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ORIGINAL ARTICLE

Effects of lanthanum carbonate on bone markers and bone mineral density in incident hemodialysis patients

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Abstract

Introduction Recent clinical studies demonstrated the favorable effects of calcium-free phosphate binders on mortality and vascular calcification in hemodialysis (HD) patients. The aim of the present study was to investigate the effects of a calcium-free phosphate binder, lanthanum carbonate (LC), on bone metabolic markers and bone mineral density (BMD), compared with those of calcium carbonate (CC), in subjects new to HD.

Materials and Methods The present study included 65 subjects from our previous randomized controlled trial (LC group, $N=31$; CC group, $N=34$). We investigated the effects of LC on serum intact parathyroid hormone (iPTH), osteocalcin (OC), bone-specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase 5b (TRACP-5b), sclerostin levels, and BMD, compared with those of CC in patients new to HD at baseline and at 12 and 18 months.

Results Serum OC levels at 18 months were significantly higher in the LC group than in the CC group. During the study period, serum BAP and TRACP-5b and iPTH levels tended to be higher in the LC group than in the CC group. At 18 months, the percentage of low bone turnover, based on a serum BAP cutoff value, was significantly lower in the LC group than in the CC group. There were no significant differences in the lumbar and femoral BMD between the two groups.

Conclusions The results of the present study suggest that LC has potential in preventing low bone turnover, in comparison to CC, in patients new to HD.

Keywords Lanthanum carbonate · Bone metabolic marker · Low bone turnover · Non-calcium-containing phosphate binder · Initiation of hemodialysis

Introduction

Bone fracture in patients with chronic kidney disease (CKD) is more prevalent compared with the general population [1, 2] and is associated with hospitalization and mortality [3]. Therefore, attempts to prevent bone fracture are important for patients with CKD. Hyperphosphatemia is one of the main therapeutic targets for CKD and mineral bone disorder (CKD–MBD), because it can result in secondary hyperparathyroidism [4] and lead to critical bone abnormalities.

Nowadays, various phosphate binders are available in the clinical setting and are broadly classified into two types, including non-calcium containing and calcium containing. Because the former seems to have more favorable effects on the progression of vascular calcification and mortality, compared with those of latter [5], the Kidney Disease: Improving Global Outcomes (KDIGO) clinical guideline updated in 2017 suggests restriction of the dose of calcium-based phosphate binders [6]. Lanthanum carbonate (LC) is one of non-calcium-containing phosphate binders that had been reported to prevent the progression of vascular calcification, compared with the effects of calcium-containing phosphate binders [7, 8]. In fact, several clinical studies have examined the effects of LC on bone metabolism, in comparison with those of calcium-containing phosphate binders [9–13]; however, these were limited by the relatively small sample size, short observational period, and the inclusion of participants who were all under maintenance hemodialysis (HD). Therefore, the effects of LC on bone mineral metabolism particularly in patients who have been newly initiated HD, were not fully elucidated. As a previous study demonstrated that changes in bone mineral metabolism during the first

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6 months of HD initiation were associated with mortality [14], newly initiated HD patients should be treated with a phosphate binder that has favorable effects on CKD–MBD.

Considering these results, we believe that it is crucial to investigate the effect of LC on bone metabolism during the early period after initiating HD. The aim of the present study was to examine the effect of LC on markers of bone metabolism and bone mineral density (BMD) compared with that of calcium carbonate (CC), in patients new to HD.

Materials and methods

Study design and data collection

The present study was a post hoc analysis from our previous randomized controlled trial [7]. In brief, 105 subjects who were started on HD at five institutions between December 2012 and June 2014 were enrolled and randomly divided into the LC and CC groups. The trial focused on the effect of LC on coronary artery calcification (CAC), compared with that of CC. The protocols were approved by the appropriate institutional review committee (no. 230019) and performed in accordance with the recommendations of the Declaration of Helsinki for Biomedical Research involving human subjects.

Patients in each group were prescribed LC or CC at a dose that keeps serum phosphate levels between 3.5 and 6.0 mg/dL according to the Japanese Society for Dialysis Therapy guidelines [15]. When serum phosphate levels could not be maintained within the target range by either one of the drugs or patients could not take a higher dose of these drugs, only sevelamer or bixalomer use was permitted. Although the administration of cinacalcet and vitamin D agent was not permitted, vitamin D agent could be used only in case of severe hypocalcemia. Attending physicians could modify their medication other than phosphate binder, vitamin D agents, and cinacalcet freely.

The current study excluded patients whose blood samples were not available for measurement of serum bone metabolic markers. From the previous study patients, 65 subjects were included in the present study (LC group, $N=31$; CC group, $N=34$). The main outcomes included changes in bone metabolic markers and BMD during the study period. We evaluated the serum levels of osteocalcin (OC), bone-specific alkaline phosphatase (BAP), tartrate-resistant acid phosphatase isoform type 5b (TRACP-5b), and sclerostin at baseline and at 12 and 18 months. At the same time of the measurement of the bone metabolic markers, assessment of BMD at the lumbar spines and femoral neck was also performed. The other laboratory data and medical history of the patients were previously collected [7].

We estimated the proportion of subjects with low bone turnover according to the cutoff values of OC (< 36.2 ng/mL), BAP (< 12.9 μg/L), and TRACP-5b (< 460 mU/dL) that were reported by previous diagnostic accuracy studies on the association between bone markers and biopsy-proven low bone turnover [16, 17].

Sample and BMD measurements

We collected blood samples at baseline, 12 months, and 18 months after starting LC. The samples were stored at − 80 °C in the freezer. The assays used for measurement were the immunoradiometric assay (BGP-IRMA; LSI Medience Corporation, Tokyo, Japan) for serum OC; chemiluminescent enzyme immunoassay (Access Ostase; Beckman Coulter, Tokyo, Japan) for serum BAP; enzyme immunoassay (Osteolinks TRAP-5b; Nittobo Medical, Fukushima, Japan) for serum TRACP-5b; and enzyme-linked immunosorbent assay (Sclerostin ELISA; Biomedica Medizinprodukte, Vienna, Austria) for serum sclerostin.

The BMD at the lumbar spines (mean of L2–L4) and at the femoral neck was measured by dual energy X-ray absorptiometry (Discovery A, Hologic, Bedford, MA, USA). The diagnosis of osteoporosis was based on the definition by the World Health Organization criteria [18].

Statistical analysis

Data are expressed as mean ± standard deviation, median and interquartile range, or proportions. We used unpaired *t* test and Chi square test to compare the characteristics of the subjects between the LC and CC groups. The variables with skewed distribution were logarithmically transformed before analyses. Bone metabolic marker and BMD changes during the study period were analyzed in both groups using the paired *t* test. A *p* value of less than 0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS statistics version 24.0 (Chicago, IL, USA).

Results

Patients' characteristics

The baseline characteristics of the subjects are summarized in Table 1. There were no statistically significant differences in age, sex, estimated glomerular filtration rate, corrected calcium, phosphate, iPTH, vitamin D use, dialysate calcium concentration, and lumbar and femoral BMD between the LC and CC groups. Serum iPTH, OC, BAP, TRACP-5b, and sclerostin levels were comparable between the two groups. Likewise, the proportions of low bone turnover, based on the cutoff values of the

Table 1 Baseline characteristics of patients

	Calcium carbonate ($n=34$)	Lanthanum carbonate ($n=31$)	p value
Age (years)	65 ± 11	64 ± 13	NS
Sex (male) (%)	23 (67.6)	26 (83.9)	NS
Body mass index (kg/m^2)	24.0 ± 3.7	24.7 ± 4.5	NS
Hypertension (%)	33 (97.1)	29 (93.5)	NS
Diabetes mellitus (%)	13 (38.2)	17 (54.8)	NS
Vitamin D (%)	13 (38.2)	11 (35.5)	NS
Dialysate calcium concentration			
3.0 mEq/L (%)	29 (85.3)	29 (93.5)	NS
2.75 mEq/L (%)	1 (2.9)	0 (0.0)	NS
2.5 mEq/L (%)	4 (11.8)	2 (6.5)	NS
Hemoglobin (g/dL)	8.5 ± 1.8	8.7 ± 1.4	NS
Urea nitrogen (mg/dL)	88.9 ± 27.1	87.5 ± 25.9	NS
Creatinine (mg/dL)	8.9 ± 2.3	8.5 ± 2.2	NS
eGFR (mL/min/1.73 m^2)	5.2 ± 1.2	5.9 ± 2.4	NS
Albumin (g/dL)	3.4 ± 0.5	3.4 ± 0.6	NS
Corrected calcium (mg/dL)	8.1 ± 0.9	8.5 ± 0.8	NS
Phosphate (mg/dL)	5.9 ± 1.2	6.0 ± 1.5	NS
iPTH (pg/mL)	265.2 (196.7–435.4)	237.9 (128.0–414.9)	NS
OC (ng/mL)	20.5 (12.8–34.2)	22.4 (10.7–34.0)	NS
BAP (μg/L)	11.2 (8.1–14.6)	11.1 (8.4–18.8)	NS
TRACP-5b (mU/dL)	529.5 (344.2–747.0)	603.0 (318.0–914.0)	NS
Sclerostin (pmol/L)	84.1 (67.3–107.4)	88.1 (66.2–122.7)	NS
Low bone turnover (%)			
Determined by OC	26 (76.5)	25 (80.6)	NS
Determined by BAP	20 (58.8)	18 (58.1)	NS
Determined by TRACP-5b	13 (38.2)	13 (41.9)	NS
Determined by iPTH	2 (5.9)	3 (9.7)	NS
Lumbar BMD (g/cm^2)	1.1 ± 0.3	1.0 ± 0.3	NS
Femoral BMD (g/cm^2)	0.7 ± 0.2	0.7 ± 0.2	NS

Values are expressed as mean ± standard deviation, median and interquartile or proportions

eGFR estimated glomerular filtration rate, *iPTH* intact parathyroid hormone, *OC* osteocalcin, *BAP* bone-specific alkaline phosphatase, *TRACP-5b* tartrate-resistant acid phosphatase 5b, *BMD* bone mineral density, *NS* not significant

bone markers, were not different between the two groups. Twenty percent of the study subjects had osteoporosis (T score $\leqq -2.5$). At the end of study, there were no significant differences in the dialysate calcium concentration between the two groups. Vitamin D use was not different between the LC and CC groups [25 (81%) vs. 22 (65%), respectively].

During the study periods, we observed adverse events/effects including diarrhea (3%), constipation (6%), rash (5%), and gastrointestinal hemorrhage (3%). Two patients received coronary artery bypass graft, one patient was diagnosed with angina pectoris, and one patient was diagnosed with heart failure. There was no statistically significant difference in these events between the two groups.

Effects of LC and CC on serum phosphate, calcium, and iPTH

Upon completion of the study, serum phosphate levels in 42 patients (65%) were controlled within the target range of the clinical guidelines in Japan [15] [LC group, $N=23$ (74%); CC group, $N=19$ (56%)]. In 20 patients (31%), at the end of study, the values of phosphate, corrected calcium, and iPTH were all within the recommended ranges [15].

The changes in serum phosphate, calcium, and iPTH levels in the two groups are shown in Fig. 1. Serum phosphate levels were comparable between the LC and CC groups. At 18 months, compared with the CC group, the LC group had lower serum calcium levels (8.8 ± 0.6 mg/

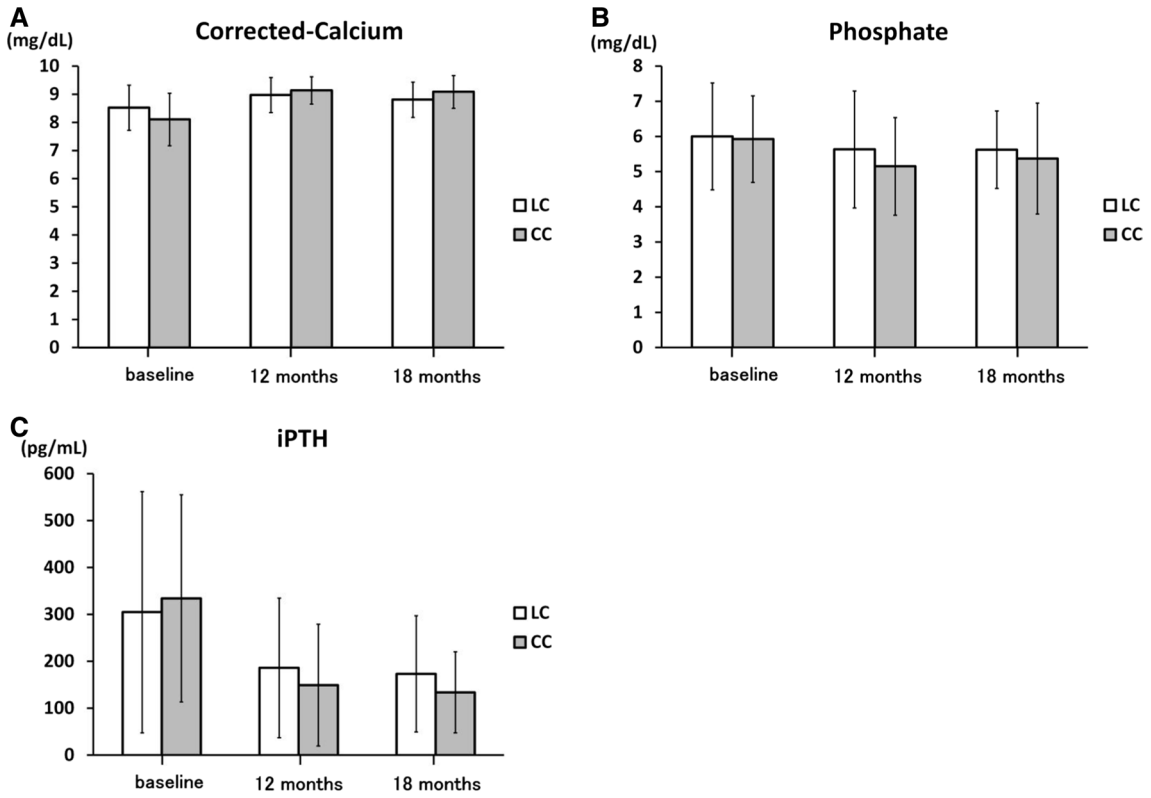

Fig. 1 Changes in the CKD–MBD parameters during the study period: **a** serum-corrected calcium levels, **b** serum phosphate levels, **c** serum intact parathyroid hormone levels. *CKD–MBD* chronic kidney disease–mineral bone disorder, *iPTH* intact parathyroid hormone

dL vs. 9.1 ± 0.6 mg/dL) and higher serum iPTH levels [149 (90–200) pg/mL vs. 113 (52–215) pg/mL] although not statistically significant.

Effects of LC and CC on bone metabolic markers and BMD

As depicted in Fig. 2, serum OC levels from baseline to 12 and 18 months increased in the LC group and remained unchanged in the CC group. Moreover, serum OC levels were significantly higher in the LC group than in the CC group at 12 months [28.4 (17.2–43.4) ng/mL vs. 20.2 (15.0–30.3) ng/mL, $p < 0.05$] and at 18 months [30.0 (18.9–53.2) ng/mL vs. 21.7 (15.3–28.3) ng/mL, $p < 0.05$]. At 18 months, compared with the CC group, the LC group had higher serum BAP [11.9 (8.1–18.5) μg/L vs. 9.5 (8.0–12.9) μg/L] and TRACP-5b levels [456.0 (228.0–644.0) mU/dL vs. 326.5 (183.3–487.5) mU/dL] although not statistically significant. Serum sclerostin levels were similar between the two groups.

The percentage of low bone turnover was significantly smaller in the LC group than in the CC group at 18 months (Fig. 3), when classified by the serum BAP cutoff value (51.6% vs. 76.5%, $p < 0.05$). The percentage of low bone turnover at 18 months, although not statistically significant, was smaller in the LC group than in the CC group, based on the other bone metabolic markers, including OC (61.3% vs. 79.4%), and TRACP-5b (51.6% vs. 67.6%). These results indicated that, at the end of study, more patients had low bone turnover in the CC group than in the LC group.

Upon completion of the study, the lumbar spines and femoral neck BMD in both groups were not significantly different from their baseline value (Fig. 4). Both lumbar and femoral BMD were comparable between the LC and CC groups. The proportion of subjects who had osteoporosis was similar between the two groups (LC vs. CC, 20.0% vs. 25.0%).

Discussion

In this study, we demonstrated that (1) serum OC levels were significantly higher in the LC group than in the CC group; (2) at 18 months, serum BAP and TRACP-5b levels tended to be higher in the LC group than in the CC group; (3) the proportion of low bone turnover based on the BAP cutoff value was significantly smaller in the LC group than in the CC group; (4) the proportion of subjects with low bone turnover, as determined by OC, TRACP-5b, or iPTH cutoff values, tended to be smaller in the LC group than in the CC group.

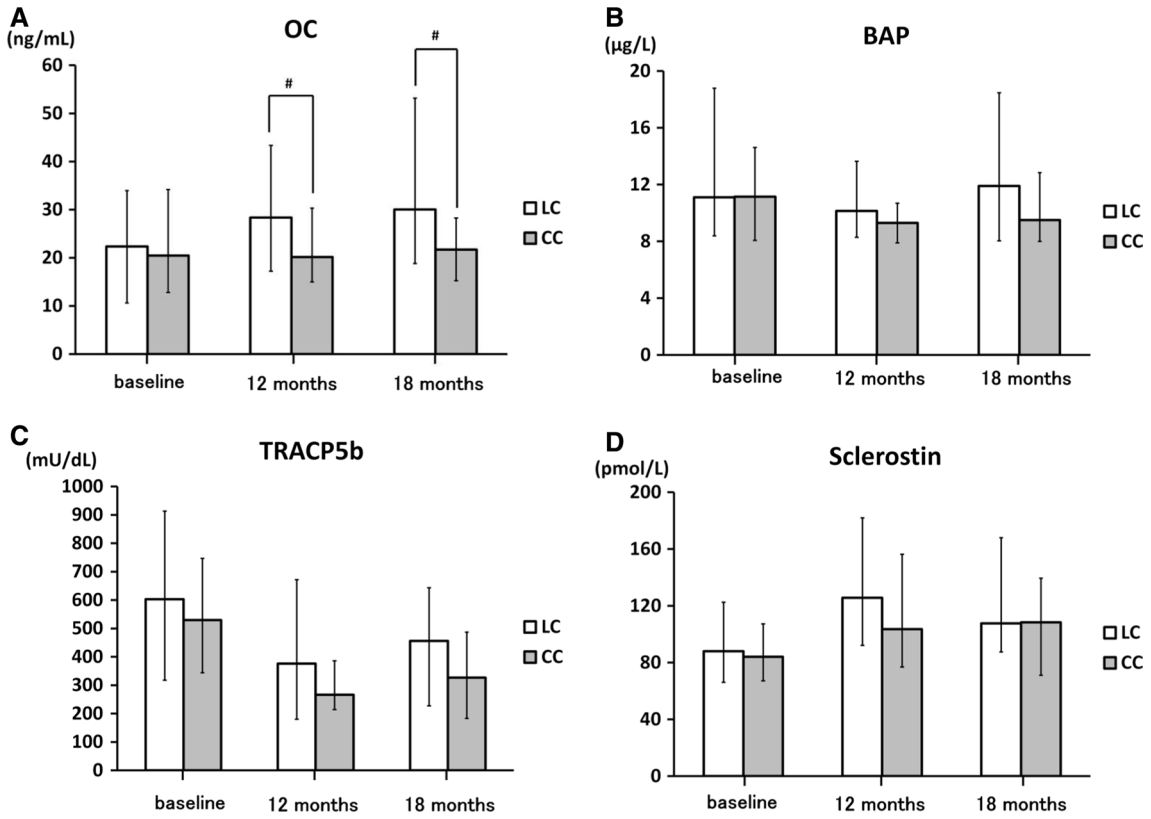

Fig. 2 Changes in serum bone metabolic markers during study period: **a** serum osteocalcin levels, **b** serum bone-specific alkaline phosphatase levels, **c** serum tartrate-resistant acid phosphatase isoform type 5b levels, **d** serum sclerostin levels. *OC* osteocalcin, *BAP* bone-specific alkaline phosphatase, *TRACP-5b* tartrate-resistant acid phosphatase isoform type 5b. #; LC vs. CC, $p < 0.05$

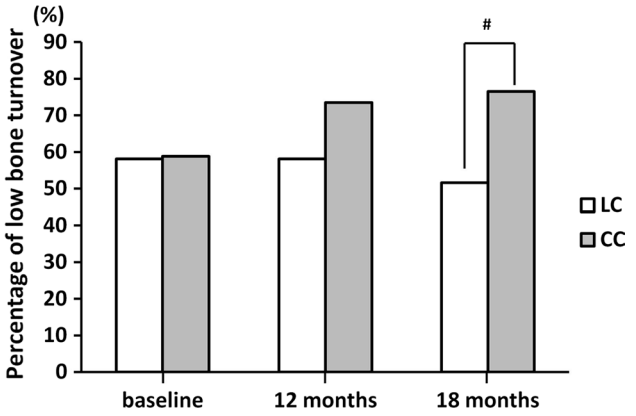

Fig. 3 Percentage of patients with low bone turnover determined using cutoff values of serum bone-specific alkaline phosphatase levels (< 12.9 μg/L). #; LC vs. CC, $p < 0.05$

Bone biopsy is useful and the gold standard test for evaluation of the state of bone abnormalities. However, it is difficult to perform routinely in the clinical setting, because it is invasive and hard to perform and analyze. On the other hand, measurements of bone metabolic markers are non-invasive and easy to perform repeatedly, therefore, they had been useful for the assessment of changes in bone metabolism over time [19]. Although the use of bone metabolic markers has several limitations, it has been reported by previous clinical trials to discriminate between high and low bone turnover [16, 17].

Low bone turnover is thought to be associated with bone fracture and progression of vascular calcification in patients undergoing HD. Several studies demonstrated that low bone turnover assessed by bone biopsy was associated with higher arterial calcification score or CAC progression [20, 21]. Among the bone metabolic markers, OC and BAP were reported to have an association with bone turnover, bone fracture and vascular calcification [16, 17, 22, 23]. PTH is also known to be a good surrogate marker for bone turnover and bone fracture in HD patients [24–26]. A previous study reported that HD patients with low serum PTH level (range, 5–61 pg/mL) had a higher prevalence of vertebral fracture, compared with those with elevated serum PTH levels [25]. The results of our study demonstrated that serum OC levels were significantly higher and serum PTH levels tended to be higher in the LC group than in the CC group. Furthermore, fewer patients had low bone turnover in the LC group than

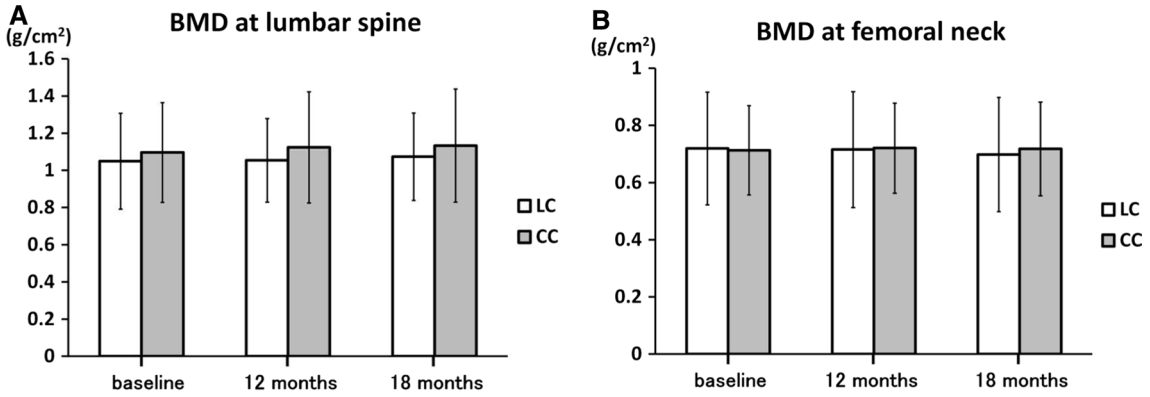

Fig. 4 Changes in BMD during the study period: **a** lumbar spine, **b** femoral neck. *BMD* bone mineral density

in the CC group. Compared with calcium-containing phosphate binders, LC does not increase the calcium load and can maintain the appropriate serum iPTH levels [10, 27].

There are several experimental studies that elucidated the detailed mechanisms of the bone-protective effects of LC [28–30]. Based on the results, LC may stimulate bone formation directly. An in vitro study showed that lanthanum ions promoted the expression of Runx2, OC, and osteopontin in stem cells derived from human adipose tissue which are precursors of osteoblasts [28]. In this study, the amount of calcium deposition evaluated by the Alizarin red and von Kossa staining was higher in the lanthanum-containing medium than in the control medium. Another in vitro study showed that lanthanum ion enhanced osteoblast differentiation through an extracellular signal-regulated kinase phosphorylation via pertussis toxin-sensitive Gi protein signaling [29]. An in vivo study using a CKD model of rats that underwent parathyroidectomy and received a constant infusion of PTH reported that bone formation on bone histomorphometry was higher in the LC group than in the non-LC group. In particular, lanthanum treatment caused a robust stimulation of bone formation, with activation of osteoblasts on the endosteal surface of the femoral diaphysis, leading to an increase in cortical bone volume. These results indicated that LC may stimulate bone formation independently of PTH [30]. Therefore, LC seems to have potential effects of directly stimulating bone formation.

Several clinical studies have investigated the association between LC treatment and bone metabolism. A study that used bone histomorphometry demonstrated that the rate of adynamic bone was smaller in the LC treatment group than in the CC treatment group [9]. In addition, a recent trial reported that the levels of bone metabolic markers in HD patients were higher in the LC group than in the CC group [13]. These findings corresponded with the results of our study and indicated that LC, compared with CC, has the potential to prevent bone fracture by avoiding low bone turnover.

Unfortunately, there were no significant differences in BMD between the two groups in the present study. However, our data about BMD were compatible with those of previous reports. A previous interventional study did not find a significant difference in lumbar spine BMD between the LC and CC groups at 18 months [8]. In addition, a 24-month randomized controlled trial showed no significant differences in BMD between the two groups [12]. Therefore, LC may not have a great impact on BMD within a relatively short period. If the observational period of these studies and our study were much longer, BMD might have been improved by LC treatment, through improvement of bone quality and reduction of the rate of low bone turnover, compared to the effects of CC.

Sclerostin is mainly produced by osteocytes and regulates bone formation via the Wingless and Integration1/beta-catenin pathway [31, 32]. Although little is known regarding the effect of LC on sclerostin, a clinical trial on a small number of patients reported that LC, compared with placebo, did not significantly alter the levels of sclerostin in patients with CKD stage 3 [33]. Likewise, our study showed that serum sclerostin levels were comparable in the LC and in CC groups. Further studies that include a larger number of subjects are required to confirm the effects of LC on sclerostin levels.

In conclusion, our data suggest that LC, compared with CC, has the potential to prevent low bone turnover in patients with CKD after initiating HD. Although future studies are required to elucidate the details, LC may provide therapeutic benefits for bone fracture and cardiovascular disease, leading to better clinical prognosis in patients new to HD.

A part of this study was presented at the annual meeting of the American Society of Nephrology in 2018.

Compliance with ethical standards

Conflict of interest This study was partly supported by Bayer Yakuhin Co, and Hideki Fujii and Shinichi Nishi have received a speaker honorarium from Bayer Yakuhin Co. The other authors declare that they have no other conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Nickolas TL, Leonard MB, Shane E (2008) Chronic kidney disease and bone fracture: a growing concern. Kidney Int 74:721–731
2. Wakasugi M, Kazama JJ, Taniguchi M et al (2013) Increased risk of hip fracture among Japanese hemodialysis patients. J Bone Miner Metab 31:315–321
3. Tentori F, McCullough K, Kilpatrick RD et al (2014) High rates of death and hospitalization follow bone fracture among hemodialysis patients. Kidney Int 85:166–173
4. Young EW, Albert JM, Satayathum S et al (2005) Predictors and consequences of altered mineral metabolism: the dialysis outcomes and practice patterns study. Kidney Int 67:1179–1187
5. Jamal SA, Vandermeer B, Raggi P et al (2013) Effect of calcium-based versus non-calcium-based phosphate binders on mortality in patients with chronic kidney disease: an updated systematic review and meta-analysis. Lancet 382:1268–1277
6. Ketteler M, Block GA, Evenepoel P et al (2017) Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) guideline update: what's changed and why it matters. Kidney Int 92:26–36
7. Fujii H, Kono K, Nakai K, Goto S, Nishii T, Kono A, Nishi S (2018) Effects of lanthanum carbonate on coronary artery calcification and cardiac abnormalities after initiating hemodialysis. Calcif Tissue Int 102:310–320
8. Toussaint ND, Lau KK, Polkinghorne KR, Kerr PG (2011) Attenuation of aortic calcification with lanthanum carbonate versus calcium-based phosphate binders in haemodialysis: a pilot randomized controlled trial. Nephrology 16:290–298
9. D'Haese PC, Spasovski GB, Sikole A et al (2003) A multicenter study on the effects of lanthanum carbonate (Fosrenol™) and calcium carbonate on renal bone disease in dialysis patients. Kidney Int 85:S73–S78
10. Malluche HH, Siami GA, Swanepoel C et al (2008) Improvements in renal osteodystrophy in patients treated with lanthanum carbonate for two years. Clin Nephrol 70:284–295
11. Inaba M, Okuno S, Nagayama H et al (2015) Restoration of parathyroid function after change of phosphate binder from calcium carbonate to lanthanum carbonate in hemodialysis patients with suppressed serum parathyroid hormone. J Ren Nutr 25:242–246
12. Wada K, Wada Y, Uchida HA, Tsuruoka S (2015) Effects of lanthanum carbonate versus calcium carbonate on vascular stiffness and bone mineral metabolism in hemodialysis patients with type 2 diabetes mellitus: a randomized controlled trial. Int J Nephrol Renov Dis 8:111–118
13. Zhang C, Wang S, Zhao S, Zhang X (2017) 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. Med (Baltim) 96:e8664
14. Soohoo M, Feng M, Obi Y et al (2016) Changes in markers of mineral and bone disorders and mortality in incident hemodialysis patients. Am J Nephrol 43:85–96
15. Fukagawa M, Yokoyama K, Koiwa F et al (2013) Clinical practice guideline for the management of chronic kidney disease-mineral and bone disorder. Ther Apher Dial 17:247–288
16. Coen G, Ballanti P, Bonucci E et al (1998) Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. Nephrol Dial Transplant 13:2294–2302
17. Salam S, Gallagher O, Gossiel F, Paggiosi M, Khwaja A, Eastell R (2018) Diagnostic accuracy of biomarkers and imaging for bone turnover in renal osteodystrophy. J Am Soc Nephrol 29:1557–1565
18. World Health Organization (1994) Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 843:1–129
19. Nishizawa Y, Ohta H, Miura M et al (2013) Guidelines for the use of bone metabolic markers in the diagnosis and treatment of osteoporosis (2012 edition). J Bone Miner Metab 31:1–15
20. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC (2004) Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol 15:1943–1951
21. Barreto DV, Barreto FC, Carvalho AB et al (2008) Association of changes in bone remodeling and coronary calcification in hemodialysis patients: a prospective study. Am J Kidney Dis 52:1139–1150
22. Ureña P, Hruby M, Ferreira A, Ang KS, de Vernejoul MC (1996) Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. J Am Soc Nephrol 7:506–512
23. Fusaro M, Giannini S, Gallieni M et al (2016) Calcimimetic and vitamin D analog use in hemodialyzed patients is associated with increased levels of vitamin K dependent proteins. Endocrine 51:333–341
24. Quarles LD, Lobaugh B, Murphy G (1992) Intact parathyroid hormone overestimates the presence and severity of parathyroid-mediated osseous abnormalities in uremia. J Clin Endocrinol Metab 75:145–150
25. Atsumi K, Kushida K, Yamazaki K, Shimizu S, Ohmura A, Inoue T (1999) Risk factors for vertebral fractures in renal osteodystrophy. Am J Kidney Dis 33:287–293
26. Iimori S, Mori Y, Akita W et al (2012) Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. Nephrol Dial Transplant 27:345–351
27. Zhai CJ, Yang XW, Sun J, Wang R (2015) Efficacy and safety of lanthanum carbonate versus calcium-based phosphate binders in patients with chronic kidney disease: a systemic review and meta-analysis. Int Uro Nephrol 47:527–535
28. Harini D, Indra R, Rajaram A, Rajaram R (2014) Induction of osteoblast differentiation in human adipose derived stem cells by lanthanum ions. J Rare Earths 32:1080–1088
29. Wang X, Yuan L, Huang J, Zhang TL, Wang K (2008) Lanthanum enhances in vitro osteoblast differentiation via pertussis toxin-sensitive gi protein and ERK signaling pathway. J Cell Biochem 105:1307–1315
30. Fumoto T, Masako I, Kyoji I (2014) Lanthanum carbonate stimulates bone formation in a rat model of renal insufficiency with low bone turnover. J Bone Miner Metab 32:484–493
31. Sabbagh Y, Graciolli FG, O'Brien S et al (2012) Repression of osteocyte Wnt/beta-catenin signaling is an early event in the progression of renal osteodystrophy. J Bone Miner Res 27:1757–1772

32. Delgado-Calle J, Sato AY, Bellido T (2017) Role and mechanism of action of sclerostin in bone. Bone 96:29–37
33. Seifert ME, de las Fuentes L, Rothstein M et al (2013) Effects of phosphate binder therapy on vascular stiffness in early stage chronic kidney disease. Am J Nephrol 38:158–167