Effect of lanthanum carbonate on coronary artery calcification and bone mineral density in maintenance hemodialysis patients with diabetes complicated with adynamic bone disease
A prospective pilot study
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Abstract
Background: The incidence of adynamic bone disease (ABD) is increasing. Coronary artery calcification (CAC) may be severe in patients with ABD on maintenance hemodialysis (MHD). The aim of this study was to evaluate the effect of lanthanum carbonate (LC) on CAC and bone mineral density (BMD) in MHD patients with diabetes complicated with ABD.

Methods: A total of 92 MHD cases were divided into the calcium carbonate (CC) and LC groups. Primary outcome measure was the changes in the degree of CAC score (CACS) and BMD in forearm from baseline to 12 months. Secondary outcomes included changes in serum markers of CKD-MBD and side-effects.

Results: After 12 months, serum levels of calcium, phosphate, FGF23, and MGP were decreased significantly, while iPTH, b-ALP, PINP and β-CTX, and CACS and BMD were increased in LC group compared with those at baseline (P < .05). After 12 months treatment, serum levels of calcium, phosphate, FGF23, and CACS were lowered, while MGP, b-ALP, PINP, β-CTX, BMD, and iPTH were higher in LC group than in CC group. Pearson correlation analyses revealed that BMD in forearm was positively correlated with iPTH and MGP, while negatively with CACS. CACS was positively correlated with serum calcium, phosphate and FGF23, while negatively with serum MGP. Multivariate linear regression revealed changes of BMD in forearm and femoral neck and changes of serum FGF23 were independent influential factors for changes of CACS (P < .05).

Conclusions: In MHD patients with diabetes complicated with ABD, lanthanum carbonate could delay CAC progress, and improve bone transport and bone density.

Abbreviations: β-CTX = C-terminal telopeptide of type I collagen, ABD = adynamic bone disease, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, b-ALP = bone alkaline phosphate, BMD = bone mineral density, BMP-2 = bone morphogenetic protein 2, BUN = blood urea nitrogen, CAC = coronary artery calcification, CACS = coronary artery calcification score, CC = calcium carbonate, COB = calcium channel blocker, CKD = chronic kidney disease, CKD-MBD = chronic kidney disease-mineral and bone disorder, DXA = dual-energy x-ray absorptiometry, FGF23 = fibroblast growth factor, HbA1C = hemoglobin A1c, HCO3− = bicarbonate ion, hsCRP = high-sensitive C-reactive protein, iPTH = intact parathyroid hormone, Kt/V = urea clearance index, LC = lanthanum carbonate, LDL-C = low-density lipoprotein cholesterol, MGP = matrix Gla protein, MHD = maintenance hemodialysis, MSCT = multislice spiral computed tomography, PINP = procollagen I N-terminal peptide, VC = vascular calcification.

Keywords: bone density, bone diseases, coronary artery calcification, lanthanum, metabolic, renal dialysis

1. Introduction
The incidence of cardiovascular calcification (namely vascular and valvular calcification) in patients with chronic kidney disease (CKD) is significantly higher than that in the general population. Moreover, calcification of the blood vessels develops faster in patients with CKD compared with the general population. Cardiovascular calcification in CKD patients is one of the strongest predictors of CKD-cardiovascular disease and all-cause mortality. Elevated serum calcium, phosphate, calcium-phosphate product, fibroblast growth factor (FGF23), intact parathyroid hormone (iPTH), and abnormal vitamin D metabolism are important factors causing and accelerating vascular calcification (VC).

Adynamic bone disease (ABD) is a variety of renal osteodystrophy and histologically characterized by a comprehensive decrease in osteocyte activity. ABD patients show a decreased number of osteoclasts and osteoblasts, reduced bone formation
rate, as well as decreased bone mineralization and collagen synthesis, but generally have normal osteoid gap. Imaging manifestations of ABD include osteopenia, bone deformation, and osteoporosis. In recent years, the incidence of ABD gradually rose by about 21% to 35%.[23] Factors that cause ABD include short hemodialysis time, advanced age, malnutrition, diabetes, and inappropriate use of calcium-based phosphate binders and active vitamin D. Prevalence of VC in maintenance hemodialysis (MHD) patients with ABD has significantly increased,[3] however, currently there is no approved treatment to reverse VC, and even renal transplantation cannot prevent VC progression.

High serum phosphate is considered to be an important factor in inducing VC, and an increase of serum phosphate levels by 1 mg/dL results in 18% increased risk of death in CKD patients.[4] Methods for controlling high serum phosphate include limited dietary phosphate, adequate hemodialysis, and phosphate-binding agents. The most common and current types of phosphate-binding agents include calcium-based phosphate binders, aluminum-based phosphate binders, and non-calcium-non-aluminum-based phosphate binders. Calcium-based phosphate binders are inexpensive, but are prone to cause hypercalcemia and VC. Hypercalcemia is a contributing factor in the progression of VC in patients with CKD.[5] Aluminum-based phosphate binders have long been used and are effective in reducing phosphate levels. But these can be used only for short term (within 2–4 weeks) as long-term use causes aluminum-related bone disease and encephalopathy. Non-calcium-non-aluminum-based phosphate binders include lanthanum carbonate (LC) and sevelamer, and can effectively reduce serum phosphate without causing elevated serum calcium. These are best suited for patients with VC and/or ABD.

At present, there is no study that described the effect of LC on coronary artery calcification (CAC) and bone mineral density (BMD) in ABD patients. CAC predicts long-term cardiovascular events in hemodialysis.[6] Hence, this study aimed to investigate the effects of LC on CAC and BMD in diabetic MHD patients with ABD.

2. Patients and methods

2.1. Subjects

Ninety-two patients who met the inclusion criteria between January 1 and December 31, 2016 from Beijing Chaoyang Hospital Dialysis Center in China were recruited. The inclusion criteria were age >20 years and <65 years; patients primarily with diabetic nephropathy (DM was diagnosed according to the WHO 1990 guideline) and whose glycemic control has been optimized and stable for at least 3 months; and hemodialysis (HD) treatment for at least 6 months. Bone biopsy is the gold standard for diagnosing renal osteodystrophy, but it is invasive. In this study, we did not perform bone biopsy, but ABD was diagnosed by using clinical criteria (iPTH <150 pg/mL and bone alkaline phosphate, b-ALP <20 ng/mL).[7] The exclusion criteria were significant gastrointestinal disorders; elevated serum transaminases (ALT or AST, greater than 3 times the normal upper limit); hypocalcemia (adjusted serum calcium level <2.1 mmol/L); poorly controlled diabetes or hypertension; taking glucocorticoids, cinacalcet, or active vitamin D; parathyroidectomy; cancer; subjects receiving extended hours or night HD; live renal transplantation within 6 months of enrollment; or life expectancy <3 months.

Written informed consent was obtained from all subjects. The study protocol was approved by the Institutional Ethics Committee of the Beijing Chaoyang Hospital (Ethics number: 2016–10–18-6; Drug clinical test number: 2009L10130). The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. The privacy right of human subjects was observed.

2.2. Study design

Patients were randomized at a ratio of 1:1 to receive either LC (Fosrenol chewable 250- and 500-mg tablets, China) or calcium carbonate (CC, Xiedali 500-mg tablets, 200 mg calcium/tablet, China) 3 times daily orally, with meals, for 12 months. During screening, patients were classified according to age, sex, HbA1C (hemoglobin A1c) and coronary artery calcification score (CACS). For randomization, dynamic allocation with CACS as regulators was carried out using SAS 9.3 (SAS Institute, Cary, NY). After screening, subjects received a 2-week washout, in which all phosphate binders were withheld. Due to the size, appearance, and taste of the tablets, the study was open-label, and investigators were not blinded to treatment allocation and patient demographics.

After randomization, subjects were initially administered with either LC or CC. Patients in the LC group received LC (Fosrenol chewable 250- and 500-mg tablets, China), with a starting dose of 250 mg/time, while patients in the CC group received CC (Xiedali 500-mg tablets, China) at 375 mg/time. Both LC and CC were given 3 times/d and chewed during the meals. The doses were adjusted every 2 weeks for the first 6 weeks, and the doses of LC and CC were increased by 250 mg and 375 mg each time, respectively. The total amount of CC did not exceed 3750 mg/d. The doses were adjusted to make the levels of serum phosphate <1.78 mmol/L within 6 weeks.[8] This study started in January 2016 and ended in December 2016, with an observation period of 12 months. No subjects were administered with cinacalcet or (aluminum- and magnesium-based) phosphate binders. Patients showed good compliance and no one withdrew from this study. There were no drug-related side effects and hemodialysis-related acute serious complications.

Hemodialysis was performed using polysulfone hollow-fiber dialyzers, 3 times/week (4 h/d) at 7 am to 11 am every day. No patients had hemodiafiltration treatment, but used arteriovenous fistula as their vascular pathway. The dialysate composition was: Na+, 138 mmol/L; K+, 2.5 mmol/L; Ca2+, 1.25 mmol/L; Mg2+, 0.5 mmol/L; Cl−, 109 mmol/L; CH3COO−, 3.0 mmol/L; citrate, 0 mmol/L; and HCO3−, 31 mmol/L. All MHD patients had the same dialysate and it was not changed during the study period. The blood flow rate was 250 mL/min and dialysate flow rate was 500 mL/min. Residual urine volume of the subjects was <100 mL/d. Monthly detection of dialysis water met the standards. All patients were clinically assessed monthly to achieve dry weight, and hypertensive patients reached a blood pressure of <140/90 mm Hg before hemodialysis by adjusting dry weight and antihypertensive drugs. Intravenous iron, erythropoetin, and insulin were administered to make hemoglobin (11–12 g/L) and glycosylated hemoglobin (<7.5%) reach the standards.

2.3. Outcome measures

The primary outcome measures were changes in the degree of CAC as determined by multislice spiral computed tomography

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(MSCT) and T score of the forearm BMD as determined by dual-energy x-ray absorptiometry (DXA) from baseline to 12 months. Other prespecified secondary outcomes include changes in serum markers of chronic kidney disease-mineral and bone disorder (CKD-MBD) and side-effects of medications.

2.4. Computed tomography

2.4.1. Coronary artery calcification score (CACS). Quantitative detection of CAC was performed using a MSCT scanner (Siemens Somatom Definition AS, Germany) on the first and the last day of the study,[12] and was operated by the same experienced physician without knowing the grouping of patients. Patients were instructed to hold their breath, and the flat scan images were then captured at 70% R-R interval of the patient’s cardiac cycle to make sure the images were mainly obtained during the diastolic period with a layer thickness of 2.5 mm. Approximately 30 to 35 tomographic images were obtained from the scan range of ascending aorta to apex, and these were used for diagnostic analysis after noise reduction and pseudo-shadow processing. The calcification of coronary arteries was assessed by Agaston scoring[10,11] and CACS analysis was performed with the Smartscore automatic analysis software. A CT value of 130 HU as the threshold and the area of 0.5 mm² for calcified lesion were taken to calculate the area of CAC lesions, which was then multiplied by a fixed coefficient (determined by maximum pixel density). Each tomographic image was independently analyzed, and the total score of CACS was obtained by adding the calcification scores of all the tomographic images.

2.5. Measurement of BMD

BMD measurement was operated by the same experienced physician who did not know the patients’ grouping. The lumbar vertebrae (L2-4), femoral neck, and forearm BMD were measured using a QDR-4500 fan beam dual-energy x-ray bone density instrument (Hologic Company, America). According to the diagnostic criteria for osteoporosis promulgated by the World Health Organization in 1994,[4,12] BMD T-score of +2.5 s to −1.0 s (not including −1.0 s), −1.0 s to −2.5 s, and <−2.5 s were regarded as normal bone mass, bone loss, and osteoporosis, respectively. The BMD T-score referred to the individual BMD when compared with the average bone density that was measured with the same race and gender of young people, and s represented the standard deviation.

2.6. Laboratory methods

Baseline serum was taken prior to hemodialysis from all patients during the start of the randomized controlled trial. Blood urea nitrogen (BUN), ura clearance index (Kt/V), hemoglobin, albumin (HbA1C), bicarbonate ion (HCO3⁻), low-density lipoprotein cholesterol (LDL-C), homocysteine, calcium, phosphate, FGF23, high-sensitive C-reactive protein (hsCRP), iPTH, b-ALP, procollagen 1 N-terminal peptide (PINP), C-terminal telopeptide of type I collagen (β-CTX), and matrix Gla protein (MGP) were measured. After a 2-week washout phase involving the discontinuation of all phosphate binders, subsequent serum samples were taken at 2, 4, and 6 weeks after the start of the medication for calcium and phosphate assessment. After which, monthly blood tests including BUN, hemoglobin, albumin, HbA1C, HCO3⁻, homocysteine, hsCRP, iPTH, phosphate, and calcium were performed according to the hospital protocol.

At 12 months, serum was taken prior to hemodialysis to measure FGF23, b-ALP, PINP, β-CTX, and MGP.

Total serum calcium was adjusted according to the albumin level using the following conversion formula: corrected calcium = serum total calcium + 0.025 × (40-albumin) mmol/L. Blood analysis was carried out using an automatic biochemical analyzer (ADVIA 2400, Siemens, Germany) and iPTH was measured using a direct chemiluminescence assay kit (Siemens, Germany). FGF23 and MGP were determined by enzyme-linked immunosorbent assay kit (Bio-Swamp Company, China). Serum b-ALP was measured using an enzyme immunoassay (ELA) kit (Quidel Company, America). PINP and β-CTX were measured using electrochemical luminescence immunoassay kit (Roche Company, Swiss). The kits were used according to the manufacturer’s instructions.

2.7. Safety

Safety was evaluated by recording the adverse events and laboratory assessments.

2.8. Statistical analysis

The 1 sample Kolmogorov-Smirnov test was used for normality test. Continuous data were presented as mean ± standard deviation. The average values of the 2 groups were compared using the t test for 2 independent samples. A paired t-test was used for comparing before and after treatment in each group. Categorical data were expressed as rates, and the 2 groups were compared with the χ² test. Correlation analysis between 2 indexes was performed using the Pearson correlation test. Multivariate correlation was analyzed by multiple linear regression analysis. P < .05 was considered to be statistically significant. Statistical analysis was performed using SPSS 17.0 (IBM, Armonk, NY).

3. Results

3.1. Baseline characteristics of the subjects

Baseline characteristics of the study participants are summarized in Table 1. Ninety-two patients were randomized in this study: 46 patients were allocated to LC group and rest in the CC group. No patients were withdrawn from this study. No significant differences were observed for age, gender, dialysis duration, DM duration, concomitant drugs, Kt/V, blood pressure, hemoglobin, homocysteine, FBG, HbA1C, HCO3⁻, phosphate, corrected calcium, iPTH, b-ALP, albumin, LDL-C, hsCRP, PINP, β-CTX, FGF23, MGP, CACS, and BMD in lumbar vertebra, femoral neck, and forearm (all P > .05).

3.2. Changes in CAC score (CACS) and BMD during the study period

Changes in CACS and BMD in all patients are summarized in Table 2. Compared with before treatment, the BMD T-score and CACs of LC group were significantly increased after 12 months, and the BMD T-score of CC group was significantly decreased and the CACS was significantly increased (P < .05). After 12 months, the BMD T-scores in lumbar vertebra (P < .001), femoral (P < .001), and forearm neck (P < .001) in the LC group were significantly higher than those in the CC group, while there was a significant decrease in the CACS of the LC group compared with the CC group (P < .001).
3.3. Changes in biochemical markers during the study period

The key biochemical markers studied in all patients are summarized in Table 2. No significant differences were observed for Kt/V, hemoglobin, homocysteine, blood pressure, FBG, HbA1C, HCO₃⁻, albumin, LDL-C, and hsCRP at baseline and at 12 months. After 12 months of treatment, serum levels of phosphate, FGF23, and MGP were decreased significantly, while serum levels of iPTH, b-ALP, PINP, and β-CTX were increased significantly in the LC group compared with baseline ($P < .05$), but the corrected serum calcium levels showed no change. After 12 months, the serum levels of phosphate, iPTH, b-ALP, PINP, β-CTX, and MGP were decreased significantly and serum levels of corrected calcium were increased significantly in the CC group as compared with those at baseline ($P < .05$), but no change was observed for FGF23. After 12 months of treatment, serum levels of calcium ($P < .001$), phosphate ($P < .001$), and FGF23 ($P < .001$) were lower, while the iPTH ($P < .001$), b-ALP ($P < .001$), PINP ($P < .001$), β-CTX ($P < .001$), and MGP ($P < .001$) were higher in the LC group than in the CC group.

3.4. Correlation analyses

Pearson correlation analysis showed a significant positive correlation between BMD T-score in forearm and iPTH ($r = 0.363$, $P = .02$) and MGP ($r = 0.389$, $P = .01$), while negative correlation with CACS ($r = -0.79$, $P < .001$), and no significant correlation with other indexes. CACS was negatively correlated with BMD T-scores in lumbar vertebra ($r = -0.58$, $P < .001$), femoral neck ($r = -0.64$, $P < .001$), forearm ($r = -0.79$, $P < .001$), and MGP ($r = -0.29$, $P < .001$), while positively correlated with FGF23 ($r = 0.54$, $P < .001$), serum calcium ($r = 0.24$, $P < .001$), and serum phosphate ($r = 0.47$, $P < .001$). No significant correlation was observed with other indexes.

Multiple linear regression was performed using changes of CACS as dependent variable, changes of serum calcium, serum phosphate, iPTH, b-ALP, PINP, β-CTX, FGF23, MGP, and BMD T-scores in lumbar vertebrae, femoral neck, and forearm as independent variables. The variables that were eventually included in the regression equation were changes of T-scores in forearm (B = -134.37, $P < .001$) and femoral neck (B = -72.21, $P < .001$), and changes of FGF23 (B = 55.01, $P < .001$).
Table 2
Indexes of before and after treatment in LC group and CC group.

| Group          | Kt/V | SBP, mm Hg | DBP, mm Hg | Hemoglobin, g/L | Albumin, g/L | HbA1C, % |
|----------------|------|------------|------------|----------------|--------------|----------|
| LC group baseline | 1.241±0.021 | 133.624±24.511 | 73.172±10.001 | 119.831±5.512 | 36.269±1.291 | 7.281±0.153 |
| (n=46) 12 mo     | 1.231±0.022 | 137.331±13.041 | 76.931±9.502  | 117.522±4.021 | 36.934±1.142 | 7.352±0.142 |
| P value          | .642      | .472        | .142        | .091          | .772         | .281     |
| CC group baseline | 1.231±0.012 | 135.327±12.361 | 76.671±9.372  | 118.391±4.781 | 36.532±1.391 | 7.222±0.633 |
| (n=46) 12 mo     | 1.222±0.021 | 139.222±10.201 | 78.771±6.852  | 117.512±4.412 | 36.369±1.261 | 7.352±0.142 |
| P value          | .241      | .182        | .331        | .552          | .583         | .251     |

4. Discussion

Our study revealed that the application of LC in diabetic MHD patients with ABD could effectively reduce serum phosphate and FGF23 without causing elevation of serum calcium compared with CC. In addition, LC increased the serum levels of iPTH and b-ALP, improved bone metabolic index, increased BMD, reduced the increase of CACS, and delayed CAC progression.

CKD-MBD involves abnormal phosphate metabolism, abnormalities of bone transformation, mineralization and bone mass, and calcification of blood vessels or other soft tissues. Bone biopsy clarifies the status of bone transformation, but its clinical application is very limited due to its invasive nature. Biochemical indexes of bone transformation reflect bone formation status at certain time point. b-ALP is produced by osteoblasts and acts as an indicator for osteoblast activity and can accurately reflect the status of bone formation. PINP is a marker of bone formation, accounting for 90% of bone matrix protein. It is an extension peptide of procollagen I amino terminal, and is synthesized by osteoblasts. Elevated PINP levels indicate active bone transformation. Serum β-CTX is a bone resorption marker and a β-collagen degradation product. It is the most valuable indicator for evaluating osteoclast activity and bone resorption. PINP and β-CTX in hemodialysis cannot be removed, and they are reliable indicators of bone metabolism in MHD patients. b-ALP is now recommended to assess bone turnover in hemodialysis patients,[113] and is associated with mortality and fracture rate in CKD subjects. When used in combination with PTH, b-ALP as a bone formation marker correlates well with bone biopsy histomorphometry in predicting ABD.[114] According to the K/DOQI guidelines,[18] iPTH is defined as the target of CKD5 phase as 150 to 300 pg/mL based on iPTH as a predictor of bone transition status. Therefore, in this study b-ALP <20 ng/mL and iPTH <150 pg/mL were used to diagnose ABD. BMD was determined using DXA, which is the gold standard for the diagnosis of osteoporosis. BMD cannot predict CKD-MBD status and mineralization degree, but can determine the abnormal bone mass. Blomquist et al[115] also demonstrated that DXA results showed acceptable diagnostic sensitivity and specificity for low bone volume by histology and can be used for diagnosis of osteopenia and osteoporosis in patients with CKD-5D. Thus, in our study, DXA was used to detect changes in bone mass in MHD patients, and b-ALP, PINP, and β-CTX were used as bone biochemical markers.

In recent years, the incidence of ABD has gradually increased year by year. Malluche et al[146] investigated bone biopsies of 630 cases with MHD and the results showed that 58% of patients with low-transformation and only 3% of patients with normal bone mineralization, while 73% of patients with low bone mass were associated with low transportation status. Selected cases in our study were <65 years old and had well nutritional status in MHD patients with diabetes (without the application of active
vitamin D treatment, calcium ion concentration in dialysis solution was 1.25 mmol/L. Lack of insulin during diabetes inhibits the secretion of iPTH, and low PTH is considered to be a risk factor for ABD. Due to excessive inhibition of PTH secretion, the rates of bone formation and resorption were decreased, the ability to buffer calcium and handle additional calcium load decreased. These suggested decreased bone reshaping ability and easy occurrence of ectopic calcification.[3]

Shigematsu et al[17] showed that the content of lanthanum in bone tissue was changed from 54.1 μg/kg to 4270.9 μg/kg after using LC in MHD patients for 3 years and bone biopsy presented normalization of ABD bone transportation during the first year of LC treatment. Yajima et al[18] applied LC to treat MHD patients with ABD, and the results revealed a significant decrease in serum phosphate, but no significant change in iPTH, and normalization of bone transportation, significant increase of bone unit mineralization on periosteal surface and endocortical surface. The study also suggested that LC could increase the cortical stability of MHD patients with ABD to reduce the occurrence of fractures. Our study showed that bone formation and resorption indexes in the LC group were significantly increased and bone transportation and BMD were significantly improved after 12 months treatment compared with the CC group.

Intimal calcification and medial calcification of vessels in VC are independent predictors of cardiovascular events and all-cause mortality in MHD patients. MSC cannot differentiate whether VC is intimal or medial, but it can quantitatively assess the degree of VC and is considered as the gold standard to compare the impact of different treatment methods on VC. In adult dialysis patients, 51% to 93% have cardiovascular calcification, especially CKD patients who show rapid progression of cardiovascular calcification. The intensity and severity of calcification and preexisting atherosclerosis and CKD-MBD are closely related. Animal experiments have shown that LC delays the progression of vascular smooth muscle cells calcification of high Pi-induction, modulating PTH synthesis, and secretion. Ciceri et al[21] found that lanthanum could strengthen the calcimimetic calindol in delaying the progression of high phosphate-induced VC in vitro. Lanthanum can also promote MGP carboxylation, reduce the expression of Na-P synergetic vector Pit-1 and the expression of aortic type I collagen (only the presence of calcified vascular medial).[22,23] Nevertheless, few of these effects of lanthanum have been carried out in clinical studies. Kalil et al[24] observed the treatment of LC and CC in MHD patients for 12 months, and compared the changes in CAC and endothelial cell function. Results showed no changes in endothelial cell function and hsCRP of patients in the 2 groups before and after treatment. However, compared with before treatment, the CACS in LC group was decreased, while that in the CC group was increased, indicating slow progression of CAC in the LC group. Wada and Wada[25] showed that the effects of LC was better than CC in postponing the progression of aortic calcification after 12 months of treatment in MHD patients with T2DM; but in the subgroup analysis, this effect was only observed in patients with light aortic calcification at baseline, while there was no significant difference between LC and CC in patients with severe aortic calcification at baseline. Nevertheless, there are some limitations in the study by Wada and Wada.[25,26] the authors did not indicate at baseline and 12 months whether there was significant difference in other factors influencing the progression of aortic calcification between light and severe aortic calcification patients; the mean age of the enrolled patients was 65 years; because the effect of vitamin D receptor agonist on promoting vascular calcification is dose-dependent, the authors did not mention the ratio of vitamin D receptor agonist at baseline and dose change during the study; phosphate binder affects blood FGF23 levels, and FGF23 can promote vascular calcification, but the authors did not monitor the FGF23 levels; combination of b-ALP and iPTH was not applied to evaluate bone metabolism status; and the authors assessed the aortic calcification, and the aortic calcification was closely related to CAC. Despite the fact that our study has some limitations, we tried to overcome those of the original study by Wada and Wada.[25] Our study also confirmed significant reduction in the increased CACS in LC group compared with the CC group.

In our study, CACS was positively correlated with FGF23, serum calcium, and serum phosphate. Compared with CC, LC significantly reduced serum phosphate and FGF23 without elevating the levels of serum calcium, and multiple linear regressions showed that the FGF23 changes were an independent influential factor of CACS changes. High serum phosphate is one of the initiators of VC and can induce vascular smooth muscle cells to osteoblast-like cell phenotypes and vascular smooth muscle cell apoptosis, and promote vascular smooth muscle cells to release matrix vesicles, directly leading to the occurrence of VC. In addition, high serum phosphate caused elevation in FGF23 levels. FGF23 levels in MHD patients were 1000 times higher than in the normal population and elevated serum FGF23 is an independent predictor of VC, incidence of cardiovascular events, and mortality of MHD patients, and these effects are independent of serum calcium and phosphate levels.[26] Chang et al[27] also found that LC could decrease serum FGF23. In addition to the direct role of lanthanum, the mechanism of LC delaying CAC progression is also related with effective control of hyperphosphatemia and lowering blood FGF23 levels but without elevating the levels of serum calcium.

Studies in the general population found that osteoporosis and VC are closely related, and regardless of age, they reinforce each other and are affected by some common factors.[28] Our study also suggests that CACS was significantly negatively correlated with BMD T-scores in lumbar vertebral, femoral neck, and forearm. Multiple linear regression analysis showed that changes of T-scores in femoral neck and forearm are independent risk factors of changes in CACS.

VC and osteoporosis share a common pathogenesis, and MGP reduction is one of the important mechanisms. MGP is a vitamin K-dependent circulatory protein that is mainly distributed in the cartilage, bone marrow, and arterial wall. It is synthesized by vascular endothelial cells, macrophages, and smooth muscle cells, and modified by vitamin K-dependent carboxylase which changes from γ-glutamate residue to active MGP. This in turn forms a complex with calcium to prevent calcium deposition, thereby inhibiting VC, particularly the medial calcification. In normal blood vessels, MGP-Gla and MGP-Glu are expressed, and mainly MGP-Gla is expressed; but MGP-Glu is mainly expressed in dialysis patients. Vascular smooth muscle cell apoptosis and dysfunction caused by dialysis reduce γ-glutamate carboxylase activity and inhibit MGP activation, reducing calcium regulation ability of MGP to promote the occurrence of VC. MGP can bind to the bone morphogenetic protein 2 (BMP-2) and blocks the occurrence of BMP-2 by promoting VC. MGP also participates in bone metabolism, and the low combination ability of MGP-Glu with mineral is considered to be a risk factor for decreased BMD. Studies have shown that the distal BMD of radius is more closely related to VC than BMD in other parts.[19,29] Neradova et al[30] performed a study in vitro
and found that while vitamin K2 and phosphate coexist in solution, LC cannot significantly bind vitamin K2 but CC can. This suggests that vitamin K deficiency limits the activation of the vascular tissue mineralization inhibitor MGP-Gla, and phosphate binders could potentially limit the bioavailability of vitamin K2. In our study, the BMD T-score in forearm was positively correlated with MGP and iPTH, which may be related to the expression of MGP in osteoblasts induced by PTH and involved in the bone mineralization inhibition process by PTH. MGP and BMD of LC group were significantly higher than those of the CC group after 12 months of treatment, CACS was significantly lower than that of the CC group, and BMD T-score in forearm was significantly positively and CACS were significantly negatively correlated with MGP. Nevertheless, in the multivariate linear regression analysis with CACS changes as a dependent variable, MGP changes were not independent variable of CACS changes, and may be related to the total MGP in the cycle detected in this study, rather than the carboxylated MGP in the cycle or in the tissue, or may be related to the short observation time and less cases.

The study has few limitations, which are as follows: A small number of cases were investigated in our study, and it was a single-center study. The study duration was short. In the future, a long-term study with longer duration time of 24 to 36 months is warranted. Blinding method could not be applied due to the different shape and taste of the tablets. Bone biopsy was not performed.

5. Conclusion
In summary, LC can delay CAC progression in MHD patients with diabetes complicated with ABD, improve bone transportation, and increase BMD. This may be related to the improvement of calcium, phosphate, and FGF23 levels, MGP metabolism, and the direct effect of lanthanum.

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