



Effects of Lanthanum Carbonate on Coronary Artery Calcification and Cardiac Abnormalities After Initiating Hemodialysis

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(Citation)

Calcified Tissue International, 102(3):310-320

(Issue Date)

2018-03

(Resource Type)

journal article

(Version)

Accepted Manuscript

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(URL)

<https://hdl.handle.net/20.500.14094/0100482889>



Word count: Abstract; 250, Text; [3470](#)
References; 44, Figures; 4, Tables; 4

Original article

Effects of lanthanum carbonate on coronary artery calcification and cardiac abnormalities after initiating hemodialysis

Running title: Effects of lanthanum carbonate on CVD

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Abstract

Purpose

It is known that calcium-containing phosphate binders are more closely associated with the progression of vascular calcification than non-calcium-containing phosphate binders. In this study, we investigated the effect of the non-calcium-containing phosphate binder, lanthanum carbonate on the progression of coronary artery calcification and cardiovascular abnormalities compared to that of calcium containing phosphate binder in chronic kidney disease patients during the early period after initiating hemodialysis.

Methods

This was a randomized open-label study in which patients were divided into the calcium carbonate or lanthanum carbonate group. We evaluated blood samples, coronary artery calcification using high-resolution computed tomography and cardiac abnormalities using echocardiography prior to and after initiating hemodialysis.

Results

Cardiac dimension and systolic function were significantly improved in the lanthanum carbonate group compared to the calcium carbonate group. Though statistically

significant differences were not observed in all the patients, only among patients with moderate coronary artery calcification, the changes in coronary artery calcification score at 18 months were significantly smaller in the lanthanum carbonate group than in the calcium carbonate group. The percent change in coronary artery calcification at 18 months was significantly correlated with the serum fibroblast growth factor 23 levels at 18 months ($r = 0.245$, $P < 0.05$). This significant correlation was particularly strong in patients with moderate coronary artery calcification ($r = 0.593$, $P < 0.001$).

Conclusions

Our study suggests that lanthanum carbonate ameliorates cardiac abnormalities, and may slow coronary artery calcification development in patients with moderate coronary artery calcification, during the early period following hemodialysis initiation.

Keywords: coronary artery calcification, lanthanum carbonate, cardiac abnormalities, FGF23, non-calcium-containing phosphate binder

Introduction

In chronic kidney disease (CKD) patients including hemodialysis patients, cardiovascular disease (CVD) is a leading cause of death [1, 2] and CVD prevention is crucial for them. A major cardiovascular lesion in CKD patients is vascular calcification. Many studies have reported that vascular calcification is strongly associated with cardiovascular events and mortality [3-5]. Experimental and clinical studies have revealed hyperlipidemia, hypertension, diabetes mellitus, aging, and mineral bone disorder to be crucial factors related to pathophysiological mechanisms of vascular calcification [6-8]. Therefore, appropriately controlling these factors is essential. Controlling serum phosphate levels is especially important for advanced-stage CKD patients [9, 10].

Several studies have demonstrated that CVD occurrence is the most frequent during the first year after initiating hemodialysis [11, 12]. As it is speculated that the physiological state remarkably changes soon after initiating hemodialysis, management during this period is very important.

In the present study, we investigated the degree of coronary artery calcification (CAC) and cardiac abnormalities in patients new to hemodialysis. Additionally, we evaluated the effect of lanthanum carbonate (LC), a non-calcium-containing phosphate binder,

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3 compared with that of calcium carbonate (CC), a calcium-containing phosphate binder,
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6 on CAC progression and change in cardiac function during the early period after initiating
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9 hemodialysis.
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11 12 13 14 15 16 **Methods**

17 18 19 ***Study design***

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22 This was a two-arm, open-label, randomized controlled trial, which compared the
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25 effect of LC with that of CC in patients new to hemodialysis. The study patients were
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28 divided into these two groups by computer-generated simple randomization. Our study
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31 was conducted prospectively in accordance with the Declaration of Helsinki Principles.
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34 Our study protocols were approved by the appropriate institutional review committee (no.
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37 230019) and registered on UMIN (ID:UMIN000006808, [https://upload.umin.ac.jp/cgi-](https://upload.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000007749)
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41 open-bin/ctr_e/ctr_view.cgi?recptno=R000007749). Informed consent was obtained
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44 from all participants.
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50 51 ***Study population and procedure***

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54 Dialysis therapy was initiated in 490 patients with end-stage renal disease (ESRD) at
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57 five institutions in Hyogo prefecture between December 2012 and June 2014. Inclusion
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3 criteria were age ≥ 20 years; presence of hyperphosphatemia; and ability to give informed
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6 consent. Exclusion criteria included contraindications to lanthanum carbonate and
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9 calcium carbonate; history of parathyroidectomy; and patient refusal. Among the
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12 remaining 108 patients enrolled initially, two patients withdrew consent, and one patient
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15 died before beginning the study. Subsequently, we randomly divided the remaining 105
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18 patients into the LC (n = 50) or CC (n = 55) group (Figure 1). The patients underwent
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21 multi-detector computed tomography prior to and at 12 and 18 months after initiating
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24 hemodialysis.
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28 All patients were receiving conventional hemodialysis therapy, 3-4.5 h, thrice per
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31 week. Patients in each group were prescribed their drug at a dose that maintained serum
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34 phosphate levels between 3.5 and 6.0 mg/dL according to the Japanese Society of Dialysis
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37 Therapy guidelines [13]. In patients in whom increasing the drug was difficult, only
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40 sevelamer or bixalomer was permitted. The administration of cinacalcet was not
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43 permitted, and the administration of vitamin D agents was avoided whenever possible.
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47 Attending physicians were free to modify the other medication except for phosphate
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50 binder, vitamin D agents, and cinacalcet and dialysate composition if needed during the
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53 study period. All patients were not prescribed specific diet. Study staff were not
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56 concerned in the treatment for the study patients. Follow-up visits were conducted at 12
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3 and 18 months after initiating hemodialysis and blood samples were collected at 6, 12,
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6 and 18 months after initiating hemodialysis. We checked study medication adherence by
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9 medical information from each hospital and dialysis clinic at 6, 12, and 18 months.
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16 ***Evaluation of Coronary Artery Calcification Using Computed Tomography***

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19 CAC evaluation was performed using a multi-detector row computed tomography
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22 scanner (Optima CT660; GE Healthcare, Aquilion ONE; TOSHIBA). CAC scoring was
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25 performed by board-certified diagnostic radiologists, who were blinded to all patients'
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28 clinical characteristics, using a computerized program that calculated the CAC score
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31 (CACS) as Agatston score [14]. CACS measurements were categorized as no/mild CAC
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34 (CACS < 10), moderate CAC (CACS = 10–400), and severe CAC (CACS > 400).
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41 ***Echocardiographic examination***

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44 Echocardiography was performed at baseline and at 12 and 18 months after initiating
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47 hemodialysis. After the initiation, echocardiography was performed on the interdialysis
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50 day. Two-dimensional guided M-mode echocardiography was performed to measure left
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53 ventricular wall mass. Left ventricular diastolic and systolic diameter (LVDd/LVDs) as
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56 well as the diastolic thickness of the left ventricular posterior wall and interventricular
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3 septum were assessed on M-mode images in the parasternal longitudinal-axis view. M-
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6 mode analysis was performed according to the American Society of Echocardiography
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9 guidelines. The left ventricular mass index (LVMI, g/m²) and relative wall thickness were
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12 calculated using these parameters [15].
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19 ***Serum measurements***

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22 Venous blood was collected from patients before dialysis. Laboratory tests were
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25 conducted using standardized clinical laboratory methods. The remaining serum samples
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28 were stored at −80°C until analysis. Serum fibroblast growth factor 23 (FGF23) levels
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31 were determined using an intact FGF23 ELISA kit (Kainos Laboratories, Inc., Tokyo,
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34 Japan).
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41 ***Sample size calculation***

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44 Based on a previous study in hemodialysis patients using lanthanum carbonate [16],
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47 change in vascular calcification on the expected population to be recruited in the present
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50 study was assumed to be -95 [SD100] HU. A total sample size of 80 patients provided
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53 90% power to detect the expected difference in change in CAC at a two-tailed 5% level
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56 of significance, allowing for a 35% dropout rate. Because change in abdominal aortic
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3 calcification was evaluated the previous study, we took the difference in change between
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6 abdominal aortic calcification and coronary artery calcification into account and
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9 estimated that 50 patients per arm (total, n = 100) would be needed for appropriate
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12 analysis.
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19 ***Statistical analysis***

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22 We used the computer software application IBM SPSS statistics version 23.0 (SPSS
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24 Inc., IL, USA) for all statistical analyses. The analysis of the present study was performed
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26 in accordance with the intention-to-treat principle. Values are presented as the median
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28 and interquartile or mean $\pm$ SD. The differences between the two groups were analyzed
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30 using the Student's t-test or Mann-Whitney U test for continuous variables and using the
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32 χ^2 test for categorical variables. Pearson's correlation coefficient was used to analyse
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34 relationships between variables. To determine the independent cardiovascular factors
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36 correlated to serum FGF23 levels, we conducted a multiple regression analysis. A *P* value
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38 of < 0.05 was considered statistically significant.
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54 **Results**

55 ***Patient characteristics***

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The main patient characteristics at baseline are shown in Table 1. The percentage of males was higher in the LC group than in the CC group. No significant differences were observed in other clinical characteristics between the two groups. At baseline, 87 patients had CAC (82.9%). Twenty-six patients had no/mild CAC (24.8%), 36 patients had moderate CAC (34.3%), and 43 patients had severe CAC (40.9%). As shown in table 1, the number of patients with each CACS in the LC and CC group was the following; 0-100 (LC: n = 19 (38.0%), CC: n = 23 (41.8%)); 101-400 (LC: n = 11 (22.0%), CC: n = 9 (16.4%)); 401-1000 (LC: n = 8 (16.0%), CC: n = 10 (18.2%)); ≥ 1000 (LC: n = 12 (24.0%), CC: n = 13 (23.6%)). There was no imbalance between study arms at baseline ($P = 0.895$).

At the end of study, serum calcium levels were significantly lower in the LC group than in the CC group (Figure 2A). However, serum phosphate and intact parathyroid hormone levels (int-PTH) were comparable between the two groups (Figure 2B, C). Serum FGF23 levels were significantly lower in the LC group than in the CC group at 6 months; the levels tended to be lower even at 12 and 18 months in the LC group than in the CC group, although there were no statistically significant differences (Figure 2D). Vitamin D, phosphate binders, and other concomitant medication were the following; vitamin D (LC: n = 33 (80.5%), CC: n = 32 (64.0%), $P = 0.105$), ACE-I/ARB (LC: n = 24 (58.5%), CC: n = 29 (58.0%), $P = 1.000$), statin (LC: n = 13 (31.7%), CC: n = 23

(46.0%), $P = 0.199$), warfarin (LC: $n = 0$ (0%), CC: $n = 3$ (6.0%), $P = 0.249$), and addition of other phosphate binders (LC: $n = 7$ (17.1%), CC: $n = 19$ (38.0%), $P = 0.036$). The kind of additional phosphate binders were sevelamer and/or bixalomer. The prescribed daily doses of LC and CC at the end of study were 750.0 mg [375.0-1500.0] and 1500.0 mg [1000.0-3000.0], respectively. There was no significant relationship between the change in CAC and vitamin D, ACE-I/ARB, statin, warfarin and addition of other phosphate binders. The dose of not lanthanum carbonate but calcium carbonate was significantly associated with CAC progression ($r = 0.386$, $P = 0.010$). As for dialysate calcium concentration, there was no significant difference between the two groups.

Effects of LC and CC on CAC progression

Table 2 shows the details of and change in CAC during the study period. At baseline, CACS of each coronary artery branches (left main trunk, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) and total CACS were comparable between the two groups. Although there was no statistically significant difference between the LC and CC groups, Δ CACS tended to be smaller in the LC group than in the CC group at the end of study ($P = 0.109$). In addition, further analysis revealed that Δ CACS ($P = 0.019$) and Δ CACS ($P = 0.017$) were significantly

smaller in the LC group than in the CC group only among patients with moderate CAC (Figure 3). Even after adjustment for gender, $\% \Delta \text{CACs}$ was significantly smaller in the LC group. On the other hand, in patients with mild and severe CAC, CACS, ΔCACs and $\% \Delta \text{CACs}$ were similar between the two groups. Eight and ten patients without CAC were included in the LC and CC group, respectively. Among them, one and four patients developed CAC at 18 months, respectively.

Effects of LC and CC on echocardiographic parameters and cardiovascular biomarkers

Table 3 shows changes in echocardiographic parameters and cardiovascular parameters including serum troponin T and asymmetric dimethylarginine (ADMA) levels. At 12 months, left atrial diameter (LA), LVDd, LVDs, and systolic function were improved in the LC group, and the improvement continued until the end of study. Serum troponin T and ADMA levels did not significantly differ between the two groups at baseline.

Correlation of CAC with clinical factors

Serum phosphate levels at 18 months were significantly correlated with ΔCACs ($r = 0.225$, $P < 0.05$) and $\% \Delta \text{CACs}$ ($r = 0.235$, $P < 0.05$). Log-serum FGF23 levels at 18

months were significantly correlated with $\% \Delta \text{CACS}$ (Figure 4A; $r = 0.245$, $P < 0.05$).

However, serum calcium, int-PTH, and low density lipoprotein cholesterol levels as well as other clinical factors at 18 months were not significantly correlated with $\% \Delta \text{CACS}$.

The significant correlation between log-serum FGF23 levels at 18 months and $\% \Delta \text{CACS}$ was particularly strong in patients with moderate CAC (Figure 4B; $r = 0.593$, $P < 0.001$).

Correlation of FGF23 with cardiovascular abnormalities

At 18 months after starting drug therapy for hyperphosphatemia, log-serum FGF23 levels were significantly correlated with LVDd, LVDs, and ejection fraction (EF), and tended to be correlated with LA in addition to $\% \Delta \text{CACS}$ (Table 4). Log-serum FGF23 levels had no significant correlation with LVMI. Multivariate regression analysis including LVMI revealed that log-serum FGF23 levels were significantly correlated with $\% \Delta \text{CACS}$ and EF. No significant correlation was observed between log-serum FGF23 levels and other cardiovascular biomarkers.

Cardiovascular events, death, and adverse and other events during the study period

Two patients, one in the LC group and another in the CC group, died during the study period. The cause of death of both patients was CVD. CVD events including CVD death

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3 occurred in the eight patients, five in the LC group and three in the CC group. Other
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6 adverse events were as follows: infection (n = 3), rash (n = 4), constipation (n = 4), and
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9 diarrhea (n = 2). In addition, six patients did not undergo follow-up examinations without
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12 any notice, three got transferred to other hospitals, two underwent kidney transplantation,
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15 and one could not have follow-up examinations because she could not keep rest because
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18 of worsening dementia. There were no significant differences in these events between the
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22 two groups.
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28 **Discussion**

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31 We demonstrated that 1) there was no significant statistical difference in CACS
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34 between the LC and CC group; 2) only in the patients with moderate CAC, the changes
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37 in CACS between baseline and 12 months as well as baseline and 18 months were
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40 significantly smaller in the LC group than in the CC group; 3) the percent change in
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43 CACS between baseline and 18 months was significantly correlated with the log-serum
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46 FGF23 levels at 18 months and the significant correlation was particularly strong in
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49 patients with moderate CAC; and 4) though serum phosphate levels were comparable
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52 between the two groups at 18 months, serum FGF23 levels tended to be lower in the LC
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57 group than in the CC group.
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Vascular calcification is frequently observed in patients at advanced CKD stages. Several factors, such as aging, diabetes mellitus, impaired renal function, inflammation, oxidative stress, uremic toxin, renin-angiotensin system, hypertension, hyperlipidemia, and mineral disorder, are related to the progression of vascular calcification [6-8]. Among them, hyperphosphatemia is thought to be the most important factor for the pathophysiology [9, 10]. Importantly, as hemodialysis patients cannot excrete phosphate into the urine, their serum phosphate levels are prone to elevation. Therefore, the removal of phosphate by hemodialysis and control of phosphate burden from the intestine using phosphate binders are needed for hemodialysis patients.

Since CT scan cannot distinguish intimal and medial vascular calcification, it is difficult to know which component is more affected in CKD patients. Though the absence of increased plaque growth at low GFR has been reported, CAC dramatically progresses in CKD patients in the clinical settings. Therefore, we think medial layer is more affected in CKD patients. In addition, we think that intimal calcification is related to atherosclerotic events such as plaque rupture and acute vessel occlusion and medial calcification is related to impaired microvascular circulation due to increase in arterial stiffness.

Previous studies have reported that higher serum phosphate levels, although still within

the normal range, are associated with greater CAC prevalence and are significantly related to CVD occurrence [10, 17, 18]. Moreover, the calcification of coronary plaque has been reported to be associated with plaque stability and lead to the occurrence of acute coronary syndrome [19, 20]. It is also known that coronary flow reserve (CFR) is impaired with decreasing renal function and vascular dysfunction due to CAC is one of the mechanisms [21, 22]. In both hemodialysis and non-hemodialysis patients, impaired CFR is significantly correlated with CVD events and death [23, 24]. Thus, CAC presence contributes to CVD progression through various mechanisms. The results of meta-analysis and large studies have revealed that vascular calcification is significantly associated with increased CVD events and all-cause mortality [3, 4]. Therefore, a strict control of serum phosphate levels is very crucial in the clinical setting.

However, attention should be paid to the method of treating hyperphosphatemia. A previous study has reported that patients with a higher dose of calcium-containing phosphate binders have severe vascular calcification [25]. In addition, several randomized controlled trials have compared the effect of sevelamer with CC on CAC progression [26-28]. These results demonstrated that sevelamer is less likely to affect CAC progression compared with CC. Similar results were observed in several studies using LC [29-31]. In the present study, although there was no significant difference in CAC progression

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3 between the LC and CC groups, the progression was significantly reduced in the LC group
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6 compared with the CC group in patients with moderate CAC. We speculated that most
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9 patients who have led to ESRD because of chronic glomerulonephritis may have a trivial
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12 or no vascular calcification because they may not have a few risks for atherosclerosis. In
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15 fact, CAC had progressed minimally in such patients at the end of study. Moreover, CAC
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18 progression appeared to be relatively mild in patients with severe CAC at baseline
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21 because change in CAC is underestimated in these patients. A recent meta-analysis has
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24 demonstrated that non-calcium-containing phosphate binders could reduce the mortality
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27 risk by 22% compared with that by calcium-containing phosphate binders [32].
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30 Furthermore, non-calcium-containing phosphate binders were demonstrated to be able to
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33 prevent CAC progression compared with that by calcium-containing phosphate binders.
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36 In the present study, outcomes, such as CVD events and death were minimal, and no
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39 significant difference was observed in the prevalence between the two groups. However,
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42 previous studies have reported that CVD events and death were most frequently observed
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45 within 1 year after initiating hemodialysis [11, 12]. Taken together, we suggest that
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48 hyperphosphatemia treatment using LC soon after initiating hemodialysis may be an
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51 effective strategy to improve the prognosis of hemodialysis patients by slowing the
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54 progression of vascular calcification especially in patients with moderate CAC.
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3 In the present study, we assessed the effects of LC on cardiac abnormalities and
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6 cardiovascular biomarkers, including FGF23 in the present study. LA, LVDd, LVDs and
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9 cardiac function were significantly improved in the LC group compared with those in the
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12 CC group. It is known that LC and other non-calcium-containing phosphate binders can
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15 reduce serum FGF23 levels [33-35]. Consistent with these results, our study results
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18 demonstrated that serum FGF23 levels were significantly lower at 6 months and tended
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21 to be lower at 12 and 18 months after initiating hemodialysis in the LC group than in the
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24 CC group. In addition, serum FGF23 levels at 18 months were significantly correlated
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27 with CAC progression and cardiac dysfunction; however, they were not significantly
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30 correlated with left ventricular hypertrophy and other cardiovascular biomarkers levels.
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33 Although we could not elucidate the pathophysiological mechanism underlying the
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36 improvement in cardiac parameters, we speculated that CAC prevention and decrease in
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39 serum FGF23 levels may be associated with the improvement. We suppose that CAC
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42 prevention can contribute to prevention of decrease in CFR. Previous study showed that
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45 CACS was significantly correlated with CFR [21]. In addition, it has been reported that
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48 FGF23 reduces nitric oxide production [36]. Thereby, the progression of myocardial
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51 damage also may be prevented in the LC group.
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57 Although FGF23 level is known to be related to the progression of ESRD, CVD, and
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1 death [37, 38], the correlation of FGF23 with vascular calcification is controversial [39-
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7 41]. However, serum FGF23 levels were remarkably elevated in hemodialysis patients;
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10 thereby the influence appeared to be greater in these patients than in non-dialyzed CKD
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12 patients. The result of multivariate analysis revealed that FGF23 was significantly and
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15 independently correlated with CAC progression in the present study. A recent
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18 experimental study has demonstrated that FGF23 enhances phosphate-induced vascular
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21 calcification by promoting osteoblastic differentiation involving the extracellular Signal-
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24 regulated Kinase 1/2 pathway [42]. Thus, it is suggested that a combination of
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27 hyperphosphatemia and high serum FGF23 levels can further induce vascular
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30 calcification. Therefore, as both hyperphosphatemia and elevated serum FGF23 levels
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33 can accelerate the progression of vascular calcification, lowering both serum phosphate
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36 and FGF23 levels may be a crucial treatment. Furthermore, although serum phosphate
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39 levels did not significantly differ between the two groups in the present study, LC is
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42 known to have a strong phosphate-lowering effect compared with that of other phosphate
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45 binders [43]. Considering these findings, hyperphosphatemia treatment using LC is a
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48 favorable strategy for hemodialysis patients.
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54 This study has some limitations. Firstly, CVD events and death were minimal during
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57 the study period, and the effect of LC on hard outcome remains unclear. This is likely
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because Japanese dialysis patients have better prognosis compared to those in other countries [44]. Further, this study included only 105 patients. In addition, these patients were observed for relatively short period. To resolve these issues, further study using a larger sample size for a longer observational period is warranted. Secondly, serum FGF23 levels were not correlated with left ventricular hypertrophy, and we could not evaluate left ventricular mass using magnetic resonance imaging (MRI). If MRI study is performed, this result may be different. Thirdly, there was a significant difference in use of other phosphate binders between the two groups. As mentioned above, we speculated that there was a possibility that use of sevelamer might partly affect the progression of coronary artery calcification. Fourthly, the study design was open-labelled. Therefore, it might also affect the strategy of phosphate control. In addition, strictly speaking, the analysis of this study is not ITT analysis because we analyzed only the participants who completed the trial. However, this study included patients who stopped the assigned drug and is similar to full analysis set, if anything. Therefore, we think the analysis of this study belongs to ITT in a broad sense. In addition, there was no significant difference in drop out rate between the two group (p=0.183).

Conclusions

Our data suggest that LC ameliorates cardiac abnormalities and is less likely to induce CAC progression in ESRD patients with moderate CAC during the early period after initiating hemodialysis. To explore utility in clinical settings, it is essential to perform a randomized controlled trial involving a large sample size.

Acknowledgement

This study was partly presented at the annual meeting of the European Renal Association - European Dialysis and Transplant Association Congress, 2016.

The authors thank the staff of Kobe university graduate school of medicine (Dr Shuhei Watanabe, Dr Kentaro Watanabe, Dr Ken Kitamura, Dr Rie Awata, Dr Mikiko Yoshikawa, Dr Yuriko Yonekura, and Kayo Tsubota) and the following faculties that participated in this study: from Joyo Ejiri Hospital, Dr Kazunari Ejiri; from Akashi medical center, Dr Susumu Sakamoto; from Kohnan Hospital, Dr Akira Fujimori; from Nishiwaki city hospital, Dr Masahide Iwai; and from Chibune Kidney and Dialysis Clinic, Dr Jong-Il Kim.

Compliance with Ethical Standards

Funding: This study was funded by Kidney Foundation, Japan (JKFB11-30).

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.

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Table 1 Baseline characteristics of patients

	LC (n = 50)	CC (n = 55)	<i>P</i>
Age (year)	65 ± 14	63 ± 13	0.383
Sex (male) (%)	44 (88.0)	38 (69.1)	0.019
Smoking (%)	19 (38.0)	26 (47.0)	0.324
HT (%)	48 (96.0)	53 (96.4)	0.924
DM (%)	26 (52.0)	23 (41.8)	0.301
CVD (%)	10 (20.0)	16 (29.1)	0.286
BMI (kg/m ²)	24.5 ± 4.0	24.3 ± 3.9	0.726
Systolic BP (mmHg)	146.7 ± 19.9	149.2 ± 22.8	0.563
Diastolic BP (mmHg)	71.8 ± 14.9	75.0 ± 14.1	0.269
ACE-I/ARB (%)	30 (60.0)	34 (61.8)	0.851
Statin (%)	14 (28.0)	24 (43.6)	0.098
Vitamin D (%)	17 (34.0)	22 (40.0)	0.530
Warfarin (%)	4 (8.0)	0 (0)	0.290
<i>Dialysate calcium concentration</i>			
3.0 mEq/L (%)	44 (88.0)	46 (83.6)	0.582
2.75 mEq/L (%)	1 (2.0)	1 (1.8)	0.946

2.0 mEq/L (%)	5 (10.0)	8 (14.5)	0.485
Hemoglobin (g/dL)	8.8 ± 1.4	8.6 ± 1.6	0.446
Cr (mg/dL)	8.8 ± 2.4	9.1 ± 2.3	0.486
eGFR (mL/min/1.73 m ²)	5.8 ± 2.3	5.2 ± 1.3	0.067
Albumin (mg/dL)	3.4 ± 0.5	3.3 ± 0.6	0.372
LDL-C (mg/dL)	87.6 ± 32.3	89.5 ± 30.2	0.760
cCa (mg/dL)	8.5 ± 0.7	8.3 ± 0.9	0.213
P (mg/dL)	5.7 ± 1.5	5.9 ± 1.5	0.348
cCa × P (mg ² /dL ²)	48.1 ± 12.0	48.8 ± 11.4	0.724
Int-PTH (pg/mL)	251.0 (129.0-523.5)	292.5 (173.0-467.6)	0.741
FGF23 (pg/mL)	732.8 (438.1-1588.2)	700.5 (275.7-1824.2)	0.918
CACS			0.895
0-100	19 (38.0)	23 (41.8)	
101-400	11 (22.0)	9 (16.4)	
401-1000	8 (16.0)	10 (18.2)	
>1000	12 (24.0)	13 (23.6)	

LC: lanthanum carbonate; CC: calcium carbonate; HT: hypertension; DM: diabetes mellitus; CVD: cardiovascular disease; BMI: body mass index; BP: blood pressure; ACE-I/ARB: angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker; Cr: creatinine; eGFR: estimated glomerular filtration rate; LDL-C: low density lipoprotein cholesterol; cCa: corrected calcium; P: phosphate; $cCa \times P$: corrected calcium-phosphate products; Int-PTH: intact parathyroid hormone; FGF23: fibroblast growth factor 23; CACS: coronary artery calcium score.

Values are presented as the median and interquartile or mean $\pm$ SD.

Table 2 Details of coronary artery calcification at baseline and change in coronary artery calcification score during the study period

	LC			CC		
(months)	0	12	18	0	12	18
	(n = 50)	(n = 43)	(n = 41)	(n = 55)	(n = 52)	(n = 50)
LMT	0	0	0	0	0	15.5
	(0-56.6)	(0-15.0)	(0-53.4)	(0-40.0)	(0-57.7)	(0-98.9)
LAD	104.3	159.7	119.0	74.2	130.6	145.7
	(2.8-470.4)	(13.2-466.7)	(19.2-479.9)	(0.4-451.0)	(8.0-555.0)	(27.6-559.0)
LCx	19.8	39.0	46.0	1.8	22.0	43.0
	(0-155.8)	(0-142.2)	(0-161.5)	(0-122.6)	(0-204.0)	(0-215.5)
RCA	13.5	15.1	8.0	11.3	58.2	125.0
	(0-183.6)	(0-213.8)	(0-231.1)	(0-208.8)	(7.5-458.0)	(2.1-564.1)
Total	207.5	320.6	349.9	213.0	433.9	500.0
	(10.3-1000.3)	(24.4-1032.7)	(65.1-981.7)	(13.8-829.2)	(116.3-1375.0)	(178.1-1512.1)
ΔCACS (from baseline)		53.3	76.0	-	64.7	164.4
	-	(1.2-179.4)	(0-250.9)		(0.9-269.0)	(5.7-331.7)
%ΔCACS (from baseline)	-	29.4	42.2	-	47.8	59.1
		(5.4-91.3)	(0-125.1)		(0-132.1)	(0.9-208.7)

LC: lanthanum carbonate; CC: calcium carbonate; LMT: left main trunk; LAD: left anterior descending coronary artery; LCx: left circumflex coronary artery; RCA: right coronary artery; CACS: coronary artery calcium score.

Values are presented as the median and interquartile.

Table 3 Echocardiographic parameters and cardiovascular biomarkers

	LC				CC			
(months)	0	6	12	18	0	6	12	18
LA (mm)	42.3 ± 6.6	-	39.5 ± 5.6*	39.4 ± 4.9*	43.1 ± 6.5	-	44.1 ± 6.8	42.4 ± 7.5
LVDd (mm)	49.2 ± 5.9	-	46.0 ± 5.9	45.7 ± 5.0*	49.4 ± 5.2	-	48.2 ± 6.6	48.3 ± 6.4
LVDs (mm)	31.2 ± 6.3	-	28.6 ± 5.2*	28.5 ± 5.4*	32.1 ± 5.1	-	31.6 ± 6.1	31.9 ± 6.4
IVST (mm)	11.8 ± 2.2	-	12.3 ± 3.1	12.1 ± 3.4	11.6 ± 1.8	-	11.8 ± 1.9	11.4 ± 2.2
LVPWT (mm)	11.5 ± 1.7	-	11.8 ± 1.7	11.7 ± 1.9	11.8 ± 1.8	-	11.7 ± 1.7	11.7 ± 1.9
FS (%)	36.7 ± 7.6	-	38.0 ± 7.3*	37.9 ± 7.1*	35.2 ± 6.2	-	34.8 ± 6.1	34.4 ± 6.2
EF (%)	64.2 ± 8.3	-	65.3 ± 7.0	66.5 ± 6.4*	62.9 ± 7.8	-	62.5 ± 8.8	62.1 ± 8.4
LVMI (g/m ²)	155.9 ± 39.0	-	150.3 ± 49.6	144.7 ± 48.5	158.7 ± 42.9	-	153.8 ± 42.2	150.2 ± 44.8
RWT	0.47 ± 0.12	-	0.50 ± 0.09	0.51 ± 0.10	0.48 ± 0.09	-	0.49 ± 0.09	0.49 ± 0.10
E/A ratio	0.97 ± 0.62	-	0.86 ± 0.32	0.80 ± 0.24	0.84 ± 0.33	-	0.84 ± 0.29	0.83 ± 0.33
DcT (msec)	213.2 ± 58.6	-	248.4 ± 61.6	242.8 ± 56.9*	226.6 ± 57.8	-	223.8 ± 67.4	215.8 ± 67.6
TRPG (mmHg)	26.8 ± 9.0	-	23.0 ± 6.1	20.1 ± 9.0	26.4 ± 9.8	-	22.4 ± 10.6	21.3 ± 11.6
IVCD (mm)	14.1 ± 4.6	-	12.6 ± 3.9	12.4 ± 4.5	14.4 ± 6.2	-	13.8 ± 5.1	12.9 ± 4.4
Troponin T (ng/mL)	0.054	0.054	0.047	0.052	0.057	0.044	0.051	0.043
	(0.043-0.075)	(0.035-0.063)	(0.036-0.069)	(0.036-0.071)	(0.034-0.088)	(0.026-0.062)	(0.027-0.064)	(0.025-0.062)
ADMA (nmol/mL)	0.55 ± 0.14	0.59 ± 0.12	0.53 ± 0.10	0.56 ± 0.10	0.54 ± 0.12	0.60 ± 0.11	0.56 ± 0.12	0.59 ± 0.11

LA: left atrial dimension; LVDd: left ventricular diastolic diameter; LVDs: left ventricular systolic diameter; IVST: intraventricular septum thickness; LVPWT: left ventricular posterior wall thickness; FS: fractional shortening; EF: ejection fraction; LVMI: left ventricular mass index; RWT: relative wall thickness; DcT: deceleration time; TRPG: tricuspid regurgitation pressure gradient; IVCD: inferior vena cava diameter; ADMA: asymmetric dimethylarginine.

Values are presented as the median and interquartile or mean $\pm$ SD.

*; LC vs CC, $P < 0.05$

Table 4 Correlation of FGF23 with cardiovascular factors at 18 months

	Univariate		Multivariate	
	R	<i>P</i>	β	<i>P</i>
CACS	-0.034	0.756	-	-
Δ CACS	0.125	0.244	-	-
% Δ CACS	0.245	0.026	0.231	0.031
LVMI	0.026	0.813	-	-
EF	-0.211	0.050	-0.132	0.224
E/A ratio	0.340	0.002	0.273	0.022
DcT	-0.232	0.032	-0.034	0.769
IVCD	0.265	0.012	0.175	0.109

FGF23: fibroblast growth factor 23; CACS: coronary artery calcification score; LVMI: left ventricular mass index; EF: ejection fraction;

DcT: deceleration time; IVCD: inferior vena cava diameter.

Figure Legends

Figure 1 Flowchart of participants in the present study

Figure 2 Change in chronic kidney disease-mineral metabolism disorder (CKD-MBD) parameters during the study period

- (A) Serum calcium levels
- (B) Serum phosphate levels
- (C) Serum intact parathyroid hormone (int-PTH) levels
- (D) Serum fibroblast growth factor-23 (FGF23) levels

#, LC vs CC, $P < 0.05$

Figure 3 Median change in coronary artery calcification in the lanthanum carbonate (LC) and calcium carbonate (CC) groups during the study period

(A) Δ CACS and % Δ CACS in the LC and CC group among all the study patients

(B) Δ CACS and % Δ CACS in the LC and CC group among the patients with moderate CAC

CAC: coronary artery calcification; CACS: CAC score

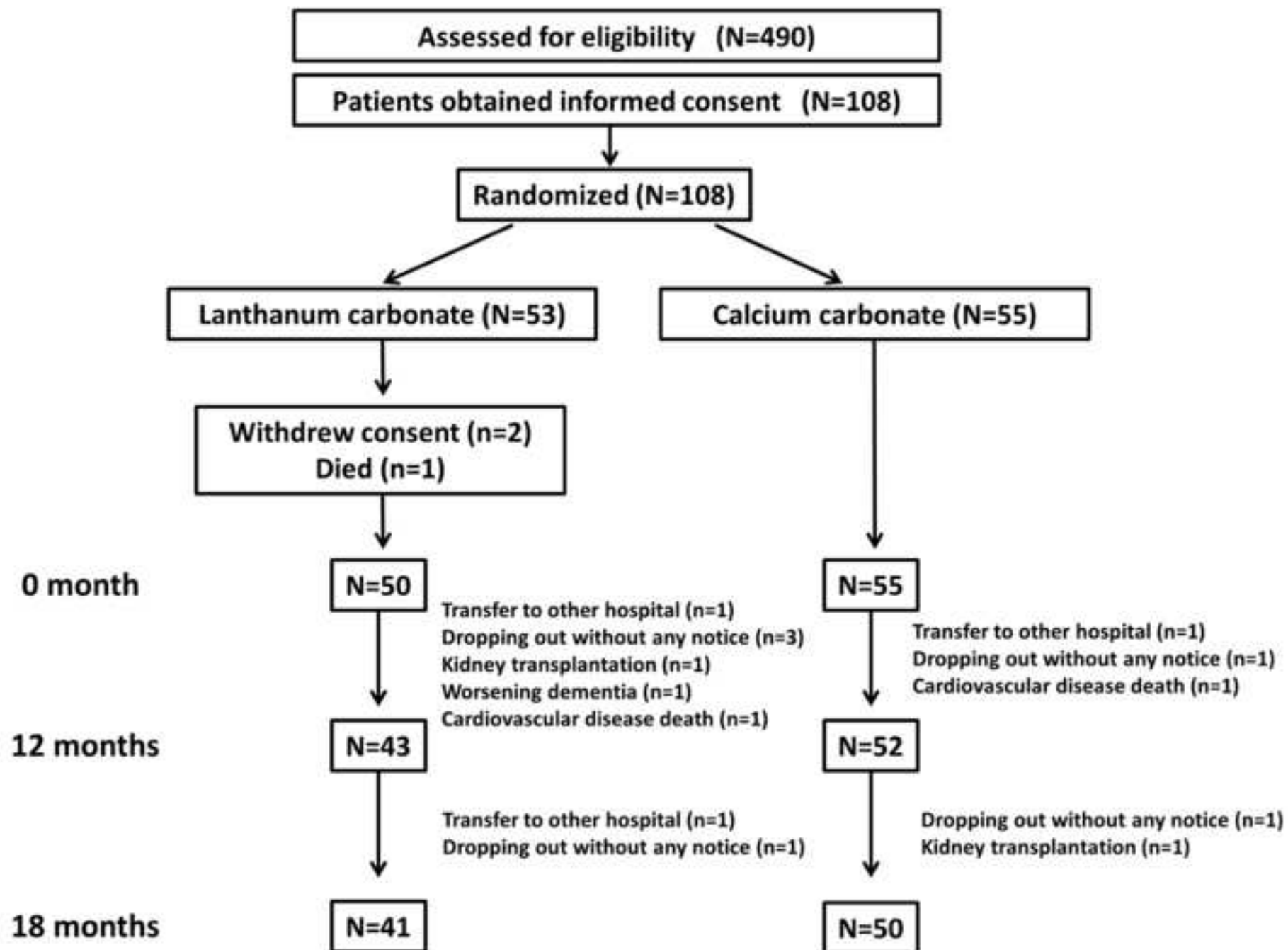
#; LC vs CC, $P < 0.05$

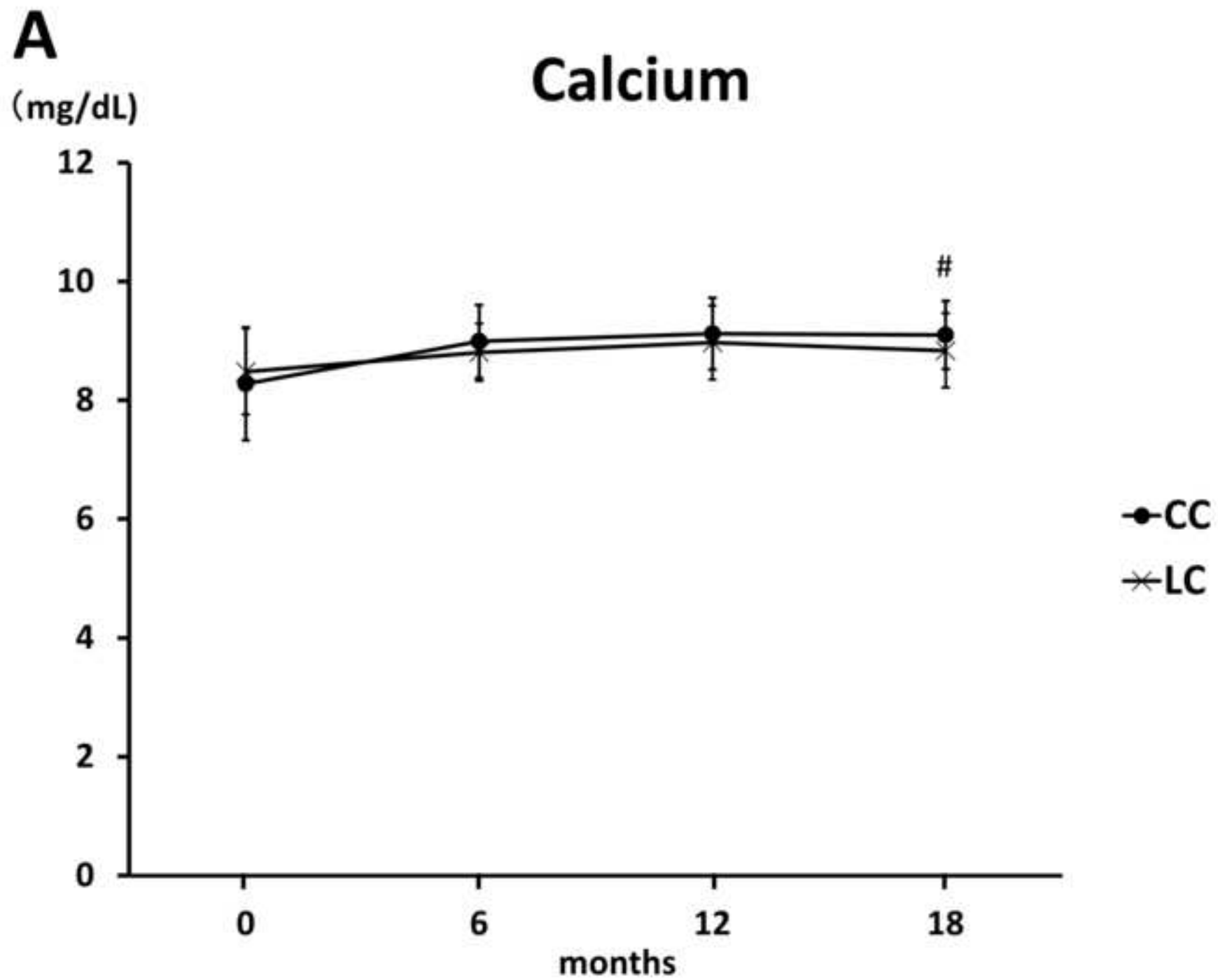
Figure 4 Correlation between log-serum FGF23 levels and % Δ CACS at 18 months

(A) Relationship between log-serum FGF23 levels and % Δ CACS among all the study patients

(B) Relationship between log-serum FGF23 levels and % Δ CACS among the patients with moderate CAC

FGF23: fibroblast growth factor 23; CACS coronary artery calcification score

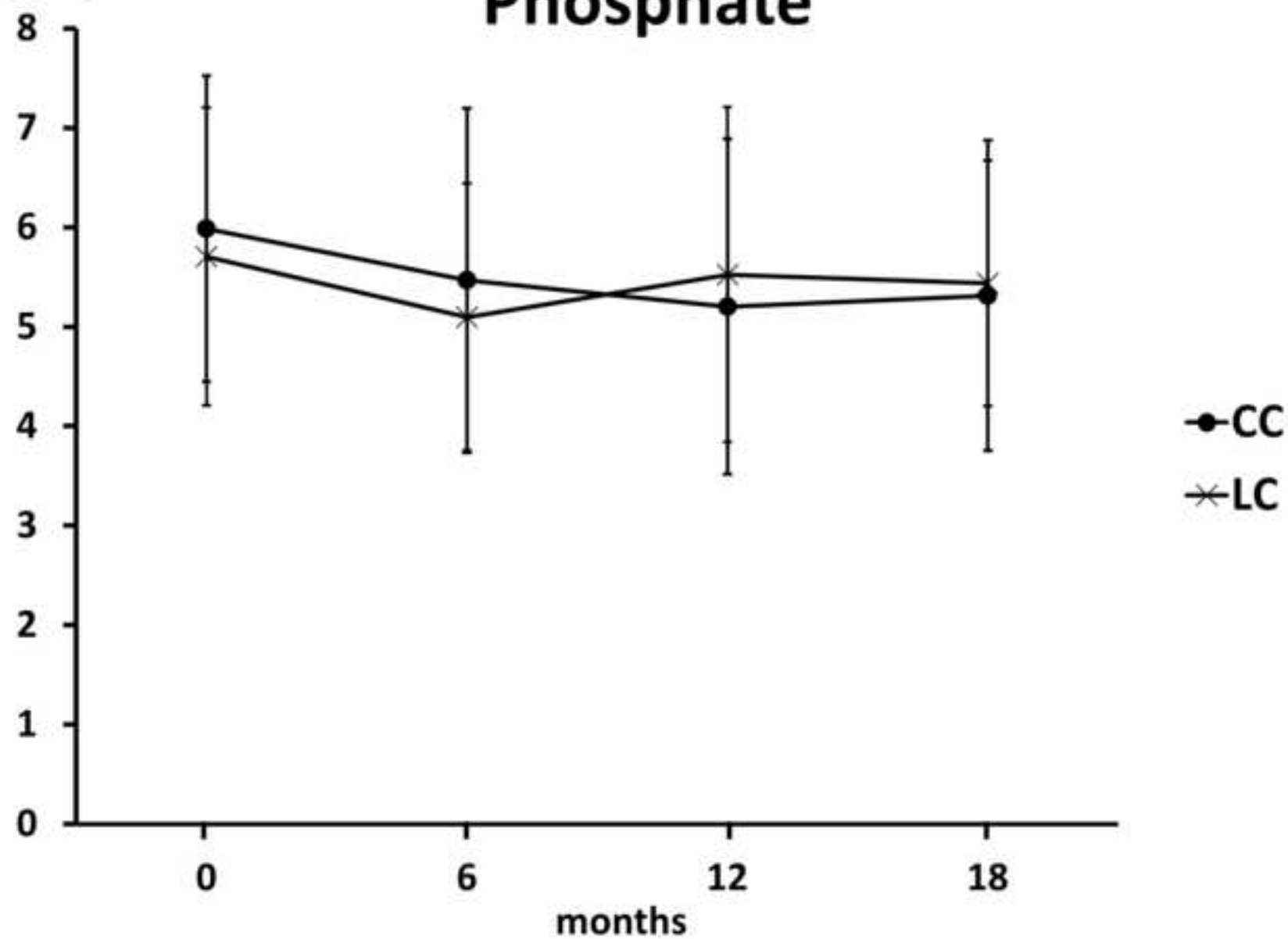


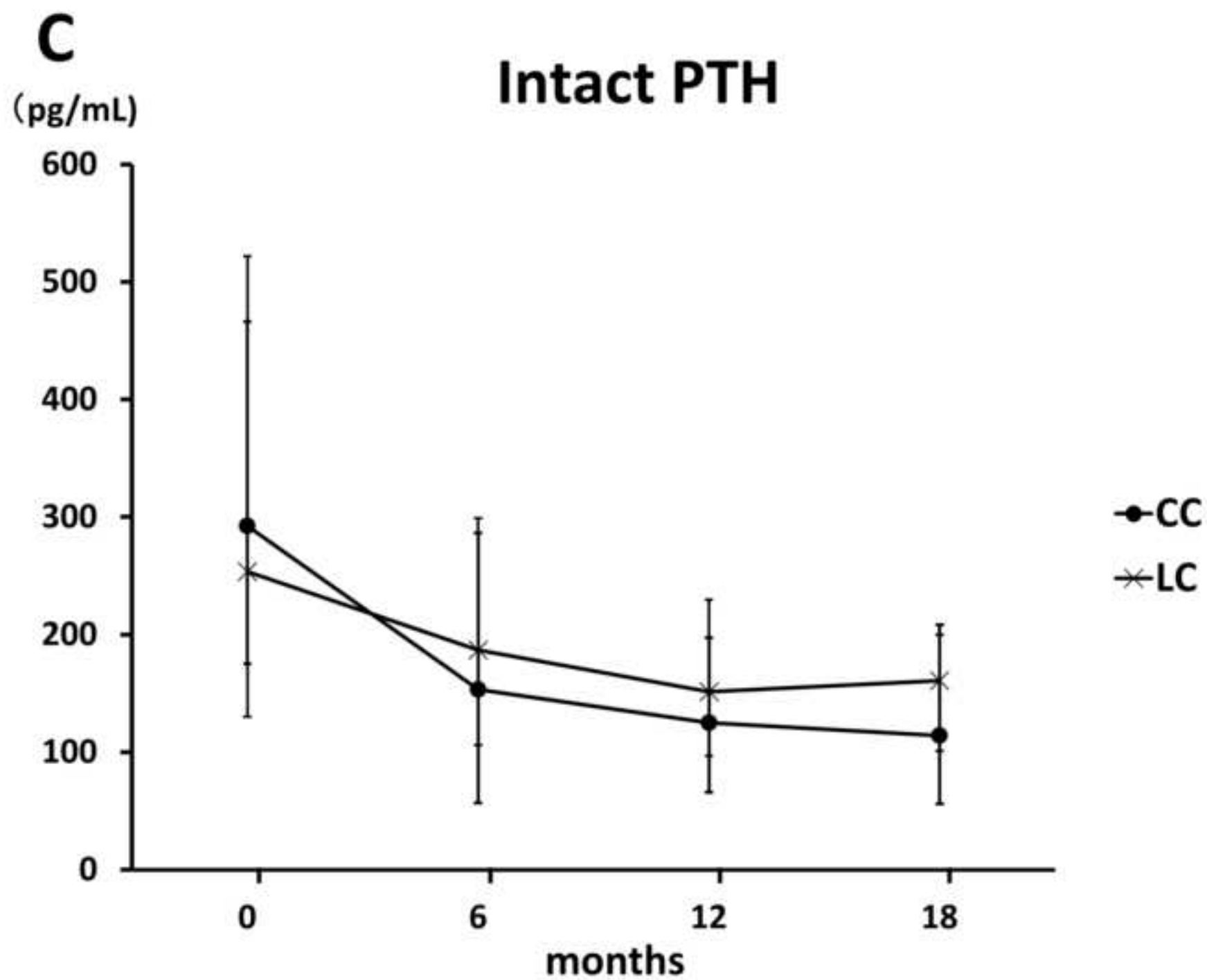


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(mg/dL)

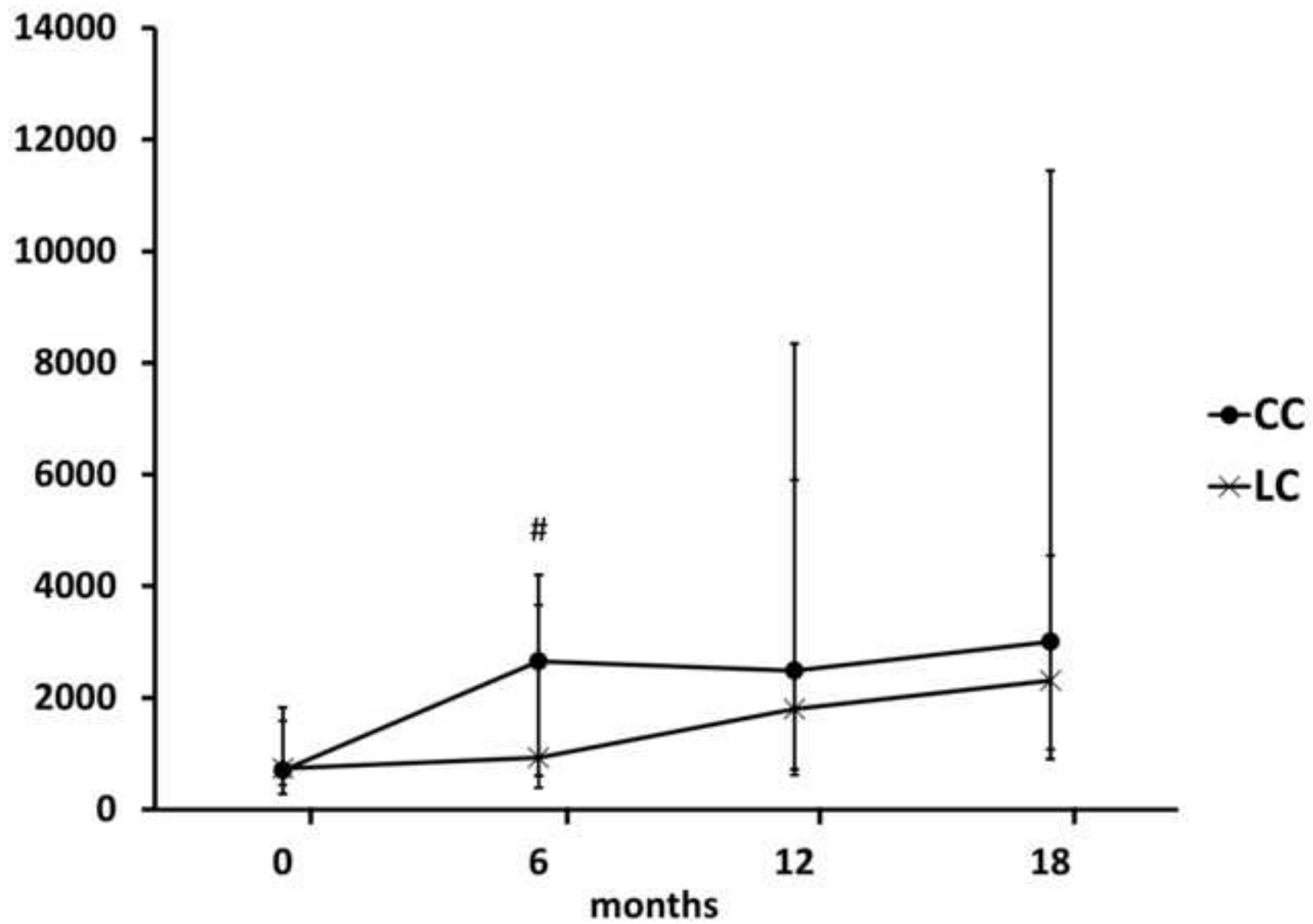
Phosphate





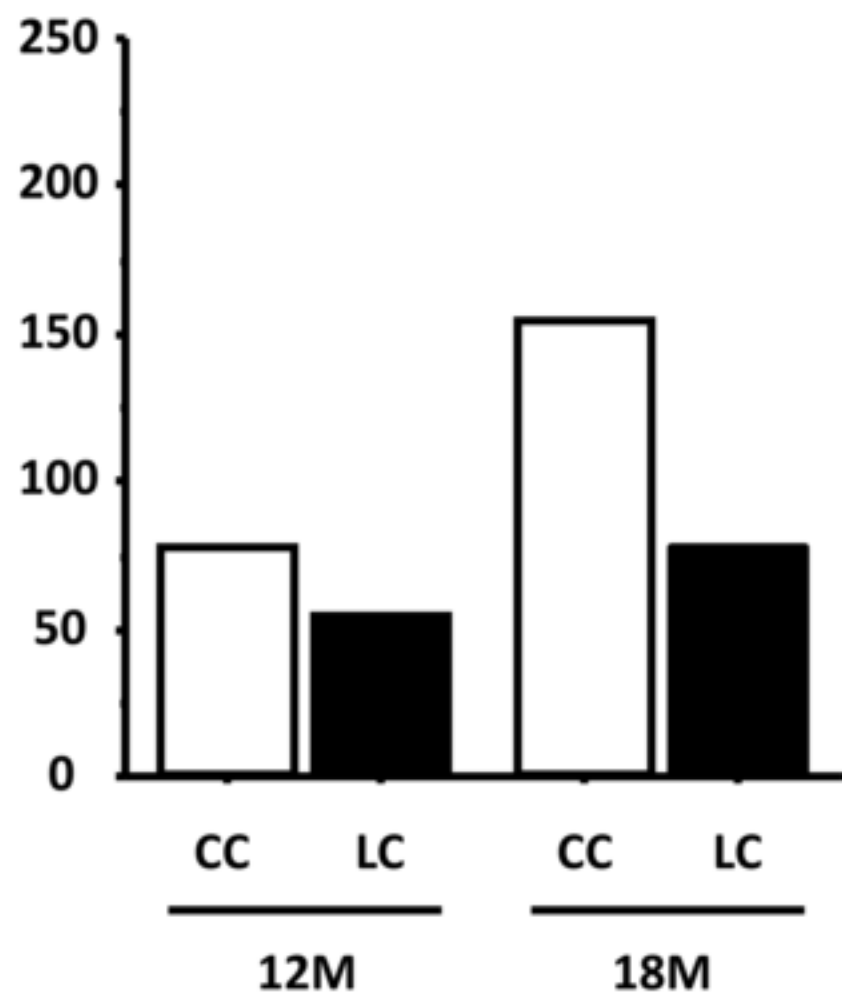
D**FGF23**

(pg/mL)

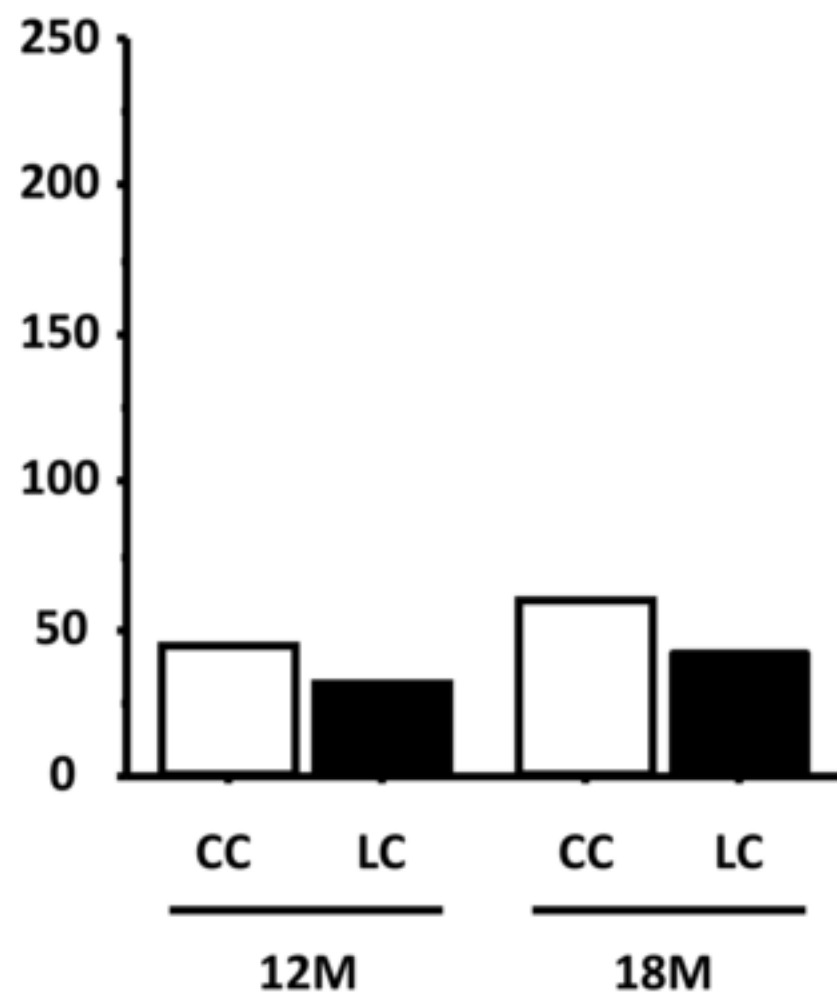


total

Δ CACS



% Δ CACS



$10 \leq \text{CACS} \leq 400$

