ORIGINAL ARTICLE

Sevelamer carbonate reduces the risk of hypomagnesemia in hemodialysis-requiring end-stage renal disease patients

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Abstract

Background: Sevelamer has been associated with less progression of vascular calcifications. This effect could be due to a reduction in serum phosphate levels but also to other additive effects. Magnesium has been also shown to prevent vascular calcification but the effect of sevelamer on serum magnesium levels has not been thoroughly evaluated. Our aim was to analyze whether the use of sevelamer reduces the risk of hypomagnesemia in hemodialysis (HD)-requiring end-stage renal disease patients.

Methods: All prevalent patients from the dialysis unit of the Hospital Italiano de Buenos Aires as of 1 June 2015 were evaluated. They were on three times per week bicarbonate/citrate-buffered HD. They were not receiving phosphate binders or magnesium-containing drugs. The average of three successive monthly magnesium serum levels was considered as the baseline magnesium concentration. Sevelamer carbonate use was retrieved from the patient's clinical records.

Results: One hundred and fifty-one patients were included. A large proportion of individuals were on proton pump inhibitors (PPIs) (66%) and more than 50% were using sevelamer carbonate. Serum magnesium levels were significantly higher in those receiving sevelamer compared with those who did not (2.05 ± 0.3 versus 1.8 ± 0.4 mg/dL; $P < 0.05$). A larger proportion of individuals receiving sevelamer were among those with normal serum magnesium ($P = 0.02$), while among those with hypomagnesemia, a larger proportion were on PPIs. In the multivariate model including the use of PPIs, sevelamer carbonate resulted in an independent protective factor for hypomagnesemia (odds ratio: 0.44; 95% confidence interval: 0.21–0.87).

Conclusions: Hemodialysis patients receiving sevelamer show higher serum magnesium levels and a reduced risk of hypomagnesemia. This effect remains even after adjustment for PPI use. This effect could contribute to the still controversial superiority of sevelamer in preventing vascular calcifications.

Key words: hemodialysis, hypomagnesemia, proton pump inhibitors, sevelamer

Introduction

Magnesium is the second most abundant intracellular cation and is essential for the regulation of several enzymes and cellular functions [1].

In the general population, hypomagnesemia has largely been associated with increased risk of diabetes mellitus [2, 3], hypertension [4–6] and cardiac arrhythmias [7], as well as with greater cardiovascular mobility and mortality [8–12].

Recent observational studies showed that hypomagnesemia could be a factor linked to the development of chronic kidney disease (CKD) [13–16], and might be associated with larger overall and primarily cardiovascular mortality in dialysis-requiring end-stage kidney disease individuals [17–20].

In patients with preserved renal function, magnesium balance is regulated through tubular reabsorption and urinary excretion [21, 22].

In contrast, in patients undergoing dialysis, magnesium levels depend on the magnitude of magnesium intake, nutritional status (serum albumin levels), dose of dialysis and the concentration of magnesium in the dialysate [1].

Two recent publications described the association between hypomagnesemia and the use of proton pump inhibitors (PPIs) in patients receiving renal replacement therapy with hemodialysis (HD) [23, 24].

Conversely, a previous report showed that the use of sevelamer hydrochloride improved magnesium absorption in patients undergoing dialysis. Unfortunately, data were not adjusted for the use of PPIs [25].

Reports regarding the effect of sevelamer carbonate and particularly its relationship with the presence of hypomagnesemia in an adequately adjusted statistical model are lacking.

The main aim of this study was to assess whether the use of sevelamer reduces the risk of hypomagnesemia in dialysis-requiring end-stage renal disease individuals.

Materials and methods

We performed a cross-sectional and observational study in prevalent HD individuals in the HD unit from the Hospital Italiano de Buenos Aires, Argentina.

All patients receiving HD as of 1 June 2015 were considered and potentially admitted to the study.

All the participants were receiving conventional HD treatment three times per week with high flux dialyzers and with a standard dialysate containing—in mEq/L—Na: 138.0; K: 2.0; Ca: 3.0; Mg: 1.0; Cl: 109.0; citrate: 3.0; bicarbonate: 32.0; and dextrose 1 g/L. Those individuals suffering from acute kidney injury or receiving HD treatment for a period shorter than 3 months, those who remained as in-patients at the time of the study or with a recent history of chronic diarrhea, or having ileostomy or colostomy were prevented from entering the study.

None of them was receiving phosphate binders or magnesium-containing medications.

The baseline magnesium concentration was assumed as the average of three consecutive monthly values obtained as part of the routine assessment scheduled by the team taking care of the patient. Magnesium intake was estimated through a previously validated food frequency questionnaire [26].

Data regarding the use of sevelamer carbonate or any other phosphate binder were retrieved from the individual clinical records.

The association between the use of sevelamer and serum magnesium concentration was evaluated. Hypomagnesemia, defined as serum magnesium <1.9 mg/dL, was assumed as a dependent variable on sevelamer use (unadjusted model) as well as on the following variables included in an adjusted statistical model: age, gender, presence of diabetes, serum albumin concentration, dialysis dose, and use of PPIs or diuretics.

Statistical analysis

Data are expressed as mean (standard deviation), median (interquartile range) or proportions, as appropriate. The Kolmogorov–Smirnov test was used to verify the normality of the study variables. Unpaired 't' test was used for those normally distributed variables whereas the Fisher exact test was used for comparison of count variables. Univariate logistic regression analysis (unadjusted model) was carried out to determine whether the presence of hypomagnesemia was a dependent variable on the following potential covariates: sevelamer use, age, gender, presence of diabetes, serum albumin concentration, dialysis dose, and use of PPIs or diuretics. A multivariate logistic regression analysis was then performed using as independent variables those that were statistically significant in the univariate model as well as those with a plausible potential biological association (adjusted model). Odds ratios (OR) with the appropriate two-sided 95% confidence intervals (CI) were reported. All tests were two sided, and P < 0.05 was considered statistically significant. The analysis was conducted with R 3.2.2, 2015 (R Development Core Team, Auckland).

Results

One hundred and fifty-one patients were included in the study. The main baseline characteristics of the studied population are displayed in Tables 1 and 2.

A large proportion of individuals (66%) were on PPIs, and all participants were receiving phosphate binders. More than 50% of them were using sevelamer carbonate, while the remaining were on calcium acetate (32%) or calcium carbonate (13%). None of them received aluminum or iron-containing phosphate binders.

Serum magnesium concentrations were significantly higher in those individuals receiving sevelamer compared with those who did not (2.05 ± 0.3 versus 1.8 ± 0.4 mg/dL, respectively; P = 0.0064) (Figure 1).

Patients receiving sevelamer showed lower serum levels of total cholesterol (143 ± 40 versus 160 ± 33 mg/dL; P = 0.005); calcium (8.5 ± 0.7 versus 8.8 ± 0.8 mg/dL; P = 0.0142), higher intact parathyroid hormone (iPTH) values (463 ± 45 versus 398 ± 47 pg/mL; P = 0.001), but similar serum phosphate concentrations (5.1 ± 1.5 versus 4.7 ± 1.2 mg/dL; P: not significant).

A larger proportion of individuals receiving sevelamer was observed among those with normal serum magnesium (P = 0.02) while among hypomagnesemic patients, a larger proportion was on PPIs (Table 3).

In the multivariate model including the use of PPIs, sevelamer carbonate resulted in an independent protective factor for hypomagnesemia (OR: 0.44; 95% CI: 0.21–0.87) (Table 4).

Discussion

Our study shows that patients using sevelamer carbonate as phosphate binder in dialysis have a lower risk of hypomagnesemia, even after correcting for the use of PPIs.

Sevelamer carbonate, a calcium-free intestinally non-absorbed polymer, is approved for hyperphosphatemic dialysis patients in the USA and hyperphosphatemic stage 3–5 CKD patients in many other countries. Sevelamer has been shown to reduce absorption of advanced glycation end products, bacterial

Table 1. Characteristics of the population studied

Characteristic[a]	Total cohort (N = 151)	Sevelamer (N = 82)	No sevelamer (N = 69)	P-value
Gender				
Male	82 (56)	50 (54)	32 (62)	0.07
Female	69 (44)	32 (46)	37 (38)	
Age (years)	53 ± 23	54 ± 19	52 ± 28	0.53
Age >65 years	59 (39)	32 (39)	27 (39)	0.98
Time in dialysis (months)	66 ± 84	68 ± 59	63 ± 107	0.71
Time in dialysis >60 months	61 (40)	35 (43)	26 (38)	0.53
Diabetes	26 (17)	15 (18)	11 (16)	0.70
Hypertension	53 (35)	30 (37)	22 (32)	0.73
Coronary artery disease	18 (12)	11 (13)	8 (11)	0.90
Hemoglobin (g/dL)	11 ± 1.4	11 ± 1.6	11 ± 1.3	0.36
Albumin (g/dL)	3.9 ± 0.7	4 ± 0.6	3.9 ± 0.6	0.74
Albumin <4 g/dL	76 (50)	43 (52)	33 (48)	0.57
URR	74 ± 8	74 ± 9	75 ± 7	0.4
URR <65	14 (9)	8 (10)	6 (9)	0.73
Low magnesium intake	34 (22)	19 (23)	15 (28)	0.84
PPI use	99 (66)	53 (64)	46 (67)	0.79
Diuretics use	6 (4)	4 (5)	2 (3)	0.83
Number of antihypertensive drugs[b]	1 (0–4)	1 (0–4)	1 (0–4)	0.93

BMI, body mass index; URR, urea reduction ratio.
[a]All data are expressed as *n* (%) or mean ± standard deviation unless otherwise indicated.
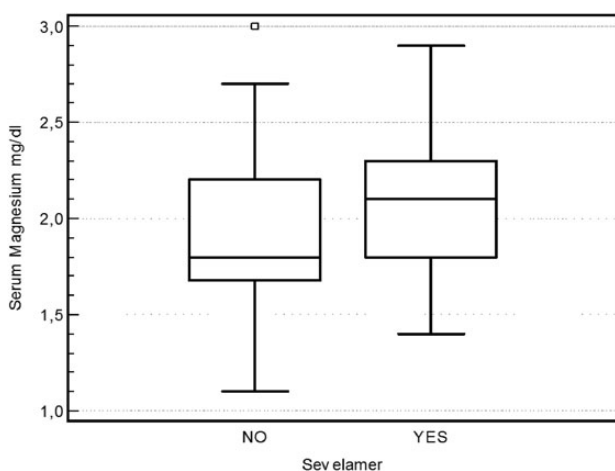[b]Median (range).

Table 2. Causes of CKD[a]

	Total cohort (N = 151)	Sevelamer (N = 82)	No sevelamer (N = 69)	P-value
Nephroangiosclerosis hypertensive	26	25	23	0.92
Diabetes nephropathy	14	15	13	0.90
Glomerulonephritis	21	19	22	0.80
PKD	9	11	10	0.94
Myeloma kidney	2	1	2	0.86
Others	15	17	16	0.96
Unknown	13	12	14	0.90

PKD, polycystic kidney disease.
[a]All data are expressed as percent.

Fig. 1. Mean serum magnesium (mg/L) in patients with and without sevelamer (P < 0.05).

Table 3. Analysis of different variables and their relationship with the presence or absence of hypomagnesemia

Variable[a]	Mg <1.9 mEq/L	Mg ≥1.9 mEq/L	P-value
Use of sevelamer	18	63	0.02
Age >65 years	43	36	0.38
Male gender	53	55	0.94
Diabetes	54	46	0.43
Time in dialysis >60 months	41	39	0.81
URR <65	8	10	0.78
Albumin <4 g/dL	53	47	0.46
Low Mg intake	29	17	0.09
PPI use	73	59	0.07
Diuretic use	6	2.5	0.52

Mg, magnesium; URR, urea reduction ratio.
[a]All data are expressed as percent.

toxins and bile acids, suggesting that it may reduce inflammatory, oxidative and atherogenic stimuli in addition to its on-label action of lowering serum phosphate [27]. Several studies have suggested that non-calcium-containing phosphate binders, such as sevelamer, are associated with less progression of vascular calcifications compared with calcium-based phosphate binders [28, 29]. A recent meta-analysis has also demonstrated that non-calcium-containing phosphate binders, including

Table 4. Adjusted multivariate model for the risk of developing hypomagnesemia

Variable	OR	95% CI	P-value
Sevelamer use	0.44	0.23–0.90	0.023
Age >65 years	1.26	0.59–2.69	0.55
Male gender	1.16	0.55–2.45	0.41
Diabetes (presence)	1.07	0.43–3.16	0.31
Time in dialysis >60 months	1.09	0.54–2.19	0.25
URR <65	0.67	0.18–2.45	0.55
Albumin <4 g/dL	1.17	0.55–2.48	0.68
Low Mg intake	2.1	0.93–4.75	0.07
PPI use	1.84	0.90–3.87	0.09
Diuretic use	4.39	0.33–58.50	0.26

Mg, magnesium; URR, urea reduction ratio.

sevelamer, reduce mortality in patients on HD more than calcium-based binders [30]. Furthermore, there is increasing evidence showing an association between magnesium and cardiovascular risk in patients without renal disease. In addition, low magnesium serum levels are associated with vascular calcification and increased cardiovascular mortality in patients with end-stage renal disease [19, 31].

Ishimura *et al.* [17] found significantly lower serum magnesium concentrations in HD patients with vascular calcifications than in those without calcification. In a multivariate logistic regression analysis, a lower magnesium concentration was a significant independent factor associated with the presence of vascular calcification after adjustment for other confounding factors, such as calcium and phosphate. Their analysis revealed that a 1 mg/dL decrease in serum magnesium increased the risk for vascular calcification by 71.6% [17]. Additionally, in a longitudinal study, Meema *et al.* [32] speculated that hypermagnesemia may retard the progression of vascular calcification in end-stage renal disease patients. They evaluated 44 continuous ambulatory peritoneal dialysis patients for the progression of vascular calcification measured by fine detail radiographs of the hands and feet. Patients were divided into those who demonstrated progression versus those who did not, and laboratory parameters were compared. There was no difference in calcium, phosphorus, PTH or alkaline phosphatase between the two groups. However, the serum magnesium was significantly higher (3.02 ± 0.51 versus 2.69 ± 0.52 mg/dL) in the group that did not show progression over an average period of 27 months. The authors concluded that hypermagnesemia might be associated with retardation or improvement of arterial calcifications in peritoneal dialysis patients [32]. Finally, Mitsopoulos *et al.* [25] investigated the effect of sevelamer on serum magnesium in HD patients to assess the association of magnesium levels with iPTH and lipid profiles. They found that HD patients receiving sevelamer have a significant increase in serum magnesium. This increase in serum magnesium is associated with a reduction in the iPTH level ($r = -0.40$, P = 0.016) [25]. It can be speculated that the rise in serum magnesium levels might also contribute to the much debated superiority of sevelamer in suppressing vascular calcifications compared with other phosphate binders.

An important difference with our study was that in the Mitsopoulos study magnesium levels were not adjusted for the use of PPIs, an adjustment that we performed in our study. This is very important as recent publications have shown an association of hypomagnesemia with the use of PPIs in HD patients [23, 24]. With respect to the mechanism by which sevelamer could exert this effect on serum magnesium, it is presumed that it could be

due to its capacity to bind biliary salts, increasing the quantity of free magnesium available for absorption [1, 25].

The present study has the strength of having considered a number of variables potentially associated with the balance of magnesium—including a dietary survey—that have not been previously included in reports that studied the association between the use of medications and the occurrence of hypomagnesemia in dialysis patients [23, 24]. On the other hand, it has the limitation of any observational study, in addition to the fact that the alimentary survey was qualitative in nature instead of quantitative.

Given these results, we assume that the use of sevelamer should be included in future studies assessing the presence of hypomagnesemia in patients undergoing dialysis.

In summary, we found that patients treated with sevelamer carbonate for the correction of hyperphosphatemia have higher serum magnesium levels with less risk of hypomagnesemia presence. This could be another additive effect of sevelamer. We could speculate that the higher serum magnesium levels could also contribute to the debated superiority of sevelamer in preventing vascular calcifications, therefore reducing cardiovascular mortality more than calcium-containing phosphate binders. Again, this should be clinically tested in a prospective way.

Conflict of interest statement

None declared.

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