Impact of sevelamer hydrochloride on serum magnesium concentrations in hemodialysis patients

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Abstract. Serum Mg levels are elevated in patients with renal insufficiency: harmful effects of hypomagnesemia have been reported in patients receiving hemodialysis (HD). In this cross-sectional study, which included 86 HD patients (male : female = 56:30, age 68 ± 12 years), we examined the clinical factors associated with serum Mg levels, with a focus on sevelamer, a phosphate binder widely used to control the hyperphosphatemia of HD patients. The mean serum Mg concentration among our patients was 2.48 ± 0.37 mg/dL (1.02 ± 0.15 mmol/L). Sevelamer was administered to 67 patients (77.9%) at a mean dose of 1.98 ± 1.64 g/day. Sex, diabetes mellitus, cardiovascular disease, anuria, and drugs other than sevelamer were not associated with serum Mg levels. HD duration, serum calcium, albumin, high-density lipoprotein cholesterol, normalized protein catabolic rate (nPCR), creatinine generation rate, and sevelamer dose correlated positively with serum Mg levels, whereas a negative correlation was observed for age and high-sensitivity C-reactive protein. A stepwise multiple regression analysis revealed that age, nPCR, and the dose of sevelamer were independently associated with serum Mg levels. Sevelamer and Mg have been reported to exhibit similar effects, such as an anti-inflammatory effect, inhibition of cardiovascular calcification, and decreased mortality. Therefore, the pleiotropic effects of sevelamer may be partly attributable to the increase in serum Mg levels caused by the drug itself.

Key words: chronic kidney disease, hemodialysis, magnesium, sevelamer hydrochloride

Serum Mg concentrations in healthy subjects are maintained within a narrow range primarily by the balance between intestinal absorption and renal reabsorption/excretion. Renal tubular reabsorption of Mg is increased by extracellular volume contraction, hypomagnesemia, and high parathyroid hormone levels [1]. Recent observational studies have shown that hypomagnesemia is a predictor of renal insufficiency and end-stage kidney disease [2, 3], but renal insufficiency decreases urinary Mg excretion and increases serum Mg levels. Mg-containing laxatives have been reported to induce hypermagnesemia in some patients with end-stage kidney disease [4, 5]. Previous studies have suggested that hypermagnesemia aggravates renal osteodystrophy [6]

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and uremic pruritus [7] in patients undergoing hemodialysis (HD). On the other hand, recent studies have shown the harmful effects of hypomagnesemia in this population, including inflammation [8], cardiovascular calcification [9, 10], and increased mortality [11-13].

Sevelamer hydrochloride is a hydrogel of crosslinked polyallylamine hydrochloride, which is resistant to digestive degradation and is not absorbed from the gastrointestinal tract. Partially protonated amines spaced one carbon from the polymer backbone interact with phosphate anions in the gastrointestinal tract by ionic and hydrogen bonding [14]. Thus, sevelamer decreases phosphate absorption from the gut, and is widely used to control hyperphosphatemia in HD patients. Recent studies have reported pleiotropic effects of sevelamer including the effect on the metabolism of minerals and trace elements [15]. In the present study, we investigated clinical factors associated with serum Mg levels in HD patients, with a focus on the effects of sevelamer.

Methods

Patients undergoing HD for ≥6 months were included in this cross-sectional study. All patients provided their informed consent, and the ethical committee of our hospital approved this study. Dialysate containing Mg^{2+} at 1.0 mEq/L was used in all patients. We recorded patients' sex; age; HD duration; Kt/V urea (efficacy of uremic toxin removal); the presence of diabetes mellitus (DM), cardiovascular disease (CVD), and anuria defined as urine volume < 100 mL/day; body mass index; creatinine generation rate (CGR), which reflects body muscle mass; normalized protein catabolic rate (nPCR), which reflects protein intake; serum levels of Ca, Mg, albumin, high-density lipoprotein cholesterol (HDL-C), intact parathyroid hormone (iPTH), and high-sensitivity C-reactive protein (hs-CRP) as well as the administration of Ca-channel blockers, β-blockers, proton-pump inhibitors (PPIs), calcium carbonate, and sevelamer hydrochloride. We compared serum Mg levels based on binary parameters including sex, the presence of DM, CVD, and anuria, and the administration of the aforementioned drugs. In addition, we tested for any correlation between serum Mg levels and continuous parameters. Blood sampling was performed before the first HD session of the week. Serum Mg levels were measured using the xylidyl blue methods. The serum samples obtained were added to xylidyl blue reagent and incubated at room temperature for five minutes. Mg ions reacted with xylidyl blue to produce a red-colored complex. The intensity of the color was measured spectrophotometrically. CGR and nPCR were calculated using the equations of Shinzato *et al.* [16, 17].

Data are shown as mean ± SD. Mann-Whitney's U test was used for comparisons between two groups. Correlations between parameters were tested using Spearman's rank correlation test. A stepwise multiple regression analysis was performed to select independent determinants of serum Mg levels. In this analysis, we included parameters that correlated with serum Mg levels in the univariate analysis. A P value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS 11.0 software.

Results

Eighty-six patients were included in this study (*table 1*), and involved 56 males and 30 females with a mean age of 68 ± 12 years. They were treated with HD for 92 ± 72 months. Thirty-four (39.5%) and 31 patients (36.0%) had DM and CVD, respectively. Fifty patients (58.1%) were anuric. PPIs were administered in 39 patients (45.3%). Sixty-seven patients (77.9%) were treated with sevelamer at a mean dose of 1.98 ± 1.64 g/day. Calcium carbonate was used in 33 patients (38.4%) to treat hyperphosphatemia. The mean value of serum calcium was similar between calcium carbonate users and non-calcium carbonate users (9.1 ± 0.5 *versus* 9.1 ± 0.6 mg/dL [2.27 ± 0.12 *versus* 2.27 ± 0.15 mmol/L], P = 0.62). None of the patients used Mg-containing drugs or supplements and the mean value of serum Mg was 2.48 ± 0.37 mg/dL (1.02 ± 0.15 mmol/L, range 1.6-4.1 mg/dL [0.66-1.69 mmol/L]).

We then compared serum Mg levels based on categorical parameters (*table 2*). Sex, DM, CVD, anuria, Ca-channel blockers, β-blockers, PPIs, and calcium carbonate were not associated with serum Mg levels. The patients treated with sevelamer showed significantly higher levels of serum Mg than those not treated with this drug (2.54 ± 0.34 *versus* 2.26 ± 0.39 mg/dL [1.04 ± 0.14 *versus*

Table 1. Clinical characteristics of 86 patients.

Age (years)	68 ± 12	(27-92)
Male:female	56:30	
Hemodialysis duration (months)	92 ± 72	(6-316)
Kt/V urea	1.48 ± 0.25	(0.92-2.13)
Anuria	50	(58.1%)
Diabetes mellitus	34	(39.5%)
Cardiovascular disease	31	(36.0%)
Body mass index (kg/m^2)	22.0 ± 4.2	(14.0-39.0)
CGR (%)	65.0 ± 18.9	(12.6-112.6)
Albumin (g/dL)	3.67 ± 0.26	(3.1-4.3)
HDL-C (mg/dL)	44 ± 14	(19-93)
Calcium (mg/dL)	9.1 ± 0.6	(7.3-10.7)
iPTH (pg/mL)	120 ± 77	(3-377)
hs-CRP (mg/dL)	0.088 ± 0.121	(0.003-0.829)
nPCR (g/kg/day)	0.85 ± 0.14	(0.49-1.22)
Calcium-channel blockers	34	(39.5%)
β-blockers	20	(23.3%)
PPIs	39	(45.3%)
Calcium carbonate	33	(38.4%)
Sevelamer hydrochloride	67	(77.9%)
Administered dose (g/day)	1.98 ± 1.64	(0-6.00)
Magnesium (mg/dL)	2.48 ± 0.37	(1.6-4.1)

CGR, creatinine generation rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate; PPIs, proton-pump inhibitors.

0.93 ± 0.16 mmol/L], P = 0.007). Correlations between serum Mg levels and continuous parameters are shown in *table 3*. Serum Mg levels correlated positively with HD duration, CGR, serum albumin, Ca, HDL-C, and nPCR, and the dose of sevelamer (*figure 1*). Negative correlations were found between serum Mg levels and age and hs-CRP, but not between serum Mg and iPTH. In the stepwise multiple regression analysis (*table 4*), age (β = -0.338, P = 0.001), nPCR (β = 0.188, P = 0.04), and the dose of sevelamer (β = 0.284, P = 0.004) were independently associated with serum Mg levels (r^2 = 0.34).

Discussion

During HD therapy, Mg is removed from the blood by diffusion, which occurs due to the concentration gradient of Mg between the blood and dialysate across the dialysis membrane. Dialysate containing Mg^{2+} of 1.0 mEq/L is commonly used in Japan, and the use of dialysate with a higher Mg^{2+} concentration increases serum Mg levels. Serum Mg levels in HD patients have recently been attracting increasing attention. We herein found that serum Mg levels were independently associated with age, nPCR, and the dose of sevelamer. A previous study reported that Mg intake was an important determinant of serum Mg levels in HD patients [18]. Mg-rich foods include green vegetables, peas, beans, nuts, seeds, and some fish [18]. However, we did not evaluate the dietary Mg intake of patients in the present study. We recorded nPCR to represent total nutrient intake, and found an independent association between nPCR and serum Mg levels. This result suggests the significant influence of Mg intake on its serum levels.

Hyperphosphatemia is a well-known risk factor for vascular calcification, and several kinds of phosphate binders, such as calcium carbonate and sevelamer, are available in the clinical practice of HD. Since hypercalcemia is also a risk factor for vascular calcification, calcium

Table 2. Comparison of serum magnesium levels based on categorical parameters.

	n	Mg levels (mg/dL)	*P*
Sex			
Male	56	2.51 ± 0.38	0.52
Female	30	2.42 ± 0.33	
Diabetes mellitus			
Yes	34	2.44 ± 0.45	0.25
No	52	2.51 ± 0.31	
Cardiovascular disease			
Yes	31	2.49 ± 0.48	0.76
No	55	2.48 ± 0.30	
Anuria			
Yes	50	2.52 ± 0.31	0.24
No	36	2.43 ± 0.44	
Calcium-channel blockers			
Yes	34	2.45 ± 0.33	0.53
No	52	2.50 ± 0.40	
β-blockers			
Yes	20	2.51 ± 0.44	0.94
No	66	2.47 ± 0.35	
PPIs			
Yes	39	2.51 ± 0.43	0.60
No	47	2.46 ± 0.32	
Calcium carbonate			
Yes	33	2.52 ± 0.34	0.11
No	53	2.46 ± 0.39	
Sevelamer hydrochloride			
Yes	67	2.54 ± 0.34	0.007
No	19	2.26 ± 0.39	

PPIs, proton-pump inhibitors.

Table 3. Correlation between serum magnesium levels and clinical parameters.

	r	*P*
Age	-0.556	<0.001
Hemodialysis duration	0.235	0.03
Kt/V urea	0.041	0.70
Body mass index	-0.117	0.28
CGR	0.383	<0.001
Albumin	0.240	0.02
HDL-C	0.315	0.003
hs-CRP	-0.238	0.02
Calcium	0.227	0.03
iPTH	-0.065	0.55
nPCR	0.309	0.004
Sevelamer dose	0.474	<0.001

CGR, creatinine generation rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; iPTH, intact parathyroid hormone; nPCR, normalized protein catabolic rate.

carbonate is not used unless patients exhibit hypercalcemia. Sevelamer is a pleiotropic, non-Ca containing phosphate binder with effects other than its phosphate-lowering effects, such as anti-inflammatory effects, improvement in lipid profiles, an antioxidant effect, a reduction in plasma levels of advanced glycation end-products [15], and a glucose-lowering effect [19]. These may lead to favorable effects of the drug on cardiovascular disease, mortality, and hospitalization [15, 20]. As described previously [21], we are attempting to control hyperphosphatemia in our HD patients with the active use of sevelamer hydrochloride. In this study, sevelamer was administered to 77.9% of our patients. We found an independent association between the dose of sevelamer and serum Mg levels. Mitsopoulos *et al.* previously reported that during an eight-week treatment with sevelamer, the mean serum Mg level increased significantly [22]. Chertow *et al.* also found a significant increase in serum Mg

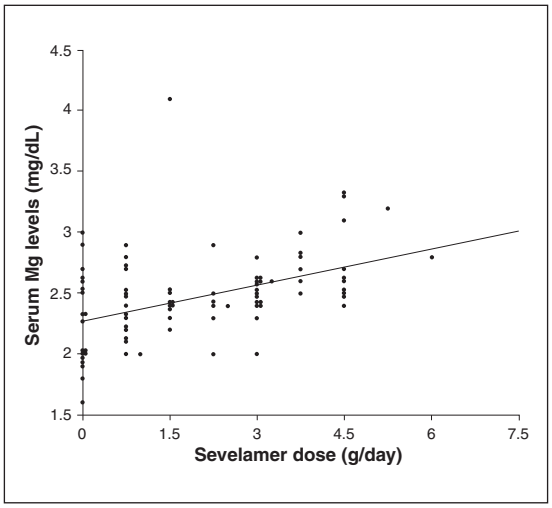

Figure 1. Correlation between dose of sevelamer and serum magnesium levels.

levels that was induced by sevelamer [23]. In a cross-sectional study by Rosa-Diez *et al.*, the use of sevelamer carbonate was identified as an independent protective factor for hypomagnesemia, defined as serum Mg levels <1.9 mg/dL [24]. It seems plausible to speculate that the pleiotropic effects of sevelamer depend on its adsorptive action on not only phosphate, but also other substances in the intestinal lumen. This drug is known to improve lipid profiles by binding to bile acid [25]. Previous studies have indicated that the anti-inflammation effect of sevelamer might be attributable to its chelation effect on pro-inflammatory compounds [26, 27]. Regarding the increase in serum Mg levels by sevelamer, Mitsopoulos *et al.* speculated that it could be due to its capacity to bind biliary salts, thereby increasing the quantity of free Mg available for intestinal absorption [22].

Table 4. Stepwise multiple regression analysis for independent determinants of serum magnesium levels.

	β	***P***
Age	-0.338	0.001
Hemodialysis duration	-0.003	0.97
CGR	0.052	0.68
Albumin	-0.021	0.83
HDL-C	0.061	0.54
hs-CRP	-0.038	0.68
Calcium	0.074	0.42
nPCR	0.188	0.04
Sevelamer dose	0.284	0.004
$r^2 = 0.34$		

CGR, creatinine generation rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; nPCR, normalized protein catabolic rate.

Previous studies have reported that Mg has favorable effects on inflammation [8], lipid profiles, glucose metabolism [28], and cardiovascular calcification [29, 30]. The same effects have been observed in sevelamer. Although the precise mechanisms responsible for these effects of sevelamer have not yet been elucidated, the increase in serum Mg levels induced by the drug itself may be included in the mechanisms.

We did not find any association between serum Mg levels and PPIs. This result was unexpected because previous studies have shown that the use of PPIs is a risk factor for hypomagnesemia [31]. This discrepancy might be explained by several drugs, such as Ca-containing phosphate binders, vitamin D receptor antagonists (VDRAs), and cinacalcet, which are used to treat hyperphosphatemia and secondary hyperparathyroidism in HD patients. The former two increase, while the latter decreases serum Ca levels. We speculate that multiple combinations of these drugs may affect serum Ca and Mg levels in a complicated manner and modify the relationship between serum Mg levels and PPIs. In addition, we found no association between Mg and iPTH. Based on *in vitro* and *in vivo* studies showing that Mg modulates PTH secretion in a similar manner to Ca [1], this result also appears to be controversial. The lack of the association between Mg and iPTH in our study may be attributable to VDRAs or cinacalcet. Furthermore, on a molar basis, Mg is a 2.5- to 3-fold less potent suppressor of PTH secretion than Ca [1].

There were some limitations in our study. A small sample size and the cross-sectional and single-center study design made it difficult to draw general conclusions and identify causal relationships. As discussed above, we did not evaluate Mg intake. Rosa-Diez *et al.* evaluated Mg intake using a food frequency questionnaire and found a marginally significant association between Mg

intake and serum Mg levels in a multivariate analysis [24].

In conclusion, we herein identified an independent association between serum Mg levels and the dose of sevelamer. Sevelamer and Mg have been reported to exhibit similar effects, such as an anti-inflammatory effect, inhibition of cardiovascular calcification, and decreased mortality. These effects of sevelamer may be partly attributable to the increase in serum Mg levels induced by the drug itself.

Disclosure

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