PLOS | ONE

RESEARCH ARTICLE

New Conclusions Regarding Comparison of Sevelamer and Calcium-Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials

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Citation: Wang C, Liu X, Zhou Y, Li S, Chen Y, Wang Y, et al. (2015) New Conclusions Regarding Comparison of Sevelamer and Calcium-Based Phosphate Binders in Coronary-Artery Calcification for Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials. PLoS ONE 10(7): e0133938. doi:10.1371/journal.pone.0133938

Editor: Carmine Pizzi, University of Bologna, ITALY

Received: April 18, 2015

Accepted: July 2, 2015

Published: July 31, 2015

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: This study was supported by the National Natural Science Foundation of China (Grant No. 813770866 and 81070612), the China Postdoctoral Science Foundation (Grant No. 201104335 and 20090460774), Guangdong Science and Technology Plan (Grant No. 2011B031800084 and 2013B021800190), the Fundamental Research Funds for the Central Universities (Grant No. 11ykpy38), and the National Project of Scientific and Technical Supporting Programs Funded by Ministry of

Abstract

Background

Sevelamer hydrochloride is used widely, but its impact upon cardiovascular calcification, cardiovascular mortality, all-cause mortality and hospitalization is not known.

Outcomes

Primary outcome was cardiovascular calcification (coronary artery calcification scores (CACS) and aortic calcification scores (ACS)). Secondary outcomes were serum characteristics, hospitalization, cardiovascular mortality and all-cause mortality. Risk ratio (RR), mean differences and standard mean difference with 95% confidence intervals (CIs) were pooled using random- or fixed-effects models.

Results

We identified 31 studies (on 23 randomized controlled trials with 4395 participants). An analysis pooling showed a significant decrease in serum levels of phosphate with calcium-based phosphate binders (CBPBs) by 0.17 mg/dL [mean difference (MD), 95% CI, 0.03, 0.31] than sevelamer. A significant difference in the change of CACS by –102.66 [MD: 95% CI, –159.51, –45.80] and ACS by –1008.73 [MD, 95% CI, –1664.75, –352.72] between sevelamer and CBPBs was observed. Prevalence of hypercalcemia (serum levels of calcium >10.2–10.5 mg/dL and >11.0 mg/dL) was significantly smaller for sevelamer (RR = 0.44, 95% CI, 0.33, 0.58; RR = 0.24, 95% CI, 0.14, 0.40). No significant difference was found in hospitalization, all-cause mortality or cardiovascular mortality.

Science & Technology of China (Grant No. 2011BAI10B00).

Competing Interests: The authors have declared that no competing interests exist.

Conclusions

This meta-analysis suggests that sevelamer benefits dialysis patients in terms of CACS, ACS and hypercalcemia.

Introduction

Chronic kidney disease (CKD) is a major public-health problem [1]. As a major therapy for patients with end-stage renal disease (ESRD), renal replacement therapy is used widely all over the world. However, dialysis patients can suffer from mineral metabolism. Also, cardiovascular disease is the most common cause of death, accounting for more than one-half of cases [2–4].

Higher levels of phosphate in serum are associated with worse outcomes in dialysis patients, so different types of therapies have been employed to deal with this problem. Phosphate binders taken with meals, which bind dietary phosphate, play an important part in the treatment of hyperphosphatemia [5]. Dietary phosphate binders are used widely. Calcium-based agents were traditionally employed as first-line therapy [6] but their use can result in hypercalcemia and high levels of calcium-phosphate products, which are associated with cardiovascular mortality and mortality in ESRD. Hence, magnesium- and aluminum-based agents have started to be used.

New non-calcium, non-magnesium, and aluminum-free phosphate-binding means agents such as sevelamer have been reported to reduce the Medicare costs of inpatients compared with calcium binders [7] without alerting serum levels of calcium. As a type of calcium-free agent, sevelamer may has less influence upon serum levels of calcium [8]. However, its impact upon cardiovascular calcification, cardiovascular mortality, all-cause mortality and hospitalization is not known.

Several reviews [9–13] have focused on sevelamer, one of which was conducted in 2010 involving 14 trials and 3271 patients [9]. In that meta-analysis, the authors included predialysis patients and evaluated the level of cardiovascular calcification using coronary artery calcification scores (CACS), graded by computed tomography (CT) and representing the progression or regression of coronary artery disease, [14, 15] in four randomized controlled trials (RCTs) in hemodialysis patients. Jamal et al. (2009) [10] also analyzed cardiovascular calcification by CACS, but found no significant differences in CACS between patient groups and controls. Three of those reviews [11–13] considered biochemical outcomes, and one review also evaluated the effect of sevelamer upon all-cause mortality, cardiovascular events, and other adverse events [11]. Since then, several trials related to this issue have been published. It seems that an updated review of the evidence would be of great use to clinicians and decision-makers. Hence, we conducted a meta-analysis of published RCTs on the effectiveness and safety of sevelamer in dialysis patients.

Materials and Methods

Data Sources and Literature Searches

We undertook a systematic meta-analysis of RCTs according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (S1 Fig) [16]. We conducted a MEDLINE literature search to identify all relevant studies using the search terms 'sevelamer hydrochloride', 'sevelamer', or 'RenaGel' from January 1998 to November 2013 and searched PUBMED, EMBASE ('sevelamer hydrochloride'/exp OR 'sevelamer hydrochloride' OR

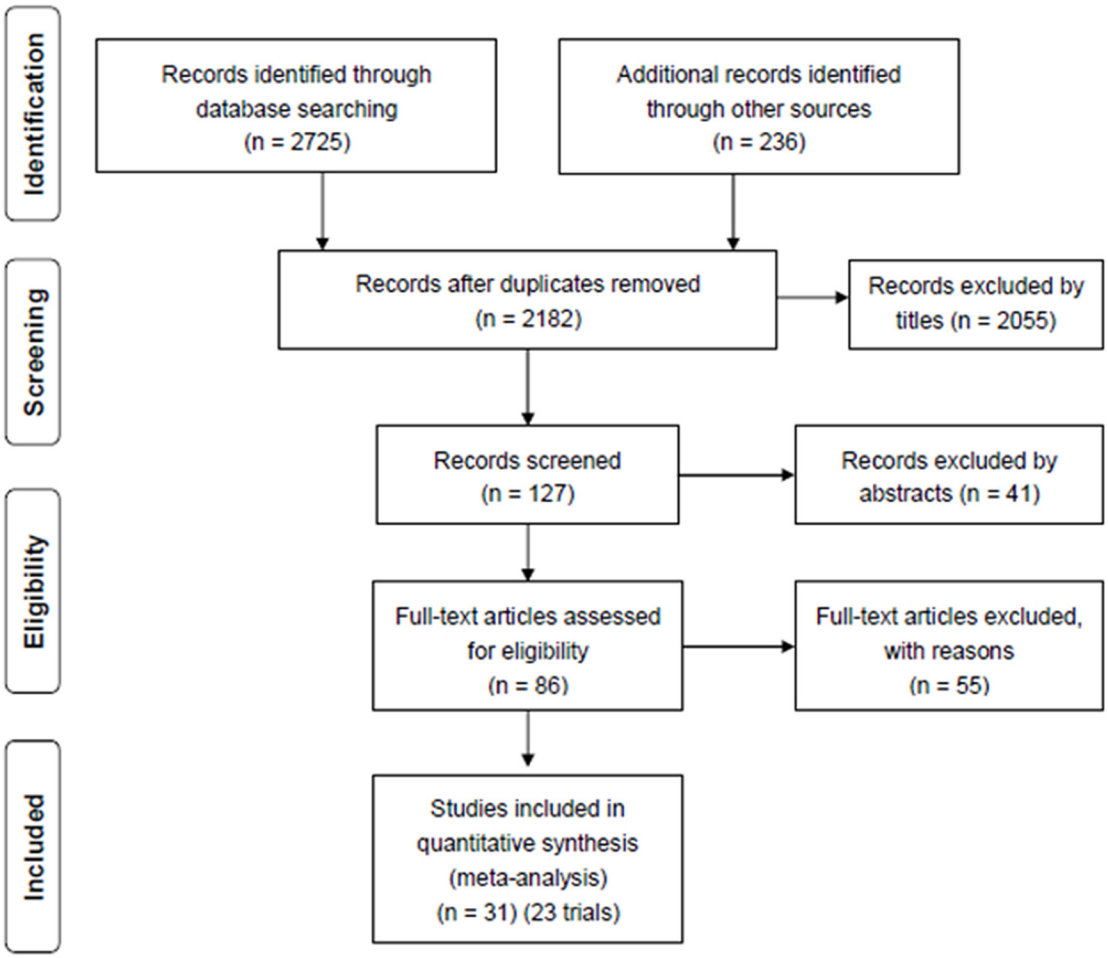

Fig 1. Flow diagram of studies considered for inclusion.

doi:10.1371/journal.pone.0133938.g001

'sevelamer'/exp OR sevelamer AND ('renagel'/exp OR renagel) 1811), the specialized register of the Cochrane Renal Group, and the Cochrane Central Register of Controlled Trials to identify all RCTs studying the effects of sevelamer hydrochloride using similar search terms.

We also searched (manually) the abstracts of conference proceedings of the American Society of Nephrology from 1998 to 2013. However, we did not have access to RCTs that were not reported.

Restrictions on language or dates were not imposed in our searches. Finally, we found 2961 studies for the analysis. After screening, 31 studies (on 23 trials) were included (Fig 1) in the analysis.

Study Selection

All RCTs that studied dialysis ESRD adults (age $\geq$18 years) and compared sevelamer to any calcium-based phosphate binder (CBPB) were included. Included studies are assumed to have analyzed the effect of phosphate binders on serum levels of phosphate or calcification of coronary arteries. Studies comparing sevelamer to any other types of phosphate binders or no phosphate binders were excluded. Titles and abstracts were reviewed by two reviewers independently, as well as the full-text articles.

Data Extraction and Quality Assessment

Data were extracted by two authors. A third reviewer checked the extracted data for accuracy. The following data were extracted: country of origin; year of publication; sample size; study design; mean age; percentage of men; mean duration of dialysis; prevalence of diabetes. The quality of trials was assessed by Review Manager 5.2 (Oxford, UK) according to the *Cochrane Handbook for Systematic Reviews of Interventions* (S2 Fig and S3 Fig) [17]. Levels of evidence were evaluated by the GRADE profiler (S4 Fig) [17]. A third person was available if there was disagreement concerning extraction and/or assessment of the quality of data.

Synthesis and Analysis of Data

We undertook meta-analyses using Review Manager 5.2 and meta-regression by comprehensive meta-analysis (CMA). Mean difference (MD) and standard mean difference (SMD) were used to pool results for continuous outcomes (e.g. serum levels of phosphate and calcium), and we also computed pooled risk ratios (RRs) for dichotomous outcomes (e.g. cardiovascular mortality, all-cause mortality). We used change-from-baseline results rather than final values in the analysis of CACS and aortic calcification scores (ACS) to evaluate the effect of phosphate binders upon vascular calcification. Pooling methods that account for the with-inpatient-correlation from crossover trials were used to combine data from crossover and parallel continuous trials [18]. A fixed- (used if $I^2 \leq 25\%$) and a random-effects model (used if $I^2 \geq 50\%$) was used to analyze data.

Ninety-five percent confidence intervals (95% CIs) were provided for all pooled estimates. Heterogeneity was assessed using the Cochrane Q test. I^2 index (which describes the percentage of total variation across studies due to true heterogeneity rather than chance) and P values were also used. Publication bias was assessed using Funnel plots.

Results

Selection and Characteristics of Studies

A total of 2961 potentially relevant citations were identified and screened. Eighty-six articles were retrieved for detailed evaluation, of which 31 (23 trials were analyzed in total) fulfilled the eligibility criteria (Fig 1). Detailed characteristics and a summary of all 31 studies (23 trials) are displayed in Tables 1 and 2. Multiple publications with no unique result were excluded from screened studies. However, unique results were extracted and studies (as well as abstracts) containing unique results were also displayed. Block 2007 [19], was a follow-up analysis of earlier studies [20–21] that compared sevelamer with CBPBs. The study of Barreto 2005 [22] was a published abstract of the study of Barreto 2008 [23], and contained some data that the full report did not mention or did not describe in detail. Chertow 2003 [24] is a short term follow-up trial which evaluated the same patients investigated in Asmus 2005 [25] which was a long term follow-up trial for them. Chertow 2002 [26], Raggi 2004 [27] and Ferramosca 2005 [28] et. al also shared data from the same patients. However, all of them (containing the same cohort of participants) were extracted only once. Sample size of studies varied from 13 patients to 2103 patients (a total of 4395 participants). Mean age was 57.9 years. Duration of dialysis was from 3 months to 18 years. Prevalence of diabetes ranged from 0% to 60%.

A total of 31 studies, including an abstract [29] and five posters [22, 30–32], were eligible for the analysis. Those studies compared sevelamer with calcium acetate, calcium carbonate, or both. One study had no baseline washout period. One study included only patients who initiated dialysis recently, and another study included only those on incident hemodialysis. All of

Table 1. Detailed characteristics of the studies.

Study	Country	Modality[a]	Duration[b] (yr)	Follow-up[c] (wk)	S dose[d] (g/d)	CBPB dose (g/d)	Sample size
Asmus 2005	USA	HD	5.1	104	6.9	4.3	72
Barreto 2005	Brazil	HD	NR	52	NR	NR	101
Barreto 2008	Brazil	HD	3.1	52	12	2.028	101
Bleyer 1999	USA	HD	NR	10	NR	NR	84
Block 2005	US	HD	0.25	78	8	2.3	129
Block 2007	USA	HD	NR	189	NR	NR	127
Braun 2004	Europe	HD	5.3	52	5.9	3.9	114
Cancela 2011	Brazil	HD	3.1	52	NR	NR	72
Chertow 1999	USA	HD	NR	16	NR	0.9	71
Chertow 2002	US, Ger, Au[e]	HD	3.3	52	6.5	4.6	200
Chertow 2003	USA	HD	2.5	52	2.4	2	108
Evenepoel 2009	NR	PD	1.2	12	4.8	4.8	143
Ferreira 2008	USA	HD	> 3.5	55	5.0	4.0	119
Francisco 2010	Europe	HD	5.0	26	3.2	1.74	255
Ferramosca 2005	USA	HD	4.8	53	6.5	4.3	108
Gallieni 2005	NR	HD	NR	12	0.403	0.403	114
Garg 2005	US, Ger, Au[e]	HD	3.3	52	NR	6.5	200
Herva's 2003	Spain	HD	4.7	34	4.09	3.9	51
Kakuta 2011	USA	HD	9.33	52	9	10.5	183
Lin 2010	Taiwan	HD	3.6	10	2.4	2.0	52
Liu 2006	USA	HD	7.3	8	0.4	0.667	70
Oliveira 2007	Brazil	HD	NR	54	NR	NR	19
Peter 2008	NR	HD	NR	104	NR	NR	2103
Qunibi 2004	USA	HD	4.3	8	6.9	7.1	100
Qunibi 2008	USA	HD	1.9	52	7.3	5.5	203
Raggi 2004	US, Ger, Au[e]	HD	3.3	52	NR	NR	200
Raggi 2005	US, Ger, Au[e]	HD	3.3	52	NR	NR	111
Sadek 2003	Europe	HD	NR	21	NR	4.85	42
Shaheen 2004	SA[f]	HD	3.4	20	2.4	1.8	20
Suki 2008	US	HD	3.2	193	6.9	5.3	2103
Takei 2008	Japan	HD	12	28	NR	NR	42

Chertow et al. 2003 and Ferramosca et al. 2005 shared the same patients, and Asmus et al. 2005 had a longer follow-up of the two studies. Block et al. 2007 had a longer follow-up than Block et al. 2007. Suki et al. 2008 and Peter et al. 2008 analyzed the same trial. Chertow et al. 2002, Raggi et al. 2004, Raggi et al. 2005 and Garge et al. 2005 analyzed the same trial. Barreto et al. 2005 is an abstract of Barreto et al. 2008, but with different types of data. Abbreviations: HD, hemodialysis; NR, not reported.

[a]Dialysis.

[b]Mean duration of dialysis

[c]Follow-up of trials

[d]Mean dose of sevelamer

[e]USA, German, Austria

[f]Saudi Arabia

doi:10.1371/journal.pone.0133938.t001

the trials were accrued on hemodialysis patients except one, which focused on patients undergoing peritoneal dialysis [33].

Table 2. Summary of the studies analyzed.

No. of studies[a]	31
No. of trials[b]	23
Sample size of the trials[b]	4395
Percentage of female participants[b]	41
Age of participants (yr)[b]	57.9
Percentage of participants with diabetes[b]	45
Body mass index (kg/m2)[b]	26.8
Percent of current smoking (%)[b]	15.6
Cause of ESRD[b]**:**	
Hypertension (%)	26.5
Diabetes mellitus (%)	41.6
Glomerulonephritis (%)	14.1
Polycystic kidney (%)	4.0
Other (%)	13.8

[a] All studies having been analyzed are included

[b] The same data were extracted for only once

doi:10.1371/journal.pone.0133938.t002

Effect of Sevelamer vs. CBPBs on Serum Measurements

In an analysis of 18 studies with 3327 participants reporting on serum levels of phosphate (duration of follow-up ranged from 8 weeks to 45 months), a significant decrease in serum levels of phosphate with CBPBs by 0.17 mg/dL (MD, 95% CI, 0.03, 0.31) was observed (Fig 2). All RCTs showed that CBPBs were better than sevelamer for the control of serum levels of phosphate.

Compared with CBPBs, the MD in serum levels of calcium (18 studies; 3425 participants; duration, 8 weeks to 45 months) and in calcium-phosphate product (14 RCTs; 3050 participants; duration, 8 weeks to 45 months) were significantly lower in patients administered sevelamer by –0.24 (95% CI, –0.34, –0.14) and by –0.14 (95% CI, –1.38, 1.10) separately.

Effect of Sevelamer vs. CBPBs upon Hypercalcemia

Level of hypercalcemia (defined in all trials as serum levels of calcium >10.2–10.5 mg/dL) reported in ten trials with 957 participants was smaller for sevelamer (RR, 0.43; 95% CI, 0.32, 0.56) compared with CBPBs (Fig 3). When hypercalcemia was defined as serum levels of calcium >11.0 mg/dL (which is viewed as "severe hypercalcemia"), the RR reported by eight trials with 605 patients was 0.22 (95% CI, 0.13, 0.37) (Fig 4). However, no trial reported on the clinical consequences or median duration of hypercalcemia.

Effect of Sevelamer vs. CBPBs on CACS and ACS

Seven studies with 731 participants, one of which had a sample size of only 52 participants, reported on the change of CACS. Considering the quality of the RCTs, we only included the six trials with 679 patients. The duration of follow-up varied from 26 weeks to 104 weeks. MD was significant, and was lower with sevelamer therapy by –102.66 (MD: 95% CI, –159.51, –45.80) (Fig 5). All RCTs analyzed showed that sevelamer was better for preventing calcification of coronary arteries than CBPB. The change in ACS was also extracted from three studies with 266 patients. Similar to the analysis of CACS, the analysis of ACS showed a significant decrease by –1008.26 (SMD: 95% CI, –1664.75, –352.72) (Fig 6).

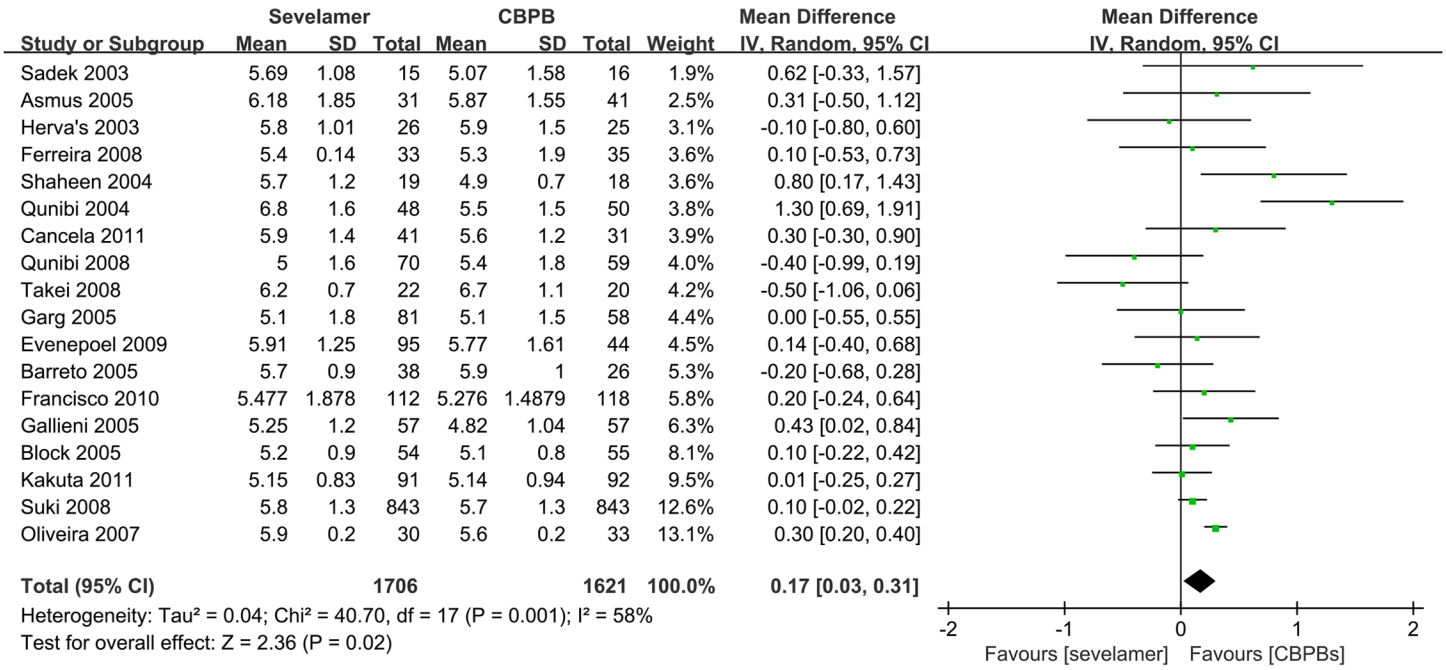

Fig 2. Forest plot of the values of phosphorus.

doi:10.1371/journal.pone.0133938.g002

Considering that the use of statins (detailed in Table 3) may have an impact on the change of CACS, we performed a linear regression on the change of CACS and the levels of low density lipoprotein (LDL) regulated mostly by statins. We found no significant relationship between CACS and LDL (Beta = -0.013; P = 0.971) (S5 Fig), which indicates that the use of statins has no significant impact on the change of CACS.

Effect of Sevelamer vs. CBPBs on Hospitalizations

Three RCTs with 2348 participants reported on the number of patients hospitalized during the study. The RR was smaller by 0.78 (95% CI, 0.61, 0.99), showing that sevelamer benefited

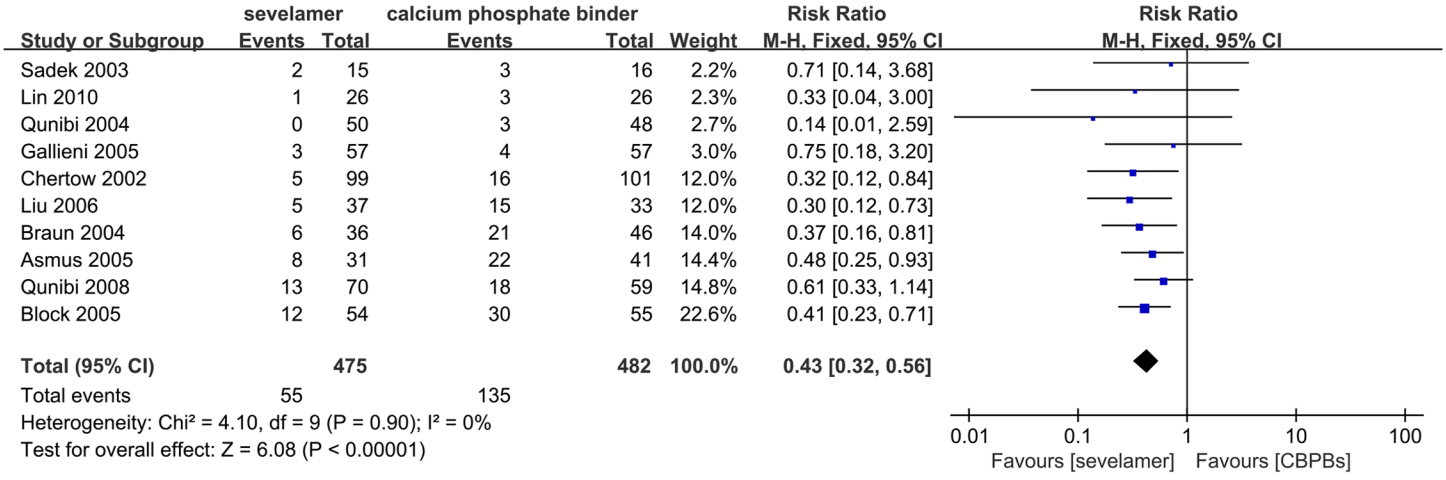

Fig 3. Forest plot of the values of hepercalcemia (above 10.2 mg-dL).

doi:10.1371/journal.pone.0133938.g003

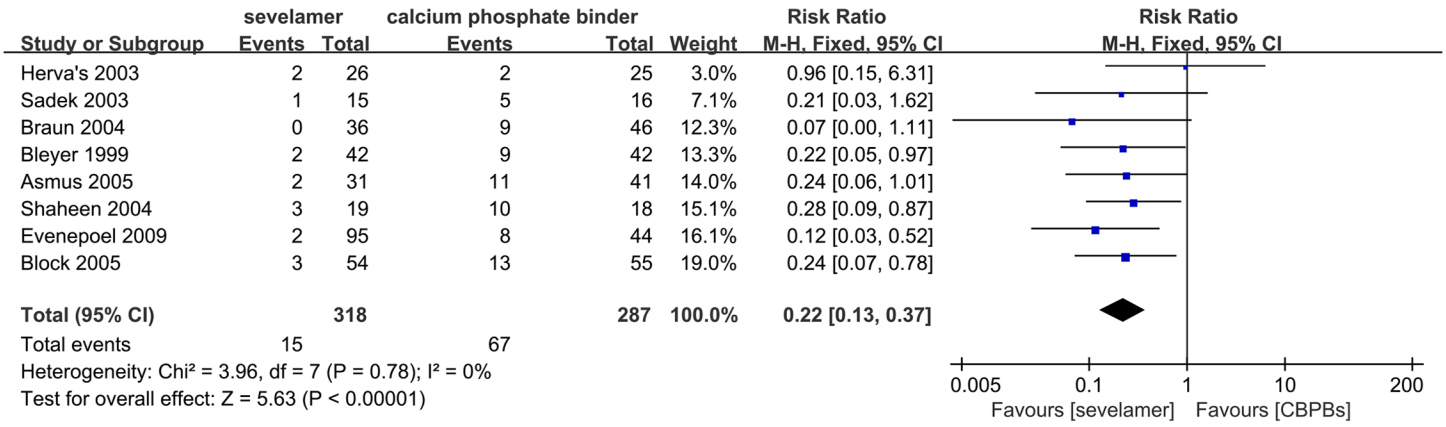

Fig 4. Forest plot of the values of hepercalcemia (above 11.0 mg-dL).

doi:10.1371/journal.pone.0133938.g004

patients with regard to hospitalization. Only one trial [34] reported on the number of days of hospitalization. Sevelamer-treated patients were hospitalized for fewer days (sevelamer (mean), 14.8±27.9; median, 5.0 hospital days/patient-year; calcium (mean), 17.4±32.0; median, 5.8 hospital days/patient-year; P = 0.09) in the trial of Suki et al. 2008 [34] but the difference was not significant.

Effect of Sevelamer vs. CBPBs on Mortality

Nine trials with 3000 participants reported all-cause mortality, and the duration of follow-up ranged from 20 weeks to 45 months. Three RCTs analyzed all-cause mortality as the primary outcome. The RR was 0.91 (95% CI, 0.79, 1.04) between sevelamer and CBPBs. Three RCTs with 2102 participants reported on cardiovascular mortality, and the RR was also non-significant by 0.94 (95% CI, 0.76, 1.16). As a result, no significant difference was found in all-cause mortality and cardiovascular mortality.

Heterogeneity and Publication Bias

All data (detailed in Table 4) were analyzed by fixed-effects ($I^2 \leq 50\%$) and random-effects ($I^2 > 50\%$) models. Between-study heterogeneity ranged from 0% to 75%. Among all the data analyzed, no between-study heterogeneity (0%) was observed in the analysis of cardiovascular mortality, all-cause mortality, change in ACS, hospitalization, and hypercalcemia. Between-study heterogeneity was low ($I^2 \leq 25\%$) in the analysis of change in CACS, and was moderate

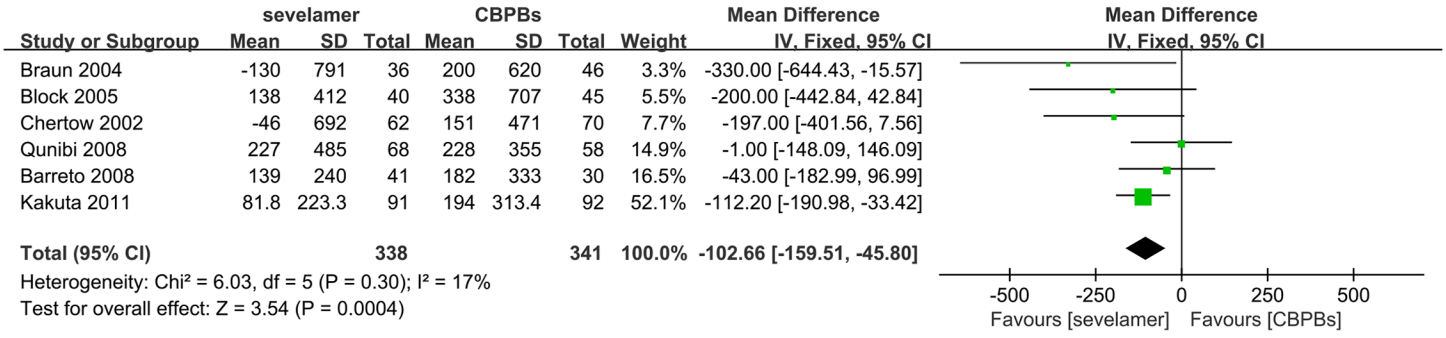

Fig 5. Forest plot of sevelamer vs. calcium phosphate binders on CACS change.

doi:10.1371/journal.pone.0133938.g005

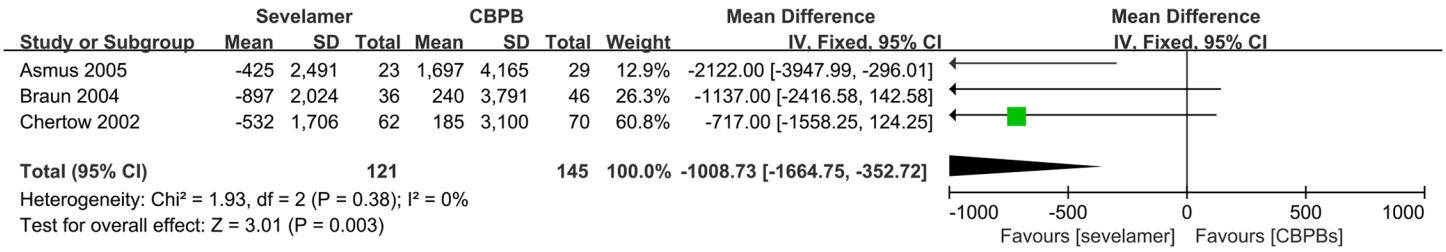

Fig 6. Forest plot of sevelamer vs. calcium phosphate binders on ACS change.

doi:10.1371/journal.pone.0133938.g006

($25\% < I^2 \leq 50\%$) in the analysis of serum calcium-phosphate product. Between-study heterogeneity of the data analyzed was high (>50%) for serum levels of phosphate and calcium. We could not undertake a subgroup analysis, so we used the random-effect model to analyze the data: serum levels of phosphorus had an $I^2 = 58\%$ and serum levels of calcium had an $I^2 = 75\%$.

Funnel plots revealed an approximately symmetrical distribution (Fig 7). Hence, publication bias was present

Meta-Regression for Baseline Variables

As a result of high heterogeneity ($I^2 = 58\%$) in the analysis of phosphorous, we undertook a meta-regression using CMA and analyzed three factors: mean duration of dialysis; designed duration of the trial; and sample size of the trial. However, we did not find a significant factor ($P > 0.1$) that contributed to heterogeneity (S6 Fig). Hence, an appropriate subgroup analysis was not carried out.

A meta-regression on CACS was performed using baseline variables: mean duration of dialysis; designed duration of the trial; and sample size of the trial. Partially because of the low heterogeneity (17%), we did not find a significant factor that contributed to the heterogeneity (S7 Fig and S8 Fig).

Discussion

We carried out a meta-analysis to estimate the impact of sevelamer upon cardiovascular calcification, cardiovascular mortality, all-cause mortality, and hospitalization in patients on dialysis,

Table 3. Details of the use of statins.

Study	Statins	Kinds	Details	Evaluation on statins
Qunibi 2008	Yes	Atorvastatin	Different statins given time[b]	No definitive conclusions[e]
Kakuta 2011	Yes	NR[a]	Different proportion of patients given statins[c]	No significant difference
Block 2005	NR[a]	NR[a]	NR[a]	NR[a]
Barreto 2008	NR[a]	NR[a]	NR[a]	NR[a]
Chertow 2002	NR[a]	NR[a]	NR[a]	NR[a]
Braun 2004	Yes	NR[a]	Different proportion of patients given statins[d]	No significant difference[f]

[a]Not reported

[b]Statins were given to calcium group at start, to sevelamer group at week 8 only if their LDL-C levels were not less than 70 mg/dL

[c]8% patients were given statins in sevelamer group, while 11% in cacium group

[d]26% patients were given statins in sevelamer group, while 33% in cacium group

[e]Definitive conclusions about the role of LDL-C lowering in the progression of CAC was unavailable

[f]Statin use was not associated with less progression of coronary artery or aortic calcification in sevelamer or calcium carbonate patients

doi:10.1371/journal.pone.0133938.t003

Table 4. Overall outcome summaries.

Outcomes	Studies	Quality[a]	Patients	Overall summary	I^2 & p	F[e] (wk)	Reference
Sevelamer vs. calcium							
Serum phosphate (mg/dL)	18	High	3327	MD R[b] 0.17 [0.03, 0.31]	58%; 0.001	49	[20, 22, 24–26, 31–46]
Serum calcium (mg/dL)	18	Moderate	3425	MD R -0.24 [-0.34, -0.14]	77%; 0.001	52	[20, 22, 24–26, 31–38, 40–46]
Serum c×p product[d] (mg^2/dL^2)	14	Moderate	3050	MD R -0.14 [-1.38, 1.10]	30%; 0.14	50	[20, 24–26, 31, 33, 34, 39–45]
Change in CACS	6	High	679	MD F[c] -102.66 [-159.51, -45.80]	17%; 0.3	62	[20, 23, 25, 26, 28, 40, 41, 47]
Change in ACS	4	High	453	MD R -1008.73 [-1664.75, -352.72]	0%; 0.80	65	[24–26, 47]
Hospitalization	3	Moderate	2348	RR F 0.78 [0.61, 0.99]	0%; 0.99	100	[24, 26, 34]
All-cause mortality	9	Moderate	3000	RR F 0.91 [0.79, 1.04]	0%; 0.44	81	[20, 23, 26, 34, 40, 41, 44, 45, 47]
Cardiovascular mortality	3	Moderate	2102	RR F 0.94 [0.76, 1.16]	0%; 0.80	84.5	[34, 44, 45]
Hepercalcemia (>10.2 mg/dL)	10	Moderate	957	RR F 0.43 [0.32, 0.56]	0%; 0.90	38	[20, 25, 26, 31, 41, 42, 44, 47–49]
Hepercalcemia (>11.0 mg/dL)	8	Moderate	605	RR F 0.22 [0.13, 0.37]	0%; 0.78	40	[20, 25, 30, 33, 39, 44, 45, 47]

Abbreviations: CACS, coronary artery calcification scores; ACS, aortic calcification scores

[a]Graduated by GRADE profiler

[b]Random-effects model

[c]Fixed-effects model

[d]Serum calcium-phosphate product

[e]Follow-up period (wk)

doi:10.1371/journal.pone.0133938.t004

and identified 31 studies (covering 23 trials with 4395 participants). Compared with CBPBs, sevelamer therapy resulted in smaller decreases in serum levels of phosphorus and a lower prevalence of hypercalcemia. A significant difference in the CACS and ACS was observed between sevelamer and CBPBs. Evidence that sevelamer reduced all-cause mortality or cardiovascular mortality was lacking. Also, there was a slight reduction in the duration of hospitalization with sevelamer therapy according to three RCTs.

Our review updates and complements the findings of earlier systematic reviews. It also includes >3000 additional participants, including a Dialysis Clinical Outcomes Revisited (DCOR) study [21] with 2103 participants—the largest randomized trial of sevelamer conducted.

Different to former meta-analyses, this meta-analysis found a significant difference in CACS and ACS. This phenomenon may be due to a better search strategy, as well as the inclusion of more trials and different types of patients. In the analysis of CACS, compared with eight RCTs on dialysis patients, a meta-analysis by Zhang 2010 [9] included four articles, and Jamal 2009 [10] included six trials in which a trial on predialysis patients was also evaluated. Similar to other reviews, CBPBs showed slightly better results for controlling serum levels of phosphate. In the analysis of serum levels of phosphate, we also undertook a meta-regression on serum levels of phosphate, and analyzed six factors but, unfortunately, factors that influenced the heterogeneity in serum levels of phosphate were found. We did not analyze the changes in sevelamer dose or CBPB dose in different treatment phases.

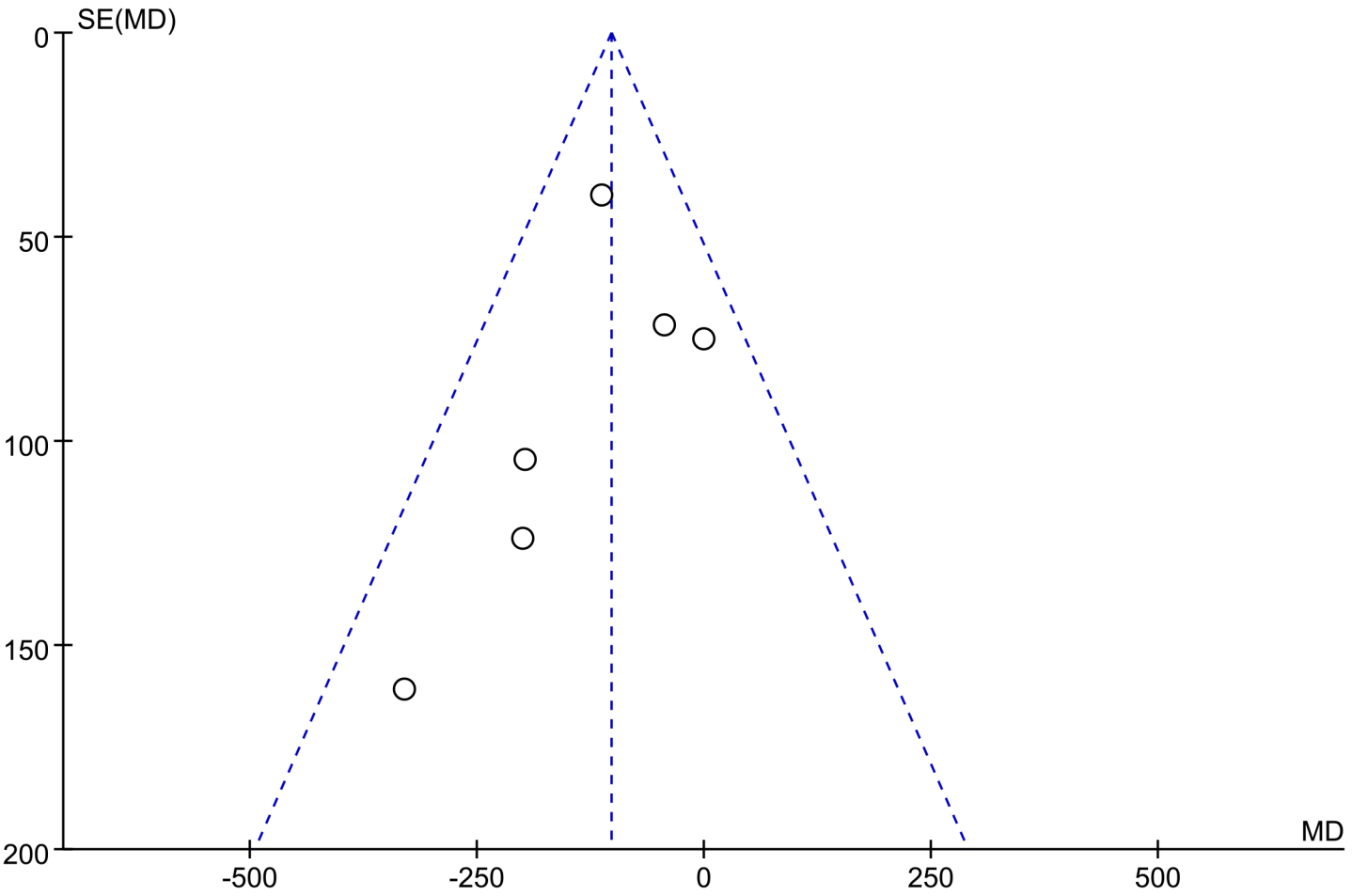

Fig 7. Funnel plot of the value of change of CACS.

doi:10.1371/journal.pone.0133938.g007

In this meta-analysis, we found a significant difference in CACS. Compared with CBPBs, sevelamer does not contain calcium, and is a type of non-calcium, non-magnesium, aluminum-free agent. As a result, sevelamer therapy can result in a smaller increase in serum levels of calcium and calcium-phosphate product. Also, the prevalence of hypercalcemia (defined as serum levels of calcium >10.2–10.5 mg/dL and serum levels of calcium >11.0 mg/dL) was also smaller. Serum levels of calcium are independent risk factors for vascular calcification, so less calcium in blood leads to a smaller increase in CACS for sevelamer therapy. However, our analysis showed no significant differences between sevelamer therapy and CBPB therapy in terms of cardiovascular mortality. A long time is required from vascular calcification to a cardiovascular event. Hence, sevelamer may reduce cardiovascular mortality in the long-term, and the fact that no significant evidence was observed for cardiovascular mortality may be due to short-term follow up.

Though sevelamer has less impact in controlling hyperphosphatemia, its use can result in a significant reduction in hospitalization. Moreover, a study showed that sevelamer-treated patients over 65 years old had a significant reduction hospitalization (P = 0.03) with a trend toward fewer hospital days (P = 0.08). In this respect, sevelamer can enhance the quality of life of patients.

Previous reviews showed no evidence to recommend use of sevelamer because there was no evidence to show that sevelamer has clinically meaningful benefits. However, our meta-analysis showed favorable use of sevelamer, especially for patients with hypercalcemia or high CACS. Also, compared with calcium-phosphate binders, the available trials mostly showed a clinically relevant beneficial effect of sevelamer.

The strengths of this meta-analysis were the number of participants and studies that we evaluated. Indeed, this is the largest systematic review of RCTs on dialysis patients to examine the effect of sevelamer compared with CBPB therapy on kidney-related serum measurements, CACS, ACS, hospitalization, and other endpoints of clinical safety.

However, several limitations must be considered. Unpublished reports could not be identified, which might have biased our results. Also, we could not assess the dosing schedules of sevelamer therapy and CBPB therapy (including dosing escalations and maximal dosing schemes), which may have contributed to the heterogeneity of our analysis (especially for the analysis of serum levels of phosphate). Patients undergoing hemodialysis or peritoneal dialysis were studied in the populations. With only four studies focusing on adequate allocation concealment, the quality of trials was not very high. Also, the duration of follow-up was short except for four Dialysis Clinical Outcomes Revisited trials. Intention-to-treat analysis was not used in some trials. In addition, some trials did not describe the number of dropouts.

In summary, compared with CBPBs, sevelamer has virtually no advantage in terms of the control of serum levels of phosphate, but it can decrease in the prevalence of hypercalcemia, and benefits vascular calcification in the long-term. We can conclude that sevelamer improves clinically relevant outcomes in ESRD patients on dialysis. Therefore, routine use of sevelamer in dialysis patients is recommended in patients that already have control of serum levels of phosphate, and if patients may suffer, or already are suffering, from hypercalcemia or cardiovascular disease. Those with severe hyperphosphatemia are recommended to choose CBPB therapy (at least in the short-term).

Supporting Information

S1 Fig. PRISMA 2009 Checklist.
(PDF)

S2 Fig. Risk of bias graph.
(TIF)

S3 Fig. Summary of risk of bias.
(TIF)

S4 Fig. Summary of findings tables.
(TIF)

S5 Fig. Linear regression of CACS and LDL.
(TIF)

S6 Fig. Meta-regression for baseline variables on serum phosphate.
(TIF)

S7 Fig. Meta-regression for baseline variables on the change of CACS.
(TIF)

S8 Fig. Regression graph of the change of CACS on total sample.
(TIF)

Author Contributions

Conceived and designed the experiments: CXW XL YMZ TQL. Performed the experiments: CXW SML YNW. Analyzed the data: CXW YBC SML. Contributed reagents/materials/analysis tools: YNW YBC CXW. Wrote the paper: CXW XL.

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Pleiotropic effects of the non-calcium phosphate binder sevelamer

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The number of chronic kidney disease (CKD) patients and related adverse outcomes has dramatically increased worldwide in the past decade. Therefore, numerous experimental and clinical studies have recently addressed the underlying mechanisms, in particular the marked increase in cardiovascular mortality. Hyperphosphatemia is a major problem in these patients with advanced stage of CKD. Its control by calcium-containing phosphate binders is effective, but at the price of potentially noxious calcium overload. Sevelamer hydrochloride is a phosphate binder that offers an effective control of hyperphosphatemia as calcium-rich binders but without increase of calcium load. Beyond the control of phosphate, sevelamer seems to exert pleiotropic effects which include the correction of lipid abnormalities and the clearance of some uremic toxins.

Kidney International (2006) **70**, S16–S23. doi:10.1038/sj.ki.50001994

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The number of chronic kidney disease (CKD) patients has dramatically increased all over the world in the past decade. At the end of 2003, about 1.1 million persons suffered from end-stage renal disease (ESRD) and received maintenance dialysis therapy.[1] CKD patients have a high risk of cardiovascular disease, with cardiovascular (CV) mortality rates being 10–20 times higher in dialysis patients than in the general population, even after stratification for age, race, gender, and the presence of diabetes.[2] Younger patients are at particularly high risk, with 30-year-old dialysis patients having a mortality risk around 500 times higher than that of an age-matched normal population.[2] Therefore, numerous experimental and clinical studies have recently addressed the mechanisms underlying this high CV mortality. Both atherosclerosis and arteriosclerosis play pivotal roles. Both types of complications involve morphological and functional arterial wall changes. Atherosclerosis is characterized by thickening of the vessel wall and progressive narrowing of its lumen owing to plaque formation, whereas arteriosclerosis is characterized by vessel wall stiffening. Both pathological processes go along with vascular calcification, which is frequently observed and rapidly progressive in ESRD patients.[3–6] Both intima and media calcification are closely associated with and predictive of cardiac events.[7]

Whereas traditional CV risk factors, such as diabetes and hypertension, are common in CKD patients, these factors alone are not sufficient to explain CKD patients increased CV burden. Studies suggest that the accelerated atherosclerotic process of CKD involves several interrelated factors, including vascular calcification, oxidative stress, endothelial dysfunction, and chronic inflammation.[8] Vascular calcification generally develops as a normal part of aging; the process is accelerated and amplified in patients with CKD resulting, in part, from hyperphosphatemia, which is observed in the majority of ESRD patients.[9] The hemodynamic and functional changes resulting from vascular calcification have a major clinical impact, in that they significantly affect morbidity and mortality in dialysis patients. Disorders of mineral metabolism appear to be involved in the pathogenesis of CKD-linked vascular calcification. The process of transformation of vascular smooth muscle cells into osteoblast-like cells is an active and highly regulated process, analogous to bone formation, and *in vitro* data support the

possibility that elevated levels of phosphate are involved in this process, which leads to the production of bone matrix proteins.[10] Vessel wall mineralization occurs if the balance of pro-mineralizing factors outweighs mineralization inhibitory factors.[10]

The control of hyperphosphatemia is a major problem in ESRD patients. Its control by calcium-containing phosphate binders is effective but at the price of potentially noxious calcium overload. Sevelamer hydrochloride (Renagel®) is a calcium-free, metal-free phosphate binder that offers control of hyperphosphatemia that is as effective as calcium-rich binders but without increasing calcium load.[11–14] Treatment with sevelamer has also been shown to attenuate the rapid progression of coronary and aortic calcification, which is often seen in dialysis patients receiving calcium-based binders. This effect may be of benefit in terms of CV events in CKD patients.[13] In addition to its phosphate binding effect and its attenuation of calcification, sevelamer also has been shown to exert a raft of potentially beneficial pleiotropic actions that may impact on CV function. These include effects on serum lipid profile, uremic toxins, degree of inflammation, and others.

EFFECT OF SEVELAMER ON LIPID PROFILE IN CKD

CKD is a clinical condition associated with abnormalities in lipoprotein metabolism in both early and advanced stages of the disease. These include increases in serum triglycerides, very low-density lipoprotein cholesterol (VLDL)-cholesterol and LDL-cholesterol, and a low serum high-density lipoprotein (HDL)-cholesterol.[15] VLDL and LDL particles are characterized by triglyceride-rich apolipoprotein B (apo B)-containing lipoproteins, which have been shown to have significant atherogenic potential.[15] The dyslipidemia of CKD patients contributes to an increased risk of CV morbidity and mortality, and may also have an adverse impact on energy metabolism and on CKD progression itself.[16] Therefore, it is important to identify therapeutic means aimed to prevent the progression of atheromatous lesions and vascular calcification seen in CKD patients. In this setting the results of the 4D study, comparing the effect of atorvastatin with placebo on CV outcomes in 1255 type II diabetic patients on maintenance hemodialysis, came as a great surprise and a challenge to widely accepted beliefs. After a median follow-up of 4 years, atorvastatin (20 mg/day) decreased the relative risk of mortality by 8% despite a high number of CV events and an overall 24% CV mortality.[17] This indicates that the risk in hemodialysis patients with type II diabetes originates from factors other than an atherogenic lipoprotein phenotype alone. However, this issue remains a matter of debate, and other clinical trials with lipid-lowering agents are under way to solve the problem.

Sevelamer has been shown to result in significant reductions in serum LDL-cholesterol and LDL: HDL cholesterol ratio in dialysis patients after 8 weeks of treatment and after a switch from calcium-containing phosphate binders.[18] It appears that sevelamer exerts these effects of LDL-cholesterol lowering primarily through its action as a bile acid binder.[19] The Treat-to-Goal study was a randomized clinical trial in 200 chronic hemodialysis patients which was conducted to determine whether sevelamer might prevent the progressive CV calcification observed in ESRD patients receiving calcium-based phosphate binders. It showed that both sevelamer and calcium-based binders provided equivalent control of phosphate levels (end of study values 5.1 ± 1.2 and 5.1 ± 1.4 mg/dl, respectively; $P = 0.33$). However, sevelamer treatment was associated with a slower progression of coronary and aortic calcification than treatment with calcium-containing phosphate binders. Median percent increase in calcium score at 52 weeks was 6% with sevelamer versus 25% with calcium-containing binders for the coronary arteries ($P = 0.02$), and 5 versus 28%, respectively, for the aorta ($P = 0.02$). Although not a primary outcome measure of the trial, LDL-cholesterol levels were decreased in the sevelamer group, from 102 mg/dl at baseline to 65 mg/dl at study completion. In contrast, LDL-cholesterol levels remained unchanged in the calcium-containing binder group (102 and 103 mg/dl, respectively, $P < 0.0001$ for change from baseline between treatment groups).[13]

In order to examine the effect of the uremic state on vascular disease progression, we and others assessed the effects of chronic renal failure on the progression of vascular calcification and atherosclerosis *in vivo*, using the uremic apolipoprotein E knockout (apo E−/−) mouse model.[20–22] We administered sevelamer to apo E−/− mice with normal and reduced renal function, respectively.[23] As expected, we found that sevelamer treatment of uremic apo E−/− mice reduced the progression of intimal and medial arterial calcification, in association with a significant decrease of serum phosphate and calcium product. This effect was observed in the absence of a change in serum total cholesterol, suggesting that sevelamer has a cholesterol-independent action on atheroma formation, for instance via positive effects on oxidative stress and/or disturbed mineral metabolism. The fact that serum total cholesterol remained unchanged does not exclude, however, possible changes of LDL- and/or HDL-cholesterol concentrations, which are abnormal in chronic renal failure. In uremic apo E−/− mice, serum VLDL, intermediate-density lipoprotein, and LDL-cholesterol concentrations are increased compared with non-uremic mice, whereas HDL-cholesterol levels are comparable.[20] Unfortunately, we were unable to perform serum lipoprotein determinations in the mice of our study because of insufficient availability of blood at the time of sacrifice.[23] Mathew *et al.* used another well-known mouse model of accelerated atherosclerosis, namely the LDL receptor-deficient ($LDLR^{-/-}$) mouse. Of interest, the severe atherosclerotic plaque formation in this model also is associated with aortic calcification. In $LDLR^{-/-}$ mice that were rendered both diabetic and uremic, the addition of sevelamer to a high-fat/high-cholesterol diet resulted in actual reversal of vascular calcification.[24] This effect exceeded that anticipated through reduction of serum phosphorus alone. The authors

found that sevelamer administration was associated with a significant reduction in serum LDL cholesterol, which might have contributed to the observed decrease in arterial calcification.[24]

In a randomized clinical trial involving 108 hemodialysis patients, total cholesterol, LDL-cholesterol, and apolipoprotein B all decreased from baseline ($P<0.0001$ in each case), whereas HDL-cholesterol increased ($P=0.036$) in sevelamer-treated patients, but not in calcium acetate-treated patients, despite the more frequent use of statins in the latter group (46 versus 22%, $P<0.05$).[25] Coronary calcification score progressed significantly from baseline in the calcium acetate group ($P=0.002$), but not in the sevelamer group ($P=0.18$). Changes from baseline to study completion were significantly different between the sevelamer and calcium groups for total cholesterol (−31 versus −4.0 mg/dl, respectively), LDL-cholesterol (−33 versus −0.9 mg/dl, respectively), and apolipoprotein B (−20 versus −0.3 mg/dl, respectively) ($P<0.0001$ in each case). Other clinical studies have also reported a beneficial effect of sevelamer on lipid profiles in dialysis patients,[11,26,27] including children.[14]

EFFECT OF SEVELAMER ON INFLAMMATION

In the CKD patient, inflammatory processes in the vessel wall may play an even more important role than in general population, with respect to both initiation and progression of atherosclerosis and vascular calcification.[25,28,29] Inflammatory processes also are important for subsequent transformations of the atheromatous plaque such as erosion, fissure, and rupture. Inflammation is considered to be a component of the major modifiable risk factors in renal disease.[30]

It has been shown that several markers of systemic inflammation, particularly acute-phase protein C-reactive protein (CRP), can be used to predict future CV events both in the general population and in hemodialysis patients.[31,32] Serum CRP levels are approximately 5–10 times higher in hemodialysis patients than in healthy subjects.[33] Elevated serum levels of high-sensitivity CRP (hs-CRP)[30] have clearly been shown to predict mortality in ESRD patients. In one study, patients in the highest hs-CRP quartile had more than double the mortality risk of those in the lowest quartile ($P<0.0001$) (Figure 1).[31]

In dialysis patients, elevated CRP levels may be the result of chronic infections or malnutrition, or may be due to dialysis-related factors, such as bioincompatible dialysis membrane or dialyzate, endotoxin exposure, back-filtration, or arterio-venous fistula infections.[34] Wanner and Metzger[33] have suggested that high serum levels of CRP reflect an increase in proinflammatory cytokine generation, such as tumor necrosis factor-α or interleukin-1β (IL-1β). These cytokines, in turn, can stimulate the production of interleukin-6, which increases expression of the CRP gene in the liver. The signal that induces endothelial and other cells to secrete tumor necrosis factor-α and interleukin-1β in the first place is not yet known, but various endogenous factors induce the generation of free oxygen radicals that, in turn,

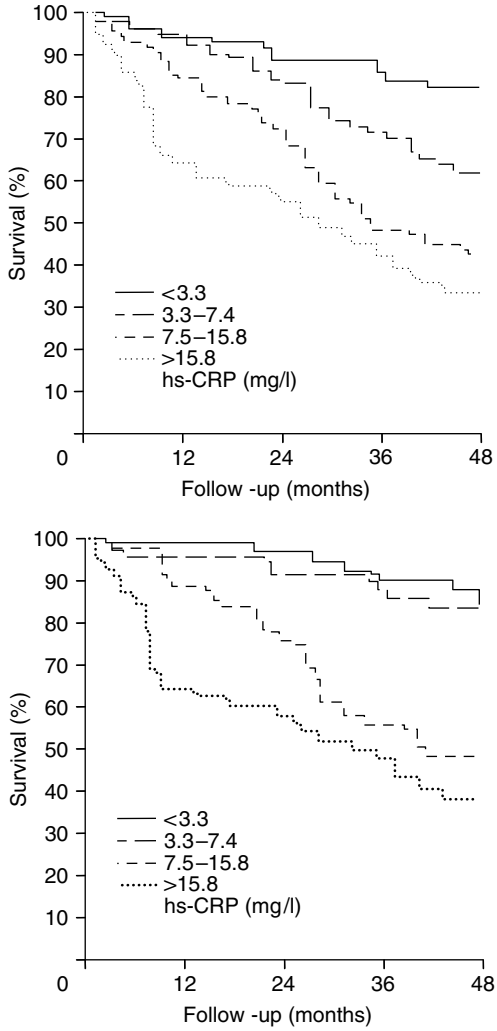

Figure 1 | Kaplan–Meier estimates for all-cause mortality (upper panel) and CV mortality (lower panel) in hemodialysis patients according to baseline hs-CRP quartile. (Reproduced with permission from Wanner *et al*. *Kidney Int* 2003).

activate a signal transduction cascade represented by the nuclear factor NF-κÂ family.[33] Potential endogenous and exogenous stimuli of CRP production are summarized in Figure 2.

Sevelamer has been shown to be associated with a reduction in inflammatory markers, compared with calcium-based binders.[25,27] In a randomized prospective study of 108 chronic hemodialysis patients, treatment with sevelamer, but not calcium acetate, resulted in significant reductions in mean ($\pm$s.d.) serum hs-CRP levels (-4.8 ± 25.8 mg/l from a baseline value of 15.3 ± 19.3 mg/l, $P=0.012$) and serum β_2-microglobulin (-0.09 ± 0.31 mg/dl from a baseline value of 3.08 ± 0.50 mg/dl, $P=0.018$).[25] As reported above, sevelamer treatment also was associated with significant improvements in serum lipid profile. However, there was no correlation between hs-CRP lowering and total and LDL-cholesterol reduction, suggesting that sevelamer may have anti-inflammatory properties mediated via non-

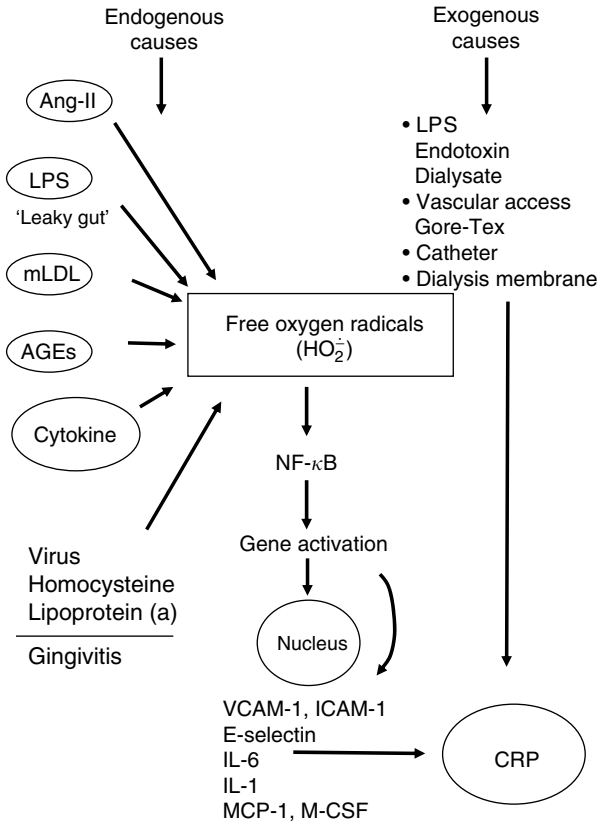

Figure 2 | Possible causes of inflammatory cascade activation in uremia and dialysis. (Reproduced with permission from Wanner and Metzger, *Nephrol Dial Transplant* 2002).

lipid-related mechanisms. The authors admitted, however, that the failure to detect an association might reflect insufficient statistical power. Nevertheless, they speculated that calcium deposition within the vessel wall could stimulate an inflammatory reaction and that inhibition of vascular damage by preventing plaque calcification could attenuate the inflammatory process.[25] This hypothesis has received recent support by the demonstration that basic calcium phosphate crystals can activate macrophages *in vitro* to secrete secretion of proinflammatory cytokines.[35]

Yamada *et al.*[27] also reported an anti-inflammatory effect of sevelamer in chronic hemodialysis patients. In this non-randomized study in 36 patients, sevelamer significantly reduced median hs-CRP from a baseline value of 1.03–0.57 mg/dl at 12 weeks and 0.38 mg/dl at 24 weeks, $P = 0.0259$, in addition to reducing non-HDL-cholesterol. Moreover, there was a significant correlation between the reduction rates of serum hs-CRP, non-HDL-cholesterol ($r = 0.451$, $P < 0.04$), and phosphate ($r = 0.453$, $P < 0.001$). The authors suggested that the anti-inflammatory properties of sevelamer could be related to prevention of ectopic calcification or the suppression of local inflammation in the vascular wall secondary to a lipid-lowering effect. It should be noted, however, that the anti-inflammatory effect of sevelamer has not *been* confirmed by all studies.[12]

When using our uremic apo E−/− mouse model with vascular calcification and atherosclerosis, we found enhanced progression of both intimal and medial vessel calcification and of atherosclerosis.[22] In response to the administration of sevelamer, these mice exhibited a slower progression of both intimal and medial calcification, in association with a significant decrease in serum phosphate and the calcium × phosphate product. At the same time, the mice had a slower progression of atherosclerosis, and this was associated with a significant decrease in the aortic root expression of nitrotyrosine, one of the local markers of oxidative stress.[23] We hypothesized from our observation that sevelamer appeared to have a protective effect on vascular inflammation via a decrease in oxidative stress, as a close relationship has *been* demonstrated between inflammation and oxidative stress in CKD patients.[36] The potential impact of our observations in an experimental animal model on the clinical outcome of hemodialysis patients still needs to be definitively demonstrated.

ROLE OF UREMIC TOXINS AND THEIR PHARMACOLOGICAL CONTROL IN CKD

The uremic syndrome is attributed to the progressive retention of large number of compounds called uremic toxins. Under normal conditions, these substances are eliminated by the kidneys, but in CKD patients they are retained in the body. Uremic toxins may interfere and interact negatively with a whole range of normal biochemical and biological functions, resulting in local and/or systemic toxicity.[37] In order to evaluate their effects they have been recently subdivided according to their physicochemical characteristics into small molecules of low molecular weight (MW), medium-size molecules of middle MW, and protein-bound solutes of low to high MW.[38] This classification provides a more systematic analytical approach than in the past and will map the varying importance of the enlisted families of uremic toxins.[39] Many of these substances are small and water-soluble compounds with low MW, including protein-bound and/or lipophilic solutes such as indoles and phenols. They are characterized by slow removal during the dialysis process and may have multiple toxic effects as a result of their accumulation in chronic renal failure, including inflammation and oxidative stress products, which are also considered uremic toxins. Uremic retention solutes may exert their toxicity especially if they are protein bound.[37,40] It has been shown that urea and creatinine are far more efficiently removed than some other uremic retention compounds, as for example indoxyl sulfate and *p*-cresol. The latter two substances interfere with endothelial proliferation and wound healing, contributing thereby to the deterioration of renal function.[40,41] Furthermore, free serum levels of *p*-cresol have been shown to be useful as a mortality prediction marker in CKD patients. Such observations have stimulated nephrologists to look beyond the effect of the small, water-soluble uremic solutes and middle molecules.[42] The successful reduction of uremic retention compounds of any type and

molecular class may help to decrease the incidence and progression of vascular calcification and related CV morbidity and mortality. It has been shown in experiments *in vitro* that the calcium-free phosphate binder sevelamer is able to adsorb uremic compounds such as indoxyl sulfate, indole, and *p*-cresol.[43] In our *in vivo* model of the uremic apo E−/− mouse, we speculated that the reduction by sevelamer of the progression of arterial calcification and atherosclerosis might be associated with a decrease in circulating uremic toxins. However, for the five retention compounds tested, there was no change in serum concentrations in response to sevelamer treatment, although the serum levels were higher in uremic than in non-uremic mice.[23] This negative finding, however, does not exclude the possible involvement of other uremic toxins.

In clinical studies in CKD patients, it was shown that sevelamer had the potential to reduce the serum levels of some low MW uremic toxins.[44] This is the case for uric acid whose serum levels were found to be significantly decreased in response to sevelamer (see below). Hyperuricemia has long been suspected to play a role in a variety of disorders, including gout, insulin resistance, dyslipidemia, hypertension, and cardiovascular disease.[44] Recent studies have strengthened previous claims that serum uric acid might independently predict CV events in the elderly with isolated systolic hypertension.[45] However, not everybody would agree. Thus, other studies showed that the odds of a favorable outcome increased by 12% per 1.0 mg/dl increase in baseline serum uric acid level, and this beneficial effect has been attributed to the antioxidant properties of uric acid.[46] Nakagawa *et al.*[47] recently proposed that high serum uric acid levels might not be only the result of hypertension and CKD, but might also contribute in some patients to the development and progression of these disease states. According to present state of the art, uric acid generated from dietary sources initiates renal microvascular disease, which in turn drives hypertension and further progression of CKD. Based on the assumption that reducing serum uric acid levels in patients with CKD might be beneficial, clinical studies have been undertaken to investigate the effect of sevelamer in this respect. It has been shown that in CKD patients with secondary hyperparathyroidism, sevelamer significantly decreased serum uric acid levels after 12 weeks of treatment.[48] In another clinical trial comparing sevelamer and calcium-based phosphate binders, a significant decrease in serum uric acid concentrations was observed among subjects randomly assigned to receive sevelamer for a time period of 52 weeks. More than one in five subjects experienced a substantial lowering of serum uric acid concentration. The degree of reduction was proportional to the baseline level. Thus, the more severe the hyperuricemia at baseline, the greater was the reduction in uric acid concentration with sevelamer[44] (Figure 3). The capacity of sevelamer to adsorb some uremic toxins has been evaluated in studies in which the authors tested sevelamer's effect on the adsorption *in vitro* of the uremic retention compounds indoxyl sulfate, indol, and *p*-cresol. It has been shown that adsorption of these three uremic toxins occurs within 3 min and does not increase over time.[43] These studies show that sevelamer might help to remove uremic toxins via non-dialytic process.

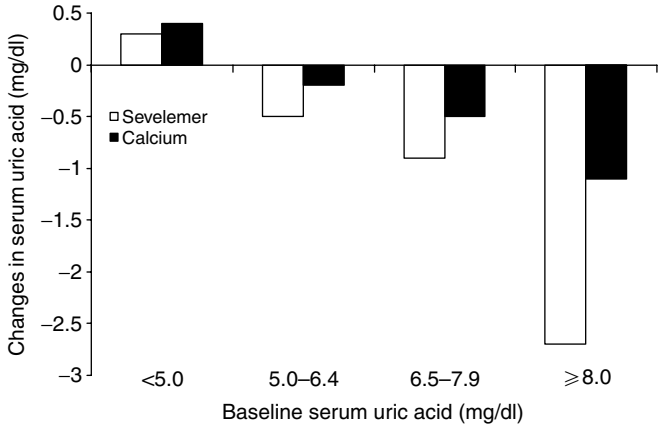

Figure 3 | Mean change in serum uric acid concentrations over 52 weeks by baseline concentration. (Reproduced with permission from Garg *et al. Arth Rheum* 2005).

As discussed above, sevelamer was also shown to reduce the expression of oxidative stress markers in our experimental model, which represent an additional class of uremic toxins. Further studies are needed to assess such pleiotropic effects of sevelamer on uremic toxins in the clinical setting and to explore new pharmaceutical approaches to clear not only one uremic toxin but, if possible, several of them at same time.

EFFECT OF SEVELAMER ON BONE STRUCTURE AND REMODELING

Disturbances of mineral metabolism and bone disease are common complications in CKD patients. They are an important cause of morbidity and decreased quality of life.[49] Increasing evidence suggests that this disorder of mineral and bone metabolism is associated with an increased risk of CV calcification, morbidity, and mortality.[50] Hyperparathyroidism develops in early stages of CKD as a compensatory mechanism in response to abnormal serum levels of calcium, phosphorus, and calcitriol.[51] This leads to a bone disorder traditionally termed 'renal osteodystrophy'. It has been proposed recently to use the term renal osteodystrophy exclusively for the alterations in bone morphology associated with CKD[52] and to use instead the term CKD-mineral and bone disorders to describe the syndrome of biochemical, osseous, and extra-skeletal calcification abnormalities in patients with CKD.[52] In order to determine the effects of different phosphate binders on bone attenuation, Raggi *et al.*[53] performed a *post hoc* analysis of data from a 52-week randomized trial comparing the effects of sevelamer and calcium-based binders in hemodialysis patients. Compared with sevelamer-treated patients, those treated with calcium-containing phosphate binders showed a significant decrease

in thoracic vertebral trabecular bone attenuation ($P = 0.01$) and a trend toward decreased cortical bone attenuation. Thirty-two percent of the patients on calcium-containing phosphate binders experienced a 10% or more decrease in trabecular and cortical bone attenuation, compared to only 10% of patients in the sevelamer group ($P = 0.006$). The latter also had significantly higher serum concentrations of total and bone-specific alkaline phosphatases, osteocalcin, and parathyroid hormone ($P < 0.0001$). The decrease in trabecular bone attenuation in the calcium-treated group was paralleled by an increase in vascular calcification, as demonstrated by electron beam CT scan (Figure 4). In contrast, the mean changes from baseline in the sevelamer-treated group were small, for both bone attenuation and vascular calcification. It is of note that, although serum bicarbonate levels were significantly lower in the sevelamer-treated group, this did not appear to have any negative impact on bone mineral content.

Recently, an open-labeled, bone biopsy study in 68 ESRD patients was conducted in order to compare the effects on bone of phosphate binder therapy with sevelamer hydrochloride versus calcium carbonate. Assessing bone mineralization by changes in mineralization lag time and osteoid thickness and determining bone turnover by changes in activation frequency, numbers of osteoblasts, and osteoclasts bone formation rate/bone surface, the authors reported that there was a trend towards less suppression of bone turnover and improvement in bone microarchitecture in sevelamer but not in calcium carbonate-treated patients.[54]

Abnormalities of bone turnover and structure continue to be among the major complications of CKD patients. Novel treatment modalities including new types of phosphate binder should allow both a better control of bone formation and mineralization and the avoidance of extra-skeletal calcification, by achieving an acceptable calcium × phosphorus product and parathyroid hormone levels within recommended target ranges, and possibly by additional pleiotropic effects.

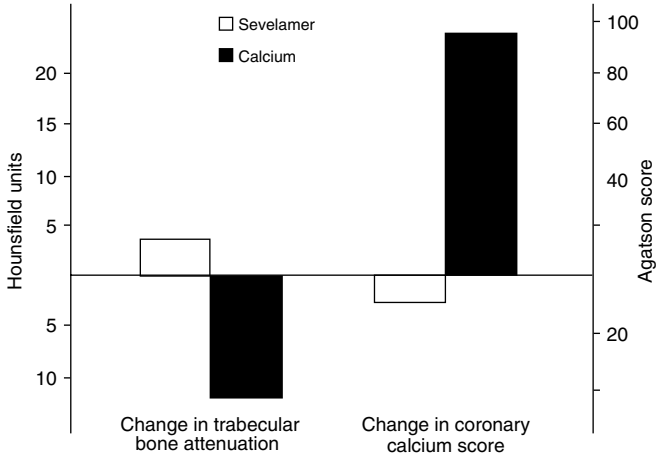

Figure 4 | A side-by-side comparison of change in mean trabecular bone attenuation and change in mean coronary artery calcification (Agatston) score in subjects randomized to calcium and sevelamer. (Reproduced with permission from Raggi *et al. J Bone Miner Res* 2005).

EFFECT OF SEVELAMER ON ESRD PATIENT OUTCOME

Sevelamer's effects on outcome could be considered as the ultimate test of its pleiotropic actions. This possibility has been tested in the Dialysis Clinical Outcomes Revisited (DCOR) trial.[55] In this 3-year trial involving over 2100 chronic hemodialysis patients, the effect of sevelamer on outcome was compared to that of calcium-based phosphate binders. All-cause mortality did not differ between the two groups of patients as a whole. However, when dividing the patients into those below and those above ages 65, a significant outcome benefit was observed in favor of sevelamer in the older, but not the younger patient cohort.

CONCLUSION AND OUTLOOK

CKD patients have high CV morbidity and mortality compared with age- and gender-matched population. Inflammation, oxidative stress, and vascular calcification represent interrelated factors that appear to contribute to this increased CV risk. The phosphate binder sevelamer interferes not only with the dramatic progression of arterial calcification in this clinical setting, but it also reduces the serum levels of atherogenic lipoproteins and of inflammation markers in CKD patients, slows the progression of vascular calcification in uremic patients and experimental animals, and reduces the progression of atherosclerosis in uremic mice. Moreover, it appears to exert beneficial effects on the progressive loss of bone density in CKD patients (Figure 5). Sevelamer's pleiotropic effects beyond that of phosphate binding resemble the beneficial effects of statins on CV outcome, which are mediated not only through lipid lowering but also a variety of non-lipid-mediated pleiotropic effects, including improvement of endothelial function, enhancement of plaque stability, and attenuation of vascular inflammation. Other studies indicate that sevelamer also has the potential to bind several of the numerous uremic toxins that currently

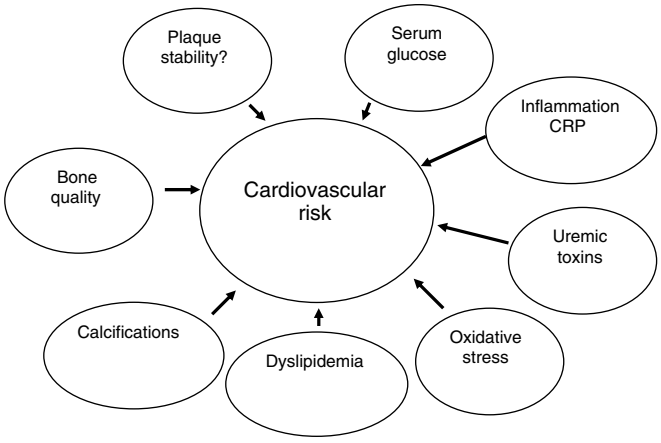

Figure 5 | Potential pleiotropic effects of sevelamer in CKD.

escape filtration by dialysis. Considering sevelamer's beneficial effects on multiple targets and possibly on patient outcome, further investigation into the pleiotropic effects of this novel compound and their clinical impact is clearly warranted.

ACKNOWLEDGMENTS

Igor G Nikolov was funded by a grant from EGIDE Foundation, Paris, France. Nobuhiko Joki was supported from Toho University funds, Japan. Tilman B Drüeke and Ziad A Massy declare having received grant support, lecture fees, and honoraria from Genzyme. Tilman B Drüeke and Ziad A Massy are members of the European Uraemic Toxin (EUTox) group.

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Pediatr Nephrol (2010) 25:373–375
DOI 10.1007/s00467-009-1328-1

BRIEF REPORT

Sevelamer carbonate increases serum bicarbonate in pediatric dialysis patients

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Received: 28 July 2009 / Revised: 3 September 2009 / Accepted: 4 September 2009 / Published online: 30 October 2009

Abstract Sevelamer hydrochloride (HCl), a calcium-free phosphate binder, is increasingly used due to concerns related to calcium exposure and the development of vascular calcifications. However, a common side effect of sevelamer HCl, metabolic acidosis, is particularly concerning in children, as it can contribute to poor growth. Sevelamer carbonate is now available and has been shown to increase serum bicarbonate in adult patients. We conducted a prospective single-center study of pediatric dialysis patients comparing serum bicarbonate before and 3 months after a switch from sevelamer HCl to sevelamer carbonate. Inclusion criteria were a minimum of 3 months of dialysis therapy and either a serum bicarbonate <20 mmol/L or the need for sodium bicarbonate supplementation. Ten hemodialysis and 14 peritoneal dialysis patients, aged 16± 3 years, were enrolled. Whereas serum calcium and phosphorus remained unchanged, serum bicarbonate increased from 20 (17.2–22.0) to 24.5 (20.75–26) mmol/L ($p<0.001$) after 3 months of sevelamer carbonate therapy. Sodium bicarbonate supplementation was stopped in all patients ($n=10$), reducing the mean daily sodium intake by an average of 2.3 g per patient. These results demonstrate that sevelamer carbonate is an effective phosphate binder that improves acid-base status in pediatric dialysis patients.

Keywords Sevelamer HCl · Sevelamer carbonate · Metabolic acidosis · Pediatric dialysis patients

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Introduction

Cardiovascular disease is now recognized as one of the leading causes of morbidity and mortality not only in adults but also in children with chronic kidney disease (CKD) [1, 2]. Indeed, several studies have shown a high prevalence of cardiovascular risk factors, such as vascular calcifications and left-ventricular hypertrophy across the spectrum of CKD in children [2–5]. Although this process is multifactorial, the use of calcium-based phosphate binders has been associated with the development of vascular calcifications in adult and pediatric patients receiving dialysis [3, 6]. Sevelamer hydrochloride (HCl), on the other hand, has been shown to be a safe and effective phosphate binder, providing the same control of skeletal lesions associated with secondary hyperparathyroidism as calcium-based binder therapy [7–9]. Furthermore, sevelamer HCl has been associated with decreased progression of vascular calcifications in adult patients undergoing hemodialysis [6, 10].

However, the use of sevelamer HCl has been associated with a dose-dependent metabolic acidosis in both pediatric and adult dialysis patients [9, 11]. This side effect is concerning in children, as chronic metabolic acidosis is considered a potential risk factor for poor growth. Sevelamer carbonate is a similar anion exchange resin in which chloride is replaced by carbonate. It has been shown to be equally effective in lowering phosphorus, with a reduced incidence of metabolic acidosis in adult patients on dialysis [12]. Therefore, this study was designed to assess the effects of sevelamer carbonate on acid-base status in pediatric dialysis patients.

Material and methods

The patient population was comprised of children receiving outpatient peritoneal or hemodialysis at the Ronald Reagan

University of California-Los Angeles (UCLA) Medical Center. This study was approved by the UCLA Institutional Review Board, and all patients/parents gave informed consent to participate. Patients were enrolled in a prospective 3-month trial with the following inclusion criteria: a minimum of 3 months on automated peritoneal dialysis or hemodialysis, sevelamer HCl as primary phosphate binder, a serum bicarbonate <20 mmol/L, or the need for sodium bicarbonate supplementation. Upon entry into the study, sevelamer HCl was replaced by an identical dose of sevelamer carbonate, and the following biochemical variables were determined every 4 weeks: phosphorus, calcium, intact parathyroid hormone (iPTH), complete blood cell count, serum glucose, sodium, potassium, chloride, bicarbonate, magnesium, creatinine, urea, albumin, and alkaline phosphatase. For patients on sodium bicarbonate supplementation, blood pressure (BP) and interdialytic weight gain (IDWG) were recorded before and every month after starting sevelamer carbonate. Results are reported as systolic and diastolic BP indexes (average BP divided by the 95th percentile for age, sex, and height). Data is presented as medians with a 25−75 percentile range. Comparisons between groups were made using nonparametric tests (Kruskal-Wallis test and Dunn's posttest for comparisons of more than two groups, and Wilcoxon signed rank test for two-group comparisons). A p value of <0.05 was considered significant.

Results

A total of 24 patients aged 16±3 years were enrolled in the study. Mean duration of dialysis therapy for the ten patients receiving hemodialysis and 14 receiving peritoneal dialysis was 9±13 months. At study entry, the dose of sevelamer HCl was 11.9±3.8 g/day. Six peritoneal dialysis and four hemodialysis patients were receiving sodium bicarbonate supplementation (average of 2.3±1 g/day). Twelve patients were treated with active vitamin D sterol therapy. Baseline serum calcium and phosphorus levels were 9.3 (9.2–9.7) mg/dl and 5.7 (4.8–7.2) mg/dl, respectively, and remained stable during the follow-up period (Fig. 1a). Intact PTH was 330 (136–668) pg/ml at the beginning of the study and 510 (258–1051) pg/ml after 3 months (p=0.076). Initial serum bicarbonate levels were 20.0 (17.2–22.0) mmol/L (20.5 mmol/L in peritoneal dialysis vs. 20 mmol/L in hemodialysis patients; p=ns). Levels increased to 24.5 (20.75–26) mmol/L at the end of the study (p<0.001) (25 mmol/L in peritoneal dialysis and 23 mmol/L in hemodialysis patients; p=ns) (Fig. 1b).

All sodium bicarbonate supplementation was discontinued by 2 months in the ten patients previously on alkali therapy. Among these ten patients, BP and antihypertensive therapy remained unchanged. Systolic and diastolic BP indexes at the beginning of the study were 0.93 (0.85–1) and 0.83 (0.78–0.99), respectively. BP indexes remained stable throughout the study and were 0.87 (0.81–1.01) and 0.8 (0.65–0.94), respectively, after 3 months (p=ns). BP indexes were not different between peritoneal dialysis and hemodialysis patients. In addition, there was no difference in mean IDWG at the beginning of the study and after 3 months [1.1 (0.2–1.2) kg and 1.1 (0.8–1.4) kg, respectively; p=ns].

Discussion

The results of this study demonstrate that sevelamer carbonate is an effective phosphate binder in pediatric dialysis patients. Serum calcium and phosphorus remained unchanged after the switch from sevelamer HCl to sevelamer carbonate. The median serum iPTH increased after the switch, but this trend did not reach statistical significance. In addition, the change to sevelamer carbonate normalized serum bicarbonate levels, eliminating the need for alkali therapy previously required with sevelamer HCl.

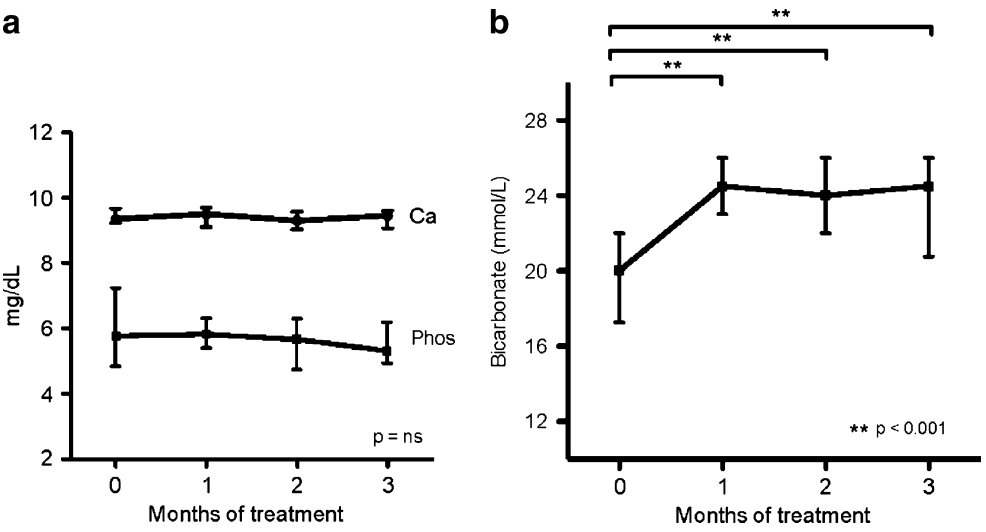

Fig. 1 **a** Serum phosphorus (*Phos*) and calcium (*Ca*) at study entry and after 1, 2, and 3 months of treatment with sevelamer carbonate. There was no significant difference in serum phosphorus and calcium at 1, 2, and 3 months of treatment compared with baseline (p=ns). **b** Serum bicarbonate at study entry and after 1, 2, and 3 months of treatment with sevelamer carbonate. There was a significant increase in serum bicarbonate levels at 1, 2, and 3 months of treatment compared with baseline (p<0.001)

Previous studies in both pediatric and adult patients have demonstrated that metabolic acidosis is a relatively common adverse side effect of sevelamer HCl. In particular, Pieper et al., in a crossover study of 18 pediatric CKD patients (17 dialysis dependent) showed that sevelamer HCl was as effective as calcium acetate in lowering phosphorus levels but was associated with a higher rate of metabolic acidosis (34.4% vs. 3.3%) [9]. Sevelamer carbonate, on the other hand, in a study of 79 adult hemodialysis patients, was equivalent to sevelamer HCl in controlling phosphorus and increased bicarbonate levels by 1.3±4.1 mEq/L over 2 months [12]. Similar findings were described in adult patients with CKD not yet on dialysis [13].

The increase and normalization of serum bicarbonate levels after the switch to sevelamer carbonate is of particular importance in children with CKD in whom growth retardation remains a significant problem [14, 15]. It is well recognized that children with chronic metabolic acidosis and normal renal function have poor growth, and in vitro studies have shown that metabolic acidosis is associated with a decrease in bone mineralization [16]. Thus, current Kidney Disease Outcomes Quality Initiative (K/DOQI) nutritional guidelines for children recommend maintaining a serum bicarbonate level >22 mmol/L [17]. Furthermore, in adult dialysis patients, metabolic acidosis has been associated with an increased risk of death and hospitalizations [5, 11].

The improvement in acid-base status had the additional advantage of allowing the discontinuation of all sodium bicarbonate supplementation. This reduction in salt intake, on average 2.3 g/day, may have a beneficial effect in a population already fluid sensitive and prone to cardiovascular disease [18]. In our study, there was no change in the IDWG, BP medications, or BP during the follow-up period. This study may have been underpowered to detect such differences, and larger trials are needed. However, discontinuation of sodium bicarbonate supplementation led to a decrease in the number of pills per day, which may have a positive impact in a population where noncompliance is an ongoing issue.

In conclusion, although sevelamer HCl and sevelamer carbonate are both effective non-calcium-based phosphate binders in pediatric dialysis patients, sevelamer carbonate has the additional advantage of maintaining serum bicarbonate within the normal range. The preferential use of sevelamer carbonate in pediatric CKD patients, including patients not yet on dialysis, could have a positive impact on growth, along with decreasing salt intake and the burden of medications.

Disclosure Dr I. Salusky receives honorarium from Genzyme.

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