Prevalence and Factors Associated with Hypomagnesemia in Southern Chinese Continuous Ambulatory Peritoneal Dialysis Patients

KEY WORDS: Continuous ambulatory peritoneal dialysis; hypomagnesemia; malnutrition; hypertonic peritoneal dialysate.

Magnesium (Mg^{2+}) is a metal element that is essential for life. It is involved in hundreds of enzymatic reactions, and it is an important cofactor in many biologic processes. Profound magnesium deficiency results in a variety of clinical manifestations, including a positive Chvostek sign or Trousseau sign, vertigo, nystagmus, tetany, cardiac arrhythmia, and bone instability (1). However, hypomagnesemia has been paid little attention in the continuous ambulatory peritoneal dialysis (CAPD) population.

Patients on CAPD dialyzed with peritoneal dialysate containing 0.25 mol/L magnesium were reported to develop a considerable fall in serum magnesium (2); however, the causes of hypomagnesemia are far more complicated. Hypertonic exchanges, different daily peritoneal dialysis (PD) exchange volumes, comorbidities, and nutrition status can also affect magnesium balance in this population. The present study was therefore designed to investigate the prevalence of hypomagnesemia and its associated factors in CAPD patients.

METHODS

Patient Selection and Clinical Information: This cross-sectional survey study enrolled prevalent CAPD patients at the PD center of The First Affiliated Hospital of Sun Yat-sen University from February to June 2011. All patients had received CAPD treatment for more than 1 month and were being regularly followed. Patients were dialyzed with a low-magnesium dextrose peritoneal dialysate (containing Mg^{2+} 0.25 mmol/L, Ca^{2+} 1.25 mmol/L or 1.77 mmol/L, Na^+ 132 mmol/L, Cl^- 96 mmol/L) produced by Baxter Healthcare (Guangzhou, China).

Demographic and clinical characteristics including age, sex, primary renal disease, PD vintage, medications, daily PD exchange volume, ultrafiltration volume, urine volume, and clinical symptoms including ostalgia or arthralgia and tetany were recorded. The use of hypertonic peritoneal dialysate was defined as the daily use of 1 or more exchanges of solution with a 2.5% or higher dextrose concentration. The use of 1.25 mmol/L (physiologic) calcium dialysate, calcium supplements, compound α -ketoacid (50 mg calcium per pill), and calcitriol were also recorded. Comorbidities, including diabetes, coronary artery disease, congestive heart failure, and cerebrovascular disease were also recorded. The Charlson comorbidity index, which has been verified as a useful predictor of survival in PD patients, was used to assess the comorbidity status of patients (3).

All biochemical tests were conducted using an automatic chemistry analyzer [Hitachi 7180 (Boehringer Mannheim, Mannheim, Germany) or Abbott Aeroset (Abbott Laboratories, Abbott Park, IL, USA)]. Serum magnesium was determined by xylidine blue method. The normal reference values for serum magnesium in this study were 0.70 – 1.10 mmol/L. Hypomagnesemia was defined as a serum magnesium level less than 0.70 mmol/L.

Statistical Analysis: Results are expressed as frequencies and percentages (categorical variables), mean $\pm$ standard deviation (continuous variables), and median and interquartile range (skewed distributions). The t-test for independent samples was used for normally distributed continuous variables. Comparisons of non-normally distributed continuous variables were performed using the Mann–Whitney U-test. For categorical variables, the chi-square test was used. The bivariate correlation test was performed to examine associations between demographic and biochemical variables and serum magnesium. Binary logistic regression was used in a multivariate analysis to explore factors associated with hypomagnesemia. All calculations were performed in the SPSS software application (version 13.0 for Windows: SPSS, Chicago, IL, USA). Bonferroni correction was used to correct the p values when performing comparisons. A p value of less than 0.05 was considered significant.

RESULTS

Demographic and Clinical Characteristics: The study recruited 402 PD patients (mean age: 49.3 ± 14.9 years), 57% of whom were men. Median PD duration was 23.3 months (range: 11.9 – 38.1 months). The leading cause of end-stage renal disease was glomerulonephritis (59.7%),

followed by diabetic nephropathy (19.4%). Mean body mass index was 22.33 ± 2.95 kg/m². Hypertonic peritoneal dialysate was used at least once daily by 242 patients (60.2%).

Prevalence of Hypomagnesemia and Characteristics of Patients With and Without Hypomagnesemia:

Mean serum magnesium in the 402 enrolled CAPD patients was 0.73 ± 0.11 mmol/L. Of those patients, 163 (40.5%) were diagnosed with hypomagnesemia, and 3 (0.7%) had serum magnesium levels less than 0.5 mmol/L. Compared with the patients having a normal level of serum magnesium, patients with hypomagnesemia more frequently used hypertonic dialysate (71.2% vs 57.0%, $p = 0.005$); had lower serum albumin (37.9 ± 4.5 g/L vs 39.5 ± 3.7 g/L, $p < 0.001$), potassium (3.89 ± 0.66 mmol/L vs 4.18 ± 0.70 mmol/L, $p < 0.001$), and phosphate (1.46 ± 0.44 mmol/L vs 1.75 ± 0.47 mmol/L, $p < 0.001$); and had a lower normalized protein equivalent of nitrogen appearance (0.94 ± 0.21 g/kg/day vs 1.00 ± 0.23 g/kg/day, $p = 0.015$). We observed no significant differences between the groups in sex, age, primary renal disease, major comorbidity, Charlson comorbidity index, body mass index, daily PD exchange volume, peritoneal equilibration test, total Kt/V, and residual renal function (Table 1).

Factors Associated with Hypomagnesemia: The bivariate correlation analysis showed that serum magnesium was positively associated with duration of dialysis ($R^2 = 0.046$, $p < 0.001$), ultrafiltration volume ($R^2 = 0.047$, $p < 0.001$), serum potassium ($R^2 = 0.082$, $p < 0.001$), serum creatinine ($R^2 = 0.059$, $p < 0.001$), serum phosphate ($R^2 = 0.136$, $p < 0.001$), serum calcium ($R^2 = 0.021$, $p = 0.003$), intact parathyroid hormone ($R^2 = 0.028$, $p = 0.017$), serum albumin ($R^2 = 0.046$, $p < 0.001$), and normalized protein equivalent of nitrogen appearance ($R^2 = 0.028$, $p = 0.002$). Serum magnesium was also negatively associated with urine volume ($R^2 = 0.011$, $p = 0.043$) and creatinine clearance ($R^2 = 0.024$, $p = 0.004$). No significant association was found with age, Charlson comorbidity index, daily exchange volume, residual renal function, or total Kt/V. Hypomagnesemia was also positively correlated with the use of hypertonic peritoneal dialysate ($R^2 = 0.021$, $p = 0.005$) and negatively correlated with the use of dialysate containing 1.25 mmol/L calcium ($R^2 = -0.012$, $p = 0.030$).

To adjust for confounding factors, a binary logistic regression analysis was performed. The results of that analysis showed that lower body mass index [odds ratio (OR): 0.868; 95% confidence interval (CI): 0.771 to 0.977; $p = 0.019$], lower serum albumin (OR: 0.909; 95%

TABLE 1
Comparison of Demographic Data and Biochemical Parameters in Patients With and Without Hypomagnesemia

Variable	Serum magnesium		<i>p</i> Value
	<0.7 mmol/L	≥0.7 mmol/L	
Age (years)	49.4±15.3	49.1±14.6	NS
Sex (<i>n</i> men/women)	101/62	128/111	NS
Duration of dialysis (months)			
Median	17.5	27.1	<0.001
Interquartile range	7.4–30.1	14.1–39.57	
Body mass index (kg/m ²)	22.0±2.9	22.5±3.0	NS
CCI score	3.67±1.87	3.64±1.70	NS
Use of vitamin D ₃ [<i>n</i> (%)]	82 (50.3)	112 (46.9)	NS
Dialysate use			
Daily exchange volume (L)	7.9±1.3	8.0±1.3	NS
Hypertonic dialysate [<i>n</i> (%)]	111 (71.2)	131 (57.0)	0.005
Dialysate with 1.25 mmol/L Ca [<i>n</i> (%)]	50 (32.1)	99 (43.0)	0.029
Daily ultrafiltration (mL)			
Median	450	550	<0.001
Interquartile range	200–700	300–850	
Daily urine volume (mL)			
Median	500	425	NS
Interquartile range	180–1000	100–800	
Serum total calcium (mmol/L)	2.32±0.19	2.36±0.19	NS
Serum phosphate (mmol/L)	1.46±0.44	1.75±0.47	<0.001
Serum potassium (mmol/L)	3.89±0.66	4.18±0.70	<0.001
Intact parathyroid hormone (pg/mL)			
Median	348.5	386.4	0.011
Interquartile range	155.8–575.9	211.3–713.1	
Serum albumin (g/L)	37.9±4.5	39.5±3.7	<0.001
Blood urea nitrogen (mmol/L)	17.7±5.3	19.8±5.3	<0.001
Serum creatinine (μmol/L)	913.0±317.8	1009.2±325.7	0.004
Total Kt/V	2.26±0.58	2.26±0.69	NS
Residual renal function (mL/min/1.73 m ²)			
Median	1.58	1.32	NS
Interquartile range	0.36–3.85	0.22–3.11	
nPNA (g/kg/day)	0.94±0.21	1.00±0.23	0.015
Creatinine clearance (L/week/1.73 m ²)			
Median	67.6	60.1	0.026
Interquartile range	53.3–83.9	50.1–77.4	

NS = nonsignificant; CCI = Charlson comorbidity index; nPNA = normalized protein equivalent of nitrogen appearance.

CI: 0.830 to 0.995; *p* = 0.040), lower serum phosphate (OR: 0.217; 95% CI: 0.087 to 0.545; *p* = 0.001), and higher use of hypertonic dialysate (OR: 3.972; 95% CI: 1.902 to 8.292; *p* < 0.001) were factors independently associated with hypomagnesemia (Table 2).

DISCUSSION

To date, epidemiologic studies concerning the prevalence of hypomagnesemia in the PD population with a larger sample size are lacking. In the present

study of 402 Chinese CAPD patients, we found that the prevalence of hypomagnesemia was 40.5%, which is consistent with the prevalence of 64% reported by Ejaz *et al.* (2). However, those prevalences are far higher than the prevalence of 8.9% in CAPD patients reported by Cho *et al.* (4). It is surprising that the prevalence of hypomagnesemia is so remarkably different in different countries, although the patients received the same low-magnesium dialysate for PD. Notably, the other two studies included only a small group of PD patients, and the prevalence of hypomagnesemia was not the primary

TABLE 2
Factors Independently Associated with
Hypomagnesemia in the Binary
Logistic Regression Model^a

Variable	Adjusted OR	95% CI	p Value
Body mass index (kg/m ²)	0.868	0.771 to 0.977	0.019
Serum albumin (g/L)	0.909	0.830 to 0.995	0.040
Serum phosphate (mmol/L)	0.217	0.087 to 0.545	0.001
Use of hypertonic dialysate	3.972	1.902 to 8.292	<0.001

OR = odds ratio; CI = confidence interval.

^a Patients with and without hypomagnesemia were compared. Parameters of age, body mass index, duration of dialysis, use of hypertonic dialysate, use of dialysate with 1.25 mmol/L calcium, diabetes mellitus, ultrafiltration volume, urine volume, serum albumin, serum potassium, serum total calcium, serum phosphate, serum intact parathyroid hormone, normalized protein equivalent of nitrogen appearance, creatinine clearance, and residual renal function were included in the model.

purpose of the investigations. Thus, they may inevitably produce biases.

The pathogenesis of hypomagnesemia in the PD population is highly complex. Our findings showed that, after adjusting for confounders, serum albumin and body mass index were independently associated with hypomagnesemia. Serum albumin had been shown to be a valid marker of nutrition status and is strongly correlated with mortality (5,6). In our study, we also found that serum magnesium is associated with many markers of nutrition (7) in PD patients, including normalized protein equivalent of nitrogen appearance, serum creatinine, and blood urea nitrogen. All of those markers were significantly lower in the patients with hypomagnesemia than in those with a normal level of serum magnesium. However, most of the R^2 values for those markers were low in the correlation analysis, indicating that the associations with serum magnesium were weak. In addition, we found that serum magnesium was independently correlated with serum phosphate. Because serum phosphate in end-stage renal disease patients depends largely on phosphate uptake (8), our results indirectly indicate that patients with hypomagnesemia have an overall reduction in oral intake, which may eventually lead to exacerbation of their nutrition status. We therefore suggest that nutrition status may be one of the most important risk factors for hypomagnesemia in PD patients. This close link between hypomagnesemia and nutrition has also been observed

by other authors, who found that magnesium depletion was closely correlated with protein-energy malnutrition in children (9,10).

Another important contributor to serum magnesium values in PD patients is the dialysate used (2,11,12). First, the use of low-magnesium dialysate (Mg^{2+} 0.25 mmol/L) is regarded as the main reason for the development of hypomagnesemia, because of increased magnesium clearance in effluent (2,13). Unfortunately, low-magnesium dialysate is the only commercially available solution in Guangzhou city, and thus, we could not compare the effect on serum magnesium of solutions with various magnesium concentrations. However, the use of low-magnesium dialysate can't explain the different serum magnesium levels in an entire PD population receiving the same low-magnesium dialysate. Second, logistic regression analysis revealed that the use of hypertonic dialysate was independently associated with hypomagnesemia, indicating that hypertonic dialysate may also play a role in magnesium balance. It has been reported that dialysate with a higher glucose concentration increases the mass transfer of magnesium in PD (14). On the other hand, the higher caloric load of hypertonic dialysate may result in a reduction of overall dietary intake, consequently leading to hypomagnesemia (15).

The implication of magnesium supplementation in asymptomatic patients with hypomagnesemia remains unknown. Hypomagnesemia might be merely a biologic marker of malnutrition or perhaps a result of inappropriate use of low-magnesium and hypertonic dialysate, and magnesium supplementation may be not favorable for PD patients. Because the appropriate serum magnesium level and dose of supplemental magnesium are still uncertain in the complex setting of PD, increasing food intake and improving a patient's nutrition status may be the proper clinical approach. Prospective studies may be needed in this respect in the future.

The main limitation of our study is the limited information provided by the cross-sectional study. The relationships between long-term clinical outcome, cardiovascular events, and hypomagnesemia need further study. Moreover, we did not precisely evaluate dietary intake of magnesium or quantitate magnesium loss in dialysate and urine. We therefore do not have a complete profile of magnesium balance in PD patients.

CONCLUSIONS

The prevalence of hypomagnesemia is high in Chinese PD patients. Nutrition status was closely associated with hypomagnesemia, suggesting that malnutrition may play an important role in the pathogenesis of

hypomagnesemia. A higher frequency of hypertonic dialysate use was also involved in the development of hypomagnesemia.

DISCLOSURES

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