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Original Article

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Accelerated vascular calcification and relative hypoparathyroidism in incident haemodialysis diabetic patients receiving calcium binders

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Abstract

Background. Vascular calcification and low bone turnover with a relatively low parathyroid hormone (PTH) often coexist in diabetic patients undergoing haemodialysis. Since calcium salts (CaS) are used extensively as primary phosphate binders and have been associated with progressive vascular calcification, we studied the effects of CaS on coronary arteries and parathyroid activity in incident haemodialysis diabetic patients.

Methods. We measured the change in coronary artery calcium scores (CACS) with sequential electron beam computed tomography (EBCT) in 64 diabetic and 45 non-diabetic patients, randomized to CaS or sevelamer within 90 days of starting haemodialysis. CACS measurements were repeated after 6, 12 and 18 months. Serum intact PTH (iPTH), calcium and phosphorus were serially tested.

Results. During the study period, serum phosphate was similar in diabetic and non-diabetic patients. Serum calcium levels were similar at baseline (2.3 ± 0.25 mmol/l for both) and increased significantly with CaS treatment ($P < 0.05$) both in diabetic and non-diabetic patients but not with sevelamer. Diabetic patients treated with CaS showed a significantly greater CACS progression than sevelamer-treated patients (median increase 177 *vs* 27; $P = 0.05$). During follow-up, diabetic patients receiving CaS were significantly more likely to develop serum iPTH values <16 pmol/l than diabetic patients treated with sevelamer (33% *vs* 6%, $P = 0.005$) and had a lower mean iPTH level (24 ± 16 *vs* 31 ± 14 pmol/l; $P = 0.038$).

Conclusions. The management of hyperphosphataemia with CaS in haemodialysis diabetic patients is associated with a significantly greater progression of CACS than with sevelamer. These effects are accompanied by iPTH changes suggestive of low bone turnover.

Keywords: calcium salt; coronary artery calcium; diabetes mellitus; phosphate binders; vascular calcification

Introduction

The use of calcium-based phosphate binders has been associated with progressive vascular calcification in dialysis patients [1,2]. Furthermore, an association between vascular calcification and bone disease has been reported both in general population [3] and uraemic individuals [4]. Indeed, patients undergoing haemodialysis experience a high rate of cardiovascular [5] and bone diseases [6]. Uraemic osteodystrophy can be classified as high or low turnover, or as a mixed form of bone pathology [7]. Interestingly, uraemic diabetic patients have been reported to suffer more frequently than other uraemic subjects from low-turnover bone disease [8]. In this form of osteodystrophy, often associated with relatively low serum parathyroid harmone (PTH) levels, the dormant bone tissue is unable to incorporate calcium and to undergo normal remodelling. In patients with low turnover (adynamic bone), calcium absorbed via the dialysate and the gastrointestinal tract may contribute to the calcification of soft and vascular tissues [4] although vascular calcification may also develop with high bone turnover subsequent to secondary hyperparathyroidism. Several reports have shown the negative prognostic impact of cardiovascular calcification [9–11], and observational studies have linked abnormal bone health to mortality in end-stage renal disease (ESRD) [12,13]. Hence, slowing down vascular calcification and avoiding bone demineralization appear to be reasonable targets of therapy. This is a subanalysis of a randomized clinical trial where we assessed the prevalence and progression of coronary artery calcification in incident haemodialysis patients randomized to calcium-based phosphate binders *vs* sevelamer [2]. The focus of the current study is

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to compare the effects the two types of binders had in diabetic and non-diabetic patients on intact PTH (iPTH) and vascular calcification progression.

Methods

Subjects

Detailed methods for this randomized clinical trial have been previously published [2]. Briefly, we randomized 109 adult (>18 years old) patients from September 2000 through December 2002 at five clinical centres in the United States (two in Denver, CO, two in New Orleans, LA and one in San Diego, CA). Patients were all naïve to haemodialysis and were excluded if they had previously undergone dialysis, kidney transplant, coronary artery stenting or coronary artery bypass surgery, and if they weighed >300 pounds [due to the weight limit of the cradle of the electron beam computed tomography (EBCT) machine] or had current atrial fibrillation or atrial flutter. The exclusion of previous coronary interventions and atrial arrhythmias was implemented to maximize the image quality on EBCT scanning by reducing the artifacts due to metal objects or motion. Written informed consent was obtained from all subjects before entering the study and approval was obtained from each institutional Internal Review Board in adherence with the Declaration of Helsinki on principles of medical research involving human subjects.

Study design

Patients were stratified by diabetes status and randomized in a 1:1 fashion to receive either open label sevelamer or calcium-based phosphate binders. EBCT was performed at baseline and repeated at 6, 12 and 18 months, and the pre-determined primary endpoint was change in absolute coronary calcium score at 18 months. The change in coronary calcium score at each time interval is based on the actual number of patients who underwent a repeat scan at that particular point in time. At 18 months, the EBCT scan was repeated in 85 of the original 109 enrolled patients. Figure 1 shows the flow chart for patient attrition between the initial and 18-month scans.

The study design pre-dated the publication of the Kidney Disease Outcomes Quality Initiative clinical practice guidelines for bone disease and mineral metabolism in chronic kidney disease [14], therefore the investigators were not instructed to aim for specific mineral serum levels although a serum calcium <2.5 mmol/l, phosphorus <2.1 mmol/l, $Ca \times P \leq 5.25\ mmol^2/l^2$ and iPTH between 16 and 32 pmol/l were clinical routine at the time of the study and had been implemented on the basis of expert opinion in a prior study [1]. No study-specific management protocols were provided except for the mandate to keep randomized patients on the phosphate binder they had been assigned to and the dialysate calcium at 1.25 mmol/l. Investigators were free to alter the phosphate binder dose and, within

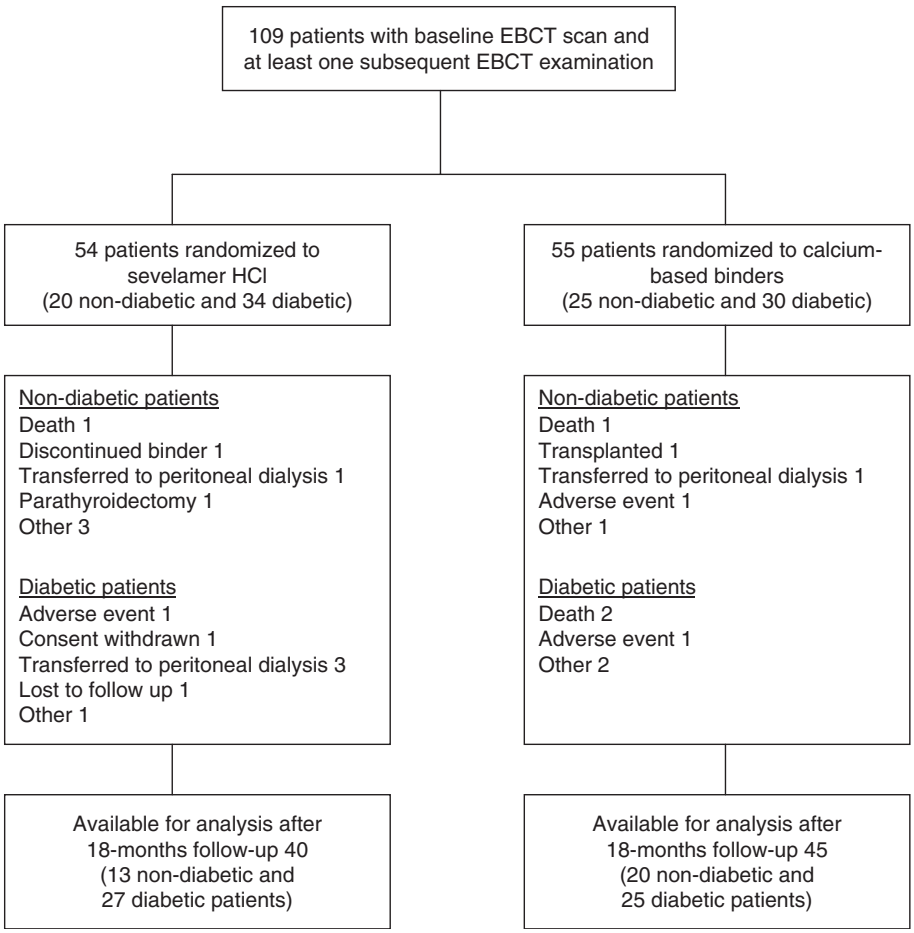

Fig. 1. Flow chart of patients' attrition from the beginning to the end of the study.

the calcium treatment arm, to alternate between calcium-acetate and calcium carbonate at their discretion. Patients randomized to sevelamer were allowed to take calcium as a nightly supplement at the discretion of the investigator but this happened in <5% of cases. Calcimimetic agents were not used in patients enrolled in this trial. Recruiting physicians were blinded to the EBCT results and no clinical decisions were made based on the results of the scans. Baseline medical conditions were assessed by chart review.

Imaging procedures

All EBCT scans were performed using a C-150 scanner (GE-Imatron, San Francisco, CA). A standard imaging protocol was used as previously described [2]. Forty to fifty contiguous slices were obtained starting at the aortic arch and extending to the diaphragm. The slice thickness was kept at 3 mm and the acquisition time at 100 ms per slice. A coronary artery calcium score (CACS) for each area of interest identified along the course of the coronary arteries was calculated as originally described by Agatston *et al.* [15]. The CACS incorporates both the density and volume of a calcified plaque. Hence, a score increase on sequential EBCT imaging may indicate either an enlargement or increased density of the plaque or both. The reverse would be true in case of a score decrease. Total CACSs were estimated as the sum of all individual CACSs. Though other scores are available, we initiated the study when the Agatston score was still the main quantitative tool utilized by the majority of investigators, and it also served well our purpose to follow changes in plaque density due to change in calcium content. The reported interscan variability for the Agatston score is about 8–10% [16].

Statistical analysis

Continuous variables were expressed as mean and SD if normally distributed, or as median and interquartile range in case of non-normal distribution. Baseline clinical characteristics were compared using a Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables. Wilcoxon rank-sum tests were used to compare the differences between treatment arms and between diabetic groups for EBCT and laboratory tests. Wilcoxon signed-rank tests were used to assess changes within groups. Episodes of hypercalcaemia were defined as any serum calcium level >2.6 mmol/l based on expert consensus as previously published [1,2].

Changes in calcium score are provided for the 6 and 12 months follow-up visits although the primary analyses of change in CACS were restricted to the 85 patients who underwent EBCT scans both at baseline and 18 months (Figure 1). The alpha level of significance was set at 0.05 for all the tests. Analyses were performed using SAS 9.1.2 (Cary, NC, USA) and SPSS 13.0 (Chicago, IL, USA) for Windows.

Results

Baseline characteristics (Tables 1 and 2)

Table 1 shows the clinical characteristics of the 109 patients randomized in this trial stratified by diabetic status and treatment assignment. Baseline and follow-up laboratory values are reported in Table 2. The average sevelamer dose was 8 g/day and the average dose of elemental calcium was 2.3 g/day. Among the calcium-treated subjects there was no difference in exposure (duration and dose) to treatment in diabetic and non-diabetic patients.

Diabetic patients had a more frequent history of atherosclerotic cardiovascular disease (including prior myocardial infarction, angina, stroke, lower extremity claudication, and aortic aneurysm) and hypercholesterolaemia and received statins more often than non-diabetic subjects. All other characteristics were similar with the obvious exception of the primary cause of chronic kidney disease. All baseline laboratory values were similar in diabetic and non-diabetic individuals with the exception of iPTH that was significantly lower in diabetic patients (28.6 ± 41 *vs* 37 ± 30 pmol/l, $P = 0.02$). The baseline CACS was significantly higher in diabetic patients (Table 3) compared with non-diabetic subjects (median 271 *vs* 29, $P = 0.019$), although the CACS distribution was balanced among patients randomized to the two treatment arms.

Laboratory values change (Table 2 and Figures 2 and 3)

Calcium- and sevelamer-treated patients achieved similar serum phosphate and calcium–phosphorus products during the treatment period (Table 2 and Figure 2). Although calcium-treated patients attained higher serum calcium levels than sevelamer-treated patients (Table 2), the increase from baseline was significant only in the non-diabetic patients (2.3 ± 0.15 *vs* 2.45 ± 0.125 mmol/l, $P = 0.014$) (Figure 2). Episodes of hypercalcaemia were more frequent in calcium-treated than in sevelamer-treated patients in both diabetic and non-diabetic cohorts (diabetic patients: sevelamer 21% *vs* calcium 63%, $P = 0.001$; non-diabetic patients: sevelamer 25% *vs* calcium 76%, $P = 0.001$).

Serum albumin increased significantly in all patients (Table 2). Sevelamer-treated patients showed a significant decline in total cholesterol and low-density lipoprotein cholesterol compared with calcium-treated subjects (Table 2). Interestingly, the C-reactive protein (CRP) level rose significantly in both treatment groups from baseline (Table 2).

There were no significant temporal-related changes in iPTH level in sevelamer-treated patients, either among the diabetic or the non-diabetic patients. In contrast, iPTH levels decreased significantly in non-diabetic patients treated with calcium, and showed a similar—although non-significant—trend in diabetic patients (Table 2 and Figure 3). During follow-up, the difference in iPTH level between diabetic patients treated with sevelamer and those treated with calcium phosphate binders became significant (30.8 ± 14 *vs* 24.1 ± 16 pg/ml, $P = 0.04$, Figure 3). The glycated

Table 1. Baseline demographic and clinical characteristics of study patients

	No diabetes mellitus			Diabetes mellitus			*P*-value
	Total $n=45$	Sevelamer $n=20$	Calcium $n=25$	Total $n=64$	Sevelamer $n=34$	Calcium $n=30$	
Age (years) mean	54 ± 15	53 ± 16	55 ± 15	60 ± 14	58 ± 14	61 ± 14	0.08
Sex (% male)	30 (67)	13 (65)	17 (68)	39 (61)	19 (56)	20 (67)	0.69
Race[a]							
White (45)	18 (51)	7 (54)	11 (50)	27 (61)	16 (67)	11 (55)	0.49
Black (34)	17 (49)	6 (46)	11 (50)	17 (39)	8 (33)	9 (45)	
Hypertension	41 (91)	18 (90)	23 (92)	64 (100)	34 (100)	30 (100)	0.05
Smoking	6 (13)	3 (15)	3 (12)	3 (5)	1 (3)	2 (7)	0.16
Atherosclerotic vascular disease[b]	9 (20)	7 (35)	2 (8)	25 (39)	15 (44)	10 (33)	0.04
Hypercholesterolaemia	8 (18)	2 (10)	6 (25)	28 (44)	15 (44)	13 (43)	0.01
Statins	7 (16)	3 (15)	4 (16)	25 (40)	16 (48)	9 (31)	0.01
ACE inhibitors	20 (44)	7 (35)	13 (52)	35 (56)	19 (58)	16 (55)	0.24
Beta blockers	21 (47)	7 (35)	14 (56)	26 (42)	14 (42)	12 (41)	0.69
Warfarin	1 (4)	1 (5)	1 (4)	1 (2)	0 (0)	1 (3)	0.57
Vitamin D	25 (56)	9 (45)	16 (64)	2 (52)	20 (61)	12 (41)	0.71
Primary cause of ESRD							
Diabetes mellitus	0 (0)	0 (0)	0 (0)	58 (91)	30 (88)	28 (93)	<0.001
Hypertension	17 (38)	8 (40)	9 (36)	4 (6)	2 (6)	2 (7)	<0.001
Glomerulonephritis	8 (18)	5 (25)	3 (12)	0 (0)	0 (0)	0 (0)	<0.001
Polycystic kidney disease	2 (4)	0 (0)	2 (8)	1 (2)	1 (3)	0 (0)	0.57
Interstitial nephritis	3 (7)	1 (5)	2 (8)	0 (0)	0 (0)	0 (0)	0.07
Unknown	15 (33)	6 (30)	9 (36)	1 (2)	1 (3)	0 (0)	<0.001

Continuous variables are expressed as mean ± SD and categorical variables as absolute value and relative frequency in parentheses. The *P*-value tests the differences between diabetic and non-diabetic group.
[a]Race distribution was tested on a total of 79 patients, white or black. The remaining belonged to several races and were too few to assess for significance. Percentage was calculated over 79 patients in total (1 missing).
[b]Atherosclerotic vascular disease was defined as one or more of the following: prior history of myocardial infarction, angina pectoris, stroke, transient ischaemic attack, claudication, lower extremity interventions for atherosclerotic vascular disease and aortic aneurysm.

haemoglobin levels were similar at baseline and after 18 months of randomization in diabetic patients treated with either sevelamer or calcium-based binders (mean ~7% for both baseline and follow-up, $P=0.25$).

Coronary artery calcium score change (Table 3 and Figure 4)

The laboratory changes described above were accompanied by parallel CACS changes. The baseline CACS was higher in the diabetic patients overall, although there was no significant difference among the patients randomized to the two treatment arms. The absolute CACS progression at 6 and 12 months showed a clear but non-significant trend for a greater increase in the calcium-treated than in the sevelamer-treated patients (Table 3 and Figure 4). The difference became significant ($P=0.05$) in diabetic patients treated with calcium binders compared with those treated with sevelamer at the end of 18 months of follow-up (Table 3 and Figure 4). Although there was a difference in progression between non-diabetic patients treated with the two binders, the difference did not reach statistical significance ($P=0.09$).

Discussion

In this study, we showed that incident haemodialysis diabetic patients treated with calcium-based phosphate binders had a greater CACS progression than those treated with sevelamer. Additionally, diabetic patients showed a lower baseline serum iPTH level than non-diabetic patients, and the treatment with calcium aggravated this condition compared with the treatment with sevelamer. Taken together, these data suggest, although they do not prove, that our diabetic patients initiating haemodialysis were more likely to suffer from low-turnover bone disease (a state of relative hypoparathyroidism) than non-diabetic subjects and that this form of osteodystrophy may worsen with the use of calcium-based phosphate binders.

It has been recently reported that low bone mineral density and low-turnover bone disease are associated with vascular calcification in ESRD [4]. The typical features of low-turnover bone disease are those of a very indolent remodelling of bone that appears unable to incorporate calcium often in the presence of low iPTH levels [7,8], though iPTH levels may also be within normal limits in the presence of adynamic bone disease.

Vascular calcification occurs in two separate locations in the arterial wall of patients affected by ESRD. The tunica media of the arterial wall is a common target of vascular calcification both in ESRD and diabetes mellitus. This type of calcification is distinct from the calcification of the sub-intimal space that typically follows the development of atherosclerosis. Medial calcification is secondary to

Table 2. Baseline and follow-up laboratory values

Variable	Mean baseline values							Mean follow-up values						
	No diabetes			Diabetes			*P*-value[a]	No diabetes			Diabetes			*P*-value[a]
	All $n=45$	Sevelamer $n=20$	Calcium $n=25$	All $n=64$	Sevelamer $n=34$	Calcium $n=30$		All $n=45$	Sevelamer $n=20$	Calcium $n=25$	All $n=64$	Sevelamer $n=34$	Calcium $n=30$	
Albumin (mmol/l)	36 (6)	35 (6)	37 (6)	36 (5)	35 (5)	36 (4)	0.41	39[b] (4)	39[b] (3)	39[b] (5)	38[b] (2)	38[b] (3)	38[b] (2)	0.01
Calcium (mmol/l)	2.3 (0.2)	2.3 (0.15)	2.3 (0.2)	2.3 (0.2)	2.3 (0.68)	2.3 (0.15)	0.94	2.4 (0.15)	2.3 (0.15)	2.45[b,c] (0.12)	2.3 (0.12)	2.27 (0.10)	2.35[c] (0.15)	0.02
Phosphorus (mmol/l)	1.7 (0.55)	1.8 (0.68)	1.7 (0.45)	1.6 (0.42)	1.6 (0.42)	1.7 (0.45)	0.29	1.6 (0.35)	1.6 (0.35)	1.7 (0.03)	1.7 (0.22)	1.7 (0.22)	1.6 (0.25)	0.50
Ca × Pi ($mmol^2/l^2$)	3.9 (0.11)	4.1 (0.10)	3.9 (0.09)	3.7 (0.84)	3.7 (0.28)	3.9 (0.06)	0.34	3.8 (0.05)	3.7 (0.05)	4.2 (0.04)	3.9 (0.03)	3.9 (0.22)	3.8 (0.04)	0.78
iPTH (pmol/l)	37.2 (29.8)	34.6 (31.8)	39.2 (28.8)	28.7 (41.3)	28.6 (35.3)	28.7 (47.9)	0.02	29.6 (15.5)	32.3 (18.7)	27.4[b] (12.2)	27.7 (15.4)	30.8 (14.3)	24.1[c] (15.9)	0.48
Total cholesterol (mmol/l)	4.5 (1.2)	4.6 (1.3)	4.4 (1.1)	4.5 (1.3)	4.5 (1.5)	4.5 (1.2)	0.71	4.2 (1.2)	3.5[b] (1.9)	4.7[c] (1.1)	4.3 (1.0)	4.1 (1.2)	4.6[c] (0.8)	0.82
LDL (mmol/l)	1.9 (0.8)	1.9 (0.9)	2.0 (0.7)	1.8 (1.0)	1.86 (1.1)	1.8 (0.9)	0.71	1.8 (0.9)	1.4 (1.1)	2.2[b,c] (0.7)	1.8 (0.8)	1.6 (1.0)	2.0[b,c] (0.7)	0.66
Triglycerides (mmol/l)	2.0 (1.0)	2.0 (0.97)	1.9 (1.1)	2.2 (1.3)	2.1 (1.3)	2.3 (1.3)	0.65	1.8 (1.1)	1.5[b] (1.0)	2.1 (1.2)	2.2 (1.2)	2.2 (1.3)	2.2 (1.2)	0.16
HDL (mmol/l)	1.1 (0.4)	1.2 (0.4)	1.1 (0.3)	1.1 (0.4)	1.1 (0.4)	1.0 (.03)	0.34	1.0 (0.5)	1.0 (0.6)	1.1 (0.4)	1.0 (0.4)	1.0 (0.5)	1.0 (0.3)	0.68
CRP (mg/l)	6.4 (6.5)	5.1 (4.1)	7.5 (7.8)	7.7 (7.6)	7.7 (7.2)	7.1 (8.2)	0.66	9.1 (9.3)	7.2 (8.4)	10.5 (9.9)	10.1[b] (10.5)	10.1 (10.4)	10.4 (10.8)	0.45
Haemoglobin (g/dl)	11.8 (1.8)	11.6 (1.5)	12.1 (2.1)	12 (2.1)	11.8 (2.1)	12.2 (2.1)	0.48	12.2 (1.1)	12.2 (0.8)	12.3 (1.1)	12.4 (0.8)	12.3 (0.8)	12.4 (0.7)	0.88

Variables expressed as mean and SD in parentheses.
[a]Mann–Whitney U-test for difference between diabetic and non-diabetic patients.
[b]$P < 0.05$ between baseline and follow up within groups (Wilcoxon sign-rank test).
[c]$P < 0.05$ for difference between sevelamer and calcium salts (Mann–Whitney U-test).

Table 3. Baseline and change in CACS after 6, 12 and 18 months of follow-up in patients stratified by diabetes mellitus

	No Diabetes			Diabetes			*P*-value[a]
	Total	Sevelamer	Calcium salts	Total	Sevelamer	Calcium salts	
Baseline CACS							
n	45	20	25	64	34	30	
Mean ± SD	490 ± 1446	589 ± 1981	412 ± 842	776 ± 1316	682 ± 1160	880 ± 1487	
Median	29	2.4	42.9	271	285	233	0.02
P-value		0.80[b]			0.46[b]		
6-month change							
n	44	19	25	60	32	28	
Mean ± SD	14 ± 294	−26 ± 360	48 ± 236	45 ± 431	43 ± 235	47 ± 586	
Median	0	0	0	1	0	21.3	0.94
P-value	0.01[c]	0.51[b]		0.03[c]			
12-month change							
n	37	15	22	55	30	25	
Mean ± SD	112 ± 185	66 ± 122	145 ± 215	140 ± 384	98 ± 389	191 ± 379	
Median	10	0	24	19	2.1	43	0.97
P-value	<0.001[c]	0.24[b]		0.001[c]	0.11[b]		
18-month change							
n	33	13	20	52	27	25	
Mean ± SD	170 ± 271	110 ± 251	210 ± 283	290 ± 726	151 ± 475	440 ± 911	
Median	19	0	36	97	27	177	0.28
P-value	<0.001[c]	0.09[b]		<0.001[c]	0.05[b]		

[a]Diabetic *vs* non-diabetic patients.
[b]Sevelamer *vs* calcium salts.
[c]Baseline *vs* follow-up.

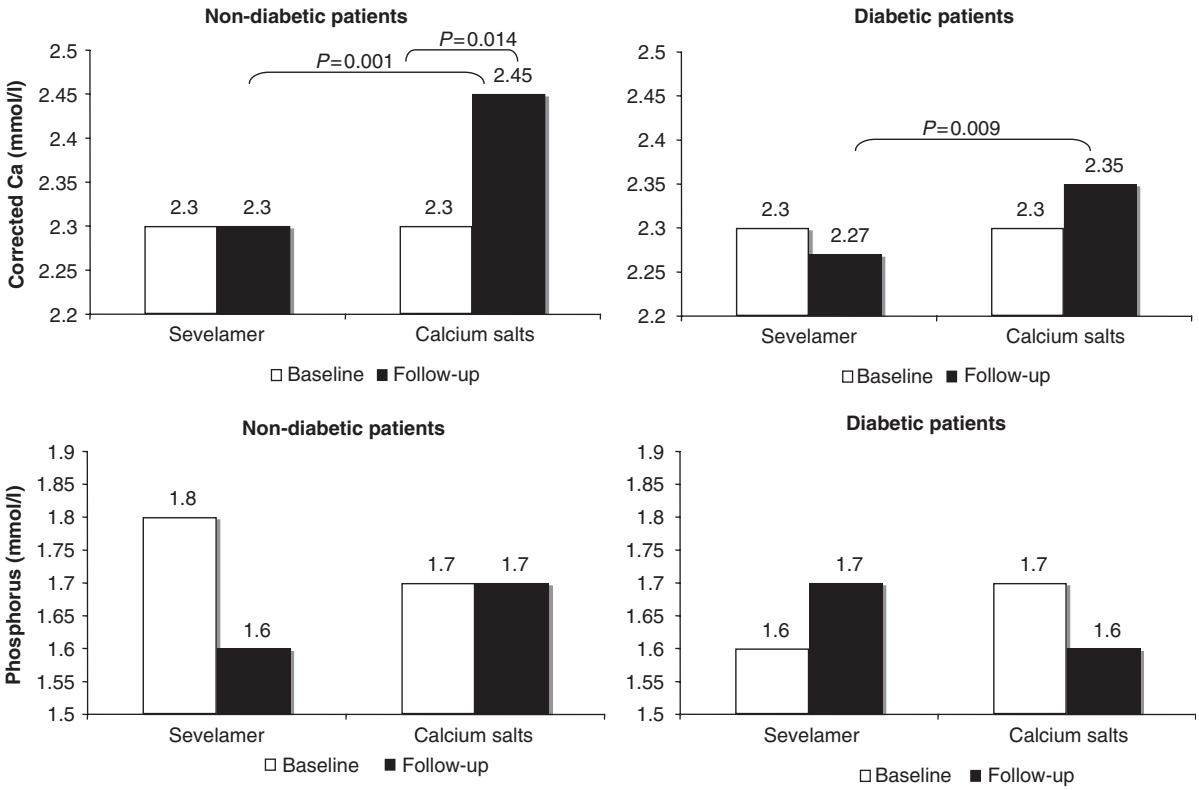

Fig. 2. Change in corrected serum calcium and phosphorus levels in diabetic and non-diabetic patients treated with either sevelamer or calcium salts.

an endochondral ossification of the matrix that shares many aspects with osteogenesis [17]. In fact, vascular smooth muscle cells (VSMCs), osteoblasts and chondrocytes derive from common mesenchymal cells [17,18]. Furthermore, similar matrix proteins are present in the arterial media layer and the skeletal tissue such as collagen type I, osteocalcin, osteopontin and matrix γ-carboxyglutamic acid (GLA) protein [19–22].

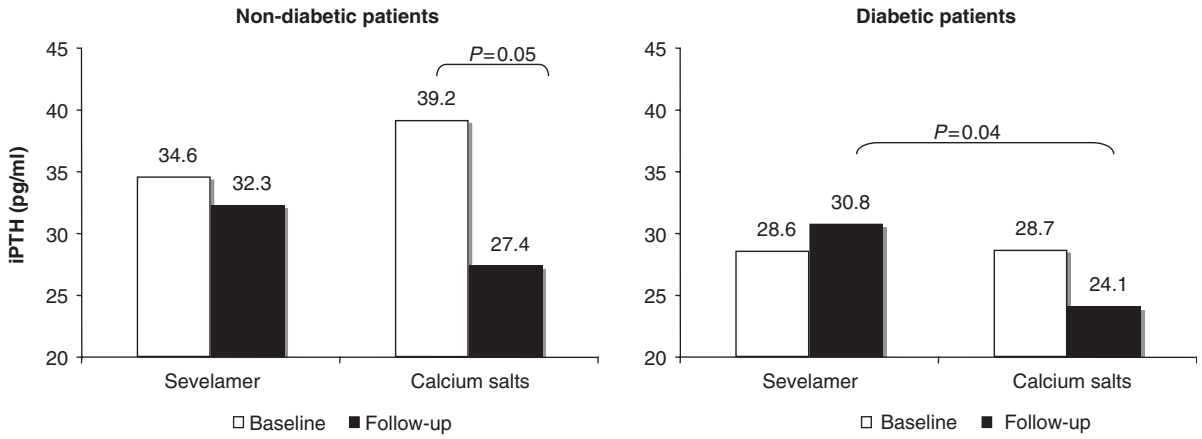

Fig. 3. Change in iPTH levels in diabetic and non-diabetic patients treated with either sevelamer or calcium salts.

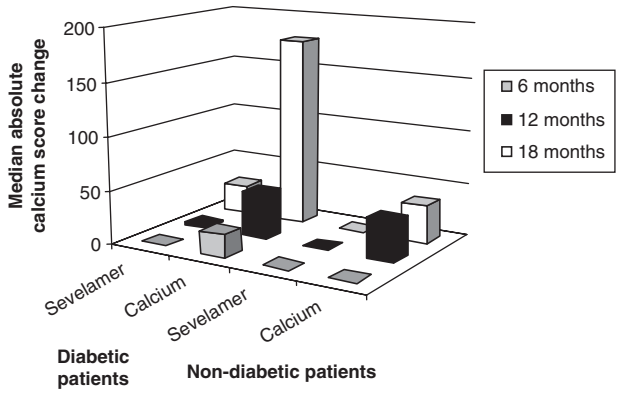

Fig. 4. Change in absolute CACS in diabetic and non-diabetic patients randomized to sevelamer and calcium-based binders at 6, 12 and 18 months.

Given a similar cellular and matrix composition, bones and arteries may be programmed to respond to various metabolic and noxious stimuli following similar pathways. Among the many candidates capable of inducing a pro-calcifying response of VSMCs are hyperphosphataemia [23–25], episodic hypercalcaemia [26], inflammation [27–29], hyperglycaemia and advanced products of end-glycation [30–32], insulin [33,34], oestrogens [3], vitamin K [35,36], low osteoprotegerin [28] and dyslipidaemia [37]. It is therefore conceivable that alterations in mineral metabolism and accrual of substantial inflammation during the course of haemodialysis, aggravated by hyperglycaemia, insulin resistance and local hypoxia may induce osteogenic differentiation of VSMCs promoting active ossification of the arterial wall. Interestingly, hyperglycaemia has been shown to inhibit PTH secretion *in vitro* [38] and—as shown in this study—PTH levels are often lower in diabetic compared with non-diabetic patients undergoing maintenance haemodialysis.

The natural trend toward developing low-turnover bone features is probably worsened in diabetic patients undergoing dialysis by treatment with calcium-based phosphate binders. In prospective, randomized trials of prevalent haemodialysis patients, calcium binders have been shown to be associated with significant progression of vascular calcification [1,2] as well as a decrease in bone mineral density [39]. The protracted administration of calcium likely suppresses the pulsatile release of PTH [40], slowing down bone remodelling and worsening the trend towards development of low bone turnover.

There were a few limitations to this investigation. This is a subanalysis of a primary study [2] that was not designed to assess the difference in CACS progression between diabetic and non-diabetic patients. The number of patients was relatively small and this limited our ability to perform multivariate analyses to assess the association of pertinent endpoints with several independent variables. Although the results reported in this analysis find support in evolving basic science concepts, the assumptions made in our discussion remain to be further elucidated.

In conclusion, control of serum phosphate with calcium-based binders, as compared with sevelamer, in incident haemodialysis diabetic patients is associated with decreasing iPTH levels and accelerated progression of vascular calcification. Further studies will be necessary to confirm our findings and verify whether non-calcium-based binders confer a survival advantage over calcium salts.

Conflict of interest statement. P.R. and G.A.B. received research grants from Genzyme Therapeutics, Cambridge, MA, and they are part of the speakers' bureau of Genzyme Therapeutics, Cambridge, MA.

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