Calcium Carbonate versus Sevelamer Hydrochloride as Phosphate Binders after Long-Term Disease Progression in 5/6 Nephrectomized Rats

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Our aim was to compare the effects of calcium carbonate and sevelamer-HCl treatments on calcium-phosphate metabolism and renal function in 5/6 nephrectomized (NX) rats so that long-term disease progression preceded the treatment. After 15-week progression, calcium carbonate (3.0%), sevelamer-HCl (3.0%), or control diets (0.3% calcium) were given for 9 weeks. Subtotal nephrectomy reduced creatinine clearance (−40%), plasma calcidiol (−25%), and calcitriol (−70%) and increased phosphate (+37%), parathyroid hormone (PTH) (11-fold), and fibroblast growth factor-23 (FGF-23) (4-fold). In NX rats, calcium carbonate diet increased plasma (+20%) and urinary calcium (6-fold), reduced plasma phosphate (−50%) and calcidiol (−30%), decreased creatinine clearance (−35%) and FGF 23 (−85%), and suppressed PTH without influencing blood pH. In NX rats, sevelamer-HCl increased urinary calcium (4-fold) and decreased creatinine clearance (−45%), PTH (−75%), blood pH (by 0.20 units), plasma calcidiol (−40%), and calcitriol (−65%). Plasma phosphate and FGF-23 were unchanged. In conclusion, when initiated after long-term progression of experimental renal insufficiency, calcium carbonate diet reduced plasma phosphate and FGF-23 while sevelamer-HCl did not. The former induced hypercalcemia, the latter induced acidosis, while both treatments reduced vitamin D metabolites and deteriorated renal function. Thus, delayed initiation influences the effects of these phosphate binders in remnant kidney rats.

1. Introduction

Cardiovascular disease is a major cause of mortality in chronic renal insufficiency (CRI) with a 20-fold increase in the risk of cardiovascular death compared with normal population [1]. Hyperphosphatemia and secondary hyperparathyroidism (SHPT) [2] significantly contribute to the cardiovascular pathology and mineral-bone disorders in CRI. In order to halt these changes, oral phosphate binders such as calcium carbonate and sevelamer are widely used.

High intake of calcium carbonate may predispose to vascular calcifications in CRI, especially if the phosphate levels remain inappropriately high [2]. Consequently, treatment with sevelamer, a calcium- and aluminium-free and nonabsorbable polyallylamine anion exchange resin, may result in less vascular calcifications and reduced mortality in dialysis patients. However, according to recent Cochrane review, the superiority of sevelamer over calcium carbonate remains unclear [3].

In experimental animal models, increased calcium intake has resulted in beneficial effects on blood pressure (BP), endothelial function, sodium-potassium balance, inflammation and thrombosis, plasma cholesterol levels, and insulin
Advances in Nephrology

2. Methods

2.1. Animals and Experimental Design. Ninety-five male Sprague-Dawley rats were subjected to surgical 5/6 nephrectomy (NX, n = 51) or Sham operation (n = 44) at 8 weeks of age under ketamine/diazepam anesthesia (75 and 2.5 mg/kg, resp.). The NX surgery comprised removal of the upper and lower poles of the left kidney followed by unilateral nephrectomy. In the Sham group both kidneys were decapsulated [5]. All rats were housed 3-4 per cage in an animal laboratory with free access to water and chow containing 0.9% calcium and 0.8% phosphate (Lactamin R34, AnalyCen, Lindköping, Sweden). Average daily chow intake was approximately 20 grams per rat, monitored in metabolic cages.

After 15 weeks of disease progression, NX and Sham rats were divided into three subgroups with equal systolic BPs, body weights, and urine outputs (Figure 1). BP was measured using tail-cuff (Model 129 BP Meter; IITC Inc., Woodland Hills, CA, USA). NX groups were matched according to plasma creatinine concentrations. Then for 9 weeks, Sham (n = 14) and NX (n = 20) groups continued on 0.3% calcium, Ca-Sham (n = 15) and Ca-NX (n = 16) rats on 3% calcium carbonate, and Seve-Sham (n = 15) and Seve-NX (n = 15) rats on 3% sevelamer-HCl. The doses of phosphate binders (estimated at 1.3 g/kg) were chosen on the basis of previous reports, none of which had reported major adverse effects with 3.0% calcium carbonate or 3.0% sevelamer-HCl ingestion [17–29, 33, 34]. Sevelamer carbonate was not available at the time this study was conducted. As 0.9% calcium content in control chow is rather high, and lower dietary calcium content has been used in several publications [19, 33, 34], the calcium content in the present control chow was reduced to 0.3% similarly to our previous reports in experimental CRI [5, 6].

During the final week, 24-hour water consumption was measured and urine output was collected in metabolic
cages. Then BPs were measured, and rats were weighed and anesthetized (urethane 1.3 g/kg, intraperitoneally). Blood and tissue samples were collected and stored at −70 °C. Due to mortality, the final numbers for analyses in the uremic NX, Ca-NX, and Seve-NX groups were 12, 11, and 10, respectively (Figure 1). In each uremic group there was one rat that survived through the 24-week experiment but expired before BP measurements and sample collections and was only included in the survival analyses.

The study design was approved by Tampere University Animal Experimentation Committee and Provincial Government of Western Finland, Department of Social Affairs and Health, Finland. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication Number 85-23, revised 1996).

2.2. Hormonal and Chemical Analyses. Sodium, potassium, creatinine, phosphate, and calcium concentrations were measured by standard clinical chemical methods (Cobas Integra 800 Clinical Chemical Analyzer, Roche Diagnostics, Basel, Switzerland). Hemoglobin was determined photometrically (Technicon H^+2, Technicon Instruments Corporation, Tarrytown, NY, USA), plasma pH was determined using an ion selective electrode (634 pH Analyzer, Ciba Corning Diagnostics, Sudbury, UK), and rat intact parathyroid hormone (PTH) levels were determined by immunoradiometric assay (ImmunoDias Inc., San Clemente, CA, USA). Plasma 1,25(OH)\(_2\)D and 25(OH)D were determined using commercial kits (IDS Ltd, Boldon, UK) and plasma fibroblast growth factor-23 (FGF-23) was determined using ELISA kit previously applied for analyses in rats (Kainos Inc., Tokyo, Japan) [35]. Ventricular atrial natriuretic peptide (ANP) mRNA was isolated and the radioimmunoassay was carried out as described previously [36].

2.2.1. Calcification Analysis in the Aorta. Altogether 20 cross-sections of the thoracic and 20 cross-sections of the abdominal aorta from each animal were cut, and every 5th of these sections were stained with the von Kossa method and these sections were stained with the von Kossa method and processed for light microscopy. An expert blinded to the treatments quantified the calcifications.

2.2.2. Data Presentation and Analysis of Results. Statistical analysis for normally distributed variables was carried out using one-way analysis of variance (ANOVA) supported by Tukey’s HSD test in the post hoc analyses (SPSS 17.0, SPSS Inc., Chicago, IL, USA). If the distribution of a variable was skewed, the Kruskal-Wallis test was applied and the post hoc analyses were performed with the Mann-Whitney U test. Results were expressed as mean ± SEM. Survival was analyzed using the Kaplan-Meier curves and the log-rank test. \( P < 0.05 \) denoted significance.

3. Results

3.1. Animal Data, Electrolytes, Renal Function, and Blood pH. Figure 2 shows the survival rates in nephrectomized rats, which were 65%, 75%, and 73% for NX, Ca-NX, and Seve-NX, respectively \( (P = 0.782) \). Table 1 shows the characteristics and laboratory findings in the study groups. There were no significant differences in body weights between the groups during the experiment \( (P > 0.114) \). The weights of the removed kidney masses did not differ between the three NX groups \( (P = 0.924) \). Before the treatments at week 15, no differences were observed in BP \( (P = 0.739) \). At week 24, BP was elevated in all nephrectomized rats \( (P < 0.001) \), while Ca-NX rats had lower BP than other uremic groups \( (P < 0.047) \). Heart weight/body weight ratios were increased in the NX and Seve-NX groups \( (P \leq 0.004) \) (Table 1). Increased left ventricular ANP gene expression was detected in all NX groups \( (P < 0.001) \), showing the cardiac load in this model (Figure 3(a)).

Plasma creatinine was equally elevated in all NX groups before the diets \( (P = 0.849) \) (Table 1). At week 24, creatinine was 1.7-fold higher in the NX than the Sham group \( (P < 0.001) \). Most likely due to the loss of the animals with the worst renal function, creatinine was not further elevated in the NX group during the final 9-week follow-up. Both Seve-NX \( (P < 0.009) \) and Ca-NX \( (P = 0.016) \) groups had higher creatinine concentrations at week 24 than untreated NX rats (Table 1). The 24-hour urine output was increased in all NX groups \( (P \leq 0.005) \) and was especially high in Seve-NX rats \( (P < 0.001) \) (Figure 3(b)). Creatinine clearance was reduced by ~40% in untreated NX rats \( (P < 0.001) \) and was further reduced in the CaNX (~35%, \( P = 0.01 \)) and Seve-NX groups.
Table 1: Characteristics and laboratory findings in the study groups.

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>Ca-Sham</th>
<th>Seve-Sham</th>
<th>NX</th>
<th>Ca-NX</th>
<th>Seve-NX</th>
</tr>
</thead>
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<tr>
<td>Weight of kidney tissue removed in the 5/6 nephrectomy (g/kg)</td>
<td>6.3 ± 0.1</td>
<td>6.2 ± 0.1</td>
<td>6.2 ± 0.2</td>
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<tr>
<td>Body weight (g)</td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Week 15</td>
<td>454 ± 11</td>
<td>452 ± 8</td>
<td>452 ± 7</td>
<td>438 ± 7</td>
<td>447 ± 11</td>
<td>442 ± 16</td>
</tr>
<tr>
<td>Week 24</td>
<td>495 ± 13</td>
<td>474 ± 8</td>
<td>504 ± 12</td>
<td>476 ± 11</td>
<td>467 ± 16</td>
<td>459 ± 17</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Week 15</td>
<td>125 ± 10</td>
<td>123 ± 9</td>
<td>118 ± 5</td>
<td>127 ± 6</td>
<td>133 ± 7</td>
<td>132 ± 5</td>
</tr>
<tr>
<td>Week 24</td>
<td>135 ± 4</td>
<td>136 ± 4</td>
<td>144 ± 7</td>
<td>169 ± 4*</td>
<td>151 ± 5*</td>
<td>167 ± 9*</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 15</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
<td>88.2 ± 5.3</td>
<td>873 ± 71</td>
<td>88.6 ± 5.5</td>
</tr>
<tr>
<td>Week 24</td>
<td>49.6 ± 2.6</td>
<td>52.5 ± 1.9</td>
<td>53.2 ± 2.5</td>
<td>84.5 ± 7.6*</td>
<td>128.8 ± 25.7*</td>
<td>161.7 ± 33.2*</td>
</tr>
<tr>
<td>pH</td>
<td>7.40 ± 0.05</td>
<td>7.43 ± 0.03</td>
<td>7.22 ± 0.07**</td>
<td>7.41 ± 0.03</td>
<td>7.34 ± 0.05</td>
<td>7.21 ± 0.04*</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>136.0 ± 0.5</td>
<td>135.7 ± 0.3</td>
<td>136.1 ± 0.5</td>
<td>136.7 ± 0.5</td>
<td>135.4 ± 0.6</td>
<td>138.2 ± 1.2</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>3.92 ± 0.09</td>
<td>3.79 ± 0.21</td>
<td>3.90 ± 0.07</td>
<td>4.49 ± 0.15*</td>
<td>4.88 ± 0.24*</td>
<td>5.12 ± 0.23**</td>
</tr>
<tr>
<td>Hemoglobin (g/L)</td>
<td>177.3 ± 2.1</td>
<td>175.0 ± 2.2</td>
<td>182.0 ± 1.3</td>
<td>158.3 ± 4.6*</td>
<td>157.3 ± 3.9*</td>
<td>143.9 ± 8.8**</td>
</tr>
<tr>
<td>Heart wt/body wt (g/kg)</td>
<td>3.48 ± 0.07</td>
<td>3.40 ± 0.06</td>
<td>3.92 ± 0.44</td>
<td>4.53 ± 0.48*</td>
<td>4.26 ± 0.23</td>
<td>5.45 ± 0.51**</td>
</tr>
<tr>
<td>Ca-Pi product (mmol²/L²)</td>
<td>3.03 ± 0.14</td>
<td>2.05 ± 0.11*</td>
<td>3.22 ± 0.17*</td>
<td>4.10 ± 0.49*</td>
<td>2.49 ± 0.26**</td>
<td>5.24 ± 0.53**</td>
</tr>
<tr>
<td>Urine sampling at close of the study (week 24)</td>
<td></td>
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</tr>
<tr>
<td>Protein (mg/24 h)</td>
<td>70.8 ± 8.0</td>
<td>74.2 ± 10.0</td>
<td>111.2 ± 26.8</td>
<td>242.3 ± 31.6*</td>
<td>260.5 ± 46.4*</td>
<td>285.2 ± 38.8*</td>
</tr>
</tbody>
</table>

Mean ± SEM; n = 10–20 (see Figure 1); n.d. = not determined.

*P < 0.05 versus Sham, †P < 0.05 versus NX, ‡P < 0.05 Ca-NX versus Seve-NX, and #P < 0.05 Ca-Sham versus Seve-Sham.
(−45%, P = 0.01) when compared with untreated NX rats (Figure 3(c)).

A blood pH reduction of approximately 0.2 units was observed in both Sham and NX rats on sevelamer-HCL (P < 0.012) (Table 1). Plasma potassium was elevated in all NX groups (P < 0.019), especially in Seve-NX rats (P < 0.001). There were no significant differences in plasma sodium concentrations between the groups (P = 0.108). Hemoglobin was decreased in all NX groups (P ≤ 0.004) and was lowest in Seve-NX rats (P < 0.001). Urinary protein excretion was equally increased in all NX groups (P ≥ 0.920) and was ~3.5-fold higher in NX than in Sham rats (P ≤ 0.003) (Table 1).

3.2. Calcium-Phosphate Metabolism. Urinary calcium excretion did not differ between the NX and the Sham groups (P = 0.830) (Figure 3(d)) but was increased 10-fold in Ca-Sham rats (P < 0.001) and 6-fold in Ca-NX rats (P < 0.001). An increase in urinary calcium excretion was documented in uremic rats which were on sevelamer-HCL (P = 0.008) (Figure 3(d)). Plasma calcium was highest in Ca-NX rats (P ≤ 0.004) but was also increased in Ca-Sham (P < 0.001) and Seve-NX rats (P = 0.023) (Figure 4(a)), so that calcium levels did not differ in the two latter groups (P = 0.964). Plasma phosphate was increased in NX (P = 0.01) and Seve-NX rats (P = 0.001) and reduced in Ca-Sham (P < 0.001) and Ca-NX rats (P = 0.002) (Figure 4(b)). Plasma Ca-Pi product was elevated in the NX (P = 0.011) and Seve-NX groups (P = 0.001) but was reduced in both calcium-supplemented groups (P ≤ 0.047) (Table 1).

Plasma calcidiol was reduced by approximately 25% in untreated NX rats (P = 0.019) and was further decreased in the Ca-NX (P = 0.032) and Seve-NX groups (P = 0.002) (by ~30% and ~40% versus the untreated NX group, resp.). Sevelamer-HCl reduced calcidiol concentration also in
Figure 4: Plasma total calcium (a), phosphate (b), 25OH-D (c), 1,25(OH)2D (d), FGF-23 (e), and PTH (f) at the close of the study. Groups as in Figure 3; *$P<0.05$ versus Sham, #$P<0.05$ versus Ca-Sham, †$P<0.05$ versus NX, and ‡$P<0.05$ versus Ca-NX.
Sham-rats by 25% \((P = 0.009\) (Figure 4(c)). Calcitriol was low in all uremic rats \((P < 0.001)\), while both treatments \((P \leq 0.001)\), especially sevelamer-HCl, decreased calcitriol even in Sham rats (Figure 4(d)). FGF-23 levels were suppressed in Ca-NX rats \((P < 0.001)\), whereas in NX and Seve-NX rats FGF-23 remained high \((P \leq 0.043)\) (Figure 4(e)). PTH was increased 11-fold in the NX group \((P = 0.001)\) and was totally suppressed in both Ca-Sham and Ca-NX rats \((P < 0.001)\). PTH was also reduced by 75% in the Seve-NX group \((P = 0.036)\), probably due to the elevated plasma calcium in these animals (Figure 4(f)).

Even though altogether 8 aortic cross-sections were analyzed from each rat, calcifications in the aortic samples were scarce. In all uremic groups there were two rats with calcifications in the thoracic aorta, while one rat in the Ca-NX and one in the Seve-NX group also had calcifications in the abdominal aorta.

### 4. Discussion

In the present study, we examined the effects of calcium carbonate and sevelamer-HCl in established experimental CRI with prolonged disease progression period preceding the treatments. Unexpectedly, the undesirable side effects of calcium carbonate and sevelamer-HCl overshadowed their positive effects, and the treatments showed no survival benefits. Calcium carbonate suppressed PTH and FGF-23 but caused hypercalcemia especially in Ca-NX rats with impaired renal excretion capacity. Sevelamer-HCl induced acidosis in both Sham-operated and uremic rats, and consequently no decreases in plasma phosphate or FGF-23 were seen. Sevelamer-HCl also increased plasma calcium and urinary calcium excretion and decreased PTH in NX rats. Both treatments reduced vitamin D metabolites and impaired kidney function. Neither calcium carbonate nor sevelamer-HCl influenced aortic calcifications or mortality. The aortic calcifications were scarce, as the NX model is quite resistant to soft-tissue calcification in the absence of excess calcitriol or phosphate loading [6, 37]. In previous studies, sevelamer-HCl treatment did not induce renoprotective effects in experimental CRI if irreversible kidney damage had already taken place [21] but was clearly beneficial if initiated right after the kidney insult [24].

The phosphate binding and FGF-23-reducing ability of sevelamer-HCl [3, 20] seemed low in our study, although estimated sevelamer-HCl intake was approximately 1300 mg/kg/day in each rat (thus clearly exceeding the maximum dose of about 140 mg/kg/day in an average 70 kg human). The acidosis of Seve-Sham and Seve-NX rats indicates that they received hydrogen ions in excess in the diet. Acidosis and consequent impairment of kidney function with reduced phosphate excreting capacity were the likely explanation for the high phosphate levels in Seve-NX rats. Acidosis can deteriorate kidney function, whereas bicarbonate treatment can delay the progression of CRI [38]. When the present results were adjusted for the differences in creatinine, plasma phosphate was numerically lower in the Seve-NX than NX group (1.61 versus 1.75 mmol/L, resp.). Creatinine clearance did not differ between Ca-NX and Seve-NX rats, but the phosphate and the FGF-23 levels were lower in Ca-NX rats, showing that calcium carbonate functioned as a phosphate binder in this model.

A reason for the elevated phosphate in Seve-NX rats may have been the calcium- and phosphate-releasing effect of metabolic acidosis on bone [9, 15]. Increased urinary calcium excretion in Seve-Sham and Seve-NX rats strongly indicates increased calcium efflux from bone in the acidic milieu [9]. As sevelamer-HCl is not absorbed and only binds phosphate in the gut [9], it is not able to influence phosphate levels resulting from increased internal release. The acidosis-induced release of bone minerals was the likely cause for increased plasma calcium and the subsequent significant decrease in plasma PTH in Seve-NX rats, since extracellular fluid calcium concentration is the primary regulator of PTH release from the parathyroid glands [39]. In the Ca-NX rats, significant dietary hypercalcemia was the most likely cause for the deteriorated kidney function.

Although plasma calcitriol and calcidiol levels are typically reduced in CRI [40], we observed a further decline of calcidiol in Ca-NX and Seve-NX rats, which may have partially resulted from accelerated CRI in these animals. The reasons for low plasma calcidiol in CRI are multiple, including urinary loss of vitamin D binding protein and vitamin D metabolites, reduced gastrointestinal absorption, and decreased 25-hydroxylation in the liver [41]. Importantly, decrease in calcidiol and calcitriol in the Seve-Sham group corresponded to the reduction observed in untreated NX rats. Changes in calcium, phosphate, PTH, creatinine clearance [14], FGF-23 [35], and urine protein excretion [42] would all potentially influence plasma vitamin D metabolite concentrations. However, these variables did not differ between Sham and Seve-Sham rats. Sevelamer-HCl also binds bile acids in the gut [31] and interferes with the absorption of fat-soluble vitamins D, E, and K [30, 32]. This may explain the decreased plasma calcidiol in Seve-Sham rats. In addition, reduced calcitriol in Seve-Sham rats may also have resulted from acidosis, which has been implicated in downregulation of 1-alpha-hydroxylation and upregulation of 24-hydroxylation [14]. In calcium carbonate-treated rats, potential mechanisms for the reduced vitamin D metabolites were hypercalcemia and subsequent suppression of PTH and impaired kidney function of the Ca-NX group.

The present model of CRI was associated with increased heart weight and left ventricular ANP mRNA expression. Such changes can be explained by higher BP, volume load, anemia, increased FGF-23, and vitamin D deficiency in the NX groups [43–45]. Highest heart weights were observed in Seve-NX rats, probably due to accelerated CRI, increased volume load, and aggravated anemia [43]. Furthermore, lowest calcitriol was seen in the Seve-NX rats and their FGF-23 was equally high as in the untreated NX rats. Both of these mechanisms have the potential to aggravate LVH [44, 45].

Acidosis may have influenced the results obtained in previous sevelamer-HCl studies. Only two [33, 34] of the fifteen experimental sevelamer-HCl studies reported blood pH [17–29, 33, 34], and these studies applied the ligation model of 5/6 nephrectomy with a disease progression period.
of only one week. Rats received 3.0% sevelamer HCl or 3.0% calcium carbonate for 12 weeks in the former study and for 24 weeks in the latter study. High mortality (about 80%) in the latter study was observed in each uremic group. In the surviving 20%, sevelamer-HCl had beneficial effects on phosphate, PTH, and kidney function. Sevelamer-HCl also increased calciuresis when compared with uremic controls [33, 34]. Of note, the ligation 5/6 nephrectomy model results in increased plasma renin activity [46, 47], while the surgical model used here is characterized by low plasma renin and reduced aldosterone [5, 48]. Low plasma aldosterone level decreases hydrogen ion excretion in the kidneys [49], and this probably exposed the present rats to acidosis. Reduced pH in Seve-Sham rats indicates that excess hydrochloride could cause acidosis even in healthy rats. In those previous experimental studies with sevelamer HCl that did not report blood pH, increased plasma calcium concentration was attributed to reduced phosphate levels [17–21, 29]. Some studies also found increased calciuresis [17, 22, 25], which was thought to result from reduced PTH [22, 25]. A dose-dependent decrease in plasma calcitriol after sevelamer-HCl treatment was observed in two previous studies [17, 25], one of which also showed a clear reduction in plasma calcidiol [17].

In conclusion, late-onset treatment with calcium carbonate or sevelamer-HCl after 15 weeks of disease progression in the 5/6 nephrectomy rat model of CRI showed no survival benefits, and both treatments deteriorated kidney function and reduced plasma calcium and calcitriol. In both Sham-operated and remnant kidney rats, sevelamer-HCl treatment induced acidosis, while calcium carbonate treatment induced hypercalcemia. Finally, oral calcium carbonate, but not sevelamer-HCl, effectively suppressed plasma phosphate and FGF-23. Altogether, the present doses of phosphate binders, albeit based on previous publications [5, 6, 48], seemed too high for this model. The present findings also indicate that the results from previous studies using sevelamer-HCl in experimental CRI should be interpreted with caution due to the possible bias resulting from acidosis-induced changes in calcium-phosphate metabolism.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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