased progressively until 2012, from 127.6 ± 324.6 pg/mL in 2002 to 426.0 ± 293.3 pg/mL in 2011 ($F = 14.300$, $p < 0.001$) (Fig. 1). There were significant differences in serum Ca concentrations over the 10 years (9.01 ± 0.98 mg/dL to 9.35 ± 0.84 mg/dL, $F = 7.245$, $p < 0.001$). The mean serum P, Ca × P, and ALP concentrations were relatively stable. Fewer than 9 % (5.5–8.7 %) of patients had all three of iPTH, Ca, and P concentrations within the target ranges of KDOQI. However, more patients could get the target ranges of KDIGO, nearly 25 % (18.4–24.1 %) for all three parameters and above 50 % (50.0–67.6 %) for iPTH.

Seventy-two patients (49 females) were still alive at the end of the 10-year analysis in cohort 1. The characteristics of the subgroup according to calendar year are shown in Table 1. The mean age of these patients was 47.54 ± 12.28 years (range 22–69) at the start of dialysis and 51.38 ± 11.48 years (range 28–75) in 2003. In December 2012, the mean duration of dialysis was 166.1 ± 51.6 months. The cause of ESRD included glomerulonephritis (GN; $n = 50$, 69.4 %), tubulointerstitial nephritis (TIN; $n = 8$, 11.1 %), diabetic nephropathy (DN; $n = 2$, 2.8 %), and other diseases ($n = 8$, 11.1 %). CKD–MBD parameters in this subgroup of 72 patients were similar to those in cohort 1 overall (Fig. 1). Serum iPTH increased significantly after decreasing the DCa from 1.75 mmol/L in 2003 to 1.5 mmol/L in 2004 and decreased significantly after increasing the DCa to 1.75 mmol/L again in 2012 (Table 1). The changes in serum Ca, P, and Ca × P were not significantly different between 2003 and 2004 or between 2011 and 2012 except for the serum P concentration, which was significantly higher in 2004 than in 2003 (5.79 ± 0.90 mg/dL vs. 5.33 ± 0.86 mg/dL, $t = 2.45$, $p = 0.017$). The mean daily doses of calcium and $VitD_3$ had a similar trend as serum iPTH. When the DCa increased to 1.75 mmol/L in 2012, the doses of calcium and $VitD_3$ were decreased significantly (Table 1).

Risk Factors for Mortality and TC

The mean age in the 120 patients (66 females) in cohort 2 at the start of dialysis was 51.0 ± 13.8 years (range 22–73). The primary diseases of ESRD included GN ($n = 87$, 72.5 %), TIN ($n = 9$, 7.5 %), DN ($n = 9$, 7.5 %), and others ($n = 15$, 12.5 %). The laboratory data included *Kt/V* 1.51 ± 0.27, Hb 112.8 ± 19.0 (g/L), albumin 4.10 ± 0.34 (mg/dL), Ca 9.24 ± 0.86 (mg/dL), P 5.77 ± 1.58 (mg/dL), Ca × P 53.0 ± 14.8 $(mg/dL)^2$, iPTH 131.8 ± 221.4 (pg/mL), ALP 71.9 ± 36.0 (U/L). Overall, 37 patients died, with an annual mortality rate of 3.08 %. Almost 50 % of the patients died because of CCVD, including cerebral hemorrhage ($n = 7$, 18.9 %) and myocardial infarction ($n = 11$, 29.7 %). Other causes of death included cachexia ($n = 8$, 21.6 %), infection ($n = 6$, 16.2 %), tumor ($n = 4$, 10.8 %), and other ($n = 1$, 2.7 %). Cox regression analysis showed

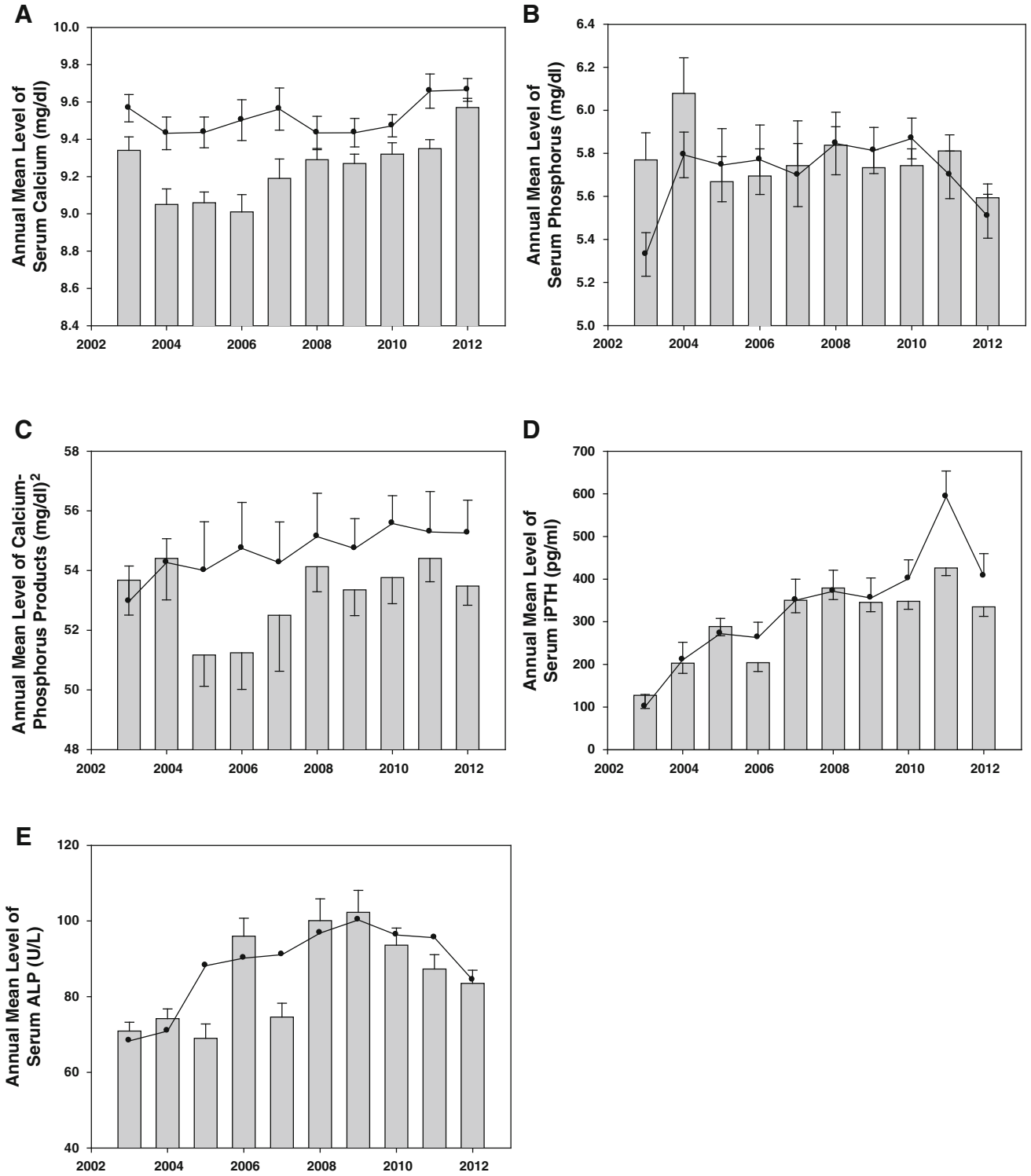

Fig. 1 Changes in clinical biochemical markers over 10 years in cohort 1. **a** Serum calcium, **b** phosphorus, **c** calcium × phosphorus, **d** iPTH, and **e** and alkaline phosphatase (ALP). Values for all patients in cohort 1 are shown as *bars*, and values for the 72 patients who survived for ≥10 years are shown as *lines*

that age at the start of dialysis (hazard ratio [HR] = 1.036, 95 % confidence interval [CI] 1.002–1.070; $p = 0.038$), male sex (HR = 0.225, 95 % CI 0.100–0.509; $p < 0.001$), and low serum albumin (HR = 0.041, 95 % CI 0.007–0.250; $p = 0.001$) were the independent risk factors for ACM. Male sex (HR = 0.043, 95 % CI 0.008–0.241; $p = 0.001$) was the

Table 1 Characteristics of 72 patients in cohort 1 who survived for ≥10 years

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Kt/V	1.50 ± 0.25	1.48 ± 0.22	1.48 ± 0.38	1.49 ± 0.23	1.50 ± 0.31	1.48 ± 0.20	1.57 ± 0.31	1.53 ± 0.27	1.49 ± 0.29	1.53 ± 0.30
Laboratory data										
Hemoglobin (g/L)	103.0 ± 13.4	102.8 ± 16.5	109.4 ± 19.1	110.4 ± 17.0	107.9 ± 15.7	110.6 ± 17.9	110.6 ± 18.3	109.6 ± 17.7	110.9 ± 15.3	110.3 ± 16.1
Albumin (g/dL)	3.86 ± 0.14	3.87 ± 0.22	3.85 ± 0.23	3.85 ± 0.25	3.82 ± 0.25	3.88 ± 0.31	3.88 ± 0.14	3.89 ± 0.17	3.84 ± 0.20	3.89 ± 0.11
Calcium (mg/dL)	9.57 ± 0.62	9.43 ± 0.74	9.44 ± 0.70	9.50 ± 0.93	9.56 ± 0.96	9.43 ± 0.76	9.44 ± 0.65	9.47 ± 0.51	9.66 ± 0.78	9.67 ± 0.52
Phosphorus (mg/dL)	5.33 ± 0.86[a]	5.79 ± 0.90	5.75 ± 1.44	5.77 ± 1.37	5.70 ± 1.24	5.85 ± 1.24	5.81 ± 0.91	5.87 ± 0.81	5.70 ± 0.94	5.51 ± 0.87
Intact PTH (pg/mL)	100.9 ± 243.1[b]	210.4 ± 350.8	272.3 ± 302.1	262.8 ± 306.0	350.5 ± 417.7	371.4 ± 419.5	355.8 ± 397.0	401.2 ± 374.9	593.0 ± 513.1	407.0 ± 446.8[c]
Ca × P product $(mg/dL)^2$	53.0 ± 10.1	54.3 ± 6.8	54.0 ± 13.9	54.7 ± 13.1	54.3 ± 11.6	55.1 ± 12.4	54.7 ± 8.5	55.6 ± 7.9	55.3 ± 11.5	53.4 ± 9.4
ALP (U/L)	68.3 ± 27.5	70.9 ± 28.9	88.2 ± 50.7	90.2 ± 70.0	91.1 ± 50.9	96.8 ± 79.4	100.3 ± 85.2	96.3 ± 73.4	95.6 ± 51.3	84.4 ± 50.2
Creatinine (mg/dL)	910.5 ± 172.4	993.6 ± 213.9	937.9 ± 163.5	890.7 ± 260.9	886.2 ± 165.1	824.1 ± 189.8	781.7 ± 138.6	780.6 ± 155.7	784.9 ± 148.5	789.6 ± 151.1
Total cholesterol (mg/dL)	174.2 ± 36.8	181.3 ± 46.2	172.7 ± 41.4	175.9 ± 71.6	198.0 ± 44.9	185.2 ± 39.1	186.8 ± 36.3	185.2 ± 36.3	177.1 ± 33.6	181.6 ± 39.5
AoACs	0.0133 ± 0.0748	0.0186 ± 0.0781	0.1184 ± 0.1702	0.1569 ± 0.2073	0.1656 ± 0.2052	0.1755 ± 0.2226	0.2427 ± 0.2441	0.2560 ± 0.2354	0.2387 ± 0.2422	0.2826 ± 0.2376[d]
Medicines										
Calcium salts (mg/day)	117.0 ± 118.6	143.8 ± 119.2	282.7 ± 272.8	535.2 ± 365.0	377.4 ± 253.0	413.3 ± 294.6	232.3 ± 226.2	276.1 ± 219.1	232.8 ± 175.5	158.8 ± 142.9[e]
Active vitamin D_3 (μg/day)	0.0176 ± 0.0226[f]	0.0297 ± 0.0239	0.0699 ± 0.1233	0.1965 ± 0.2437	0.2526 ± 0.1711	0.3807 ± 0.3657	0.4595 ± 0.3564	0.3911 ± 0.2379	0.3498 ± 0.1892	0.1327 ± 0.1022 [g]

Seventy-two MHD patients in cohort 1 who survived for ≥10 years were analyzed. Their clinical data were compared between 2003 and 2004 (corresponding to a decrease in the DCa from 1.75 to 1.50 mmol/L) and between 2011 and 2012 (corresponding to an increase in DCa concentration from 1.50 to 1.75 mmol/L)

[a] Serum phosphorus concentrations increased significantly between 2003 and 2004 ($t = -2.45$, $p = 0.017$)

[b] Serum iPTH concentrations increased significantly between 2003 and 2004 ($t = -4.88$, $p < 0.001$)

[c] Serum iPTH decreased significantly between 2011 and 2012 ($t = 4.804$, $p < 0.001$)

[d] The AoACS increased significantly between 2003 and 2012 ($t = -7.81$, $p < 0.001$)

[e] Daily doses of elementary calcium decreased significantly between 2011 and 2012 ($t = 3.222$, $p = 0.002$)

[f] Daily doses of active vitamin D increased significantly between 2003 and 2004 ($t = -3.114$, $p = 0.003$)

[g] Daily doses of active vitamin D decreased significantly between 2011 and 2012 ($t = 10.652$, $p < 0.001$)

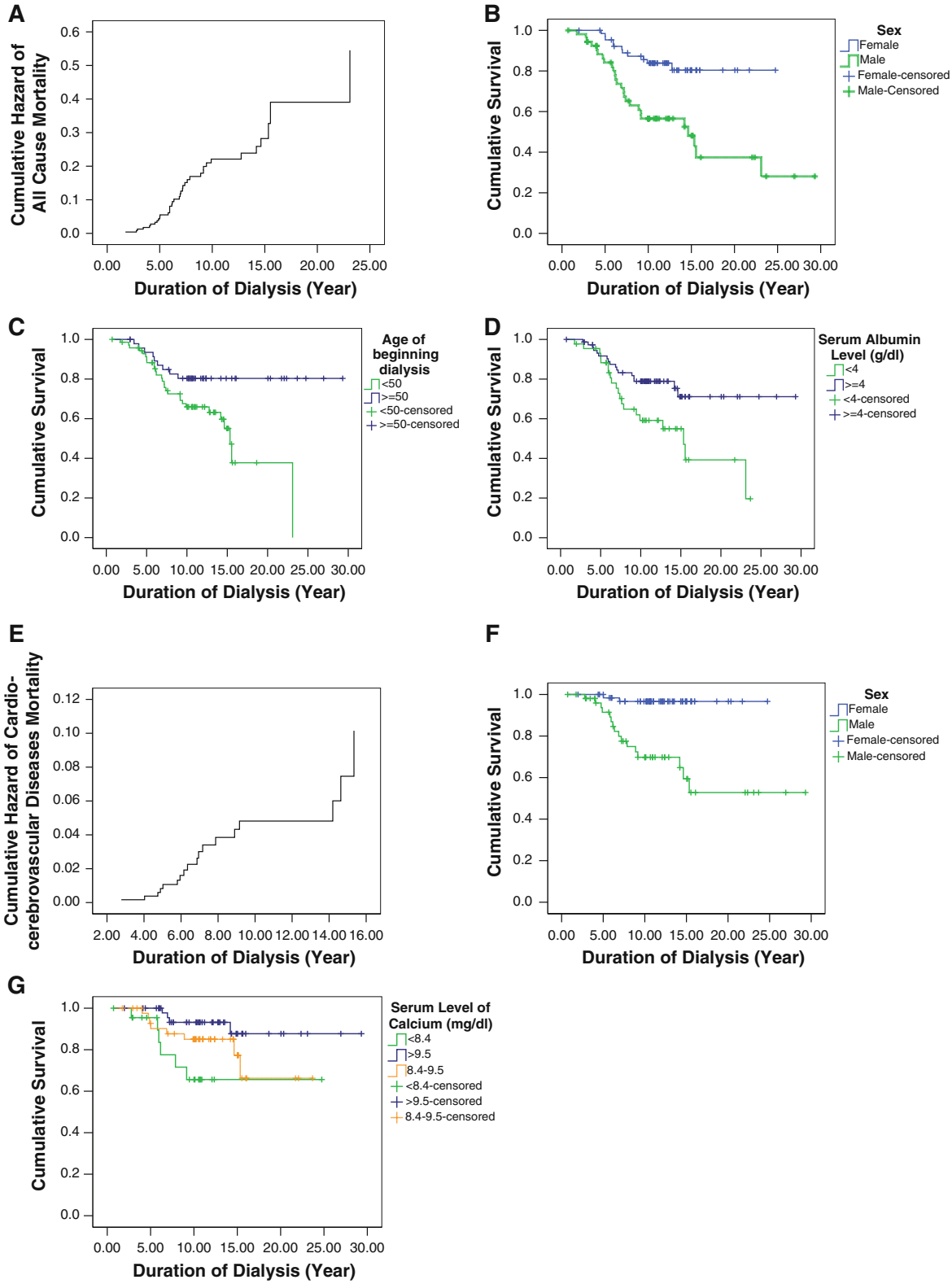

Fig. 2 Kaplan–Meier analysis of risk factors for ACM and CCVM in cohort 2 ($n = 120$). **a** Cumulative incidence of ACM in cohort 2. **b** Males versus females ($\chi^2 = 13.73$, $p < 0.001$). **c** Dialysis started at <50 versus ≥50 years of age ($\chi^2 = 6.88$, $p = 0.009$). **d** Serum albumin concentration <4.0 versus ≥4.0 g/dL ($\chi^2 = 6.59$, $p = 0.010$). **e** Cumulative incidence of CCVM in cohort 2. **f** Males versus females ($\chi^2 = 17.95$, $p < 0.001$). **g** Serum calcium concentrations of <8.4, 8.4–9.5, and >9.5 mg/dL ($\chi^2 = 7.57$, $p = 0.006$)

Table 2 Characteristics of patients in cohort 3

	Group DCa 1.75 ($n = 285$)	Group DCa 1.5 ($n = 223$)	t/χ^2	p
Age (years)	61.2 ± 14.7	63.9 ± 15.8	–1.384	0.167
Dialysis vintage (months)	64.8 ± 51.6	61.6 ± 55.5	0.480	0.632
Gender female (%)	152 (53.3 %)	100 (44.8 %)	3.280	0.070
Cause of ESRD (%)			8.270	0.082
Glomerulonephritis	170 (59.6 %)	113 (50.7 %)	–	–
Diabetic nephropathy	73 (25.6 %)	63 (28.3 %)	–	–
Tubulointerstitial nephritis	17 (6.0 %)	19 (8.5 %)	–	–
Hypertension	16 (5.6 %)	11 (4.9 %)	–	–
Other	9 (3.2 %)	17 (7.6 %)	–	–

Stable MHD patients treated at BFH, Beijing Chao-Yang Hospital, or Beijing Fu-Xing Hospital were enrolled into cohort 3 in January 2011. These patients were divided into two groups and received DCa of 1.75 or 1.5 mmol/L. In the DCa 1.75 group, DCa was increased from 1.5 to 1.75 mmol/L in January 2012. Patients were followed up for 2 years. Changes in parameters within each group were compared by paired t tests or χ^2 tests. There were no significant differences between the two groups at baseline

independent risk factor for CCVM. By contrast, higher serum Ca (HR = 0.275, 95 % CI 0.096–0.788; $p = 0.016$) was associated with reduced risk for CCVM. However, none of the factors determined in this study were risk factors for TC. We next performed Kaplan–Meier analysis to determine differences in both ACM and CCVM in patients stratified by risk factors (Fig. 2).

In the subgroup of 72 patients from cohort 1, AoACS increased significantly from 0.0133 ± 0.0748 to 0.2826 ± 0.2376 during the 10-year follow-up period ($t = -7.81$, $p < 0.001$). Logistic regression analysis showed that age (in 2003) was the only factor associated with TC (relative risk = 0.942, $\beta = -0.059$, $p = 0.011$). None of the other parameters determined in this study was associated with TC.

Effects of Short-Term Changes in DCa on CKD–MBD

The baseline characteristics of the two groups of patients (DCa 1.75 and 1.5) in cohort 3 were similar (Table 2). The serum Ca concentrations in 2012 were significantly different between the two groups. In the DCa 1.75 group, serum P, iPTH, and 25(OH)D concentrations decreased and serum Ca increased significantly between two calendar years. Furthermore, the mean daily doses of both calcium and $VitD_3$ were reduced significantly between 2011 and 2012 in group DCa 1.75 (Table 3). There were no significant differences in clinical outcomes between the two groups or between the two calendar years in each group.

Discussion

In China, the current situation of CKD–MBD control is very serious. Indeed, the proportions of patients with optimal serum Ca, P, and iPTH among Chinese MHD patients were significantly lower than in the Dialysis Outcomes and Practice Patterns Study (DOPPS) 3 (2007) and DOPPS 4 (2010) [16]. In the present study, <9 % of patients had serum Ca, P, and iPTH concentrations within the target ranges of KDOQI in each calendar year.

In China, the most common medicines used to treat CKD–MBD are calcium salts (calcium carbonate and calcium acetate) and $VitD_3$ agents (calcitriol and alpha-hydroxyvitamin D_3). All other intestinal phosphate binders, vitamin D analogues, and calcimimetics could not be bought freely in the Chinese mainland market before 2012. Indeed, our study provided clear evidence for progressive deteriorations in SHPT-related morbidity and metabolic disorders over 10 years among patients treated at BFH whose DCa was reduced from 1.75 to 1.5 mmol/L (Table 3; Fig. 1). The present study examined the potential of an effective method [16–18] of controlling high P and iPTH concentrations simply by changing the DCa. It was also demonstrated that the doses of both calcium and $VitD_3$ were reduced by using DCa 1.75 mmol/L in the present study. Although many clinical practice guidelines recommend against this method, we believe it may be beneficial for Chinese MHD patients considering the current clinical status.

Prior studies have demonstrated the clinical benefits of a high DCa that included significant reductions in serum P and iPTH concentrations [17] as well as maintaining a stable hemodynamic state [18]. Al-Hejaili et al. [19] confirmed that DCa 1.25 mmol/L stimulated iPTH production and DCa 1.75 mmol/L suppressed iPTH levels during both single and long-term nocturnal hemodialysis. Our findings suggest that 1.75 mmol/L DCa could reduce serum iPTH concentrations, whereas 1.5 mmol/L DCa could increase it (Table 3; Fig. 1).

The main danger of high DCa is the increased Ca load, which is associated with TC, such as coronary calcification [20, 21], peripheral arterial calcification [22], CVC [23], increased arterial stiffness changes [24, 25], and increased risk of mortality [4, 26]. Notably, in the present study and another study [27], serum Ca, P, and iPTH were not independent risk factors for TC or ACM [28]. Traditional risk factors [27, 29–31], such as age, sex, smoking, diabetes, hypertension, history of cardiovascular disease, total cholesterol, and high-sensitivity C-reactive protein, are still leading risk factors for ACM and cardiovascular mortality in CKD patients with or without dialysis. A prospective study demonstrated that high DCa was not associated with mortality, unlike the findings of the DOPPS [32]. In our

Table 3 Comparison of DCa of 1.5 and 1.75 mmol/L in cohort 3

	Group DCa 1.75 ($n = 285$)				Group DCa 1.5 ($n = 223$)				t/χ^2	p
	2011	2012	t/χ^2	p	2011	2012	t/χ^2	p		
Laboratory data										
Kt/V	1.50 ± 0.29	1.50 ± 0.29	0.116	0.908	1.51 ± 0.29	1.52 ± 0.26	−0.473	0.636	−0.627	0.531
Hemoglobin (g/L)	114.7 ± 15.4	114.9 ± 13.6	−0.118	0.906	114.9 ± 19.1	115.1 ± 13.0	−0.135	0.893	−0.169	0.866
Albumin (g/dL)	3.82 ± 0.22	3.83 ± 0.37	−0.710	0.480	3.80 ± 0.36	3.82 ± 0.31	−0.800	0.425	0.449	0.654
Creatinine (mg/dL)	836.2 ± 168.7	817.5 ± 184.3	1.050	0.295	825.6 ± 211.5	798.4 ± 239.8	1.180	0.240	0.892	0.373
Total cholesterol (mg/dL)	163.0 ± 35.2	161.6 ± 35.6	0.570	0.569	162.6 ± 44.0	161.6 ± 35.6	0.481	0.632	0.152	0.879
Calcium (mg/dL)	9.38 ± 0.84	9.59 ± 0.89	−2.910	0.004	9.30 ± 0.79	9.22 ± 0.64	1.050	0.297	5.187	<0.001
Phosphorus (mg/dL)	5.85 ± 1.30	5.57 ± 1.21	2.530	0.012	5.80 ± 1.42	5.75 ± 1.21	0.380	0.703	−1.670	0.095
Ca × P product $(mg/dL)^2$	55.0 ± 13.7	53.4 ± 12.0	1.330	0.186	54.0 ± 14.4	53.1 ± 12.3	0.680	0.500	0.216	0.829
Intact PTH (pg/mL)	425.7 ± 365.1	340.9 ± 390.1	6.360	<0.001	379.9 ± 378.1	366.6 ± 341.0	1.380	0.170	−0.780	0.438
ALP (U/L)	105.7 ± 45.4	106.8 ± 45.5	−0.287	0.774	100.0 ± 47.0	110.6 ± 56.9	−0.836	0.405	0.416	0.678
BAP (U/L)	17.54 ± 16.57	16.03 ± 11.18	1.304	0.195	17.12 ± 14.80	17.21 ± 16.90	−0.189	0.856	−0.674	0.501
25(OH)D	14.58 ± 7.65	12.86 ± 7.29	4.587	<0.001	14.24 ± 8.30	14.39 ± 6.12	−0.186	0.853	2.261	0.024
Medicines										
Calcium salts (mg/day)	444.7 ± 375.3	383.5 ± 309.4	6.025	<0.001	392.0 ± 345.6	402.8 ± 341.3	−0.601	0.549	−0.664	0.507
Active vitamin D_3 (μg/day)	0.2679 ± 0.1783	0.1953 ± 0.1248	13.990	<0.001	0.2531 ± 0.1817	0.2498 ± 0.1783	0.473	0.637	−4.005	<0.001

Stable MHD patients treated at BFH, Beijing Chao-Yang Hospital, or Beijing Fu-Xing Hospital were enrolled into cohort 3 in January 2011. These patients were divided into two groups and received DCa concentrations of 1.75 or 1.5 mmol/L. In the DCa 1.75 group, DCa was increased from 1.5 to 1.75 mmol/L in January 2012. Patients were followed up for 2 years. Changes in parameters within each group were compared by paired t tests or χ^2 tests. There were no significant differences between the two groups at baseline

study, Cox regression analysis revealed that a high level of serum Ca even might be a protective factor for CCVM.

It is possible that the duration of follow-up after increasing the DCa to 1.75 mmol/L was too short to detect changes in TC. In the present study, AoACS, ACM, and CCVM did not increase significantly over 1 year after increasing the DCa. Although previous studies have examined the factors associated with TC and the clinical consequences of TC, the risk factors for the progression of TC in MHD patients are largely unknown. Additionally, the effects of TC progression on the outcomes of MHD patients have not been assessed. An earlier study by Sigrist et al. [33] determined that age, male sex, and serum ALP concentrations were associated with progressive calcification in patients with CKD4–5. Kim et al. [34] found that age, duration of dialysis, and the presence of AoAC were associated with AoAC progression. Several previous studies showed that age [20, 35, 36], sex [20], and duration of dialysis [20, 35] were independent risk factors of coronary artery calcification (CAC), whereas age [20] was the only predictor of AAC in HD patients. Notably, serum iPTH concentration was not a risk factor for CAC [36, 37]. In the present study, we did not find risk factors for TC among several common parameters.

Overall, it is very difficult for many MHD patients in China to achieve the combined targets of serum Ca, P, and iPTH concentrations, according to KDOQI. Although >25 % of patients could get the accommodating target ranges of the KDIGO guidelines, it was confirmed that iPTH levels increased after using DCa 1.5 mmol/L in the present study. Considering the advantages and disadvantages, we think that changing the DCa may be a useful method in China. High DCa was widely used in China until 2003, following widespread adoption of the KDOQI guidelines published in 2002. Overall, 11.4 % of MHD patients in China [38] and 12.3 % of patients in a French cohort [32] are currently using a DCa of 1.75 mmol/L. Although the mortality rate of Chinese MHD patients had not improved over the last few decades, the mortality rate of <8 % in China [14, 39] is still much lower than that in Western countries (20 %) [40]. However, at BFH, the morbidity of SHPT has deteriorated in the last 10 years, after we started using a DCa of 1.5 mmol/L. It is also notable that both the elevated serum P and iPTH concentrations and the increased doses of calcium and $VitD_3$ did decrease in the year after the DCa was increased at BFH. Additionally, there were no significant signs of TC and the mortality rate did not increase. Seyffart et al. [41] proposed that a high DCa could be used for a long period of time. Certainly, the long-term outcomes of a high DCa for MHD need to be followed up, and our research will continue to focus on this issue. With recent advances in technology and

the opening of new markets, we may find better ways to solve the current situation regarding CKD–MBD in China.

Some limitations of this study warrant discussion. First, the present study may be subject to selection bias because the patients in the three centers were not randomly divided into two groups in the prospective component of the study. Second, we did not taken into account variations in laboratory values over time. Third, we did not analyze dietary factors, but these factors may affect biomarkers of CKD–MBD. Fourth, the correlation factors of serum 25(OH)D levels were not analyzed. Nevertheless, our study has some strengths, including a moderately large sample size, a long follow-up period of up to 10 years, and comprehensive laboratory and imaging evaluations. Additionally, to minimize variability, we calculated the mean values for each calendar year.

Conclusion

It is very difficult to control CKD–MBD in Chinese MHD patients because of the scarcity of effective treatments. Our present results suggest that increasing the DCa to 1.75 mmol/L effectively reduces the elevated serum iPTH and P concentrations in MHD patients and that this method shows good short-term safety without increased risk of mortality, CCVD, or TC.

Acknowledgments This project was supported by the Capital Health Research and Development Project (2011-2002-02), the Beijing Municipal Science and Technology Commission Funds (Z121107001012138), and the Beijing Natural Science Foundation (7132091).

References

1. Jadoul M, Albert JM, Akiba T et al (2006) Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. Kidney Int 70:1358–1366
2. Block GA, Klassen PS, Lazarus JM et al (2004) Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol 15:2208–2218
3. Kalantar-Zadeh K, Kuwae N, Regidor DL et al (2006) Survival predictability of time-varying indicators of bone disease in maintenance hemodialysis patients. Kidney Int 70:771–780
4. Tentori F, Blayney MJ, Albert JM et al (2008) Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis 52:519–530
5. Floege J, Kim J, Ireland E et al (2011) Serum iPTH, calcium and phosphate, and the risk of mortality in a European hemodialysis population. Nephrol Dial Transpl 26(6):1948–1955
6. Goodman WG, Goldin J, Kuizon BD et al (2000) Coronary artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med 342:1478–1483
7. Raggi P, Boulay A, Chasan-Taber S et al (2002) Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol 39:695–701
8. National Kidney Foundation (2003) K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis 42(Suppl 3):S1–S202
9. Guideline Working Group, Japanese Society for Dialysis Therapy (2008) Clinical practice guideline for the management of secondary hyperparathyroidism in chronic dialysis patients. Ther Apher Dial 12:514–525
10. Kidney Disease: Improving Global Outcomes (KDIGO) CKD–MBD Work Group (2009) KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of chronic kidney disease–mineral and bone disorder (CKD–MBD). Kidney Int 76(Suppl 113):S1–S130
11. Lezaic V, Pejanovic S, Kostic S et al (2007) Effects of lowering dialysate calcium concentration on mineral metabolism and parathyroid hormone secretion: a multicentric study. Ther Apher Dial 11:121–130
12. Spasovski G, Gelev S, Masin-Spasovska J et al (2007) Improvement of bone and mineral parameters related to adynamic bone disease by diminishing dialysate calcium. Bone 41:698–703
13. Toussaint N, Cooney P, Kerr PG (2006) Review of dialysate calcium concentration in hemodialysis. Hemodial Int 10:326–337
14. Beijing Hemodialysis Record Data System (2011) 2010 Annual report on hemodialysis in Beijing. Chin J Blood Purif 10:19–21
15. Ogawa T, Ishida H, Matsuda N et al (2009) Simple evaluation of aortic arch calcification by chest radiography in hemodialysis patients. Hemodial Int 13:301–306
16. Dialysis Outcomes and Practice Patterns Study (2010) DOPPS annual report. http://www.dopps.org/annualreport/index.htm. Accessed 23 Feb 2013
17. Hwang JC, Chen CA, Wang CT et al (2008) Long-term effect of different dialysate calcium concentrations on parathyroid hormone levels in hemodialysis patients. Ren Fail 30(10):943–949
18. Gabutti L, Bianchi G, Soldini D et al (2009) Haemodialysis consequences of changing bicarbonate and calcium concentrations in haemodialysis fluids. Nephrol Dial Transpl 24(2):973–981
19. Al-Hejaili F, Kortas C, Leitch R et al (2003) Nocturnal but not short hours quotidian hemodialysis requires an elevated dialysate calcium concentration. J Am Soc Nephrol 14:2322–2328
20. Asci G, Ok E, Savas R et al (2011) The link between bone and coronary calcifications in CKD-5 patients on haemodialysis. Nephrol Dial Transpl 26:1010–1015
21. West SL, Swan VJ, Jamal SA (2008) Effects of calcium on cardiovascular events in patients with kidney disease and in a healthy population. Clin J Am Soc Nephrol 5(Suppl 1):S41–S47
22. Yamada K, Fujimoto S, Nishiura R et al (2007) Risk factors of the progression of abdominal aortic calcification in patients on chronic haemodialysis. Nephrol Dial Transpl 22:2032–2037
23. Dabrowski J, Stazka J, Janicka L et al (2004) Calcification of heart valves in hemodialyzed patients and their cardiosurgical correction. Kardiol Pol 61(8):151–155
24. Kim J-K, Moon SJ, Park HC et al (2011) Effects of lowering dialysate calcium concentrations on arterial stiffness in patients undergoing hemodialysis. Korean J Intern Med 26:320–327
25. LeBeouf A, Mac-Way F, Utescu MS et al (2009) Effects of acute variation of dialysate calcium concentrations on arterial stiffness and aortic pressure waveform. Nephrol Dial Transpl 24(2):3788–3794
26. Goodkin DA, Bragg-Gresham JL, Koenig KG et al (2003) Association of comorbid conditions and mortality in hemodialysis patients in Europe, Japan, and the United States: the Dialysis Outcomes and Practice Patterns Study (DOPPS). J Am Soc Nephrol 10:3270–3277

27. Hou F, Jiang J, Chen J et al (2012) China collaborative study on dialysis: a multi-center cohort study on cardiovascular diseases in patients on maintenance dialysis. BMC Nephrol 13:94–102
28. Floege J, Kim J, Ireland E et al (2011) Serum iPTH, calcium and phosphate, and the risk of mortality in a European haemodialysis population. Nephrol Dial Transpl 26:1948–1955
29. Joosen IA, Schiphof F, Versteylen MO et al (2012) Relation between mild to moderate chronic kidney disease and coronary artery disease determined with coronary CT angiography. PLoS One 7(10):e47267
30. Lee MJ, Shin DH, Kim SJ et al (2012) Progression of aortic arch calcification over 1 year is an independent predictor of mortality in incident peritoneal dialysis patients. PLoS One 7(11):e48793
31. Markaki A, Kyriazis J, Stylianou K et al (2012) The role of serum magnesium and calcium on the association between adiponectin levels and all-cause mortality in end-stage renal disease patients. PLoS One 7(12):e52350
32. Jean G, Lataillade D, Genet L et al (2013) Higher dialysate calcium is not associated with mortality in hemodialysis patients: results from the French ARNOS study [in French]. Nephrol Ther 9:103–107
33. Sigrist MK, Taal MW, Bungay P et al (2007) Progressive vascular calcification over 2 years is associated with arterial stiffening and increased mortality in patients with stages 4 and 5 chronic kidney disease. Clin J Am Soc Nephrol 2:1241–1248
34. Kim HG, Song SW, Kim TY et al (2011) Risk factors for progression of aortic arch calcification in patients on maintenance hemodialysis and peritoneal dialysis. Hemodial Int 15:460–467
35. Pencak P, Czerwieńska B, Ficek R et al (2013) Calcification of coronary arteries and abdominal aorta in relation to traditional and novel risk factors of atherosclerosis in hemodialysis patients. BMC Nephrol 14:10–18
36. Coen G, Pierantozzi A, Spizzichino D et al (2010) Risk factors of one year increment of coronary calcifications and survival in hemodialysis patients. BMC Nephrol 11:10–18
37. Dukkipati R, Kovesdy CP, Kim Y et al (2010) Association of relatively low serum parathyroid hormone with malnutrition–inflammation complex and survival in maintenance hemodialysis patients. J Ren Nutr 20(4):243–254
38. Kong X, Zhang L, Zhang L et al (2012) Mineral and bone disorder in Chinese dialysis patients: a multicenter study. BMC Nephrol 13:116–123
39. Beijing Dialysis and Transplantation Registration Group (2001) The report about the registration of dialysis and transplantation in Beijing 1999. Chin J Nephrol 17(2):79–82
40. US Renal Data System (2012) Atlas of ESRD 2010. http://www.usrds.org/2012/view/v2_05.aspx. Accessed 23 Feb 2013
41. Seyffart G, Schulz T, Stiller S (2009) Use of two calcium concentrations in hemodialysis—report of a 20-year clinical experience. Clin Nephrol 71(3):296–305