Short-Term Treatment with Sevelamer Increases Serum Fetuin-A Concentration and Improves Endothelial Dysfunction in Chronic Kidney Disease Stage 4 Patients

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Background and objectives: Vascular calcification and endothelial dysfunction contribute to the development of cardiovascular disease in patients with chronic kidney disease (CKD). Sevelamer, a non–calcium-based phosphate binder, has been shown to attenuate cardiovascular calcification in CKD patients, although the exact mechanism has not been clarified. This study was designed to investigate the effect of short-term sevelamer treatment on both serum fetuin-A concentrations and endothelial dysfunction seen in CKD patients.

Design, setting, participants, & measurements: Fifty nondiabetic stage 4 CKD patients whose phosphate levels were ≥5.5 mg/dl were enrolled in this 8-wk randomized prospective study. Thirty-six healthy volunteers served as matched controls. Patients were treated with either sevelamer (n = 25, 12 males) or calcium acetate (n = 25, 13 males). Fetuin-A, high-sensitivity C-reactive protein, Ca × PO₄ product, flow-mediated dilation (FMD), insulin, and homeostasis model assessment (HOMA) were obtained at baseline and after the treatment period.

Results: As expected, CKD patients had significantly lower levels of fetuin-A and FMD, and significantly higher levels of intact parathyroid hormone, Ca × PO₄ product, and high-sensitivity C-reactive protein than controls (P < 0.001 for all). The use of sevelamer led to a significant increase in the fetuin-A concentration with improvement in FMD, whereas no significant difference was observed in the calcium acetate group. In a multiple regression analysis, FMD levels were independently related to fetuin-A both before (β = 0.63, P < 0.001) and after (β = 0.38, P = 0.004) treatment.

Conclusions: This small, randomized, prospective study shows that short-term sevelamer treatment significantly increases fetuin-A levels and improves FMD in nondiabetic stage 4 CKD patients.


Cardiovascular disease (CVD) is prevalent in patients with chronic kidney disease (CKD) (1). Strong correlation between the derangement in mineral metabolism, such as hyperphosphatemia, hyperparathyroidism, as well as elevated calcium × phosphorus product (Ca × PO₄) and mortality has been reported in hemodialysis (HD) patients (2). These derangements have also been shown to result in vascular calcification, an independent risk factor for cardiovascular mortality (3,4). Elevated Ca × PO₄ product and higher doses of oral calcium ingestion significantly predicted coronary artery calcification (CAC) in patients with end-stage kidney disease (5). Moreover, London et al. (4) have shown significant association between the uses of calcium-based phosphate binders and arterial medial calcification in HD patients. Based on the deleterious effect of high calcium intake on vascular calcification, a calcium-free non-absorbed phosphate binder, sevelamer hydrochloride, has been developed for the treatment of hyperphosphatemia in CKD patients (6). Studies have shown that sevelamer provides effective control in serum PO₄ levels without inducing hypercalcemia (6,7). Additionally, these studies have also shown beneficial effects of sevelamer on the progression of vascular calcification, although the underlying mechanisms were not clarified (8). Recent studies on vascular calcification have evaluated a number of circulating systemic calcification inhibitors, such as fetuin-A, matrix-Gla protein, osteoprotegrin, etc. (9). Fetuin-A, the major circulating inhibitor of vascular calcification, has been shown to be lower in dialysis patients and to be associated with cardiovascular mortality (10).

Recent data have shown a relationship between vascular calcification and endothelial dysfunction (ED) in vascular dis-
Concise Methods

Subjects

CKD stage 4 patients >18 yr of age and willing to participate to the study were screened. Those who had serum PO$_4$ $>$5.5 mg/dl were evaluated for the study. Patients with diabetes mellitus, hypercalcinemia (serum Ca >11 mg/dl), and history of CAD, and smokers and those taking statins or renin-angiotensin blockers were excluded because of the putative effect of these factors on ED. Of 62 screened patients, 50 met the study criteria and were included in this study. The primary renal diseases were glomerulonephritis in 12 patients (24%), hypertension in 11 patients (22%), polycystic kidney disease in 6 patients (12%), reflux nephropathy in 4 patients (8%), and unknown in 17 patients (34%). Sixteen of the patients were on antihypertensive therapy (9 patients were treated with calcium-channel antagonists, 2 patients with β-blocker agents, and 5 patients with loop diuretics). The study also recruited a control group comprising 36 healthy, unrelated subjects matched for age, sex, and body mass index by advertisement in the hospital of Gülhane School of Medicine in Ankara, Turkey. The ethical committee of Gülhane School of Medicine approved the study, and written informed consent was obtained from all patients.

Study Design

This was a randomized study conducted from 2005 through 2006 in Gülhane School of Medicine. The Outpatient Clinic of the Department of Nephrology is a tertiary referral center. At admission, most patients were untreated (including phosphate binders) or treated only with antihypertensive agents. After the first evaluation, 9 patients receiving phosphate binders underwent a 2-wk washout period. Patients who developed a phosphate level $>$5.5 mg/dl during this period were included in the study. Patients were randomly assigned in a 1:1 ratio to receive sevelamer (Renage® capsule) or calcium acetate (PhosEx® tablet) (Figure 1). The treatment phase was 8 wk. During the study period, serum calcium and phosphorus concentration were measured every 2 wk and the dose of phosphate binders were titrated to achieve a serum phosphorus concentration $<$5.5 mg/dl. The starting dose for sevelamer was two capsules (800 mg) three times a day and for calcium acetate one tablet (1000 mg) three times a day. The average dose of sevelamer treatment was two tablets three times a day (4800 mg/d). The medications were given with meals and the doses were increased as needed. Patients were not given calcitriol during the study period. If hypercalcinemia (serum Ca > 11 mg/dl) occurred during the study, phosphate binder doses were decreased according to a fixed algorithm. The primary end point was defined as an increase in serum fetuin-A levels and FMD levels after 8 wk of treatment. Secondary end points were a decrease in PO$_4$ levels and Ca × PO$_4$ product in serum.

Fasting blood samples were taken before and after the study to measure serum creatinine, serum albumin, hs-CRP, insulin, intact parathyroid hormone (iPTH), lipid profile, and serum fetuin-A concentration. Flow-mediated dilation (FMD) was evaluated before and after the study.

Blood Chemistry

All samples were obtained from patients and controls between 8:00 and 8:30 a.m. after 12 h of fasting for measurement of fasting plasma glucose (FPG), serum albumin, total cholesterol, triglyceride, HDL cholesterol, and LDL cholesterol. Total plasma cholesterol, triglyceride, and HDL cholesterol were measured by the enzymatic colorimetric method with an Olympus AU 600 auto analyzer using reagents from Olympus Diagnostics, GmbH (Hamburg, Germany). LDL cholesterol was calculated with use of Friedewald’s formula (14). Hemoglobin levels were measured with an automated analyzer (Abbott Cell-Dyn 4,000, Abbott Park, IL).

The serum basal insulin value was determined by the coated tube method (DPC-USA). An insulin resistance score Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) was computed by the following formula(15):

$$HOMA-IR = \frac{FPG (mg/dl)}{405} \times \frac{immunoreactiveinsulin(IRI)(\mu U/ml)}{405}$$

Serum total Ca was measured by the Cresolphthalein complexone method using Menagent Calcium 60-s kits (Menarini Diagnostics, Florence, Italy). Serum PO$_4$ was measured by the ammonia molybdate complex method using Menagent Phosphofix kits (Menarini Diagnostics). iPTH was measured by IRMA, using kits (Immulate iPTH) from Diagnostic Product Corporation (Los Angeles, CA) with a sensitivity of 1 pg/ml.

Serum concentrations of fetuin-A (AHSG) were measured by using a human fetuin-A ELISA kit (BioVendor Laboratory Medicine, Inc., Brno, Czech Republic) in an ELISA plate reader (Synergy HT, Multidetection Multi-Plate Reader, Bio-tek Instruments, Inc., Winooski, VT). Interassay and intraassay coefficients of variations were $<$9%. For the measurement of hsCRP, serum samples were diluted with a ratio of 1/101 with the diluents solution. Calibrators, kit controls, and serum samples were all added on each microwell with an incubation period of 30 min. After three
was defined by Levey formula [GFR version of the Modification of Diet in Renal Disease prediction equation amount of serum samples was calculated as mg/L with a graphic that was photometric measurement was performed at the 450-nm wavelength. The temperature in dark. The reaction was stopped with a stop solution, and was added on each microwell for additional 15 min incubation in room Table 2.

Comparison of the effects of sevelamer and calcium acetate on the parametera

|                             | Controls (n = 32) | Sevelamer (n = 25) | Calcium acetate (n = 25) | p
|-----------------------------|------------------|-------------------|--------------------------|---
| **BMI (kg/m²)**             | 24.9 ± 2.1       | 24.9 ± 2.6        | 24.7 ± 2.4               | NS
| **Total cholesterol (mg/dl)** | 182.7 ± 16.6     | 189.8 ± 18.8      | 190.1 ± 19.2             | NS
| **Triglycerides (mg/dl)**   | 134.6 ± 13.8     | 137.7 ± 12.4      | 128.7 ± 21.3             | NS
| **LDL cholesterol (mg/dl)** | 114.0 ± 12.3     | 113.5 ± 16.0      | 117.8 ± 19.2             | NS
| **HDL cholesterol (mg/dl)** | 41.4 ± 5.1       | 38.6 ± 5.9        | 38.9 ± 6.9               | NS
| **Hemoglobin (g/dl)**       | 14.0 (13.0 to 15.4) | 11.4 (10.5 to 13.5) | 11.0 (10.2 to 13.4) | <0.05
| **SBP (mmHg)**              | 127 ± 7          | 132 ± 7           | 129 ± 8                  | <0.05
| **DBP (mmHg)**              | 81 ± 3           | 83 ± 5            | 82 ± 4                   | NS
| **eGFR (ml/min)**           | 111 (95 to 126)  | 25 (17 to 30)     | 24 (15 to 29)            | <0.001
| **HOMA-IR**                 | 1.24 ± 0.33      | 1.34 ± 0.34       | 1.31 ± 0.31              | NS
| **Serum Ca (mg/dl)**        | 9.1 ± 0.5        | 8.1 ± 0.4         | 8.0 ± 0.4                | <0.001
| **Serum PO₄ (mg/dl)**       | 3.6 ± 0.4        | 7.8 ± 0.6         | 7.8 ± 0.7                | <0.001
| **Ca × PO₄ product**        | 34 (23 to 41)    | 62 (54 to 73)     | 63 (46 to 71)            | <0.001
| **Serum albumin (g/dl)**    | 4.2 ± 0.3        | 3.9 ± 0.3         | 3.9 ± 0.3                | <0.01
| **iPTH (pg/ml)**            | 42 (21 to 65)    | 155 (120 to 183)  | 148 (148 to 186)         | <0.001
| **hs-CRP (mg/L)**           | 2 (1 to 4)       | 15 (9 to 18)      | 14 (10 to 24)            | <0.001
| **FMD (%)**                 | 8.8 (7.3 to 12.4) | 6.0 (4.3 to 6.8)  | 5.8 (4.7 to 7.0)         | <0.001
| **Fetuin-A (g/L)**          | 0.40 (0.34 to 0.46) | 0.27 (0.23 to 0.34) | 0.27 (0.24 to 0.31) | <0.001

aBML, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FMD, flow-mediated dilatation; FPG, fasting plasma glucose; HOMA-IR, homeostasis model assessment-insulin resistance; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; NS, not significant. Data are means ± SD or median.
bP values determined by t test.

data were with 100 µL enzyme conjugate (peroxidase-labeled anti-CRP) was added on each microwell for additional 15 min incubation in room temperature in dark. The reaction was stopped with a stop solution, and photometric measurement was performed at the 450-nm wavelength. The amount of serum samples was calculated as mg/L with a graphic that was made by noting the absorbance levels of the calibrators.

Estimated GFR (eGFR) was calculated according to the simplified version of the Modification of Diet in Renal Disease prediction equation formula [GFR = 186 × Pre−1.154 × age−0.203 × 1.212 (if black) × 0.742 (if female)] was defined by Levey et al. (16).

**Table 2. Comparison of the effects of sevelamer and calcium acetate on the parametera**

<table>
<thead>
<tr>
<th></th>
<th>Sevelamer (n = 25)</th>
<th>Calcium Acetate (n = 25)</th>
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<tr>
<td></td>
<td>BT</td>
<td>AT</td>
</tr>
<tr>
<td><strong>Fetuin-A (g/L)</strong></td>
<td>0.27 (0.23 to 0.34)</td>
<td>0.35 (0.24 to 0.43)b</td>
</tr>
<tr>
<td><strong>FMD (%)</strong></td>
<td>6.0 (4.3 to 6.8)</td>
<td>6.8 (5.5 to 8.8)b</td>
</tr>
<tr>
<td><strong>LDL cholesterol (mg/dl)</strong></td>
<td>113.5 ± 16.0</td>
<td>103.7 ± 17.0b</td>
</tr>
<tr>
<td><strong>Serum albumin (g/dl)</strong></td>
<td>3.9 ± 0.3</td>
<td>4.0 ± 0.4</td>
</tr>
<tr>
<td><strong>hsCRP (mg/L)</strong></td>
<td>15 (9 to 18)</td>
<td>10 (5 to 14)b</td>
</tr>
<tr>
<td><strong>iPTH (pg/ml)</strong></td>
<td>155 (120 to 183)</td>
<td>164 (117 to 232)b</td>
</tr>
<tr>
<td><strong>Serum Ca (mg/dl)</strong></td>
<td>8.1 ± 0.4</td>
<td>7.9 ± 0.5</td>
</tr>
<tr>
<td><strong>Serum PO₄ (mg/dl)</strong></td>
<td>7.8 ± 0.6</td>
<td>5.9 ± 0.9b</td>
</tr>
<tr>
<td><strong>Ca × PO₄ product</strong></td>
<td>62 (54 to 73)</td>
<td>48.0 (29.6 to 59.5)b</td>
</tr>
</tbody>
</table>

aData are mean ± SD and median. Paired samples t test.
bP < 0.001

ED. The determination of ED was performed according to Ceremias et al. (17). Measurements were made by a single observer using an ATL 5000 ultrasound system (Advanced Technology Laboratories, Inc., Bothell, WA) with a 12-MHz probe. All vasoactive medications were withheld for 24 h before the procedure. The subjects remained at rest in the supine position for at least 15 min before the examination started. Each subject’s arm was comfortably immobilized in the extended position to allow consistent recording of the brachial artery 2 to
ANOVA, considered to be statistically significant. One-sample Kolmogorov-calculated by the Power and Sample Size V.2.0 program (Vanderbilt was used to assess the predictors for FMD levels. Sample size was with continuous variables. Stepwise multivariate regression analysis data. Spearman rank correlation was used to determine correlations Changes of important parameters after phosphate binding with sevelamer and calcium acetate over 8 wk Table 3.

Figure 2. Fetuin-A, high-sensitivity C-reactive protein (hsCRP), and flow-mediated dilation (FMD) levels in calcium acetate and sevelamer groups before and after 8 wk of treatment.

4 cm above the antecubital fossa. Three adjacent measurements of end-diastolic brachial artery diameter were made from single two-dimensional frames. All ultrasound images were recorded on S-VHS videotape for subsequent blinded analysis. A pneumatic tourniquet was inflated to 200 mmHg with obliteration of the radial pulse. After 5 min the cuff was deflated. Flow measurements were made 60 seconds postdeflation. The maximum FMD diameters were calculated as the average of the three consecutive maximum diameter measurements. The FMD was then calculated as the percent change in diameter compared with baseline resting diameters. To assess the reproducibility of our technique, the same operator repeated brachial artery studies. The operator was blinded to the FMD result and medications remained unchanged between the initial and repeated scans.

Statistical Analyses
All statistical analyses were performed by using the SPSS 11.0 statistical package (SPSS, Inc., Chicago, IL). Non-normally distributed variables were expressed as median (range) and normally distributed variables as mean±SD as appropriate. A P value <0.05 was considered to be statistically significant. One-sample Kolmogorov-Smirnov test was used for analysis of distribution of data. One-way ANOVA, t test, and paired-sample t test were used to compare numeric data. Spearman rank correlation was used to determine correlations with continuous variables. Stepwise multivariate regression analysis was used to assess the predictors for FMD levels. Sample size was calculated by the Power and Sample Size V.2.0 program (Vanderbilt University, Department of Biostatistics, Free Software). The criteria for sample size calculation were as follows; 95% confidence intervals, 80% power, decrease in fetuin-A levels (0.1 g/L for sevelamer treatment group and 0.025 g/L for calcium acetate group, according to clinical experience). According to these criteria, 22 patients were to be recruited in each group. Considering the possibility of laboratory and other process mishaps, we decided to include 25 patients in each group.

Results
Basic Characteristics
Baseline clinical and laboratory characteristic as well as vascular measurements for the study population are shown in Table 1. There were no differences between CKD patients and controls with respect to age, sex, insulin levels, HOMA index, lipid profiles, and body mass index. Also, these variables were not significantly different between the sevelamer (n = 25) and calcium acetate (n = 25) groups. As expected, serum Ca, fetuin-A, and albumin concentrations and eGFR levels were lower and serum PO4, iPTH, Ca × PO4 product and hs-CRP levels were higher in CKD patients. FMD levels were lower in CKD patients than in controls. There were no significant basal differences in the sevelamer and calcium acetate groups’ treatment according to serum fetuin-A concentration and vascular measurements (Table 1).

Effects of Sevelamer on Fetuin-A Concentrations and FMD Levels
Whereas median serum fetuin-A concentration increased significantly in the sevelamer-treated group (0.27 g/L to 0.35 g/L, P < 0.001) no significant difference (0.27 g/L to 0.28 g/L) was observed in the calcium acetate–treated group (Table 2). Figure 2 shows the effects of sevelamer and calcium acetate treatment on serum fetuin-A, FMD, and hs-CRP levels. The mean change in serum fetuin-A concentration was 0.07 ± 0.04 g/L in the sevelamer-treated group. Thus, at the end of the 8-wk treatment period, there was a statistically significant (P < 0.001) difference in fetuin-A between the sevelamer- and calcium acetate-treated groups. In parallel, whereas FMD significantly improved in the sevelamer-treated group (5.7 ± 0.8% to 6.7 ± 0.8%, P < 0.001), no significant change was observed in the calcium acetate–treated group (5.7 ± 0.4% to 5.7 ± 0.6%) (Table 3).

At the end of the study period there were no significant differences in serum albumin, Ca, or PO4 levels with respect to binder assignment (Table 2). However, although not statisti-

| Table 3. Changes of important parameters after phosphate binding with sevelamer and calcium acetate over 8 wk |
|-----------------------------------------------|-----------------|------------------|------------------|
| Fetuin-A (g/L)                              | 0.07 ± 0.04     | 0.01 ± 0.03      | <0.001           |
| FMD (%)                                      | 1.1 ± 0.9       | 0.01 ± 0.55      | <0.001           |
| hs-CRP (mg/L)                                | −4 (−11 to 0)   | −1 (−13 to 6)    | 0.002            |
| iPTH (pg/ml)                                 | 9.8 ± 23.2      | 33.2 ± 33.3      | 0.003            |
| Serum Ca (mg/dl)                             | −0.06 ± 0.58    | 0.17 ± 0.56      | NS               |
| Serum PO4 (mg/dl)                            | −1.9 ± 0.8      | −1.8 ± 0.7       | NS               |
| Ca × PO4 product                             | −15.6 ± 8.8     | −13.2 ± 7.7      | NS               |
cally significant, serum Ca levels and Ca × PO₄ product were lower in the sevelamer-treated group than in the calcium acetate–treated group. In both treatment groups iPTH levels increased during the study period.

Baseline median hs-CRP levels did not differ between sevelamer- and calcium acetate–treated groups. However, whereas sevelamer therapy significantly decreased median hs-CRP levels (15 mg/L to 10 mg/L, P < 0.001), calcium acetate–based therapy had no significant effects on median hs-CRP levels (14 mg/L to 14 mg/L). Whereas sevelamer treatment significantly decreased LDL-cholesterol levels (113.5 ± 16.0 mg/dl to 103.7 ± 17.0, P < 0.05), calcium acetate–based therapy had no such effect (117.8 ± 19.2 mg/dl to 123.2 ± 15.8 mg/dl, P = NS).

Correlations
At baseline, FMD was positively correlated with serum fetuin-A levels and negatively correlated with hs-CRP levels. As expected, a negative correlation was observed between serum fetuin-A and hs-CRP levels (rho = −0.43, P = 0.002). The changes in FMD were positively correlated with basal serum fetuin-A levels (rho = 0.51, P < 0.001) (Figure 3). In parallel, the reduction in hs-CRP levels correlated with the changes in serum fetuin-A concentration (rho = 0.40, P = 0.005). A multiple regression model incorporating variables expected to influence FMD (sex, age, Ca × PO₄ product, hs-CRP, and iPTH), as well as fetuin-A was performed both before and after treatment. The results showed that FMD levels were independently related to fetuin-A levels both before (P < 0.001) and after (P = 0.004) treatment (Table 4).

Whereas three patients experienced hypercalcemic episodes during treatment with calcium acetate, no patient experienced hypercalcemia with sevelamer. Some patients experienced abdominal pain (n = 1 for calcium acetate; n = 1 for sevelamer), nausea (n = 1 for calcium acetate; n = 1 for sevelamer) and muscle cramps (n = 1 for calcium acetate; n = 0 for sevelamer) during the study period. No patients withdrew from the study as a result of adverse events.

Discussion
This randomized controlled study shows that short-term (8 wk) sevelamer treatment significantly increases serum fetuin-A concentration in CKD stage 4 patients. In contrast, calcium acetate had no significant effect on fetuin-A levels during the observation period. This study also shows that ED improves in parallel with the increase in serum fetuin-A concentration in sevelamer-treated CKD patients. On the basis of the present observation one could speculate that an increment in fetuin-A during sevelamer treatment may be one underlying mechanism by which this drug attenuates progression of vascular calcification (18) and improves outcome (19) in CKD patients.

Fetuin-A, a circulating glycoprotein synthesized by liver cells, has been shown to be one of the major calcification inhibitors. Notably, fetuin-A also has several other properties, such as inhibition of TGF-β and impact on insulin sensitivity (20). Fetuin-A has been suggested to be responsible for approximately 50% of the precipitation inhibitory effect of serum PO₄ (20). Recently, Westenfeld et al. (21) showed that fetuin-A deficiency, CKD, and a high-PO₄ diet synergistically acts in the pathogenesis of extraosseous calcification in a mouse model. Thus, fetuin-A knockout mice have been shown to develop severe vascular and other tissue calcifications (22). Because vascular calcification is a common event even in young CKD patients (23) and is one of the predictors of cardiovascular mortality (3), several studies have examined the role of serum fetuin-A levels in various CKD populations. Our study shows that fetuin-A levels are significantly reduced in nondiabetic CKD stage 4 patients, which confirms previous studies in CKD stage 5 patients (10,24–26). In contrast, in 970 CAD patients

Table 4. Analysis of association between FMD and some different parameters by univariate and multivariate linear regression both before and after treatment

<table>
<thead>
<tr>
<th></th>
<th>Univariate β (P)</th>
<th>Multivariate β (P)</th>
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<tbody>
<tr>
<td>Before treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetuin A (g/L)</td>
<td>0.65 (&lt;0.001)</td>
<td>0.63 (&lt;0.001)</td>
</tr>
<tr>
<td>Ca × PO₄ product</td>
<td>−0.12 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>−0.02 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>−0.17 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.03 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>0.07 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>After treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetuin A (g/L)</td>
<td>0.48 (0.001)</td>
<td>0.38 (0.004)</td>
</tr>
<tr>
<td>Ca × PO₄ product</td>
<td>−0.10 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>−0.30 (0.04)</td>
<td>NS</td>
</tr>
<tr>
<td>hs-CRP (mg/L)</td>
<td>−0.39 (0.005)</td>
<td>NS</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>0.24 (NS)</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>0.03 (NS)</td>
<td>NS</td>
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</table>

![Figure 3. Scatter plot shows the significant positive relationship between the change in fetuin-A and FMD.](image-url)
with mild CKD, Ix et al. (27) reported that serum fetuin-A concentration was not reduced. In a cross-sectional study, Mehrotra et al. (28) reported that the significance of correlation between fetuin-A and GFR was lost after adjusting the data for serum albumin in nondialized patients with diabetic nephropathy. On the basis of these observations, it could be suggested that serum fetuin-A levels decline only late during the course of progression of patients with CKD.

The fact that low levels of fetuin-A are associated with vascular calcification (29) and mortality (10) in prevalent HD patients has resulted in a lot of interest in this calcification inhibitor. Subsequent studies show that a reduction in serum fetuin-A levels is associated with both all-cause and cardiovascular mortality in CKD stage 5 patients starting dialysis treatment (24) as well as prevalent continuous ambulatory peritoneal dialysis patients (25). These findings were recently corroborated by Hermans et al. (26) who demonstrated in prospective multicenter cohort study of 987 Dutch dialysis patients that low fetuin-A is a general predictor of mortality.

Vascular calcification is a common finding both in dialysis patients (30) and CKD patients not yet on dialysis therapy (31,32). Given the strong association between the development of vascular calcification and cardiovascular mortality in patients with CKD (3), elucidating this process seems to be very important. Chertow et al. (8) have shown that, compared with Ca-based PO₄ binders, sevelamer attenuated the progression of coronary and aortic calcification in 200 HD patients. In accordance, Braun et al. (33) reported that HD patients on Ca-based therapy showed greater progression in coronary and aortic calcification than patients on sevelamer therapy. However, the exact mechanism(s) by which sevelamer attenuates the calcification process have not been elucidated. Although normalization of Ca and PO₄ metabolism may be a major contributor, other beneficial effects of sevelamer, such as lipid reduction (34) and uric acid reduction (35), may also be of potential benefit. In addition, sevelamer may have beneficial effects on uremic toxin absorption, such as p-cresol (36). The mechanism(s) by which sevelamer therapy increased serum fetuin-A concentration in this study is not evident. However, because fetuin-A is a negative acute-phase reactant (37) and because we observed that sevelamer therapy was associated with a reduction in hs-CRP levels, a nonspecific antiinflammatory effect of sevelamer therapy may explain the observed increase in fetuin-A. Indeed, Ferramosca et al. (38) demonstrated that sevelamer treatment had antiinflammatory and potential antiatherogenic effects in HD patients. In addition, Phan et al. (39) showed that sevelamer prevented uremia-enhanced atherosclerosis in apolipoprotein E–deficient mice. Given the observed reduction in LDL cholesterol levels, it could also be speculated that favorable effects on uremic dyslipidemia may also contribute to less inflammation in sevelamer-treated patients. Finally, given the structure of the sevelamer molecule, nonspecific binding in the gut of one or several factors that inhibit fetuin-A synthesis could also theoretically contribute to the observed finding.

Another important observation in this study was the small but significant improvement in ED in sevelamer-treated patients. Notably, FMD increased in parallel with increased fetuin-A concentration, and in a multiple regression analysis fetuin-A was independently associated with FMD. In accordance, we have previously shown that the improvement in FMD after successful kidney transplantation was associated with increased fetuin-A levels (40). Taken together, because this study suggests that sevelamer has a beneficial effect on endothelial function, further mechanistic studies are needed to confirm this finding and elucidate potential pathophysiological mechanism(s).

The results of our study must be considered with the following caveats. First, the number of patients was limited and studies in larger populations are needed to confirm this finding. Second, because the observation period was short, additional studies with longer observation time are needed. Third, because diabetic patients and smokers were not included in this study, it should be emphasized that this is a selected group of CKD patient with a low degree of comorbidities. Thus, these findings cannot be generalized to the whole CKD patient population. Fourth, endothelial-independent function as measured by response to glyceryl trinitrate as alterations in calcification was not evaluated. Fifth, we should have measured pH or serum bicarbonate levels because metabolic acidosis could be exacerbated by sevelamer, which in turn could lead to increased nitric oxide production and improved endothelial function. Finally, it should be acknowledged that the observed effects on both inflammatory markers and endothelial function were modest and its relevance for cardiovascular morbidity and mortality is unknown.

In conclusion, this 8-wk, prospective, randomized trial shows that treatment with sevelamer (in contrast to calcium acetate) was associated with less inflammation, increased levels of the circulating inhibitor of vascular calcification fetuin-A, and an improvement of endothelial function in nondiabetic CKD stage 4 patients. Further studies are needed to investigate whether these effects, at least in part, could contribute to less vascular calcification and better outcomes in sevelamer-treated CKD patients.

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Disclosures

B.L. is an employee of Baxter Healthcare, Inc. P.S. is a member of the scientific advisory board of Gambro AB.

References


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