Nonphosphate-Binding Effects of Sevelamer—Are They of Clinical Relevance?

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ABSTRACT

Sevelamer is an ion-exchanging resin that binds phosphate in the gut. Because it does so without increasing the calcium load, treatment with sevelamer may lead to less vascular calcification and better survival in chronic kidney disease patients. However, the results of available clinical studies have not been consistent; recent observations challenge the hypothesis that the extra calcium load inherent in calcium-based phosphate binder therapy increases cardiovascular mortality by accelerating vascular calcification. This reemphasizes the fact that we still lack detailed understanding on the complex relationships between vascular calcification, bone metabolism, vascular disease and outcome in the context of uremia. Thus, the role of phosphate binders may be more complex than initially anticipated and not limited to the extra calcium load. Even if detailed mechanisms of action for sevelamer are not yet clearly established (except for its lipid-lowering action), sevelamer may have a number of additional nonphosphate-lowering actions (including lipid lowering as well as improvement in endothelial function, modulation of inflammation and oxidative stress and binding of uremic toxin absorption). Whether these potentially very interesting pleiotropic effects of sevelamer may be translated into significant clinical benefits remains to be established.

Does Sevelamer Treatment Affect Outcome, Vascular Calcification, and Bone Health?

Sevelamer is an orally administered calcium-free, metal-free phosphate binder proved to be as effective as calcium-based phosphate binders for the control of hyperphosphatemia (1,2). The role of hyperphosphatemia in the genesis and progression of vascular calcification has been demonstrated in experimental studies (3,4). Moreover, hyperphosphatemia is associated with vascular calcification (5,6) and worse outcome both in the general (7) and renal (8) population. The in vitro observation that elevated calcium and phosphate independently and synergistically induce calcification of human vascular smooth muscle cells has suggested an important role for calcium in the calcification process (9). Indeed, in one clinical study of 150 hemodialysis (HD) patients, treatment with calcium-based phosphate binders was associated with progressive coronary artery and aortic calcification (10). Thus, because sevelamer binds phosphate without increasing the calcium load, it has been speculated that treatment with sevelamer leads to less vascular calcification and better survival in chronic kidney disease (CKD) patients. Indeed, in five of six nephrectomized rats fed a high phosphate diet for 6 months, sevelamer treatment attenuated vascular and kidney calcification in comparison with calcium carbonate (11). However, the results of available clinical studies have not been consistent (12).

In the randomized Treat-to-Goal (TTG) study (13) it was shown that despite slower progression of vascular calcification with sevelamer, there was no correlation between calcification scores and parameters of bone metabolism. This is important information as emerging evidence suggests an inverse correlation between vascular calcification and bone mass as minerals released from bone may find their way to the vasculature (14). In a subsequent study of 114 European HD patients (of whom 93 patients were included in the TTG-study) Braun et al. (15) reported that patients on sevelamer treatment had less progression in aortic and coronary calcification than patients on calcium-based therapy. In the Renagel In New Dialysis (RIND) trial (16), only patients presenting with at least mild vascular calcification at baseline had significant progression in calcification scores, with a more rapid progression in the group treated with a calcium-based phosphate binder. However, the lipid-lowering effect associated with the use of sevelamer may have contributed to the observed results. Thus, neither of these two studies can prove that an increased calcium load plays a role in the pathogenesis of vascular calcifica-

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tion. Indeed, changes in calcification scores did not differ in the sevelamer and calcium-based phosphate binder groups in preliminary results from the Calcium Acetate Renagel Evaluation-2 (CARE-2) study (17). Moreover, a recent study on apo-E-deficient mice showed that calcium-based phosphate binder supplementation actually protected against vascular calcification (18). This implies that phosphate and not calcium may be the main culprit in the vascular calcification process.

In contrast to the noninterventional open-label extension analysis of the RIND study examining mortality as a secondary endpoint (19), the randomized Dialysis Clinical Outcomes Revisited (DCOR) trial did not show any difference in all-cause mortality examined as primary endpoint (20). Although an advantage in all-cause mortality was observed in the sevelamer-treated subgroup of patients aged >65 years, no difference in cardiovascular mortality was observed. Thus, based on these studies, any survival advantage associated with sevelamer is not readily explained by an improvement in cardiovascular outcome from a decrease in vascular calcification. Moreover, according to a meta-analysis by Tonelli et al. (2), there is no current evidence that sevelamer influences the rate of hospitalization, the frequency of symptomatic bone disease, or health-related quality of life. On the other hand, a recent secondary analysis of DCOR provided evidence for a beneficial effect of sevelamer on all-cause hospitalizations and hospital days (21).

The skeletal effects of sevelamer have been the subject of less intense study than other areas. A recent randomized open-label study in 119 HD patients showed that sevelamer increased bone formation and improved trabecular architecture (22); further studies are required to assess whether these benefits also lead to fewer fractures. A posthoc analysis of the TTG-study showed that compared to sevelamer, treatment with a calcium-based phosphate binder was associated with a significant decrease in thoracic vertebral trabecular bone attenuation (23). In accordance, sevelamer reversed CKD-induced trabecular osteopenia in a murine CKD model by increasing osteoblast surface, osteoid surface, and bone formation rates (24).

Taken together, the conflicting results reported in the literature reemphasize the fact that we still lack detailed understanding of the complex relationships between vascular calcification, bone metabolism, vascular disease and outcome in the context of uremia. To better understand the role of sevelamer in relation to calcium-based phosphate binders in this complex scenario, studies on the additional nonphoshate-lowering pleiotropic effects of sevelamer are needed.

Effects of Sevelamer on Arterial Stiffness and Circulating Inhibitors of Calcification

Arterial stiffness is an established vascular risk factor in CKD (25,26) that (in addition to vascular calcification) may be the consequence of chronic volume overload, endothelial dysfunction, inflammation, and oxidative stress (27). So far, not many studies have investigated the independent role of phosphate binders on vascular function. In one relevant report, 25 nondiabetic CKD stage 4 patients were randomized to receive sevelamer or a calcium-based phosphate binder for a period of 8 weeks. Only the patients receiving sevelamer experienced a significant improvement in endothelial function (assessed by flow-mediated dilatation) (28), a finding that correlated with increased levels of fetuin-A, a circulating inhibitor of calcification. Another clinical study, reported in abstract form (29), also found that sevelamer treatment was associated with an increase in fetuin-A levels. On the other hand, sevelamer treatment did not affect serum fetuin-A levels in an animal model (apolipoprotein-E-deficient mice) (30).

Further support for the as yet difficult to explain vascular effect came from two studies. In one, calcium-based phosphate binders in 15 HD patients were replaced by sevelamer for 6 months; it was followed by a significant decrease in heart-tibial pulse wave velocity (31). In the second study, 13 HD patients had their calcium-based phosphate binders replaced by sevelamer; carotid-femoral pulse wave velocity decreased significantly after an almost 1-year follow-up. Notably, in this small study the decrease in pulse wave velocity was not related to any changes in serum levels of inhibitors of calcifications.

Well-Established Effects of Sevelamer on Lipid Metabolism

The lipid-lowering effect of sevelamer is well established, especially concerning total cholesterol and LDL cholesterol (1,32). On the other hand, no significant effect on HDL cholesterol and triglyceride levels has been demonstrated (1). The mechanism of

TABLE 1. Established and proposed effects and mechanisms of action of sevelamer

Established effects (mechanisms understood)	Probable effects (mechanisms not clearly understood)	Possible effects (mechanisms unknown)	Other hypothetical effects
Phosphate-binding Lipid-lowering effect (bile acid binder) Hyperchloremic metabolic acidosis (ion-exchange)	Slowing vascular calcification (calcium-free phosphate binder, modulation of vascular calcification mediators and inflammation, lipid-lowering effects, induces metabolic acidosis)	Improvement in vascular stiffness (slowing vascular calcification, absorption of uremic toxins) Modulation of oxidative stress and inflammation Improvement in bone structure	Improvement in survival, cardiovascular or general outcomes Absorption of uremic toxins in the gut

action (Table 1) is most probably related to the bile acid-binding effect of sevelamer (33). Although the contribution of this lipid-lowering effect on the vascular calcification process has not been evaluated in the TTG (13) and RIND (16) trials, the preliminary result of the CARE-2 study (17) confirms the importance of lipid control. Considering the conflicting results from both the DCOR study (20) and the extension-analysis from the RIND study (19), the role of the lipid-lowering effect of sevelamer on survival is not clear, especially considering the results of the prospective, randomized "4D study," which found that atorvastatin-induced improvements in lipid profile in HD patients were not associated with a survival benefit (34).

Effects of Sevelamer on Inflammation and Oxidative Stress—Inconsistent Results

The role of persistent low-grade inflammation in the pathogenesis of atherosclerosis is now well accepted (35); it has also been linked with outcome in CKD (36). The potential capacity of sevelamer to modulate the inflammatory process has been investigated in several studies. A significant decrease in high-sensitivity C-reactive protein (hs-CRP) was observed in 25 nondiabetic CKD stage 4 patients who had been randomized to treatment with sevelamer (28). Moreover, in a nonrandomized study, 283 HD patients on sevelamer had lower CRP (but no difference in interleukin-6, tumor necrosis factor-α, and homocysteine levels) compared with patients on calcium-based phosphate binders (37). In another nonrandomized study, 28 patients treated with sevelamer also experienced a significant reduction in CRP at 12 and 24 weeks (38). As the reduction in CRP correlated to changes in phosphate and non-HDL cholesterol, the authors hypothesized that modulation of inflammation by sevelamer could be related to either the prevention of ectopic calcifications or the lipid-lowering effect. A reduction in hs-CRP in sevelamer-treated subjects compared with calcium-based phosphate binder treated subjects was also found in a posthoc analysis of the TTG study (39), although the reduction was not correlated with lipid change (39,40).

Although inflammation is interrelated with oxidative stress (41), the role of sevelamer in modulating oxidative stress markers has, to the best of our knowledge, only been investigated in a single (animal) study. In apolipoprotein-E-deficient mice, sevelamer reduced nitrotyrosine expression (a marker of oxidative stress) in atheromatous plaques but, in contrast to other reports, had no effect on serum inflammation markers (30). Thus, the putative anti-inflammatory action of sevelamer is currently speculative and is not a consistent finding in experimental studies.

Effects of Sevelamer on Gut Uremic Toxin Absorption—An Emerging Area of Interest

Among numerous uremic toxins, p-cresol and indoxyl sulfate are probably the most studied molecules of the protein-bound uremic solute family. Their adverse effects include immune dysfunction (42,43), endothelial dysfunction (44), oxidative stress (45), and inhibition of endothelial proliferation or wound repair (46)—all mechanisms that are potentially involved in the atherosclerotic process. Indeed, the free serum concentration of p-cresol has been shown to be a predictive marker of mortality in prevalent HD patients (47).

As the removal of p-cresol and indoxyl sulfate by dialysis is poor (45), various strategies blocking their absorption from the gut have attracted interest (48). The hypoglycemic agent acarbose, an α-glucosidase inhibitor, effectively reduces serum p-cresol in healthy volunteers (49). Another agent, the oral carbonaceous absorbent AST-120, binds indoxyl sulfate in uremic rats and undialyzed uremic patients (50). As sevelamer has been shown to bind uremic toxins in vitro (51) some of the favorable effects of sevelamer may be attributable to binding of toxins in the gut. However, in the apolipoprotein-E-deficient mice model, sevelamer therapy was not associated with a measurable improvement in any of the uremic toxins assessed (including uric acid) (30).

Sevelamer may have a beneficial effect on serum uric acid, a substance with an evolving but still putative role in the pathophysiology of CKD and its complications. A significantly higher proportion of patients treated with sevelamer (23%) compared to those treated with a calcium-based phosphate binder (10%) experienced a decrease in serum uric acid concentration during follow-up in a post hoc analysis of the TTG-study (52). In contrast, sevelamer did not change serum uric acid in the apolipoprotein-E-deficient mice model study cited above (30). Although the exact mechanism(s) by which sevelamer might reduce serum uric acid concentration are unknown, it could be related to sevelamer's potential capacity to bind either uric acid itself or precursor compounds involved in the purine metabolic pathway in the gut. These observations should definitely stimulate further studies.

Sevelamer-induced Metabolic Acidosis—Could it Actually Be of Benefit?

Metabolic acidosis may contribute to, or interfere with, a number of biochemical and metabolic functions and its link with wasting and inflammation in CKD has been reviewed elsewhere (53,54). As sevelamer hydrochloride is an ion-exchange resin (one mole of chloride is released for each mole of phosphate bound in the gut), hyperchloremic metabolic acidosis often ensues (54). Indeed, significant differences in bicarbonate levels have been observed in many studies comparing sevelamer and calcium-based phosphate binders, though the alkaline nature of the latter probably contributes as well (23,52,55–57). The use of sevelamer carbonate, which has no acidemia-inducing effects (and, very likely, the opposite impact) now represents an alternative to sevelamer hydrochloride (58).

While numerous adverse effects are associated with metabolic acidosis, epidemiologic studies in dialysis patients have reported a paradoxically inverse relation-

ship between metabolic acidosis and markers of improved nutritional state (59–61). This makes metabolic acidosis one of a growing family of factors that exhibit the so-called "reverse epidemiology" phenomenon in CKD (53), i.e., factors that show the opposite relation with clinical outcome compared with that found in the general population. The beneficial effect of mild metabolic acidosis on the vascular calcification process may also represent such a counterintuitive effect. As metabolic acidosis contributes to a decreased bone content of minerals it seems reasonable to hypothesize that metabolic acidosis may worsen vascular calcification. However, metabolic acidosis decreases calcium deposition in cultured rat aortas (62) and, in five of six nephrectomized rats, prevents aortic calcium and phosphate accumulation (63). Actually, this observation is not unexpected considering that calcified vascular tissue share many similar features with bone tissue.

There are a number of different mechanisms by which metabolic acidosis could inhibit the vascular calcification process including (i) increased calcium and phosphate solubility, (ii) increased mineral clearance in the arterial wall by monocyte macrophages, and (iii) decreased production of osteogenic proteins by calcified vascular smooth muscle cells. A particularly attractive finding demonstrated in the same model (63) is that metabolic acidosis decreases cellular phosphate uptake by preventing the upregulation of vascular sodium-dependent phosphate co-transporters Pit-1; these are reported to be essential for calcification of vascular smooth muscle cells (4). Taken together, sevelamer's potential to modulate the vascular calcification process may be based, in part, on metabolic acidosis—a mechanism that needs to be considered in future studies.

Conclusion

Some considerable enthusiasm was provoked by studies suggesting that sevelamer slows the progression of vascular calcification compared with calcium-based phosphate binders. Recent observations challenge the hypothesis that it is the extra calcium load inherent in calcium-based phosphate binder therapy that is responsible for any differences in the vascular calcification rate. Thus, the nature of the relationship between improvement in surrogate markers and patient outcomes is uncertain; very likely, the interactions between bone metabolism, vascular calcification, vascular diseases or outcomes and phosphate binder therapy are more complex than initially anticipated. Even if detailed mechanisms of sevelamer action are not yet clearly established (except for its lipid-lowering action), this drug remains a very interesting substance as it presents a number of putative benefits "not" related to its phosphate-binding property. It could be speculated that these pleiotropic effects may be related to the potential capacity of sevelamer to inhibit the absorption from the gut of molecules involved in atherogenic processes. However, whether these potentially very interesting pleiotropic effects of sevelamer are translated into clinically beneficial effects should be pursued in further investigations.

Conflicts of Interest

Peter Stenvinkel has been speaking at scientific meetings sponsored by Genzyme and is on the Scientific Advisory Board of Gambro. Bengt Lindholm is employed by Baxter.

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