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Authors
Shantouf, R
Ahmadi, N
Flores, F
et al.

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Impact of phosphate binder type on coronary artery calcification in hemodialysis patients

R. Shantouf1,2,3, N. Ahmadi1, F. Flores1, J. Tiano1, A. Gopal1, K. Kalantar-Zadeh1,2,3 and M.J. Budoff2,3

1Division of Cardiology, 2Harold Simmons Center for Kidney Disease Research and Epidemiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, and 3David Geffen School of Medicine, University of California Los Angeles, Los Angeles, CA, USA

Abstract. Aims: In individuals with chronic kidney disease (CKD), including those undergoing maintenance hemodialysis (MHD), coronary artery calcification (CAC) is common. We hypothesized that, in MHD patients, intake of the calcium-free phosphate binder sevelamer is associated with lower CAC compared to calcium-based phosphate binders (CBPB). Material and methods: This is a cross-sectional study of MHD patients, who underwent computerized tomography to assess coronary artery calcium scores (CACS). Patients were stratified into two mutually exclusive groups based on taking only a CBPB vs. sevelamer. Logistic regression was used to calculate adjusted odds ratio (OR) of CACS < 400, CACS 100 < CACS < 400, 10 < CACS < 100 vs. CACS < 10. Results: 117 MHD patients were either on a CBPB alone (n = 60) or sevelamer alone (n = 57). Despite increased prevalence of DM in the sevelamer group (58%) as compared to the CBPB group (35%), CACS was significantly lower with sevelamer use (283 ± 83 vs. 494 ± 94, p = 0.02). The OR of significant CACS < 400 vs. CACS < 10 was 4.35 (95% confidence interval: 1.5 – 9.9, p = 0.008) for CBPB compared with sevelamer, after controlling for case-mix, cholesterol-lowering medication, DM, and inflammatory markers. Conclusion: In our cohort, significant CAC was significantly more prevalent among MHD patients taking CBPB compared to sevelamer monotherapy.

Introduction

More than 400,000 Americans suffer from chronic kidney disease (CKD) Stage 5, also known as end stage renal disease (ESRD), and require maintenance hemodialysis (MHD) [1]. Almost half of these individuals have developed CKD as a complication of diabetes mellitus (DM) [2]. Cardiovascular disease (CVD) is one of the leading causes of death in the ESRD population [3, 4]. The all-cause and cardiovascular (CV) mortality in this population is as high as 10- to 30-fold that of the general population even after accounting for age, race, gender, and presence of DM [5, 6]. In the general population, traditional CV risk factors, such as hypertension, elevated low-density lipoprotein cholesterol (LDL-C), smoking, DM, and family history of CVD, are used to delineate those at risk for a CV event. However, with the exception of DM, most other conventional CV risk factors fail to explain the high burden of CVD and mortality in the MHD population, even though some factors such as hypertension and obesity are quite common among these patients [7].

In individuals with CKD there are several traditional risk factors such as age, gender, and DM and several non-traditional risk factors such as malnutrition, inflammation, and disturbances in mineral metabolism, specifically calcium and phosphorus homeostasis, that appear to contribute to the vascular calcification and the high incidence of CVD [8, 9]. Hyperphosphatemia and secondary hyperparathyroidism are common complications of CKD that, when untreated, may result in increased morbidity and mortality [10]. Advances in electron beam computerized tomography (EBCT) have enabled the quantification of calcification of the vasculature including in coronary arteries. The prevalence and degree of vascular calcifications have been shown to be predictors of CV and all-cause mortality in MHD patients [11]. The extent of CAC is not only higher in CKD patients but also seems to progress at a more rapid rate [12, 13]. Recent studies have indicated that the presence of DM, in a diabetic population, was the single most important risk factor of increased coro-
nary artery calcification score (CACS) in that CKD population [14].

Among phosphate binders that are administered to CKD patients, sevelamer has been suggested to have cardioprotective effects, based on studies demonstrating slower CACS progression [15], lower C-reactive protein [16], and better lipid profiles [17, 18, 19]. In the Treat to Goal study by Chertow et al. [15] in which 200 hemodialysis patients were randomized to either sevelamer or a CBPB, they showed median CACS increased significantly in the CBPB subjects but not the sevelamer group and that subjects on sevelamer had less CACS progression compared to those on a CBPB.

Given the above-mentioned associations, we hypothesized that intake of sevelamer is associated with lower CACS prevalence even after controlling for DM, mineral metabolism, surrogates of malnutrition, and other potential confounders including inflammatory cytokines. We studied a sub-group of MHD patients from the “Nutritional and Inflammatory Evaluation of Dialysis Patients” (NIED) study [20] who underwent EBCT and were taking either only a calcium-based phosphate binder (CBPB) or the calcium-free phosphate binder sevelamer hydrochloride (Renagel™, Genzyme, Boston, MA, USA). We compared the degree of CACS ≥ 400, CACS 100 ≤ CACS < 400, 10 ≤ CACS < 100 with the lower risk group defined as CACS < 10.

Materials and methods

Patients

This is a cross-sectional analysis of participants of the NIED study [20] who underwent EBCT. The NIED study (www.NIEDstudy.org) was a prospective cohort study to determine whether nutritional and inflammatory states in MHD patient population affect mortality, morbidity, and other clinical outcomes. Patients who were included in the NIED study were 18 years or older and signed a written consent. Patients with malignancy or other terminal diseases with less than a 6-month life expectancy were excluded. The subjects were all receiving thrice weekly MHD via high-flux dialyzers, and their dialysis membranes were routinely re-used. New subjects were recruited semi-annually and followed with repeated measures for up to 5 years or 10 semi-annual rounds with each round consisting of a semi-annual assessment of malnutrition and inflammatory variables including biochemical markers, anthropometric measurements, hospitalization rates, and mortality. For example, Round 1 was defined as Time 0 to Time 6 months and Round 2 was defined as Time 6 months to Time 12 months. Medical chart review, including co-morbidities and outpatient medication usage were performed on all new recruits and then on a yearly bases thereafter. All subjects underwent medical chart review by a physician to evaluate for current outpatient medication usage. CBPB included calcium carbonate (Tums™), calcium acetate (PhosLo™) and other forms of calcium-based binders. Non-calcium-based binder included only sevelamer-hydrochloride.

Of the enrolled NIED participants from 10/2001 to 7/2005, 163 patients underwent EBCT and thus were candidates for this study. Laboratory data collected at the beginning of Round 1 (defined as initial enrollment time) for the 163 subjects was used to assess use of phosphate binders, HMG-Co-reductase inhibitors (statins), concurrent biochemical markers, along with typical demographics and cardiac risk factors via extracting information from the NIED database. Subjects on none or both types of binders were excluded from further analyses.

Dialysis and laboratory data

The single-pool Kt/V was used to represent the weekly dialysis dose of each subject. Dialysis vintage time was calculated based on the time between first dialysis date and beginning of Round 1 (initial enrollment time) upon quarterly enrollment. Serum levels of calcium, phosphorus, intact parathyroid hormone (iPTH), and albumin were obtained through routine laboratory measurements performed by DaVita Laboratories (Deland, FL, USA) using automated methods. The average value for each laboratory test within a 13-week period, coinciding with study Round 1 was calculated and used for the data analysis in the study.

Study-specific laboratory tests

Serum high-sensitivity C-reactive protein (hs-CRP) and two proinflammatory cyto-
kines interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), serum total cholesterol, LDL-C and high-density lipoprotein cholesterol (HDL-C), as well as homocysteine levels were measured from fasting samples in all patients during each semi-annual Round of the NIED study. Single lab measures were continuously obtained on a semi-annual basis. For example, each “Round” was defined as a 6-month period. As part of the NIED study, at the beginning of each round, the noted measurements were obtained from a single fasting lab draw. For this particular study, Round 1 (initial study samples) values were used for this cross-sectional analysis. The hs-CRP was measured by a turbidometric immunoassay where a serum sample is mixed with latex beads coated with anti-human CRP antibodies forming an insoluble aggregate (WPCI, Osaka, Japan; mg/l, normal range < 3.0 mg/l) [21]. High-sensitivity IL-6 and TNF-α immunoassay kits based on a solid-phase sandwich enzyme-linked immunosorbent assay (ELISA) using recombinant human IL-6 and TNF-α were used to measure the serum proinflammatory cytokines (R&D Systems, Minneapolis, MN, USA; normal range IL-6, < 9.9 pg/ml; TNF-α, < 4.7 pg/ml) [22].

EBCT

The EBCT studies were performed with an E-Speed electron beam scanner (GE-Imatron, South San Francisco, CA, USA). Coronary arteries were imaged with rapid acquisition of approximately 30 – 40 contiguous images of 3 mm slice thickness without gap during end-diastole using ECG-triggering during a single 35-second breath hold. CAC was quantified using the previously described Agatston scoring method [23]. Calcium was considered present in a coronary artery when a density of > 130 Hounsfield units (HU) was detected in > 3 contiguous pixels (≥ 1 mm²) overlying that coronary artery. The CACS was computed from the product of the attenuation factor and the area of calcification (mm²), with the total CACS of each coronary artery being equal to the sum CACS of all the lesions from that artery. The total calcium score was calculated by summing CACS from the left main, left anterior descending, left circumflex, and right coronary arteries.

Statistics

Conventional Student’s t-test, and χ²-test were used, as appropriate, to detect significant differences among groups using sevelamer and CBPB. Multivariate regression analysis and analysis of covariance were performed to obtain adjusted p values controlled for case-mix and other covariates. Case-mix covariates included gender, age, race (black versus other), dialysis vintage (number of months on MHD treatment), and DM (yes/no). Other covariates include statin use (yes/no). Laboratory covariates in fully adjusted multivariate models included homocysteine, hs-CRP, IL-6, TNF-α, and albumin concentrations, as well as all lipid variables and mineral metabolism measures including iPTH, calcium, phosphorus, and calcium-phosphorus product (Ca × P). Odds ratios include 95% confidence intervals (CI). A p value less than 0.05 or a 95% CI that did not span 1.0 is considered statistically significant. p values between 0.05 and 0.20 are listed with 2 decimals for consideration of potential Type II errors. Logistic regression analysis was used to assess the odds of significant CAC (CACS ≥ 400 vs. CACS < 10) in the CBPB group vs. sevelamer controlling for multiple factors. Multivariable stepwise models adjusted for age and gender, DM, statin therapy, race, ethnicity, BMI, albumin, iPTH, calcium, phosphate, Ca × P, vintage, Kt/V, and inflammatory markers. Multivariable models were limited to only those factors that were significant in univariate analysis to avoid model overfitting. Cut off values of CACS ≥ 400, CACS 100 ≤ CACS < 400, 10 ≤ CACS < 100, and CACS < 10 were used based on large observational studies such as by Shaw et al. [24] which demonstrated an incremental increase risk of all-cause mortality (CACS 11 – 100, 101 – 399, 400 – 1,000, > 1,000 vs. CACS ≤ 10) in a cohort of asymptomatic subjects undergoing EBCT screening. Baber et al. [25] also demonstrated that cut off value of ≥ 100 notes a moderate-to-high 10-year risk of cardiovascular events. Descriptive and multivariate statistics were carried out using the statistical software SAS, version 9.13 (SAS Institute Inc., Cary, NC, USA).

Results

Of the 163 MHD patients in the CAC study, 117 were either on a CBPB alone (n = 60) or...
Sevelamer monotherapy (n = 57). The average time from Round 1 lab collection to EBCT date was 13.1 months. Table 1 summarizes the characteristics of the 117 subjects on sevelamer or CBPB monotherapy. There were no significant differences in gender, ethnicity, statin use, mean BMI, mean vintage time, and Kt/V among the CBPB vs. sevelamer group (p > 0.05). There were significant differences in age, race, and diabetes. Although DM was 1.6 times more prevalent among the sevelamer group than the CBPB (58% vs. 35%, p = 0.01), and although the baseline serum calcium and calcium phosphorus product (C × P) levels were lower in the CBPB group than the sevelamer group (p = 0.0001 and p = 0.001, respectively), the CACS was significantly lower in the sevelamer group compared to the CBPB group (p = 0.02).

Among inflammatory biochemical markers; hs-CRP, IL-6, and homocysteine concentrations were significantly greater in the CBPB group than sevelamer (p < 0.05), but TNF-α was not significantly different between the two groups. The sevelamer group had lower total cholesterol and LDL-C compared with CBPB (p < 0.05). After logistic regression analysis, the odds ratio of CACS vs. CAC < 10 was 4.35 (95% CI: 1.5 – 9.9, p = 0.008) for CBPB compared with sevelamer independent of age, gender, vintage, DM, statin therapy, race, ethnicity, BMI, iPTH, albumin, calcium, phosphate, Ca × P, Kt/V, and inflammatory markers hs-CRP, IL-6, and TNF-α (Table 2).

**Discussion**

Our results indicate that MHD subjects in this study who were on sevelamer monotherapy were noted to have lower significant CACS than CBPB despite significantly higher levels of serum calcium and Ca × P, and significantly higher prevalence of DM (Table 1). This difference persisted after logistic regression analysis with multivariate adjustment (Table 2). The sevelamer group had lower total cholesterol and LDL-C compared with CBPB (p < 0.05). This difference may be attributed to pleiotropic effects of sevelamer beyond controlling serum phosphorus and Ca × P concentrations. However, the lower CACS in the sevelamer group was independent of the foregoing factors.

The vast majority of MHD patients are on some form of a phosphorus binder to lower phosphorus absorption through the intestine. The choice of binder type was independent of vintage time (Table 3). Both CBPB and sevelamer effectively lower serum phosphorus and Ca × P levels. Achieving control of serum phosphorus without increasing serum calcium is an important goal for MHD patients. However, what this study highlights, is even though serum levels of Ca × P were at goal (Ca × P < 55 mg²/dl²) based on the National Kidney

<table>
<thead>
<tr>
<th>Variables</th>
<th>CBPB n = 60</th>
<th>Sevelamer n = 57</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57 ± 12</td>
<td>52 ± 10</td>
<td>0.04</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>70%</td>
<td>64%</td>
<td>0.08</td>
</tr>
<tr>
<td>Race (African-American)</td>
<td>26%</td>
<td>45%</td>
<td>0.03</td>
</tr>
<tr>
<td>Ethnicity (Hispanic)</td>
<td>46%</td>
<td>34%</td>
<td>0.14</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>35%</td>
<td>58%</td>
<td>0.01</td>
</tr>
<tr>
<td>Statin therapy</td>
<td>78%</td>
<td>75%</td>
<td>0.7</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4 ± 2.5</td>
<td>26.1 ± 3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Vintage (months)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 6 months</td>
<td>20%</td>
<td>21%</td>
<td>0.3</td>
</tr>
<tr>
<td>6 – 24 months</td>
<td>55%</td>
<td>55%</td>
<td></td>
</tr>
<tr>
<td>&gt; 24 months</td>
<td>25%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Kt/V</td>
<td>1.6 ± 0.3</td>
<td>1.6 ± 0.27</td>
<td>0.9</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>257 ± 184</td>
<td>323 ± 225</td>
<td>0.1</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.3 ± 0.6</td>
<td>9.8 ± 0.57</td>
<td>0.0001</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>5.4 ± 1.1</td>
<td>5.9 ± 1.3</td>
<td>0.05</td>
</tr>
<tr>
<td>Ca × P (mg²/dl²)</td>
<td>50 ± 10</td>
<td>58 ± 14</td>
<td>0.001</td>
</tr>
<tr>
<td>Hs-CRP (mg/l)</td>
<td>6.8 ± 2.4</td>
<td>3.9 ± 1.3</td>
<td>0.003</td>
</tr>
<tr>
<td>Interleukin-6 (pg/l)</td>
<td>8.8 ± 3.4</td>
<td>6.3 ± 2.5</td>
<td>0.035</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>24.9 ± 3.4</td>
<td>21.8 ± 3</td>
<td>0.03</td>
</tr>
<tr>
<td>TNF-α (pg/ml)</td>
<td>7.1 ± 3.5</td>
<td>6 ± 2</td>
<td>0.24</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>159 ± 49</td>
<td>137 ± 11</td>
<td>0.007</td>
</tr>
<tr>
<td>HDL-C (mg/dl)</td>
<td>35 ± 11</td>
<td>40 ± 11</td>
<td>0.14</td>
</tr>
<tr>
<td>LDL-C (mg/dl)</td>
<td>97 ± 36</td>
<td>73 ± 19</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>144 ± 84</td>
<td>138 ± 60</td>
<td>0.7</td>
</tr>
<tr>
<td>CAC score</td>
<td>494 ± 283</td>
<td>283 ± 83</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Values expressed as mean ± SD for continuous variables. CBPB = calcium-based phosphate binders; iPTH = intact parathyroid hormone; Ca × P = calcium-phosphorus product; hs-CRP = high sensitivity C-reactive protein; TNF-α = tumor necrosis factor-α; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; CAC = coronary artery calcium. Statistical significance defined as p value < 0.05.
Foundation K/DOQI guidelines for the CBPB group, they still had significantly higher CACS. Furthermore, this difference was present despite the sevelamer group having a much higher prevalence of DM (58% vs. 35%, p = 0.01). Previous studies have shown that diabetic nephropathy is both a stronger predictor of CAC than mineral metabolism among non-dialysis CKD patients, and a strong independent predictor of CAC progression among both non-dialysis- and dialysis-dependent CKD patients [26]. Hence, getting Ca × P to goal, even with favorable DM status, may not be adequate to hinder or slow the process of vascular calcification in MHD patients.

Sevelamer’s pleiotrophic effects, including potentially altering the lipid profile and inflammatory states of CKD patients, might be contributing to the reduction and extent of CACS. In most studies, sevelamer consistently and significantly decreased LDL-C and increased HDL-C [17, 18, 19]. Sevelamer has been associated with a lower inflammatory burden and a favorable lipid profile in MHD patients [11, 16, 17, 27].

The randomized controlled trial, Treat to Goal [15], showed an association of increased arterial calcification among patients on CBPB. Another recent randomized trial measured all-cause mortality among 127 new to MHD patients assigned to either CBPB or sevelamer; 34 deaths occurred during a median follow-up of 44 months from randomization, 23 in CBPB and 11 in sevelamer group. Baseline CACS was a significant predictor of mortality after adjustment for age, race, gender, and diabetes with increased mortality proportional to baseline scores (p = 0.002). In the randomized trial, mortality was significantly lower in the sevelamer group compared to the CBPB group. The greater risk of death for patients treated with CBPB persisted after full multivariable adjustment (hazard ratio 3.1, 95% CI: 1.23 – 7.61, p = 0.016) and showed that the baseline CACS was a significant predictor of all-cause mortality, and treatment with sevelamer was associated with a significant survival benefit as compared to CBPB [28]. Another randomized study by Suki et al. [29], comparing sevelamer and CBPB in hemodialysis patients, did not show a statisti-

| Table 2. Odds of significant CAC in CBPB vs. sevelamer. |
|-------------|-------------|-------------|-------------|
| Logistic regression covariates | CAC < 10 | 10 ≤ CAC < 100 | 100 ≤ CAC < 400 | CAC ≥ 400 |
| Unadjusted | 1.0 (Ref) | 1.02 (0.4 – 1.8) p = 0.96 | 3.44 (1.2 – 11.4) p = 0.01 | 4.75 (1.7 – 13.5) p = 0.003 |
| + Case-mix | 1.0 (Ref) | 1.07 (0.5 – 2.1) p = 0.90 | 3.39 (1.1 – 11.2) p = 0.01 | 4.68 (1.7 – 10.7) p = 0.004 |
| + Statin | 1.0 (Ref) | 1.15 (0.5 – 2.2) p = 0.88 | 3.14 (1.2 – 11.6) p = 0.02 | 4.56 (1.6 – 11.9) p = 0.006 |
| + Kt/V, albumin, Ca, Phos, Ca × P, iPTH | 1.0 (Ref) | 1.19 (0.5 – 2.7) p = 0.67 | 3.21 (1.3 – 2.3) p = 0.009 | 4.62 (1.4 – 10.3) p = 0.003 |
| + TNF-α, IL-6, CRP | 1.0 (Ref) | 1.17 (0.5 – 2.8) p = 0.72 | 3.09 (1.1 – 10.6) p = 0.01 | 4.35 (1.5 – 9.9) p = 0.008 |

Stepwise logistic regression analysis (n = 117). Definitions: Unadjusted: CAC, Case-Mix: CAC, age, gender, vintage, DM, ethnicity, race, BMI. Abbreviations are: CBPB = calcium-based phosphate binders; Ca = calcium; Phos = phosphorus; Ca × P = calcium-phosphorus product; iPTH = intact parathyroid hormone; IL-6 = interleukin-6; hs-CRP = high-sensitivity C-reactive protein; TNF-α = tumor necrosis factor-α. Statistical significance defined as p value < 0.05.

| Table 3. Odds of elevated CAC and CBPB use among vintage categories. |
|-------------|-------------|-------------|
| Models | Vintage < 6 months | 6 ≤ vintage ≤ 24 months | Vintage > 24 months |
| Odds of CAC ≥ 100 vs. <10 | Odds ratio (95% CI) | Odds ratio (95% CI) | Odds ratio (95% CI) |
| Odds of CBPB vs. sevelamer | 1.0 (Ref) | 1.13 (0.6 – 3.5) p = 0.8 | 1.22 (0.8 – 2.3) p = 0.5 |

Statistical significance defined as p value < 0.05.
cally significant reduction in mortality among the study population. However, survival benefit with sevelamer was observed among patients ≥ 65 years of age.

This study depicts a real world cross-sectional analysis comparing early baseline characteristics of MHD patients in a larger cohort in relation to EBCT. Majority of subjects had been on dialysis for greater than 6 months. When comparing odds of CAC ≥ 100 vs. CAC < 10 there was no significant difference among vintage time (Table 3) yet there was a trend in increased percentage of subjects on MHD for > 24 months as CACS increased (Figure 1), which may have potentially contributed to the CAC burden. Thus vintage was adjusted for in the logistic regression analysis. A potential limitation of the present study is that medications were collected upon enrollment in the trial and subsequently on a yearly basis. If patients changed medications or doses in between collection times, this may not have been captured. The strengths of this study include the comprehensive clinical and laboratory evaluations, and the inclusion of many individuals with DM. Unlike previous cohorts that have been studied, ours has been extensively characterized for markers of inflammation and nutritional status, including inflammatory cytokines. The availability of these measures allowed us to demonstrate that the type of phosphorus binder was able to predict higher risk of CAC independent of influences from other known inflammatory markers or comorbid states in this group of MHD patients. Another strength of this cohort is that the subjects were selected randomly without having any prior knowledge of their CACS or inflammation status.

In conclusion, our study showed that despite at goal mineral metabolism levels and favorable DM status, increased CACS was more prevalent among subjects on CBPB compared to sevelamer. Decreasing the burden of CAC, while on sevelamer, may reduce the risk of CVD and death in this population. What remains to be answered are the effects both binder types have on, not just mineral metabolism, but lipid profiles, inflammatory profiles, potentially the diabetic milieu and how those affect CAC. Larger randomized controlled trials and observational studies are needed to further clarify phosphate-binder roles in augmenting risk factors, markers, and how that translates into cardiovascular complications and mortality.

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Conflict of interest

KKZ and MJB have received grants and/or honoraria from Genzyme (manufacturer of Hectoral™, Renagel™ and Renvela™), Abbott (manufacturer of Calcijex™) and Zemplar™), Amgen (manufacturer of Sensipar™), and/or Shire (manufacturer of Fosrenol™). Other authors have not declared conflicts of interest.

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