Differences in gastrointestinal calcium absorption after the ingestion of calcium-free phosphate binders

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Behets GJ, Dams G, Damment SJ, Martin P, De Broe ME, D’Haese PC. Differences in gastrointestinal calcium absorption after the ingestion of calcium-free phosphate binders. Am J Physiol Renal Physiol 306: F61–F67, 2014. First published November 6, 2013; doi:10.1152/ajprenal.00219.2013.—Both calcium-containing and noncalcium-containing phosphate binders can increase gastrointestinal calcium absorption. Previously, we observed that lanthanum carbonate administration to rats with renal failure is not associated with increased calcitria. Additionally, lanthanum carbonate treatment in dialysis patients has been associated with a less pronounced initial decrease in serum parathyroid hormone compared with other phosphate binders. For 8 days, male Wistar rats received a diet supplemented with 2% lanthanum carbonate, 2% sevelamer, 2% calcium carbonate, or 2% cellulose. Calcitria was found to be increased in animals with normal renal function treated with sevelamer or calcium carbonate but not with lanthanum carbonate. In animals with renal failure, cumulative calcium excretion showed similar results. In rats with normal renal function, serum ionized calcium levels were increased after 2 days of treatment with sevelamer, while calcium carbonate showed a smaller increase. Lanthanum carbonate did not induce differences. In animals with renal failure, no differences were found between sevelamer-treated, calcium carbonate-treated, and control groups. Lanthanum carbonate, however, induced lower ionized calcium levels within 2 days of treatment. These results were confirmed in normal human volunteers, who showed lower net calcium absorption after a single dose of lanthanum carbonate compared with sevelamer carbonate. In conclusion, these two noncalcium-containing phosphate-binding agents showed a differential effect on gastrointestinal calcium absorption. These findings may help to improve the management of calcium balance in patients with renal failure, including concomitant use of vitamin D.

Due to their low cost and relatively good efficacy, calcium-containing phosphate binders (calcium acetate and calcium carbonate) are widely used. However, the use of these agents may go along with a positive calcium balance incidentally expressed by hypercalcemia. The increased gastrointestinal calcium absorption in patients receiving vitamin D supplements can further aggravate the calcium load, particularly when, in addition, the dialysate calcium is not adapted properly (22). It has been widely recognized that increased calcium loading in patients with end-stage renal disease is associated with increased vascular calcification, which is an independent mortality risk factor in this population (9, 16). As a result of the concerns regarding the use of calcium-containing phosphate binders, noncalcium-containing phosphate binders (such as sevelamer and lanthanum carbonate) could prove beneficial in some patients.

An important, although possibly overlooked, issue going along with the use of phosphate-binding agents consists of the fact that during phosphate complexation in the gut, calcium phosphate complexes already present will become dissociated. While the phosphate is subsequently captured by the phosphate-binding agent, more free calcium becomes available for intestinal absorption (i.e., the counter-ion effect), which, in turn, may augment the calcium load leading to hypercalcemia and hypercalciuria (13). Hence, whereas in CKD an increased calcium load is traditionally regarded as a problem inherent to the use of calcium-containing phosphate binders, it also occurs with the use of noncalcium-containing phosphate binders. Indeed, in an elegant balance study (20) in subjects with normal renal function and CKD at stages 1–3, a pronounced decrease in phosphaturia along with a striking increase of calcitria was observed within 6 days of use of aluminum hydroxide gels. Lotz et al. (14) performed calcium and phosphate balance experiments in patients with (pseudo)hypoparathyroidism and in normal volunteers using antacids (aluminum/magnesium hydroxide and aluminum hydroxide). All investigated subjects demonstrated a substantial decrease of phosphaturia, increase in calcitria and a tendency to hypophosphatemia. The sources of urinary calcium include both the gastrointestinal tract and bone. Indeed, fecal calcium fell from control values of ~200 to 75–90 mg/day. Using Ca47, it could be shown that this decline represented an actual increase in gastrointestinal absorption (75% calcium absorption under antacids). Calcium phosphate binding agents, which, by binding phosphate in the gut, limit its absorption and accumulation, hence contributing to the prevention of the development of secondary hyperparathyroidism.

Proper management of mineral metabolism remains an important challenge in the treatment of patients with chronic renal failure (12a, 25). The declined renal function inevitably leads to an increase in serum FGF-23 levels and a decrease in vitamin D levels, which, in turn, result in secondary hyperparathyroidism and mineral disturbances, generally termed as chronic kidney disease-mineral and bone disorder (CKD-MBD) (12a). An important tool in the clinical management of these patients are orally administered phosphate-binding agents, which, by binding phosphate in the gut, limit its absorption and accumulation, hence contributing to the prevention of the development of secondary hyperparathyroidism.
sevelamer or lanthanum carbonate, in doses having the same effect on phosphatemia and phosphaturia, showed different effects on calcitriol. Whereas sevelamer treatment resulted in the “classical” increase of calcitriol, inherent to gastrointestinal phosphate binding, this increase was not seen in animals that received lanthanum carbonate (1). Concomitantly, experimental as well as clinical studies have reported a modest decrease in parathyroid hormone (PTH) levels at the start of treatment using sevelamer, whereas similar studies using lanthanum carbonate showed no decrease (8, 17, 21), although these differences could be partly due to differences in study design. Second, a comparison of the evolution of the type of renal osteodystrophy during treatment with sevelamer versus calcium carbonate showed no differences in the prevalence of adynamic bone disease in both groups, whereas in a separate study that compared calcium carbonate with lanthanum carbonate, a significantly higher number of patients treated with calcium carbonate developed adynamic bone disease after a 1-yr treatment period (5, 7).

A possible explanation for the observation that lanthanum carbonate apparently induces less calcium loading may be that lanthanum also is an efficient calcium channel blocker. An in vitro study (11) has shown that lanthanum at a 0.5 mM (70 mg/l) concentration can inhibit up to 90% of calcium transport, as studied in two different types of 1,25-(OH)2 vitamin D-responsive epithelia. In the systemic circulation, this effect is unlikely to occur since the gastrointestinal absorption of lanthanum is very low (<0.002%) and >95% of the absorbed fraction circulates as protein bound, resulting in free lanthanum concentrations of <20 ng/l (0.15 nM) in patients who received lanthanum-based phosphate binder treatment (3, 6).

Furthermore, since the majority of lanthanum is excreted in the bile, end-stage renal disease patients are not at increased risk for accumulation of the element. However, in the gut, the situation may be different. Although not yet investigated, one may anticipate that a 0.5 mM concentration of lanthanum could be present along the gastrointestinal tract in patients treated with 3–4 g/day elemental lanthanum (~20 mmol/day). As a result, calcium channels in the gut may be (partially) blocked, thereby diminishing gastrointestinal calcium absorption.

Takemori, the observations made on calcitriol in rats, the serum PTH values in patients, the evolution of bone disease after 1 yr of treatment, and the potential effects of lanthanum on calcium channel-mediated transport form the base of the working hypothesis of the present study, which aimed to present further evidence showing that two noncalcium-containing phosphate binders (i.e., sevelamer and lanthanum carbonate) may have different effects on gastrointestinal calcium absorption. These issues were approached via an experimental setup as well as a clinical setup.

The important role of calcium balance and PTH among other factors in the generation and/or progression of vascular calcifications and the development of low bone turnover in renal failure patients with calcium overload strongly support the clinical relevance of this investigation.

MATERIALS AND METHODS

Animal Study

Experimental procedures were conducted according to the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Ethical Committee of the University of Antwerp. Male Wistar rats (body weight: 200 g at the start of the study) were used for the animal study. In the first setup, animals with normal renal function were used, whereas in the second setup, chronic renal failure was induced by 5/6th nephrectomy. In either setup, after a 1-wk stabilization period, animals were divided into four groups (n = 6 animals/group) that received lanthanum carbonate, sevelamer, calcium carbonate, or cellulose (2% each) in regular rodent diet containing 0.7% phosphorus and 1.0% calcium for 8 consecutive days. Animals were housed in metabolic cages to perform daily 24-h urine collections, which were stored at −20°C pending analysis for calcium and phosphorus levels. After the 8-day treatment period, all animals were given regular food without phosphate binders for a 6-day washout period, during which time the urine collections continued. To avoid loss of urine during blood sampling, four parallel groups (n = 10 animals/group) were treated similarly, but not housed in metabolic cages, and used for regular blood collections every 2 days. Half of these animals (n = 5 animals/group) were euthanized immediately after the treatment period to allow collection of a large blood volume for PTH measurements.

Hematocrit and serum ionized calcium were monitored using a Vitros autoanalyzer. Urinary calcium was measured using flame atomic absorption spectrometry, and urinary phosphorus levels were measured using a colorimetric-based method. Intact PTH levels were analyzed using a rat PTH IRMA (Immunotopics) performed according to the manufacturer’s instructions.

Clinical Study

In the clinical study, which was initially set up to evaluate the phosphate-binding efficacy of lanthanum carbonate versus sevelamer (15), calcium balance was also determined. In brief, 31 volunteers (age: 19–45 yr) with normal renal function were randomized to one of six treatment sequences, each consisting of four treatment periods separated by a 7- to 14-day washout. In each of the first three periods, participants received a meal standardized for phosphate and calcium content, the standard meal plus lanthanum carbonate (a single tablet containing 1,000 mg elemental lanthanum), or the standard meal plus sevelamer carbonate (2,400 mg, 3 × 800-mg tablets). The sequence of these treatments was also randomized. After checking into the Clinical Research Centre on day −1, subjects received a clear liquid dinner. After dinner on day −1, subjects fasted and were restricted to deionized water. No liquids other than deionized water were allowed for ~2 h before and 2 h after dosing. Subjects fasted until the lunchtime meal on day 1. Medicinal product was administered with lunch and accompanied by 250 ml deionized water containing 10 g polyethylene glycol as a nonabsorbable marker. Identically prepared meals were served to subjects on day 1 of the first three treatment periods. Additional, identically prepared meals were analyzed for calcium and phosphorus content. Mannitol solution administration was initiated (by nasogastric tube) ~4 h before the administration of the medicinal product with lunch as well as 10 h postadministration. Rectal effluent samples were collected for at least 4 h after the administration of the second mannitol solution until the subject’s stool was clear of solid material. Participants repeated the study procedures while fasting in the fourth period. Doses were chosen based on those typically used in clinical trials of sevelamer hydrochloride and lanthanum carbonate. Calcium and phosphorus were measured in the rectal effluent.

Statistical Analysis

Animal study. Results are shown as mean ± SD. Statistical analysis was performed using SPSS (version 16.0). A Kruskall-Wallis test was
used to test for differences between treatment groups followed by a Mann-Whitney U-test with the Bonferroni correction when appropriate.

Clinical study. Statistical analysis was performed using SAS (version 9.2) using a standard mixed-effect linear model (15) with adjustment for group sequence, period, and treatment as fixed effects; subject within sequence was included as a random effect.

RESULTS

Animals With Normal Renal Function

Food and water consumption as well as animal weight did not differ between treatment groups (results not shown). Serum hematocrit values showed a decline during the first treatment days in all treatment groups, which stabilized after 3 days (results not shown).

Total serum calcium levels showed no significant differences between treatment groups at any of the time points (Table 1). Lanthanum carbonate treatment did not induce statistically significant changes in ionized calcium levels compared with the control group. In contrast, treatment with calcium carbonate induced a slight elevation of ionized calcium levels versus the control group (statistically significant after 2 and 3 days of treatment), whereas treatment with sevelamer induced a statistically significant increase in ionized calcium levels from day 2 until the end of treatment. During washout, ionized calcium levels returned to baseline within 24 h in both treatment groups (Fig. 1, top). Serum PTH levels did not show statistically significant differences between treatment groups (Table 1).

After lanthanum carbonate treatment, urinary calcium excretion showed no statistically significant differences compared with the control group. Calcium carbonate treatment resulted in a small increase, which was statistically significant only on days 4 and 5 of treatment. Sevelamer treatment resulted in statistically significant increases after 4 days of treatment, which persisted until 24 h after washout. After 48 h of washout, all values returned to normal (Fig. 1, bottom).

Serum phosphorus levels showed no differences between treatment groups at any time point (results not shown). Phosphate binder treatment resulted in decreased urinary phosphate excretion, which became statistically significant in calcium carbonate- and sevelamer-treated animals (Fig. 1, middle). After washout, all values returned to control values within 24 h.

Animals With Chronic Renal Failure

Serum hematocrit levels showed a similar decline as noted in animals with normal renal function. No statistically significant differences between treatment groups were noticed (results not shown).

Total serum calcium and PTH levels showed no statistically significant differences between treatment groups (Table 1). However, throughout the treatment period, animals treated with lanthanum carbonate showed consistently lower mean serum ionized calcium levels compared with animals in the other treatment groups, although statistical significance was not achieved at all time points. Twenty-four hours after the end of treatment, serum ionized calcium levels in the lanthanum-treated group rose again, and no further differences with other treatment groups were found. Treatment with calcium carbonate or sevelamer did not induce statistically significant changes in serum ionized calcium levels versus baseline (Fig. 2, top).

Urinary calcium excretion showed a high variability during treatment, which stabilized during washout. Although statistical significance was not consistently reached, vehicle-treated animals showed the lowest urinary calcium excretion, whereas calcium carbonate and sevelamer treatment resulted in the highest urinary calcium excretion during treatment. By calculating the cumulative calcium excretion, differences become clearer. After 8 days of treatment with calcium carbonate or sevelamer, cumulative calcium excretion was significantly higher (P < 0.05) compared with treatment with vehicle. Lanthanum carbonate treatment did not result in an increase in calcium excretion versus the control group, which received vehicle only (Fig. 2, middle).

After 8 days of treatment, phosphorus excretion in vehicle-treated animals was significantly higher (P < 0.05) than in animals treated with one of the phosphate-binding agents. Again, no differences in cumulative phosphaturia between phosphate binders were found (Fig. 2, bottom).

Clinical Study

Of the 31 randomized volunteers, 18 volunteers completed the study and were eligible for the primary analysis. Of the 13 subjects not included, 4 subjects had an adverse effect leading to discontinuation of the study drug, 2 subjects refused further participation in the study, and a further 6 subjects discontinued due to other reasons: problems with collection of rectal effluent

Table 1. Serum total calcium and PTH levels in male Wistar rats treated with phosphate-binding agents for 8 days followed by a 6-day washout period

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Calcium, mg/dl</th>
<th>PTH, pg/ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before treatment</td>
<td>After Treatment</td>
</tr>
<tr>
<td>Normal renal function</td>
<td></td>
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<tr>
<td>Vehicle</td>
<td>6.7 ± 0.7</td>
<td>9.0 ± 0.8</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>7.7 ± 0.9</td>
<td>8.9 ± 1.3</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>7.7 ± 0.6</td>
<td>10.2 ± 0.4</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>7.8 ± 0.4</td>
<td>8.3 ± 1.2</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td>7.6 ± 0.4</td>
<td>7.6 ± 0.4</td>
</tr>
<tr>
<td>Lanthanum carbonate</td>
<td>8.0 ± 0.5</td>
<td>8.3 ± 1.8</td>
</tr>
<tr>
<td>Sevelamer</td>
<td>7.9 ± 0.5</td>
<td>7.9 ± 0.4</td>
</tr>
<tr>
<td>Calcium carbonate</td>
<td>7.6 ± 0.6</td>
<td>7.9 ± 0.5</td>
</tr>
</tbody>
</table>

Values are means ± SD. ND, not determined.
The least-square mean ± SD of net calcium absorption (calculated as the difference between ingested and excreted calcium) was 49.2 ± 47.35 mg in subjects who received a single lanthanum carbonate dose versus 70.4 ± 47.04 mg in subjects who received sevelamer carbonate. The lower calcium absorption in lanthanum carbonate-treated subjects (−20.67 mg) was statistically significant ($P = 0.049$). The least-square mean ± SD of net phosphorus absorption was 156.0 ± 14.16 mg after

![Graphs showing calcium and phosphorus levels](image-url)
a single lanthanum carbonate dose (1,000 mg) versus 221.8 ± 14.11 mg after sevelamer carbonate (2,400 mg), corresponding to a difference between least-square means of −65.75 mg (P < 0.001).

DISCUSSION

The aim of this study was to investigate whether two noncalcium-containing phosphate-binding agents, i.e., sevelamer and lanthanum carbonate, have differential effects on gastrointestinal calcium absorption. For this purpose, an experimental setup using animals with normal renal function and animals with chronic renal failure was used as well as a clinical balance study setup in which healthy volunteers received a single dose of these phosphate binders in combination with a standardized meal.

Experimental Study

All animals showed a drop in serum hematocrit levels. The most likely explanation for this is the blood sampling itself. Daily, −50–100 µl of blood were taken for the measurement of serum ionized calcium levels, and, every 2 days, an additional 500-µl sample volume was taken for other measurements. This most likely resulted in the drop in hematocrit and hemoglobin levels in animals.

In animals with normal renal function, sevelamer treatment resulted in statistically significant increased serum ionized calcium levels and increased calcitria, with a concomitant (not statistically significant) decrease in PTH. After the cessation of treatment, values rapidly returned to normal, within 1–2 days. According to current knowledge in mineral metabolism, these effects can reasonably be expected. Indeed, in the gut, part of phosphate occurs complexed with calcium (23). A phosphate-binding agent will bind to phosphate, thereby liberating calcium ions from these complexes. Hence, a larger amount of free calcium is available for intestinal absorption, leading to increased ionized calcium levels and decreased PTH levels. Moreover, in the presence of normal renal function, calcium excretion by the kidney increases to maintain proper calcium balance. Treatment with calcium carbonate induced similar changes. Contrastingly, lanthanum carbonate treatment did not induce a rise in serum ionized calcium levels and calcitria remained comparable with control animals.

In animals with renal failure, lanthanum carbonate induced a consistent, albeit nonstatistically significant, decrease in serum ionized calcium levels compared with untreated control animals during the whole treatment period, whereas sevelamer or calcium carbonate treatment showed no differences. Cumulative urinary calcium excretion over time showed a steeper slope in animals treated with sevelamer or calcium carbonate compared with those treated with lanthanum carbonate or vehicle, indicative of increased urinary calcium excretion in the former groups. These findings corroborate our initial hypothesis that lanthanum carbonate and sevelamer have differential effects on gastrointestinal calcium absorption/metabolism.

In in vitro experiments, lanthanum has been shown to block calcium transport in epithelia at a concentration of 0.5 mM (11, 12, 18). Since patients are treated with doses of up to 3 g/day lanthanum (21 mmol/day), free lanthanum concentrations in the millimolar range can be expected in the gut, thereby leading to a (partial) blockade of gastrointestinal calcium channels [transient receptor potential vanilloid (TRPV)5/6 channels]. The reduced calcium absorption due to this blockade counteracts the increased availability of calcium in the gut due to phosphate binding, resulting in no net difference in calcium absorption during treatment with lanthanum carbonate. Due to the very low bioavailability of lanthanum (<0.002%) and the high protein binding (up to 99%) (19), free lanthanum concentrations in the serum at steady state are more than one million times lower (pM to nM range). Furthermore, since the majority of the absorbed fraction of lanthanum is excreted in the bile and <2% via the kidney, patients with renal failure are not at an increased risk for lanthanum accumulation compared with subjects with normal renal function. Thus, no systemic interference of lanthanum with calcium channels occurs, and, so far, no pharmacological or clinical effects of lanthanum related to calcium channel blockade have been reported. To what extent the reduced gastrointestinal calcium absorption might be due to the potential calcimimetic action of lanthanum at the level of the calcium-sensing receptor in the gut is not known; however, this has to be taken into account since the calcium-sensing receptor has been identified at either or both the apical and basolateral membranes along the gastrointestinal tract (10).

Interestingly, no significant changes in total calcium levels were detected in any of the treatment groups. This is not surprising since the magnitude of the differences in ionized calcium between treatments groups was relatively small (±10%). Such changes, however, might have a significant effect on PTH levels, as it has been shown that changes as low as 2% in ionized calcium levels have a significant impact on PTH secretion (4). Vehicle- and lanthanum carbonate-treated animals showed consistently lower urinary calcium excretion in animals with normal renal function as well as in animals with chronic renal failure. In the latter group, this was further evidenced by calculating the cumulative urinary calcium excretion over the whole treatment period, which showed a significantly and consistently higher urinary calcium excretion in animals treated with sevelamer or calcium carbonate compared with vehicle- or lanthanum carbonate-treated animals.

Differences in phosphate binding efficacy would also lead to a difference in availability of free calcium in the gut. The doses

<table>
<thead>
<tr>
<th></th>
<th>Lanthanum Carbonate</th>
<th>Sevelamer</th>
<th>Meal Only</th>
<th>Fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Meal</td>
<td>272.3 ± 10.48</td>
<td>273.2 ± 12.96</td>
<td>272.2 ± 12.93</td>
<td>12.2 ± 21.00</td>
</tr>
<tr>
<td>Rectal effluent</td>
<td>235.3 ± 55.9</td>
<td>215.1 ± 49.17</td>
<td>217.8 ± 36.27</td>
<td></td>
</tr>
<tr>
<td>Net absorption</td>
<td>49.2 ± 47.35</td>
<td>70.4 ± 47.04</td>
<td>66.6 ± 28.07</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SD of total calcium contents (in mg); n = 18 volunteers. Net absorption was calculated as follows: average meal calcium per cohort – (effluent calcium – effluent calcium after fasting).
used in this study were aimed to achieve a similar phosphate binding with each of the phosphate binders. Serum phosphorus levels did not show significant differences between treatment groups. This finding is in agreement with our previous studies on phosphate-binding agents, which showed that phosphaturia is a better indicator of phosphate status. Urinary phosphorus excretion showed the expected reduction during calcium carbonate and sevelamer treatment in animals with normal renal function. In animals with renal failure, cumulative phosphorus excretion was significantly lower in animals treated with any of the phosphate-binding agents versus control animals, and no differences were found between agents. Differences in phosphate-binding efficacy are thus unlikely to play a major role in these observations.

The findings of the experimental study were confirmed in a one-dose, one-meal balance study in which healthy human volunteers received a single, clinically relevant dose of lanthanum (1,000 mg) or sevelamer (2,400 mg) (15). These doses were chosen to reflect common doses used in the clinic. Although this study was initially intended to compare phosphate-binding efficiency, calcium balance was also studied. Lanthanum carbonate was found to significantly reduce net calcium absorption compared with sevelamer, despite the superior phosphate-binding efficiency of lanthanum carbonate. In this highly controlled setup, volunteers received a standardized meal with a known and constant calcium content. Furthermore, every effort was made to ensure accurate results by performing bowel cleansing before and after treatment. For the purpose of the latter, patients received mannitol. Limited data from an experimental study (24) have shown mannitol to possibly increase the gastrointestinal absorption of calcium. As the compound was administered to subjects who received lanthanum carbonate as well as those who received sevelamer and the sequences of treatments were randomized, the observed differences on gastrointestinal calcium cannot be due to an isolated effect of mannitol on calcium absorption in lanthanum carbonate-treated subjects. On the other hand, to what extent lanthanum carbonate might have directly inhibited the stimulatory effect of mannitol on calcium absorption by, e.g., binding to the compound, cannot be deduced from data in the present study; however, this is unlikely to have occurred given the time of mannitol administration, which was 4 h before and 10 h after the administration of lanthanum carbonate.

In conclusion, the present study shows clear differences in calcium handling during treatment with two noncalcium-containing phosphate-binding agents: lanthanum carbonate and sevelamer. Whereas sevelamer treatment results in increased ionized calcium levels, lanthanum carbonate treatment does not induce this rise. The clinical relevance of these findings is supported by bone biopsy-based studies on the evolution of renal osteodystrophy after 1 yr of treatment with sevelamer (7) or lanthanum carbonate (5). In the first study, the prevalence of adynamic bone disease among the patients did not change substantially after treatment with either sevelamer or calcium carbonate. In the latter study, however, the prevalence of adynamic bone disease was significantly lower after 1 yr of treatment with lanthanum carbonate versus calcium carbonate. These findings open further perspectives for the treatment of patients with an increased calcium load and patients with an increased risk for low bone turnover disease.

DISCLOSURES
This work was funded by Shire Development LLC. S. J. Damment and P. Martin are employees of Shire.

AUTHOR CONTRIBUTIONS

REFERENCES


