Sevelamer Prevents Uremia-Enhanced Atherosclerosis Progression in Apolipoprotein E–Deficient Mice

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**Background**—The novel phosphate binder sevelamer has been shown to prevent the progression of aortic and coronary calcification in uremic patients. Whether it also decreases the progression of atheromatous plaques is unknown. The aim of our study was to examine the effect of sevelamer administration on the development of atherosclerosis and aortic calcification in the uremic apolipoprotein E–deficient mouse as an established model of accelerated atherosclerosis.

**Methods and Results**—Female mice were randomly assigned to 4 groups: 2 groups of nonuremic mice (sevelamer versus control) and 2 groups of uremic mice (sevelamer versus control). Sevelamer was given at 3% with chow. The increases in serum phosphorus concentration and calcium-phosphorus product observed in uremic control mice were prevented by sevelamer. Serum total cholesterol was increased in the 2 uremic mouse groups and remained unchanged in response to sevelamer. After 8 weeks of sevelamer treatment, uremic mice exhibited a significantly lower degree of atherosclerosis ($P<0.001$) and vascular calcification than uremic control mice. Of interest, sevelamer exerted an effect on both intima and media calcification ($P=0.005$) in uremic mice. Among possible mechanisms involved, we found no evidence for the modulation by sevelamer of inflammation or selected uremic toxins. In contrast, nitrotyrosine staining as a measure of oxidative damage was significantly decreased in response to sevelamer treatment in control and uremic mice ($P<0.005$).

**Conclusions**—Sevelamer delays not only vascular calcification but also atherosclerotic lesion progression in uremic apolipoprotein E–deficient mice. It opens the possibility of a cholesterol-independent action of sevelamer on atheroma formation via effects on mineral metabolism, oxidative stress, or both. (Circulation. 2005;112:2875-2882.)

**Key Words:** atherosclerosis ■ calcium ■ oxidative stress ■ uremia ■ phosphates

**Clinical Perspective p 2882**

Until recently, it seemed impossible to slow or even halt the progression of uremic arteriopathy and arterial calcification. The result of the prospective, randomized Treat-to-Goal study changed this view. It showed that it was possible to retard the progression of vascular calcification on the basis of an electron-beam CT technique allowing a quantitative and reproductive assessment of calcium deposition in the vessel wall. In this study, the administration of the calcium-free and aluminum-free phosphate binder sevelamer hydrochloride to patients with chronic hemodialysis for 12 months effectively led to a significantly slower progression of aortic and carotid calcification than the administration of calcium-containing phosphate binders. The electron-beam CT technique, however, cannot distinguish whether calcium deposits are localized in plaques (intima) or in the vascular media. Even more importantly, it does not enable a concomitant assessment of the progression of atherosclerotic vessel wall lesions.

*The first 2 authors contributed equally to this work.

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Therefore, we addressed these questions more directly in a uremic mouse model of accelerated atherosclerosis\(^7\)\(^–\)\(^9\) and vascular calcification.\(^9\) We used one of the most common models for the study of atherogenic mechanisms, namely, the apolipoprotein E--deficient (apoE\(^{−/−}\)) mouse. This genetically engineered animal generates atherosclerotic lesions within weeks after birth that exhibit features similar to those found in humans.\(^7\)\(^–\)\(^9\) We created CRF in these mice according to a recently established method and reported increased atheroma progression compared with non-CRF controls.\(^9\) In addition, uremia was associated with more extensive aortic calcium deposits in both the media and the intima.

The goal of our study was to examine the effect of sevelamer administration on the development of atherosclerosis and aortic calcification in the aforementioned experimental mouse model of CRF.

Methods

Animals
Female apoE\(^{−/−}\) mice were primarily obtained from Charles Rivers Breeding Laboratories (Wilmington, Mass). All procedures were in accordance with NIH guidelines for the care and use of experimental animals (NIH publication No. 85-23). The mice were housed in polycarbonate cages in a pathogen-free, temperature-controlled (25°C) facility with a strict 12-hour light/dark cycle. The mice had free access to chow diet and water. The diet (Harlan Teklad Global Diet 2018) contained 18% protein, 6% fat, 1.01% calcium, 0.65% phosphorus, and 1.54 IU/g vitamin D\(_3\).

Experimental Procedure and Diet
At the age of 8 weeks, mice were randomly assigned to 1 of the following 4 groups, with 12 animals in each group: 2 groups of non-CRF animals (sevelamer group versus placebo group) and 2 groups of CRF animals (sevelamer CRF group versus placebo CRF group). As previously described, we used a 2-step procedure to create uremia.\(^9\) Briefly, we applied cortical electrocautery to the right kidney through a 2-cm flank incision and performed left total nephrectomy through a similar incision 2 weeks later; control animals received sham operation that included decapsulation of both kidneys. Special care was taken to avoid damage to the adrenals. Blood samples were taken 2 weeks after nephrectomy, and animals of the CRF group with a urea level \(>20\) mmol/L (normal mouse serum urea, \(≤10\) mmol/L) were subsequently randomized to 2 CRF subgroups: One CRF subgroup was fed for 8 weeks on a sevelamer-containing diet, whereas the other CRF subgroup received a placebo diet for the same period of time. Likewise, control non-CRF mice were fed on sevelamer- or placebo-containing diets. Sevelamer was administered together with the diet as a 3% mix with animal chow. At the end of the study, each mouse was anesthetized with ketamine/xylazine anesthesia (100 mg/kg, 20 mg/kg), and whole blood was collected via cardiac puncture. The heart and aorta were dissected free down to the renal arteries and removed. For immunohistochemistry and aortic calcification, the heart with the aortic root was separated from more distal aorta, as reported previously.\(^9\) The rest of the aorta was used for quantification of atherosclerotic lesions (see below).

Serum Biochemistry
Serum urea, total cholesterol, phosphorus, and calcium were measured with the use of a Hitachi 917 autoanalyzer (Roche), and intact parathyroid hormone (iPTH) was measured by enzyme immunoassay (Immunotopics) as reported previously.\(^9\)

For the analysis of circulating fetuin-A at day of euthanasia, mouse sera were fractionated on 10% polyacrylamide gels, blotted to nitrocellulose, and probed with polyclonal rabbit anti-mouse fetuin-A antibody at a dilution of 1:5000 in hybridization buffer (PBS with 5% skim milk and 0.1% Tween 20) for 1 hour at 37°C. After the blots were washed with PBS including 0.1% Tween 20, a secondary antibody conjugated with horseradish peroxidase (Vector Laboratories) was added at a dilution of 1:5000 in hybridization buffer for 1 hour at 37°C. Bound antibody was detected by chemiluminescence with the use of luminol and x-ray film. Fluorographs were analyzed with the use of a flatbed scanner and the MultiAnalys software package (Bio-Rad). We performed dilutions of the serum in the range of 100-fold or 200-fold. All samples were measured on 1 day with the use of the same blot with the same antibodies and identical luminol to circumvent any interassay variability.

Analysis of uremic toxins was performed in placebo and sevelamer CRF mice and in placebo control non-CRF mice: Uric acid, indoxyl sulfate, hippuric acid, indole acetic acid, and 3-carboxy-4-methyl-5-propyl-2-furanpropionic acid (CMFP). After deproteinization of the serum samples by heat denaturation, analyses were performed with reversed-phase high-performance liquid chromatography. Indoxyl sulfate and indole acetic acid concentrations were determined by fluorescence detection (excitation 280 nm, emission 340 nm). Uric acid, hippuric acid, and CMFP were analyzed by UV detection at 254 nm. Calibration curves of the 5 compounds were used to calculate the concentrations in each sample.\(^10\)

We used enzyme immunoassay for the determination of mouse serum amyloid A (SAA) in mouse serum (ELISA kit MG45182, IBL Hamburg) to evaluate inflammation in CRF apoE\(^{−/−}\) mice.\(^11\)

Quantification of Atherosclerotic Lesions
Evaluation of the atherosclerotic plaque area was made by the en face method.\(^12\) Briefly, the aortas were carefully freed of connective and adipose tissue under a dissection microscope, opened longitudinally, and stained with Oil red O. The quantification was made with Histolab software (Microvision Instruments) as reported previously.\(^13\) The extent of atherosclerosis was expressed as the percentage of surface area of the aorta covered by lesions.\(^12\)

Quantitative and Qualitative Evaluation of Aortic Calcification
We performed von Kossa staining in cryosections of aortic tissue to evaluate calcium deposits inside and outside atheromatous plaques. These locations of calcification are supposed to reflect intima and media calcification. The precision and the accuracy of this method have been reported elsewhere with semiautomated measurement software.\(^14\) Data were expressed as the relative proportion of calcified area to total surface area of either atherosclerotic lesions or vessel area outside atheromatous plaques, as reported previously.\(^9\)

Quantification of Nitrotyrosine, Monocyte-Macrophage Infiltration, and Collagen in Aortic Root Lesions
Lesion nitrotyrosine expression, monocyte-macrophage infiltration, and collagen content were assessed as described previously.\(^13\) Briefly, for nitrotyrosine analysis the sections were preincubated in peroxidase blocking solution (Dako Cytomation) before incubation with biotinylated nitrotyrosine monoclonal mouse antibody (Cayman Chemical, SpiBio, Massy, France). The sections were treated with peroxidase-labeled streptavidin (Dako) for 15 minutes followed by reaction with diaminobenzidine/hydrogen peroxidase. For monocyte-macrophage infiltration, aortic sections were incubated with 10% normal goat serum at room temperature and incubated with a primary rat monoclonal antibody against mouse macrophages (clone MOMA-2; BioSource International, Camarillo, Calif). The secondary antibody was a biotin--horseradish peroxidase--conjugated goat anti-rat IgG (Vector Laboratories, Biovalley, Marne la Vallée, France). Immunostaining were visualized after incubation with a peroxidase detection system (Vectastain ABC kit, Vector Laboratories) with 3-amino-9-ethyl carbazole (Sigma Aldrich) used as substrate. The lesion collagen content was determined by staining with Sirius red.
Statistical Analysis
Data were analyzed by ANOVA, with 1 or 2 factors (treatment and uremic state) taken into account as appropriate, and χ² test. Results were expressed as mean±SEM. Differences between groups were considered significant at *P*<0.05.

Results

Serum Biochemistry
At time of euthanasia (10 weeks of uremia), serum urea concentration was significantly increased in CRF mice com-

<table>
<thead>
<tr>
<th>TABLE 1. Effect of CRF and Sevelamer on Body Weight and Serum Biochemistry</th>
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<tr>
<td><strong>Non-CRF</strong></td>
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<tr>
<td><strong>Control</strong></td>
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<tr>
<td>Body weight, g</td>
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<tr>
<td>Urea, mmol/L</td>
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<td>Calcium, mmol/L</td>
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<td>Phosphorus, mmol/L</td>
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<td>Ca×P, mmol/L²</td>
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<tr>
<td>iPTH, μg/mL</td>
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<td>Total cholesterol, mmol/L</td>
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Values are those at time of euthanasia (n=6 to 12 per group). Ca×P indicates calcium-phosphorus product. Data were analyzed by ANOVA with 2 factors (CRF state and sevelamer treatment) taken into account.

Figure 1. Serum uremic toxins and SAA concentrations in apoE⁻/⁻ mice without CRF, with CRF, and with CRF plus sevelamer treatment (CRF-Sev) (n=7 to 9 animals per group for uremic toxins analysis; n=5 animals in the CRF-Sev group for SAA analysis). Indoxyl sulfate, hippuric acid, and SAA levels were increased in CRF apoE⁻/⁻ mice compared with control apoE⁻/⁻ mice (*P*<0.05 by ANOVA). In contrast, uric acid, indole acetic acid, and CMPF levels were similar in CRF and control apoE⁻/⁻ mice. Sevelamer treatment did not modify any of these parameters (*P*=NS).
pared with non-CRF mice (Table 1). Serum urea concentration was slightly higher in CRF mice treated with sevelamer than in CRF mice receiving a placebo diet (Table 1). The body weight of CRF mice was 10% lower than that of nonuremic mice; no difference in body weight was observed between the 2 uremic groups (Table 1).

Total serum cholesterol was 24% higher in CRF mice than in non-CRF mice (Table 1). However, no difference was observed between the sevelamer-fed and the placebo-fed CRF groups. Sevelamer was effective in decreasing serum phosphorus, the calcium-phosphorus product, and iPTH concentration in uremic mice (Table 1). Western blot analysis of serum fetuin-A did not show a significant change in response to uremia or sevelamer treatment (data not shown). SAA and serum uremic toxin concentrations were significantly increased in CRF mice (except for uric acid, indole acetic acid, and CMPF). Sevelamer treatment did not lead to a change of SAA or uremic toxin concentrations in CRF sevelamer mice (Figure 1).

Quantification of Atherosclerotic Lesions
At the time of euthanasia, the thoracic aorta lesion area (percentage) of apoE<sup>−/−</sup> mice on a placebo diet increased 2-fold compared with nonuremic control littermates on a placebo diet. The administration of sevelamer led to a decrease in aortic lesion area in uremic mice to the level of nonuremic controls fed a placebo diet (Figure 2 and Figure 3). Figure 3 shows a typical feature of thoracic aorta plaques in CRF mice with or without sevelamer treatment. Sevelamer did not modify aortic lesion area in nonuremic mice.

Quantification of Aortic Calcification
Uremic apoE<sup>−/−</sup> mice on a placebo diet exhibited a marked increase in aortic intima (Figure 4), media (Figure 5), and both combined (Figure 6) compared with nonuremic control mice and exhibited a dramatic decrease in the progression of type of calcification in response to sevelamer, down to the level of nonuremic mice fed a placebo diet. Figure 7 shows calcium deposits in characteristic features of CRF mouse aorta with or without sevelamer treatment. Interestingly, prevention of the progression of intima calcification was more effective than that of media calcification. No effect of sevelamer on aortic calcification was observed in nonuremic mice.

![Figure 2](http://circ.ahajournals.org/)

**Figure 2.** Atherosclerotic lesion cross-sectional area in thoracic aorta in apoE<sup>−/−</sup> mice without CRF and with CRF. By ANOVA, effect of uremia on atherosclerosis progression was \( P=0.02; \) effect of sevelamer on atherosclerosis prevention, \( P<0.001; \) interaction, \( P=0.03 \) (n=7 to 11 per group).

![Figure 3](http://circ.ahajournals.org/)

**Figure 3.** Representative images of regression of atherosclerotic lesions in thoracic aorta in control apoE<sup>−/−</sup> mice with CRF (a) compared with sevelamer-treated apoE<sup>−/−</sup> mice with CRF (b). Magnification \( \times2.5 \) of the object after 2% eosin staining.
Quantification of Nitrotyrosine Expression, Monocyte-Macrophage Infiltration, and Collagen in Aortic Lesions

Sevelamer treatment led to a highly significant reduction in nitrotyrosine expression in atheromatous plaques in uremic and nonuremic mice (Table 2) (by Fisher exact test, \(P < 0.005\)). The percentage of cross-sectional lesion area occupied by macrophages, as revealed by MOMA-2 staining, was comparable for the 4 groups (by ANOVA, effect of uremia on MOMA-2 staining, \(P = \text{NS}\); effect of sevelamer on MOMA-2 staining, \(P = 0.051\); interaction, \(P = \text{NS}\)). Aortic collagen content was markedly increased in uremic mice on a placebo diet compared with nonuremic control mice. However, sevelamer treatment did not lead to a change in collagen content in either nonuremic or uremic mice (by ANOVA, effect of uremia on collagen deposition, \(P = 0.001\); effect of sevelamer on collagen deposition, \(P = \text{NS}\); interaction, \(P = \text{NS}\)).

Discussion

The present study shows for the first time that the phosphate binder sevelamer is capable of preventing uremia-enhanced atherosclerosis progression in apoE\(^{-/-}\) mice.

This effect was observed in the absence of a change in serum total cholesterol levels. In addition, our study confirms the inhibitory effect of sevelamer on the progression of vascular calcification, as reported in end-stage renal disease patients,\(^6\) and shows for the first time an effect on both intima and media calcification. The fact that the observed beneficial effect of sevelamer was apparently cholesterol independent was unexpected because this drug binds not only phosphate but also cholesterol in the intestinal lumen and thereby exerts cholesterol-lowering effects, at least in humans.\(^{15}\) The fact that serum total cholesterol remained unchanged in uremic apoE\(^{-/-}\) mice in response to sevelamer treatment does not, however, exclude possible changes of low-density lipoprotein and/or high-density lipoprotein cholesterol concentrations, which are abnormal in uremic animals.\(^{16}\) In CRF mice, serum very low-density lipoprotein, intermediate-density lipoprotein, and low-density lipoprotein cholesterol concentrations were increased compared with non-CRF mice, whereas high-density lipoprotein cholesterol remained the same in the 2 groups.\(^7\) Unfortunately, we were unable to perform serum lipoprotein determinations in the mice of this study because of insufficient availability of blood at the time of euthanasia. Alternatively, one could also envisage mechanisms other than a reduction of lipoprotein cholesterol subfractions in the observed antiatherosclerotic effect of sevelamer. The observation that its administration did not lead to changes in atheromatous lesion progression in nonuremic apoE\(^{-/-}\) mice might point to a beneficial action on the process of the uremia-linked acceleration of atherosclerosis. An interference with the enhanced oxidative stress and/or the inflammatory state of CRF represents possible alternative mechanisms.

Oxidative stress is increasingly being suggested to play a central role in the pathogenesis of cardiovascular disease in
uremic arteriopathy, and in particular to the accelerated atherosclerosis in uremia. However, in the present mouse model, Western blot analysis of serum fetuin-A did not show significant changes in response to uremia and/or sevelamer. Fetuin-A may not play the same role in mice as in humans. It is also of note that sevelamer treatment did not decrease serum SAA, which is a major acute phase protein in vertebrates and has been associated with atherosclerosis in mice, and that it did not modify vascular infiltration by inflammatory monocytes/macrophages. When these negative findings are considered, the beneficial effect of sevelamer on atherosclerosis progression and vascular calcification in the apoE−/− mouse model seemed to be independent from an anti-inflammatory effect.

Because post hoc analyses of the Treat-to-Goal study showed that sevelamer-treated dialysis patients experienced a relative reduction in highly sensitive C-reactive protein, the extent to which the beneficial effects of sevelamer on atherosclerosis and calcium deposition in mice involve arterial wall inflammation remains unclear.

Hyperphosphatemia and an increased calcium-phosphorus product are recognized factors of cardiovascular morbidity and mortality in advanced CRF. To what extent high serum phosphorus, calcium, or calcium-phosphorus product contributes to uremic arteriopathy, and in particular to the accelerated atherosclerosis of uremic apoE−/− mice, in addition to the induction of marked vascular calcification, remains to be evaluated. In uremic apoE−/− mice treated by sevelamer, the serum phosphorus concentration was well controlled compared with placebo-treated uremic mice, as was the calcium-phosphorus product and iPTH. Because the rapid progression of vascular calcification was inhibited by sevelamer in CRF apoE−/− mice in association with the reduced progression of atherosclerosis, one could think of a possible link between these 2 processes. We observed a more marked effect of sevelamer on intima vascular calcification compared with media calcification. Together with the disturbances in lipid metabolism and inflammation, calcification is now generally recognized as an integral part of the atherosclerotic process. The majority of atheromatous lesions in CRF patients are calcified, much more frequently than in the general population, and this may be an aggravating factor in lesion progression. Whether the slowed progression of arterial calcification in dialysis patients treated by sevelamer was mainly due to reduced intima calcification, media calcification, or both cannot be determined on the basis of the electron-beam CT imaging technique. In the uremic apoE−/− mice of the present study, calcium deposition at both vascular sites was decreased by sevelamer, particularly inside athero- plaque nitrotyrosine staining was also observed in response to sevelamer treatment in both CRF and control mice compared with placebo treatment. The mechanisms by which sevelamer might modify oxidative stress or whether it indirectly influences local inducible NO synthase activity in the vessel wall remains to be defined.

In regard to the possible implication of inflammation, we wondered whether fetuin-A deficiency might be involved. Fetuin-A is associated with inflammation and links vascular calcification to mortality in patients on dialysis. Activated acute phase response and fetuin-A also may account for accelerated atherosclerosis in uremia. However, in the present mouse model, Western blot analysis of serum fetuin-A did not show significant changes in response to uremia and/or sevelamer. Fetuin-A may not play the same role in mice as in humans.

TABLE 2. Antioxidative Sevelamer-Dependent Decrease in Nitrotyrosine Expression in Plaques of Non-CRF and CRF ApoE−/− Mice

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<tr>
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<th>Non-CRF</th>
<th>Non-CRF</th>
<th>CRF</th>
<th>CRF</th>
<th>CRF Sevelamer</th>
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<tr>
<td>Mice with positive nitrotyrosine staining</td>
<td>64%*</td>
<td>0%</td>
<td>94%†</td>
<td>37%</td>
<td>&lt;0.005</td>
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Data were analyzed by Fisher exact test for global evaluation; n = 6 to 12 per group.

*P<0.001 vs non-CRF sevelamer group; †P<0.001 vs CRF sevelamer group.
matous lesions. Because serum calcium, which was elevated in uremic placebo-treated mice, remained unchanged in sevelamer-treated mice, the beneficial effect of sevelamer on vascular calcification could be explained at least partially by the better control of phosphorus, the serum concentration of which decreased. Of note, high phosphorus concentrations have been shown to induce the expression of osteoblast-specific proteins in vascular smooth muscle cells in vitro and to promote the deposition of apatite into extracellular matrix.25–27 The clinical relevance of these in vitro data was recently confirmed in arterial media calcifications of dialysis patients.28 Whether these or similar effects play a role in atheroma calcification and perhaps even progression as well is unclear.

Other mechanisms explored in the present study include the effects of sevelamer on uremic toxins. Interestingly, it was shown that sevelamer could adsorb partially lipophilic uremic compounds such as indoxyl sulfate in the intestinal lumen.29 Recently, indoxyl sulfate–induced endothelial toxicity was reported.30 In the present study, we failed to observe a reduction of the serum concentration of 4 different uremic toxins in response to sevelamer in CRF apoE−/− mice. Of note, serum uric acid was not elevated in CRF mice. Moreover, sevelamer did not decrease it, in contrast to its effect in uremic patients.31 This discrepancy is probably due to the fact that rodents, but not humans, are equipped with uricase activity. Because there is a substantial number of defined and as yet undefined uremic toxin molecules,32 it remains possible that sevelamer exerts beneficial effects on other uremic toxins.

In conclusion, sevelamer prevents not only vascular calcification but also atherosclerotic lesion progression in uremic apoE−/− mice. The observed reduction of atherosclerosis progression in the absence of changes of serum total cholesterol in uremic mice may be of both theoretical and practical importance. It opens the possibility of a cholesterol-independent action of sevelamer on atheroma formation, possibly via effects on mineral metabolism or oxidative stress. It may thus be of major importance for patients with CRF if the findings obtained in mice can be extrapolated to the condition in humans.

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Disclosure

Dr Vanholder has received a modest research grant from Genzyme. Dr Lacour has received a significant research grant from Genzyme. Dr Drüke has received a significant research grant and honoraria from and has served as a consultant to Genzyme. Dr Massy has received a significant research grant from Amgen and has received honoraria as a consultant and speaker from Genzyme.

References


**CLINICAL PERSPECTIVE**

Chronic renal failure is associated with numerous metabolic and endocrine disturbances, including abnormalities of calcium and phosphate metabolism and an inflammatory syndrome. The latter occur early in the course of renal failure and contribute to the development and progression of atherosclerosis and vascular calcification. After stratification for age, gender, race, and the presence or absence of diabetes, cardiovascular mortality in dialysis patients is 10 to 20 times higher than in the general population. Until recently, it seemed impossible to slow or even halt the progression of uremic arteriopathy and arterial calcification. The present experimental study shows for the first time that the phosphate binder sevelamer is capable of preventing the progression of uremia-enhanced atherosclerosis and vascular calcification in the model of the apolipoprotein E–deficient mouse, in the absence of changes in serum total cholesterol. Among possible cholesterol-independent mechanisms, oxidative stress is thought to play a central role in the pathogenesis of cardiovascular disease in uremia. In the present study, the inhibitory effect of sevelamer on atherosclerosis and calcification was associated with a decrease not only in circulating calcium-phosphorus product but also in aortic nitrotyrosine expression, a marker of oxidative stress. The observed reduction of atherosclerosis progression by sevelamer in uremic mice may be of both theoretical and practical importance. It opens the possibility of a cholesterol-independent action on atheroma formation, possibly via effects on mineral metabolism or oxidative stress. It may thus be of major importance for patients with chronic renal failure if the present findings obtained in mice can be extrapolated to the condition in humans.
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