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ORIGINAL ARTICLE

Lanthanum carbonate, a phosphate binder, inhibits calcification of implanted aortic allografts in a rat model

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Abstract

Objectives Calcification is one of the major postoperative problems after aortic allograft implantation. We hypothesized that phosphate binders, lanthanum carbonate and calcium carbonate inhibit calcification of implanted aortic allografts and verified this hypothesis using a rat model.

Methods Aortas were harvested from 4-week-old Brown Norway rats and implanted into the subdermal space of 4-week-old Lewis rats. Twenty-seven recipient Lewis rats were divided into Group N, Group L, and Group C (9 rats per group), which were fed a normal diet, a normal diet containing 3% lanthanum carbonate, and a normal diet containing 3% calcium carbonate, respectively. Implanted aortic allografts were explanted 2 weeks later. Calcification of aortic allografts was evaluated using von Kossa staining and calcium content assay. Calcification score was defined in von Kossa staining as 0 (none), 1 (mild), 2 (moderate), and 3 (severe). Serum calcium and phosphorus levels at euthanasia were measured.

Results Calcification scores were 2.6, 1.2, and 0.8, and calcium content was 48.9, 15.8, and 8.9 mg/dry·g, in Groups N, L, and C, respectively. Calcification was significantly reduced in Groups L and C. Serum calcium level was 11.5, 12.2, and 13.5 mg/dl, and serum phosphorus level was 15.4, 12.5, and 11.7 mg/dl, in Groups N, L, and C, respectively. Serum calcium level in Group C was significantly higher than in the other two groups.

Conclusions Lanthanum carbonate and calcium carbonate significantly reduced calcification of implanted aortic allografts in young rats. Although calcium carbonate induced hypercalcemia, lanthanum carbonate has significant potential to inhibit calcification of implanted aortic allografts.

Keywords Aortic allograft · Calcification · Phosphate binder · Lanthanum carbonate

Introduction

Allograft valve/vessel replacement offers superior resistance to infections and has better antithrombotic performance compared to prosthetic valves and vessels [1, 2]. Procured from a donor after cardiac arrest or brain death, allograft valve/vessels are harvested and cryopreserved for use in patients with severe infective endocarditis/infective aortic aneurysm, prosthetic valve infection, vascular prosthesis infection, and some congenital heart diseases [3–6].

Heart valve/vessel allografts, however, gradually degenerate after implantation, and aorta and pulmonary artery allografts often develop severe medial calcification, consequently causing stenosis or pseudoaneurysms; graft dysfunction or rupture sometimes necessitates corrective surgery [7–11]. Young patients—neonates, infants and children—who receive allografts are known to be especially likely to experience allograft degeneration due to calcification in the early stages after implantation. O'Brien et al. collected 1022 cases of aortic valve allografts spanning over 29 years and reported that 93–97% of recipients who were aged 21 or older did not require corrective surgery 10 years after implantation, whereas 47% of those who were aged 20 or younger needed redo surgery [7]. Tweddell et al. studied 205 patients with congenital heart disease who received heart valve/vessel allografts for right ventricular outflow tract reconstruction, and reported that allograft durability was 95% after 1 year, 74% after 5 years, and 54% after 10 years. However, recipients younger than 1 year had a significantly lower rate of graft durability relative to those aged 1 and older [8].

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Regarding the fact that young recipients developed allograft degeneration, primarily due to calcification, in the early stages at a higher rate, Yamauchi et al. have reported that in an animal experiment using rats, one of the causes was physiological hyperphosphatemia in juveniles [12].

Hyperphosphatemia promotes vascular calcification in part by promoting smooth muscle cells to undergo an osteochondrogenic phenotype change through a mechanism requiring sodium-dependent phosphate cotransporters [13]. Phosphorus metabolism is dominated by absorption from the intestines and excretion in the urine; in humans, the reference value for serum phosphorus levels is 2.5–4.5 mg/dl for adults, but about 1.5 times higher, at 4.0–7.0 mg/dl, in children; phosphorus levels gradually decrease with growth. Hyperphosphatemia in children is a physiological phenomenon associated with growth; growth hormone promotes phosphorus reabsorption in the renal tubules [14]. On the contrary, for patients with chronic renal failure who are incapable of full excretion of phosphorus through urine, hyperphosphatemia poses a problem. As serum phosphorus levels increase, the risk of death climbs significantly [15]. Hemodialysis, at the degree that is usually performed, is too inefficient to remove phosphorus to yield sufficient phosphorus excretion; thus, patients with chronic renal failure often take phosphate binders, which bind to phosphates in food to form poorly soluble salts to reduce phosphorus absorption from the intestinal tract.

Even in the reference value for serum phosphorus levels the upper limit is nearly twice as high as the lower limit; thus, it is possible that bringing serum phosphorus levels closer to the lower limit of the reference value might make it possible to curb calcification after aortic allograft implantation. Thus, we used an animal experimental model with healthy rats to examine the hypothesis that "phosphate binders inhibit calcification of implanted aortic allografts". After consulting previous reports [12, 16] studying calcification after aortic allograft implantation, we used a model of abdominal subdermal implantation of an aortic allograft in a young rat as our animal experimental model. The phosphate binders used were lanthanum carbonate, which offers excellent efficacy in lowering serum phosphorus levels with relatively rare side effects, such as gastrointestinal symptoms, having little effect on medication compliance [17], and calcium carbonate, which is inexpensive and has long been clinically used and has no impediments to medication compliance. The dose of phosphate binders in this experiment was set as 3% according to the previous study using uremic rats [18].

Materials and methods

Animal experimental model

A young rat subdermal implantation of an aortic allograft model was used to verify our hypothesis. This study was approved by the animal experimentation committee of the University of Tokyo (Approval no. P07-87).

Three-week-old male Brown Norway (BN) rats and Lewis (LEW) rats were obtained from Japan Charles River, Co., Ltd. and were fed a normal diet containing 0.9% phosphorus and 1.12% calcium (MF®; Oriental Yeast, Co., Ltd, Japan) and tap water ad libitum, unless otherwise stated. BN rats were used as donors, and LEW rats were used as recipients. One week later (at the age of 4 weeks), the rats were anesthetized using intraperitoneal injections of pentobarbital (35 mg per 100 g body weight) and kept under sterile conditions. The whole descending thoracic and abdominal aorta (30–35 mm long) was harvested en bloc from the donor BN rats. Periaortic connective tissues were carefully removed and the aortic allografts were irrigated with normal saline to wash away donor blood. Subsequently, these aortic allografts were immediately implanted into abdominal subdermal space of recipient LEW rats. Following the injection of pentobarbital (35 mg per 100 g body weight) and keeping under sterile conditions, two small mid-abdominal skin incisions were made. A thin stylet was inserted between the two incisions and a subdermal tunnel was made. The donor aortic graft was inserted into the subdermal tunnel and the two incisions were suture-closed.

Twenty-seven recipient LEW rats were divided into three groups according to their postoperative diet. The three groups included Group N: fed the normal MF® diet, Group L: fed the MF® diet containing 3% lanthanum carbonate (FOSRENOL®; Shire plc, USA), and Group C: fed the MF® diet containing 3% calcium carbonate (Caltan®; Fuso Pharmaceutical Industries, Ltd., Japan). Each group consisted of 9 recipient LEW rats.

All recipient LEW rats were anesthetized and euthanized 2 weeks after implantation. Aortic allografts implanted in subdermal spaces were explanted, and the bilateral edges of the allografts were cut and removed. Approximately 5-mm sections of each graft were cut and preserved in 10% formalin for more than 24 h for histopathological examination. The remaining grafts were used for calcium content assay after removing internal fibrin clots and connective tissues on the adventitia. Blood samples were then taken by the right atrial puncture and centrifuged immediately to obtain serum.

Measurement of body weight

Body weight of recipient LEW rats was measured just before and at 1 week after implantation, and 2 weeks later just

before euthanasia. Body weight gain from implantation was expressed as percentage of the body weight at implantation.

Histopathological examination

Hematoxylin–eosin (HE), Elastica-van Gieson (EVG), and von Kossa staining were performed using formalin-fixed allograft samples. Calcium phosphate, which is the main element involved in calcification, was stained black by von Kossa staining. Calcification score was defined semi-quantitatively as follows (Table 1). The ring-shaped sample was estimated by two blinded examiners. Grade 0 represented no calcification, grade 1 represented mild calcification: less than one-fifth of the circle was calcified, grade 2 represented moderate calcification: one-fifth to half of the circle was calcified, and grade 3 represented severe calcification: more than half the circle was calcified.

Graft tissue calcium content assay

Calcium content of explanted aortic allografts was measured using atomic absorption spectroscopy in the laboratory of SRL Inc. (Tokyo, Japan). Explanted aortic allografts were air-dried and weighed. The allografts were dissolved in nitric acid and hydrogen peroxide solution. Calcium content of this solution was measured by absorbance of the calcium atom and was standardized by dividing by the dry weight of the sample.

Blood biochemistry testing

Serum calcium and phosphorus levels were measured in the laboratory of SRL Inc. (Tokyo, Japan).

Statistical analysis

Statistical analyses were performed with JMP 8 (SAS Institute Japan Ltd., Tokyo, Japan). Continuous variables are expressed as mean ± standard error of mean. The results between two groups were compared with *t* tests and $p < 0.05$ was considered statistically significant.

Table 1 Calcification score

Calcification score	
0	None: no calcification
1	Mild: less than one-fifth of the circle was calcified
2	Moderate: one-fifth to half the circle was calcified
3	Severe: more than half the circle was calcified

A ring-shaped histopathological sample was evaluated using von Kossa staining, and amount of calcification in each sample was given a calcification score by two blinded examiners

Results

Histopathological examination

Figure 1 shows representative histopathological images with HE, EVG and von Kossa staining for each group. HE and EVG staining showed several ruptures of the medial elastic lamina in Group N, and von Kossa staining showed strong calcification at the same site (top of Fig. 1). Such rupturing of the medial structure was only mild in Group L (middle of Fig. 1) and Group C (bottom of Fig. 1), which are the groups that received phosphate binders.

The calcification score was 2.6 ± 0.2 in Group N, 1.2 ± 0.4 in Group L, and 0.8 ± 0.4 in Group C, representing a significant difference between Groups N and L, and between Groups N and C, but no significant difference between Groups L and C (Fig. 2). The calcification score established in the von Kossa staining for assessing calcification histopathologically was significantly lower in groups that received phosphate binders.

Graft tissue calcium content assay

The calcium content (mg) per 1 g of dried allograft tissue, measured using atomic absorption spectroscopy, was 48.9 ± 8.7 in Group N, 15.8 ± 3.4 in Group L, and 8.9 ± 3.4 in Group C, representing a significant difference between Groups N and L and between Groups N and C, but no significant difference between Groups L and C (Fig. 3). Calcium content in the allograft tissue was also significantly lower in the groups that received phosphate binders.

Blood biochemistry testing

Serum calcium levels (mg/dl) were 11.5 ± 0.3 in Group N, 12.2 ± 0.2 in Group L, and 13.5 ± 0.4 in Group C, with serum calcium levels significantly higher in Group C than in Groups N or L (Fig. 4a).

Serum phosphorus levels (mg/dl) were 15.4 ± 0.3 in Group N, 12.5 ± 0.5 in Group L, and 11.7 ± 0.4 in Group C, with equivalent decreases in serum phosphorus levels observed in Groups L and C compared to Group N, and no significant difference between Groups L and C (Fig. 4b).

The product of serum calcium and phosphorus levels ($Ca \times P$; mg^2/dl^2) was 176.5 ± 6.8 in Group N, 152.3 ± 4.9, in Group L, and 157.5 ± 8.8 in Group C. It was highest in Group N, and significantly lower in Group L. Though it was lower in Group C than in group N, there was no significant difference between the two groups (Fig. 4c).

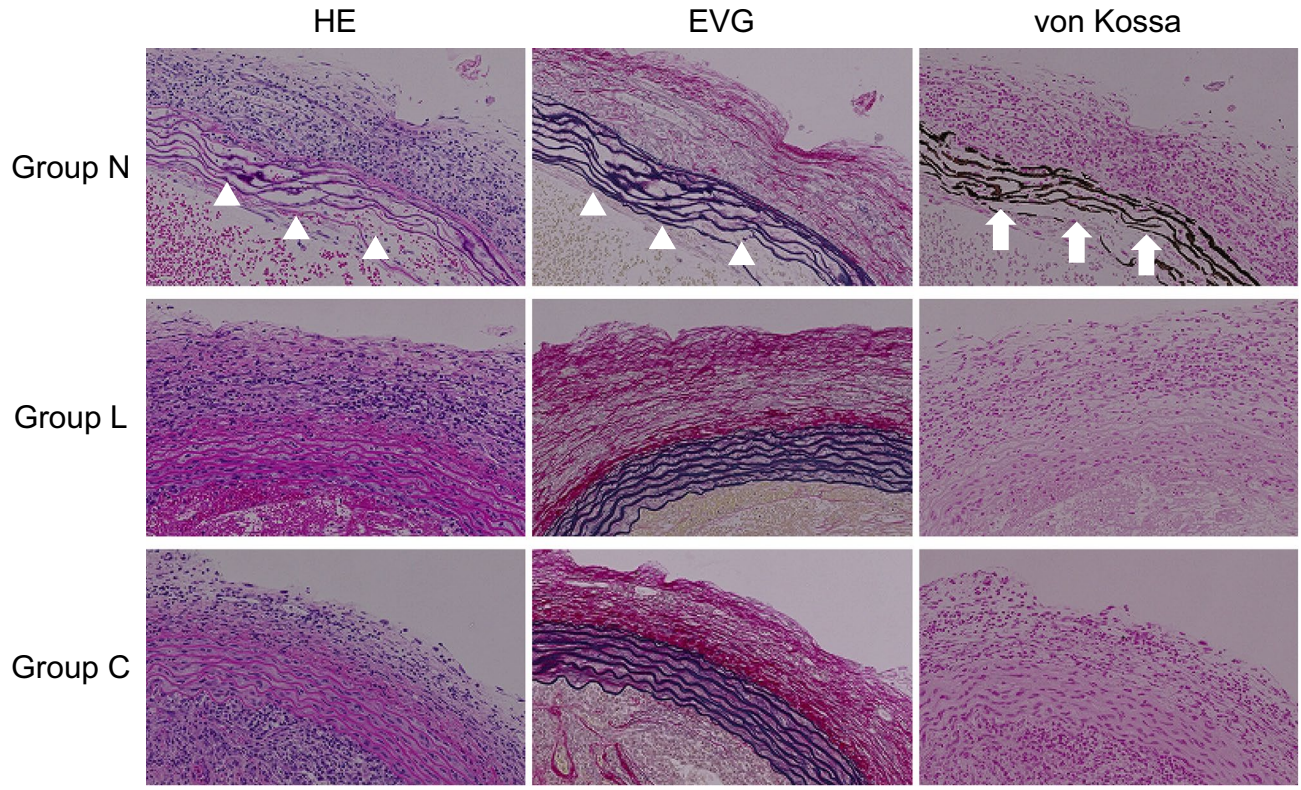

Fig. 1 Representative histopathological images. *HE* hematoxylin–eosin, *EVG* Elastica-van Gieson. HE and EVG staining showed several ruptures of the medial elastic lamina (white arrowheads) in Group N, and von Kossa staining showed strong calcification at the same site (white arrows) (top). Such rupturing of the medial structure was only mild in Group L (middle) and Group C (bottom), which are the groups that received phosphate binders

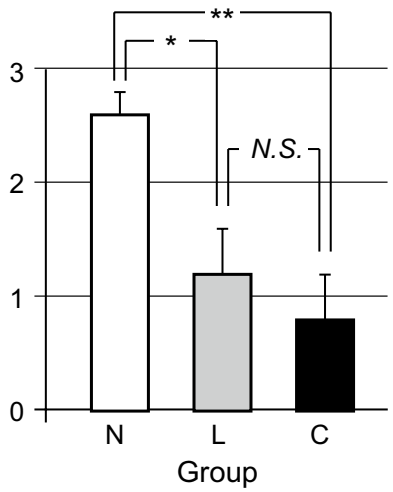

Fig. 2 The calcification score. Box: mean, bar: standard error of mean, $n=9$ per group. *$p<0.05$, **$p<0.01$. *NS* not significant. The calcification score was significantly lower in Groups L and C than in Group N, but there is no significant difference between Groups L and C

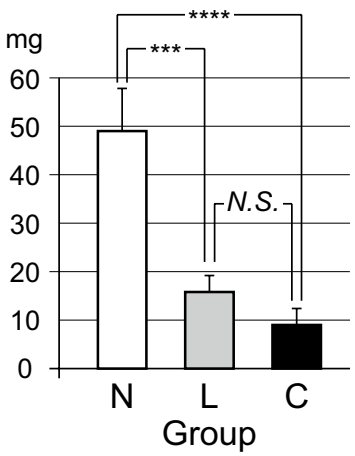

Fig. 3 Calcium content per 1 g of dried allograft tissue. Box: mean, bar: Standard error of mean, $n=9$ per group. ***$p<0.001$, ****$p<0.0001$. *NS* not significant. Calcium content was significantly lower in Groups L and C than in Group N, but there is no significant difference between Groups L and C

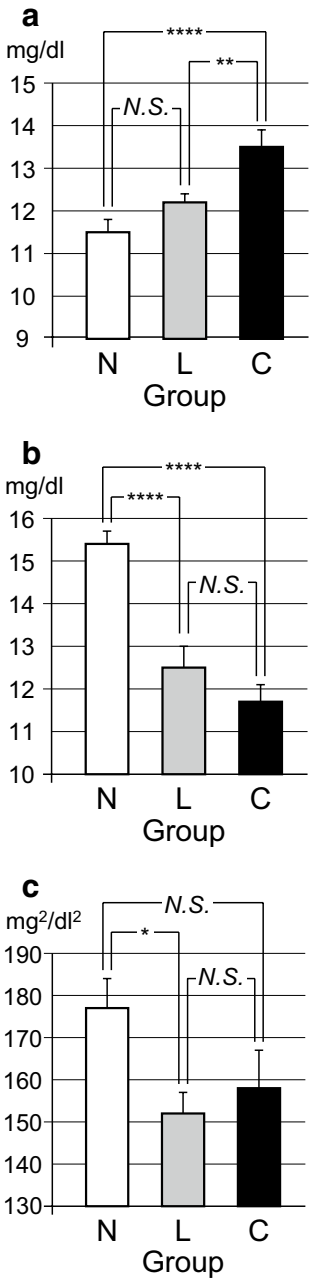

Fig. 4 Blood biochemistry testing. **a** Serum calcium levels. **b** Serum phosphorus levels. **c** The product of serum calcium and phosphorus levels (Ca×P). Box: mean, bar: standard error of mean, $n=9$ per group. *$p<0.05$, **$p<0.01$, ****$p<0.0001$. *NS* not significant. **a** It showed significant hypercalcemia in Group C. **b** Equivalent decreases in serum phosphorus levels were observed in Groups L and C. **c** It was highest in Group N, and significantly lower in Group L. Though it was lower in Group C than in group N, there was no significant difference between the two groups

Body weight gain

Body weight gain of recipient LEW rats was expressed as percentage of the body weight at implantation (Fig. 5a, b).

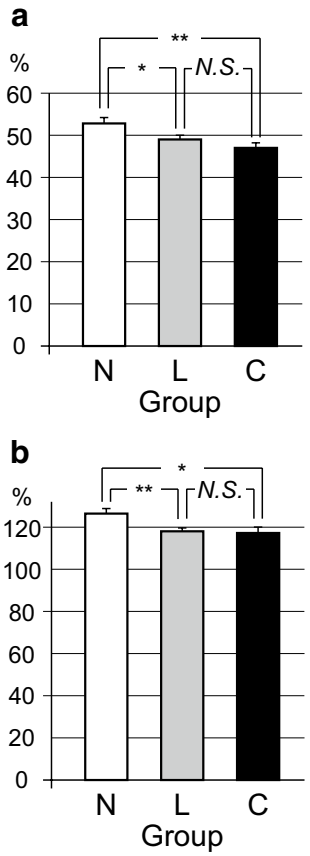

Fig. 5 Body weight gain. **a** 1 week after implantation. **b** 2 weeks after implantation just before euthanasia. Box: mean, bar: standard error of mean, $n=9$ per group. *$p<0.05$, **$p<0.01$. *NS* not significant. Body weight gain of Groups L and C was less than Group N statistically both at 1 week and 2 weeks after implantation

Body weight gain of Groups L and C was less than Group N statistically, though the actual difference of body weight gain between the groups was small. Any pathological bone fracture was not observed during the experimental period.

Discussion

In this young rat subdermal implantation of an aortic allograft model, the calcification score (Table 1)—a quantification of the extent of calcification in the histopathological samples of explanted allografts—was significantly lower in Groups L and C, which were the groups that received phosphate binders, than Group N (Fig. 2), suggesting that calcification had been suppressed in the groups that received phosphate binders. The groups that received phosphate binders—Groups L and C—also had significantly lower calcium content in the explanted allograft tissue than Group N (Fig. 3), also implying that calcification was suppressed in the groups that received phosphate binders.

Meanwhile, Group C exhibited a significant increase in serum calcium levels, which was attributed to an increase in calcium absorption from the administration of calcium carbonate (Fig. 4a). Hypercalcemia is a concern because it may increase the risk of impaired consciousness, arrhythmia, and other problems. Although calcium carbonate significantly suppressed serum phosphorus levels (Fig. 4b), the elevated serum calcium levels eliminated significant difference in Ca × P—though it did tend to be lower—when compared to Group N (Fig. 4c). In contrast, lanthanum carbonate significantly suppressed Ca × P as compared to Group N (Fig. 4c). An elevated Ca × P is generally known to raise the risk of ectopic calcification [15, 19] and higher Ca × P has also been implicated in a higher risk of death due to cardiovascular disease in epidemiological research in general population cohorts [20]. Though the present animal experimental model showed that calcium carbonate suppressed calcification of implanted aortic allografts equivalent to lanthanum carbonate, lanthanum carbonate is potentially safer and more useful than calcium carbonate in points of hypercalcemia and decreased Ca × P.

It has not been previously reported that long-term administration of phosphate binders to healthy individuals reduces serum phosphorus levels. If phosphorus levels are reduced too much, it could lead to phosphorus deficiency-based osteomalacia or rickets. In particular, hyperphosphatemia in juveniles is a physiological phenomenon associated with growth, and excessive suppression of phosphorus absorption due to administering phosphate binders that would impair growth or cause pathological bone fractures is a concern. In this experiment, body weight gain was less in groups L and C that received phosphate binders than in group N (Fig. 5). The difference of body weight gain was statistically significant, but no pathological bone fracture was observed, and it was not clear whether the difference was clinically significant. Because this experiment was short, at only 2 weeks, further and long-term evaluation is required. And also the dose of phosphate binders in this experiment was decided according to the previous study using uremic rats [18]. Lower dose of phosphate binders might be enough for healthy rats to reduce aortic allograft calcification. Actually, the difference between the upper and lower limits of the reference values for serum phosphorus levels in healthy humans is close to twofold, and adjusting the phosphate binder dosage to achieve mild long-term phosphorus suppression targeting the lower limit of the reference value may offer the ability to suppress calcification of grafts without impairing growth or causing osteomalacia; this should be the topic of a future study.

The adverse events from long-term administration of lanthanum carbonate or calcium carbonate to healthy individuals are also noteworthy. Calcium carbonate has long been used for patients with chronic renal failure, and adverse events have not caused much concern beyond an elevated likelihood of hypercalcemia [21]. Long-term administration of lanthanum carbonate creates the risk of toxicity or accumulation of lanthanum, which is a rare earth transition element, but almost no lanthanum is absorbed from the digestive tract [22, 23]. What little lanthanum is absorbed is mostly excreted in bile [24], with no hepatotoxicity observed from accumulation in the hepatobiliary system [25]. Bone or central nervous system toxicity—a problem that has appeared with aluminum hydroxide gel, which had been used as a phosphate binder [26]—has not been reported and even long-term administration may be safe [27–30].

The present study focused on the acceleration of aortic allograft calcification in young recipients to study how phosphate binders can suppress calcification in light of the involvement of physiological hyperphosphatemia. However, in actual clinical practice, calcification after aortic allograft implantation is also frequently observed in middle-aged and elderly patients, though not as early or frequently as with young individuals. Middle-aged and elderly humans also have close to a twofold difference between the upper and lower limits of the reference values for serum phosphorus levels, and mild phosphorus suppression may, similar to young individuals, potentially suppress calcification after aortic allograft implantation.

There are limitations in this study. First, though the presence of blood flow and blood pressure of the vessels is an important factor for the degeneration such as calcification, subdermal implantation model was adopted for the present animal experiment, because previous reports which adopted this model showed calcification was reproducibly yielded in the control group in short study period [12, 16]. Validation in larger animals having blood flow and blood pressure that clinically resemble humans more closely will be required. Second, since the period of aortic allograft implantation in this experiment was short (2 weeks), further evaluation with longer term is also necessary.

Conclusion

Phosphate binders, lanthanum carbonate and calcium carbonate significantly reduced calcification scores and calcium content of implanted aortic allografts in a young rat subdermal implantation model. Although calcium carbonate induced hypercalcemia, lanthanum carbonate has significant potential to inhibit calcification of implanted aortic allografts. This should be verified by large animal experimental models having blood flow and blood pressure or using adult animals in the future.

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Compliance with ethical standards

Conflict of interest The authors have declared that no conflict of interest exists.

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