Review

Emerging Effects of Sevelamer in Chronic Kidney Disease

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Key Words

Cardiovascular disease • CKD-MBD • Phosphate binder • Sevelamer

Abstract

Sevelamer, a non-absorbable anion exchange resin, is used to control hyperphosphatemia in chronic kidney disease (CKD) by binding to dietary phosphate in the gastrointestinal tract. Lipid-lowering effect is a widely recognized pleiotropic effect of sevelamer. In addition, many studies have reported that sevelamer leads to reduced vascular calcification compared with calcium-containing phosphate binders, which is attributed to the improved lipid profiles and decreased calcium load. In addition, recent studies have suggested novel pleiotropic effects on bone structure, inflammation, oxidative stress, anemia, fetuin-A, and trace element metabolism in CKD patients. All of these effects have the potential to suppress the development/progression of cardiovascular lesions and reduce mortality. This review summarizes novel findings from recent studies and discusses the potential pleiotropic effects of sevelamer on non-traditional cardiovascular risk factors in CKD patients.

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Introduction

Disturbances in mineral metabolism and bone disease are common complications of chronic kidney disease (CKD) and lead to an increased risk of cardiovascular morbidity and mortality [1]. The term 'CKD-mineral bone disorder (CKD-MBD)' is increasingly widely recognized. Phosphate binders, vitamin D receptor activators (VDRA), and calcimimetics play pivotal roles in the management of CKD-MBD. Recently, the pleiotropic effects of these agents have been widely examined. Among these agents, VRDA seem to attract the most

attention. The reported pleiotropic effects of VDRA include improvement of proteinuria, immune regulation, the renin-angiotensin system, cardiac function, vascular calcification, and mortality [2]. On the other hand, less attention has been paid to the effects of sevelamer despite its unique characteristics.

Sevelamer is a non-absorbable, calcium-free and aluminum-free anion exchange resin, which binds to dietary phosphate in the gastrointestinal tract. There are two salts of sevelamer, sevelamer hydrochloride and sevelamer carbonate, and the former was used in most previous studies investigating its effects. Early studies have found that sevelamer hydrochloride and calcium-containing phosphate binders produce comparable decreases in serum phosphorus level in patients on hemodialysis (HD) [3, 4]. The calcium-free nature of sevelamer means that it is associated with a reduced incidence of hypercalcemia [4], which allows the safe use of VDRA and better control of secondary hyperparathyroidism. In addition, improvement of lipid profiles by sevelamer is well established [3-5]. Compared with calcium-containing phosphate binders, sevelamer hydrochloride is associated with slow progression of cardiovascular calcification [5-10]. Various mechanisms as well as reduced calcium load and lipid-lowering effect might be responsible for suppression of cardiovascular lesions. Sevelamer binds to not only phosphate but other substances, which would explain its pleiotropic effects.

Effects on cardiovascular disease, mortality and hospitalization

Many studies have been demonstrated improved cardiovascular function and structure by sevelamer hydrochloride [5-14]. For example, In the RIND study, a randomized trial including 129 incident HD patients, Block et al. compared the progression of coronary and aortic calcification detected by electron beam computed tomography (CT) between sevelamer hydrochloride and calcium-containing phosphate binder [7]. The median increase in calcification score at 18 months was 11-fold greater in those treated with calcium-containing phosphate binder compared with those treated with sevelamer ($P = 0.01$). Also in prevalent HD patients, Chertow et al. found similar findings in the Treat-to-Goal study [5]. In 132 prevalent HD patients, Raggi et al. compared the progression of heart valve calcification between sevelamer hydrochloride and calcium-containing phosphate binder in a 1-year follow-up [10]. Heart valve calcification progressed more slowly in the sevelamer group after adjustment for baseline calcification and the time-averaged $\text{Ca} \times \text{P}$ product. On the other hand, 2 randomized trials, the BRiC study including 101 prevalent HD patients [15] and the CARE-2 study including 203 prevalent HD patients [16], did not find a significant difference in the progression of vascular calcification between calcium acetate and sevelamer hydrochloride. In the former study, the inconsistent result might be attributable to a higher mortality in the calcium acetate group (8 of 49 patients in the calcium acetate group and 1 of 52 patients in the sevelamer group died in a 12-month follow-up). Patients with severe calcification might have been eliminated from the study. In the latter study, the high dropout rate, the higher frequencies of diabetes mellitus and smokers at baseline might be confounding factors.

Regarding the effect of sevelamer on mortality in HD patients, some studies have shown that sevelamer decreases mortality compared with calcium-containing phosphate binders [14, 17, 18], but others have not [19, 20]. In the RIND extension study, a randomized trial including 127 incident HD patients, Block et al. showed a trend towards increased mortality in the patients treated with calcium-containing phosphate binders compared with those treated with sevelamer hydrochloride ($P = 0.06$) in a median follow-up of 44 months [17]. After adjustment for multiple factors, the difference in mortality between the groups reached statistical significance ($P = 0.02$). In addition, 2 cohort studies using a propensity-matched method detected decreased mortality in HD patients treated with sevelamer hydrochloride [14, 18]. In CKD patients not requiring HD, one randomized trial showed lower all-cause mortality in those treated with sevelamer compared with those treated with calcium carbonate [21]. However, the DCOR study, a randomized trial including 2103 prevalent HD

patients, there was no significant difference in all-cause or cause-specific mortality between those treated with sevelamer hydrochloride and those treated with calcium-containing phosphate binders during a follow-up period of 20 months [19]. In addition, secondary analysis of the DCOR study did not detect the benefit of sevelamer in terms of mortality except in the patients aged ≥ 65 years [20]. The limitation of the DCOR study was that 49.2% of the subjects were lost to follow-up, and those lost early were only followed for 90 days. The inconsistencies between the results of the RIND study and those of the DCOR study could be attributable to the difference in the follow-up period and patient selection.

Regarding hospitalization, secondary analysis of the DCOR study reported a beneficial effect of sevelamer on all-cause hospitalization compared with calcium-containing phosphate binder [20], but other studies did not [5, 19]. As available data are limited, it seems difficult to draw a conclusion.

Thus, the effect of sevelamer on mortality is not conclusive. However, many pieces of evidence suggest that sevelamer has favorable effects on non-traditional cardiovascular risk factors in CKD patients. We discuss this issue and the possibility of improvement of patient's prognosis by sevelamer in the following sections.

Effect on bone structure

Several studies have shown that sevelamer favorably affects renal bone disease. In a randomized trial including 72 HD patients [6], the patients treated with calcium carbonate showed a significant decrease in trabecular bone density at 24 months after the therapy. In contrast, sevelamer therapy was associated with a significant increase in trabecular bone density. Raggi et al. performed a post-hoc analysis of a 52-week randomized trial comparing sevelamer hydrochloride with calcium acetate in HD patients [22]. In this study, they investigated bone attenuation obtained by CT, which reflects bone mass density. During the study period, the calcium acetate group showed significantly decreased bone attenuation compared with the sevelamer group despite having an increased serum calcium level. Ferreira et al. provided histological support to the results of the aforementioned studies. In a 54-week randomized trial, bone formation determined by bone biopsy increased and trabecular architecture improved in the sevelamer group, but not in the calcium carbonate group [23]. The authors suggested that the higher use of VDRA in the sevelamer group could explain the increased bone formation, but the precise mechanisms remain to be elucidated.

Effect on FGF-23

Fibroblast growth factor (FGF)-23 is produced by osteocytes and plays an important role in the metabolism of phosphate and vitamin D. Recent studies have shown that increased serum FGF-23 level is associated with left ventricular hypertrophy [24] and mortality [25] in HD patients. Also in an experimental study, FGF-23 induced left ventricular hypertrophy in animal models [26].

Oliveira et al. examined the effect of sevelamer on FGF-23 in a 6-week randomized trial including 40 patients with CKD stage 3 to 4 [27]. After the therapy, the patients treated with sevelamer hydrochloride showed significantly decreased serum FGF-23 level ($P < 0.05$), whereas those treated with calcium acetate did not ($P < 0.05$ between two groups). Similarly, Yilmaz et al. found a 27.1%-decrease in serum FGF-23 level at 8 weeks after sevelamer therapy in CKD patients [11]. In HD patients, Brandenburg et al. did not detect improvement of serum FGF-23 level after sevelamer therapy [28]. Although the results regarding the effect of sevelamer on FGF-23 are somewhat inconsistent, the effect would be an issue of increasing interest in CKD patients.

Anti-inflammatory effect

Several studies have shown that sevelamer improves inflammation marker level. In a randomized trial including 108 HD patients, Ferramosca et al. observed a significant decrease in serum high-sensitivity C-reactive protein (hs-CRP) level in the patients treated with sevelamer hydrochloride (-0.48 ± 2.58 mg/dL from a baseline value of 1.53 ± 1.93 mg/dL, $P = 0.012$) one year after the therapy, but no such decrease was detected in those treated with calcium acetate [8]. Navarro-Gonzalez et al. compared the changes in pro-inflammatory cytokine levels as well as hs-CRP level between HD patients treated with sevelamer hydrochloride and those treated with calcium acetate in a randomized trial [29]. In those treated with sevelamer hydrochloride, serum levels of hs-CRP, interleukin (IL)-6, and soluble CD14 significantly decreased at 3 months after the therapy. Anti-inflammatory IL-10 showed a significant increase. In contrast, the patients treated with calcium acetate showed significantly increased serum IL-6. Multiple regression analysis demonstrated that the change in $\text{Ca} \times \text{P}$ product was an independent predictor of serum IL-6, even after adjustment for serum endotoxin level. The authors suggested that control of $\text{Ca} \times \text{P}$ product with sevelamer might be associated with modulation of inflammation [29]. However, the $\text{Ca} \times \text{P}$ products after therapy were almost similar between the sevelamer group and the calcium acetate group (45.3 ± 11.7 vs 44.5 ± 7.8 mg^2/dL^2). Their speculation seems somewhat questionable. Another speculation of the anti-inflammatory effect of sevelamer is that sevelamer might have a chelation effect on pro-inflammatory compounds in the intestinal lumen [8, 30].

Other inflammatory substances reduced by sevelamer include tumor necrosis factor (TNF)- α [30] and endotoxin [29, 31]. It appears that the anti-inflammatory effect of sevelamer leads to increased serum albumin level reported in some studies [28, 30]. In these studies, however, the authors did not mention the change in protein intake after sevelamer administration. Whether sevelamer might increase serum albumin level independently of protein intake remains to be elucidated.

Antioxidant effect

Oxidative stress is highly prevalent in CKD patients and has been linked to several surrogate markers of atherosclerosis, such as endothelial dysfunction and intima-media thickness [32]. In a randomized trial including 52 HD patients [33], there was a significant decrease in plasma hydrogen peroxide-related radicals detected by chemiluminescence measurement 8 weeks after the therapy in the sevelamer group ($P < 0.001$), but not in the calcium acetate group. In another randomized study including 31 HD patients, Peres et al. detected a significant decrease in *in vitro* reactive oxygen species production 12 months after sevelamer therapy [30]. Furthermore, in an intention-to-treat crossover study including 20 diabetic patients with CKD stage 2-4, Vlassara et al. found that those treated with sevelamer demonstrated decreased level of 8-isoprostanes [34]. Future studies including a larger number of patients are required to confirm the antioxidant effect of sevelamer.

Effect on fetuin-A

Fetuin-A has been noted as a vascular calcification inhibitor and is associated with mortality in HD patients [35]. Brandenburg et al. examined the effect of sevelamer on fetuin-A level in a prospective study with an intention-to-treat analysis including 57 HD patients [28]. After phosphate binder was changed from calcium-containing binder to sevelamer hydrochloride, serum fetuin-A level significantly increased (+21%). Lower sevelamer dose was associated with lower serum fetuin-A level compared with higher sevelamer dose ($P < 0.05$). Caglar et al. showed that in an 8-week randomized study including 50 non-diabetic patients with CKD stage 4, sevelamer induced a significant increase in serum fetuin-A level

along with improved endothelial dysfunction detected by flow-mediated dilation [12]. This effect was not observed in those treated with calcium acetate. Further studies should confirm these observations, but the relationship between sevelamer and fetuin-A seems fascinating.

Anemia control

In CKD patients, anemia is another important complication associated with decreased quality of life and cardiovascular morbidity and mortality [36, 37]. Erythropoiesis-stimulating agents (ESA) play a pivotal role in the management of renal anemia. Recently, we reported an independent association between sevelamer dose and ESA responsiveness in a cross-sectional study including 45 HD patients [38]. In this study, higher sevelamer hydrochloride dose was independently associated with ESA responsiveness ($P = 0.002$), even after adjustment for male sex, hs-CRP level, transferrin saturation rate, and VDRA dose. Our findings are supported by subsidiary results of a recent study by Panichi et al. including 653 HD patients [39]. In their study, the proportion of patients treated with sevelamer differed significantly between the lowest and the highest ESA resistance quartiles (36.4% vs 18.5%, $P = 0.001$) and multivariate analysis demonstrated an independent association between sevelamer use and the lowest ESA resistance quartile ($P < 0.001$). The mechanisms responsible for these results remain to be elucidated, but the decreases in serum levels of certain cytokines, such as IL-6 and TNF- α [29, 30], might improve anemia, as these cytokines are known to interfere with erythropoiesis [40].

In contrast, some studies reported a decrease in serum folic acid level by sevelamer [41, 42], which might exacerbate anemia. Schiffl et al. showed a significant decrease in serum folic acid level (from 12 ± 5 to 8 ± 3 ng/mL, $P < 0.05$) and an increase in ESA dose (from 52 ± 9 to 68 ± 15 IU/kg/week, $P < 0.05$) at 1 year after sevelamer therapy in 19 HD patients [42].

Only limited data are available on the relationship between sevelamer and anemia. Randomized controlled trials are required to investigate the causal relationship between sevelamer and ESA responsiveness.

Effect on advanced glycation end products

In a 12-month randomized trial including 183 HD patients, Kakuta et al. compared the change in plasma pentosidine level between the patients treated with sevelamer hydrochloride and those treated with calcium carbonate [9]. After the therapy, the calcium carbonate group showed significantly increased plasma pentosidine level (from 1.845 ± 0.907 to 2.121 ± 0.930 nmol/mL, $P < 0.001$), but the sevelamer group did not (from 1.861 ± 0.761 to 1.882 ± 0.860 nmol/mL, $P = 0.6$). In addition, Vlassara et al. examined the changes in plasma levels of advanced glycation end products (AGE) in diabetic patients with CKD stage 2-4 in an intention-to-treat crossover study [34]. Compared with calcium carbonate, sevelamer carbonate decreased serum methylglyoxal and 6 N-carboxymethyl-lysine. Thus, the relationship between sevelamer and AGE is worthy of further study.

Effect on trace element metabolism

In an in vitro study, Takagi et al. found that sevelamer hydrochloride adsorbed Cu^{2+} and Zn^{2+} , particularly at acid pH [43]. In our recent cross-sectional study, sevelamer hydrochloride dose inversely correlated with serum copper level in HD patients [44]. Veighey et al. compared serum levels of zinc, copper, and selenium between HD patients treated with sevelamer hydrochloride and those treated with calcium- or lanthanum-containing phosphate binder [45]. As a result, there was no difference in all of these trace element levels.

Some studies have suggested associations between trace element metabolism and

inflammation, oxidative stress, or atherosclerosis in HD patients [44, 46, 47]. The effect of sevelamer on trace element metabolism should be examined by further studies.

Clinically-relevant side effects

As mentioned above, sevelamer has been suggested to have many favorable pleiotropic effects. However, some characteristics of sevelamer, such as lower adsorbing capacity for phosphorus and higher incidence of gastrointestinal symptoms [48, 49] should be improved. In addition, unfavorable effects might occur through its adsorption of various substances, such as folic acid. In addition, serum levels of uremic toxins such as indoxyl sulphate, indole acetic acid, and hippuric acid were not improved by sevelamer administration [28, 41].

Sevelamer hydrochloride can also exacerbate metabolic acidosis. Sevelamer hydrochloride acts like an ion-exchange resin in the gastrointestinal tract and releases one mole of chloride for every mole of phosphorus that it binds to. The released chloride is buffered by bicarbonate, which leads to reduced serum bicarbonate level, and hence, metabolic acidosis. Metabolic acidosis is an important problem of CKD and is associated with increased protein catabolism, insulin resistance, systemic inflammation, bone disease, and probably increased serum β_2 -microglobulin [50]. However, sevelamer carbonate, another salt of sevelamer, might solve this problem. Fan et al. recently showed that sevelamer carbonate well controlled hyperphosphatemia and increased serum bicarbonate level [51]. Although the data on pleiotropic effects of sevelamer carbonate are limited, the effect on AGE has been reported in the aforementioned study by Vlassara et al. [34].

Comparison with lanthanum carbonate

Lanthanum carbonate is another calcium-free phosphate binder. Two crossover studies compared phosphorus-lowering effects between sevelamer hydrochloride and lanthanum carbonate, and reported no difference in serum phosphorus levels at an adequate prescribed dose [49, 52]. As reported in the previous studies, lanthanum carbonate would show a favorable effect on metabolic acidosis [53] and an unfavorable effect on lipid profiles compared with sevelamer hydrochloride [45]. Nikolov et al. examined vascular calcification in uremic apolipoprotein E-deficient mice [54], and both drugs suppressed the progression of vascular calcification. Their data regarding oxidative stress and bone formation suggested that this vascular protective effect would result from different mechanisms between the drugs.

The calcium-free nature of lanthanum carbonate seems beneficial, but clinicians should pay an attention to the fact that the safety of lanthanum administration has not been ascertained after a long-term use for more than 10-20 years.

Conclusion

Sevelamer with various pleiotropic effects seems a promising agent in CKD patients, but its effect on mortality is not conclusive. Further studies are required to clearly show the beneficial effects. As sevelamer hydrochloride improved vascular calcification and mortality in incident HD patients [7, 17], sevelamer administration in an early phase of CKD/ESRD might be required to improve patient's prognosis. In addition, the benefit of sevelamer hydrochloride might be concealed by metabolic acidosis exacerbated by the drug itself. Sevelamer carbonate might more evidently demonstrate beneficial effects.

Conflict of Interests

None to declare.

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