ORIGINAL ARTICLE

Magnesium levels and magnesium containing phosphate binders in haemodialysis patients

Koulouridis E, Kostimpa I, Klonou E, Koulouridis I, Tsilimpari B, Nikolaidou Z, Goudeli X, Krokida A, Liapi E, Bregova I

Nephrology Department and Biochemistry Laboratory. General Hospital of Corfu. Greece.

Abstract

Background and aim: Sufficient evidence suggests that serum magnesium exerts beneficial effect upon cardiovascular status and arterial calcification among dialysis patients. Magnesium containing salts are as effective as the usual phosphate binders in lowering serum phosphorus in haemodialysis patients and posses the advantage of increasing serum magnesium levels which may play an important role in cardiovascular outcome. The aim of this study was To investigate serum magnesium levels among dialysis patients before and after administration of magnesium containing phosphate binders and its clinical significance. Hippokratia 2011; 15 (Suppl 2): 21-26

Patients and Methods: In this prospective cohort we investigated 70 patients (45 men, 25 women) undergoing standard bicarbonate dialysis, thrice weekly (3-4 hours) for longer that 6 months. Age 66.1±13.2 (33-88) years, dialysis duration 62.6±57.9 (7-267) months. Presence of coronary artery disease (CAD) was established by previous history of acute myocardial infarction or coronary angiography. Chronic use (>1 year) of proton pump inhibitors (PPIs) was sought from previous history of the patients. Patients with serum magnesium levels lower than 3 mg/dl were eligible to be administered calcium acetate-magnesium carbonate (CalMag) as phosphate binder. We estimated serum calcium, phosphorus, magnesium and calcium-phosphate product monthly and iPTH every three months. In order to avoid hypermagnesaemia after two months patients receiving CalMag underwent dialysis with low magnesium dialysate (0.75 mEq/L) while the rest continued dialysis with usual magnesium dialysate (1 mEq/L).

Results: Lower magnesium levels were identified among patients with coronary artery disease (p=0.01) as well as among patients chronically receiving proton pump inhibitors (p=0.03). Administration of CalMag showed a considerable increase in the magnesium level (p=0.0004) and a significant decrease of phosphate level (p=0.01). Substitution with low magnesium dialysate (0.75 mEq/L) showed a considerable decrease of serum magnesium level (p=0.005). Variations in the levels of calcium, phosphate and calcium-phosphate product between the individual phosphate binders (PBND) showed no statistically significant difference. The estimated three month cost for the individual phosphate binders was lower for calcium carbonate and CalMag compared to the other phosphate binders.

Conclusions: The results of this study suggest that presence of coronary artery disease and chronic use of PPIs is related to lower serum magnesium levels. Administration of CalMag in haemodialysis patients is related to lower phosphorus levels and increased magnesium levels. Low dialysate magnesium concentration reduces effectively serum magnesium levels. The efficacy of CalMag in lowering serum phosphorus level is comparable with the usual phosphate binders. The lower cost of CalMag suggests its more frequent use in clinical practice among selected patients.

Key words: magnesium, haemodialysis, coronary artery disease, proton pump inhibitors, magnesium containing phosphate binders

Corresponding author: Efstathios Koulouridis, Spirou Rath 41 – TK 49100**,** Corfu, Greece, Tel: 003026610-33923, Fax: 003026610-22660, e-mail: koulef@otenet.gr

Serum magnesium levels among patients undergoing haemodialysis has been neglected for a long time because of minor effect upon bone mineral disorders and because of very rare clinical syndromes related to hyper or hypo-magnesaemia. In early sixties it has been evident that magnesium absorption is normal among dialysis patients and diminished excretion from the kidneys produce hypermagnesaemia which may be dangerous especially in cases that magnesium containing drugs administered. This notion has led to the elimination of magnesium containing drugs such as antioxidants, laxatives and phosphate binders from the regimens of end stage renal disease (ESRD) patients as well as use of low magnesium dialysate concentration (0.5-0.7 mmol/L)[1]. One decade later it became evident that increased magnesium levels suppress parathyroid hormone (PTH) production and arterial calcification. There after increased evidence in literature pointed to the possible beneficial effect of

magnesium upon bone metabolism, arterial calcification and atherosclerosis not only among ESRD patients as well as among healthy individuals[2-4]. The advent of aluminum intoxication among patients receiving aluminum hydroxide as phosphate binder prompted the necessity to use other less toxic but effective drugs and so magnesium salts, mainly magnesium carbonate, was used in order to control hyperphosphataemia among ESRD patients and proved effective and safe[5-7]. In order to avoid hypermagnesaemia, either among dialysis or peritoneal dialysis patients who receive magnesium containing phosphate binders, it was necessary to lower the dialysate or peritoneal fluid content of magnesium[8,9]. Accumulating evidence suggest that magnesium apart from its efficacy as phosphate binder may exert pleiotropic actions upon intradialytic blood pressure stability, cardiac arrhythmias and heart ischemic attacks but it has to be proved[10,11]. The aim of this study was to investigate serum magnesium levels among dialysis patients before and after calcium-magnesium salts administration its clinical significance and the efficacy of these salts as phosphate binders among a limited number of patients.

Subjects and methods.

Study design

In this prospective cohort we investigated 70 patients (45 men, 25 women) suffering from ESRD and undergoing standard bicarbonate dialysis for longer than six months. Dialysis schedule was thrice weekly (3-4 hours) with magnesium dialysate concentration of 1 mEq/L. The mean age of the patients was 66.1±13.2 (33-88) years and the mean dialysis duration 62.6±57.9 (7-267) months. Presence of coronary artery disease (CAD) was established by previous history of acute myocardial infarction or coronary angiography. Presence of calcification in the hand interosseous arteries was established by x-rays. Chronic use (greater than one year) of proton pump inhibitors (PPIs) was sought from medical records of the patients and by personal communication with each one of them (Table 1).

Table 1: Demographic characteristics of the patients (n=70).

Age: 66.1±13.2 (33-88) years.
Gender: 45 men, 25 women.
Haemodialysis duration: 62.6±57.9 (7-267) months.
Dialysis schedule: Standard bicarbonate, thrice weekly.
Coronary artery disease: 15/70 (21.4 %).
Chronic use of PPIs: 41/70 (58.7 %).
Arterial calcification (hands): 23/68 (33.8 %).
Phosphate binders:
Calcium acetate (435 mg)/Magnesium carbonate (235 mg): n=12 (17.1 %).
Calcium carbonate (420 mg)/Glycine (180 mg): n=4 (5.7 %).
Lanthanum carbonate (750 mg): n=16 (22.8 %).
Sevelamer hydrochloride (800 mg): n=38 (54.**2 %).**

Patients with serum magnesium level lower than 3 mg/dl were eligible to administer calcium acetate/magnesium carbonate (CalMag) phosphate binders. After a two weeks washout period CalMag was administered in 12 patients (seven men and five women), 1-2 tablets per meal according to phosphate levels. After two months patients receiving CalMag underwent dialysis with low magnesium dialysate (0.75 mEq/L) instead of 1 mEq/L for all the others. We used the following phosphate binders: Calcium acetate (435 mg)/Magnesium carbonate (235 mg) (OsvaRen, Fresenius Medical Care Nephrologica, Deutschland GmbH, Homburg v.d.H. Germany) 12 patients (17.1 %), Calcium carbonate (420 mg)/Glycine (180 mg) (Titralac, Meda Pharmaceuticals SA, Chalandri Attikis, Greece) 4 patients (5.7 %), Lanthanum carbonate (750 mg) (Fosrenol, Shire Pharmaceuticals Ltd, Hampshire, United Kingdom)) 16 patients (22.8 %) and Sevelamer hydrochloride (800 mg) (Renagel, Genzyme Europe B.V., Naarden, Netherlands) 38 patients (54.2 %). We estimated pre-dialysis serum calcium, phosphorus, magnesium and calcium-phosphate product monthly and iPTH every three months. Pre-dialysis serum magnesium level with usual dialysate magnesium concentration before and after CalMag administration was estimated as well as after substitution of low dialysate magnesium concentration. Serum magnesium (mg/dl) was estimated by using the xylidyl blue method, serum phosphorous (mg/dl) by molybdate UV method, serum calcium (mg/dl) by arsenazo III pigment method all the above calculations were performed by AU 600/OLYMPUS equipment. Intact iPTH (pg/ml) was estimated by two site sandwich type chemiluminescence immunoassay (CLIA, DiaSorin Inc, Stillwater, MN 55082, USA).

Statistical analysis

One-way ANOVA was used in order to test the rela-

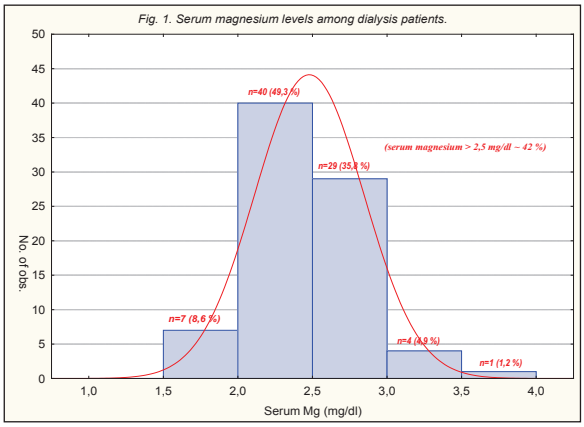

Figure 1: Pre-dialysis serum magnesium levels among ESRD patients. About 42 % of them exhibited magnesium levels greater than 2,5 mg/dl.

tionship between serum magnesium and coronary artery disease, the effect of PPIs upon magnesium level as well as the effect of magnesium upon interosseous arteries calcification. No post-hoc analysis was conducted because categorical predictors were binary and ANOVA converts to independent sample t-test. One-way ANOVA was also used with Bonferroni correction in order to compare the variation of calcium, phosphorus and calcium/phosphorus product between patients receiving various phosphate binders. Student's t-test for dependent samples was used in order to test the variation of magnesium level before and after CalMag administration as well as with high and low dialysate magnesium concentration. Multiple regression analysis was used in order to test the effect of magnesium (Mg) and calcium (Ca) levels as well as CaXP product upon iPTH. All calculations are expressed as means ± 1 standard deviation, all analysis have been conducted on the level p=0.05 of statistical significance.

Figure 2: Patients suffering from coronary artery disease exhibited lower levels of serum magnesium than the remainders.

Results

Laboratory determinations before and after CalMag administration, with dialysate magnesium concentration at 1 mEq/L and 0.75 mEq/L are shown in table 2. Dialysate composition with high (=1 mEq/L) and low (=0.75 mEq/L) magnesium concentration is shown in table 3. Detailed analysis of magnesium levels showed that seven patients (8.6 %) exhibited magnesium level between 1.5 and 2.0 mg/dl and thirty two patients (42 %) exhibited magnesium level greater than 2.5 mg/dl (Figure 1).

Fifteen out of seventy patients (21.4 %) suffered from CAD, analysis of variance between magnesium level and CAD (F=6.35, p=0.01) showed that patients suffering from CAD exhibited the lower magnesium level (Figure 2). Forty one patients (58.7 %) received PPIs for longer than one year, analysis of variance between magnesium level and PPIs (F=4.5, p=0.03) showed that patients receiving PPIs exhibited the lower level of serum magnesium (Figure 3). Twenty three patients, out of sixty eight with radiographic data (33.8 %), exhibited interosseous arteries calcification (CALC) of the hands, analysis of variance showed no significant effect of age, haemodialysis duration (HDUR), Mg, Ca, P, CaXP product and iPTH levels upon vascular calcification but the most pronounced effect, although not statistically significant, was exhibited by iPTH, haemodialysis duration and Mg (iPTH vs CALC: F=3.53, p=0.06 NS, HDUR vs CALC: F=2.19, p=0.1 NS and Mg vs CALC: F=1.09, p=0.2 NS). Correlation between magnesium level and iPTH showed no relationship of these two variables (n=70, r=0.006, p=0.9 NS). Twenty two patients received cinacalcet and four additional patients underwent parathyroidectomy by excluding these patients from the model showed again no relationship (n=44, r=0.08, p=0.5 NS). Moreover multiple regression analysis between iPTH as depended variable and Mg, Ca, P and CaXP product as independent variables showed no significant effect (n=70, F=0.94, p<0.44 NS).

CalMag administration under basal conditions (dialysate magnesium concentration 1 mEq/L) was coupled with a significant increase of serum magnesium level (n=12, t= -4.9, p=0.0004), substitution of dialysate with low magnesium concentration (0.75 mEq/L) produced a

Table 2: Laboratory determinations before and after CalMag administration.

Parameters	All patients (n=70)	No CalMag + dialysate Mg=1 mEq/L (n=12)	CalMag + dialysate Mg=1 mEq/L (n=12)	CalMag + dialysate Mg=0,75 mEq/L (n=12)	p
Magnesium (mg/dl)	*2.5 ± 0.35*	*2.25 ± 0.29*	*2.52 ± 0.34 (p=0.0004)*	*2.25 ± 0.27*	*0.005*
Calcium (mg/dl)	*9.6 ± 0.8*		*9.51 ± 1.09*	*9.8 ± 0.8*	*0.1*
Phosphate (mg/dl)	*5.3 ± 1.4*		*5.7 ± 1.9*	*4.7 ± 1.4*	*0.01*
CaXP product (mg^2/dl^2)	*51.7 ± 14.1*		*53.6 ±17.7*	*46.2 ±12.7*	*0.06*
iPTH (pg/ml)	*277.3 ± 246.1*		*131.8 ± 83.6*	155.3 ± *123.5*	*0.3*

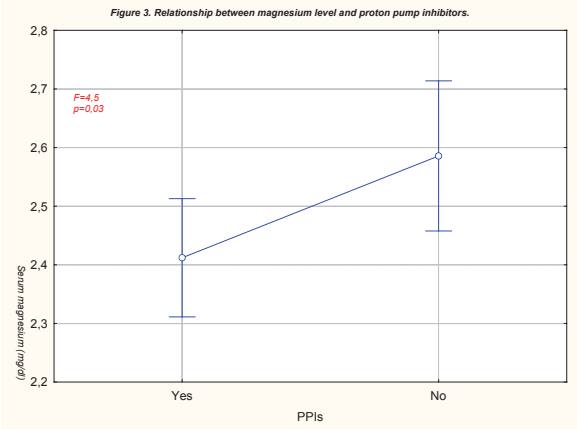

Figure 3: Patients receiving chronically (more than one year) proton pump inhibitors (PPIs) exhibited lower levels of serum magnesium.

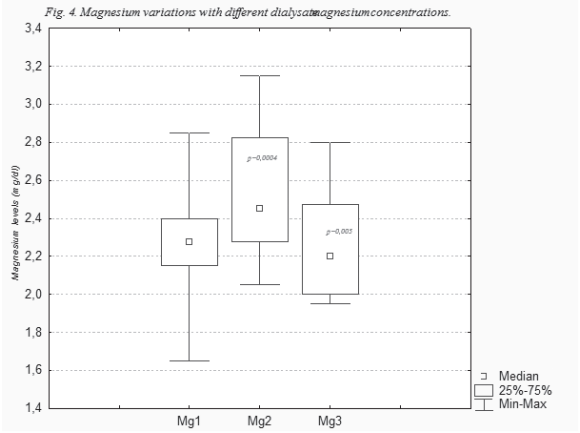

Figure 4: Variations of serum magnesium levels before and after CalMag administration and with various dialysate magnesium concentrations. (Mg1 = Dialysate magnesium concentration 1 mEq/L before Cal/Mag administration. Mg2 = Dialysate magnesium concentration 1 mEq/L + CalMag. Mg3 = Dialysate magnesium concentration 0,75 mEq/L + CalMag).

Table 3: Dialysate composition.

High Magnesium dialysate (1 mEq/L)		Low Magnesium dialysate (0,75 mEq/L)	
Na^+	138	Na^+	138
K^+	2	K^+	2
Ca^{++}	3.5 (=1.75 mmol/L)	Ca^{++}	3.5 (=1.75 mmol/L)
Mg^{++}	1 (=0.5 mmol/L)	Mg^{++}	0.75 (=0.375 mmol/L)
Cl^-	109.5	Cl^-	109.5
$CH3COO^-$	3	$CH3COO^-$	3
$HCO3^-$	35	$HCO3^-$	35

Table 4: Effect of individual phosphate binders upon Ca, P and CaXP product.

	OsvaRen (n=12)	Titralac (n=4)	Fosrenol (n=16)	Renagel (n=38)
Ca1 (mg/dl)	9.5 ± 1.09 (95 % CI=8.8-10.2)	9.6 ± 0.5 (95 % CI=8.6-10.5)	9.8 ± 0.7 (95 % CI=9.4-10.1)	9.5 ± 0.7 (95 % CI=9.3-9.8)
Ca2 (mg/dl)	9.8 ± 0.88 (95 % CI=9.2-10.3)	9.3 ± 0.7 (95 % CI=81-10.4) ***‡: (F=1.0, p=0.2 NS)***	9.5 ± 0.7 (95 % CI=9.1-9.9)	9.5 ± 0.5 (95 % CI=9.3-9.7) ***†(F=1.21, p=0.3 NS)***
P1 (mg/dl)	5.7 ± 1.9 (95 % CI=4.4-6.9)	5,2 ± 0,5 (95 % CI=4,2-6,2)	5,9 ± 1,4 (95 % CI=5,1-6,7)	5,0 ± 1,3 (95 % CI=4,6-5,5)
P2 (mg/dl)	4.7 ± 1.4 (95 % CI=3.8-5.6)	4.8 ± 0.8 (95 % CI=3.4-6.2)	5.7 ± 1.7 (95 % CI=4.8-6.7)	5.0 ± 1.2 (95 % CI=4.6-5.4) ***††: (F=1.8, p=0.08 NS)***
CaXP1 (mg^2/dl^2)	53.6 ± 17.7 (95 % CI=42.3-64.9)	50.2 ± 5.5 (95 % CI=41.4-59.0)	58.1 ± 15.0 (95 % CI=50.0-66.1)	48.5 ± 12.5 (95 % CI=44,.4-52.6)
CaXP2 (mg^2/dl^2)	46.2 ± 12.7 (95 % CI=38.0-54.3)	45.1 ± 7.4 (95 % CI=33.2-56.9)	55.4 ± 17.0 (95 % CI=46.3-64.4)	48.1 ± 11.5 (95 % CI=44.3-51.9) ***†††: (F=1.5, p=0.1 NS)***

†: Variation of calcium level between individual phosphate binders.
††: Variation of phosphate level between individual phosphate binders.
†††: Variation of calcium X phosphate product between individual phosphate binders.
‡: Comparison of calcium level between OsvaRen and Titralac.

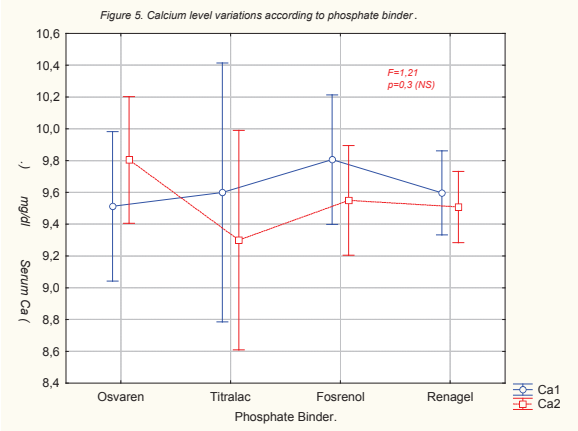

Figure 5: Calcium level variation with various phosphate binders showed no statistically significant difference between individual medications. Although it is noted a slightly increased calcium level among patients receiving Cal/Mag (Ca2) it has not reached statistical significance.

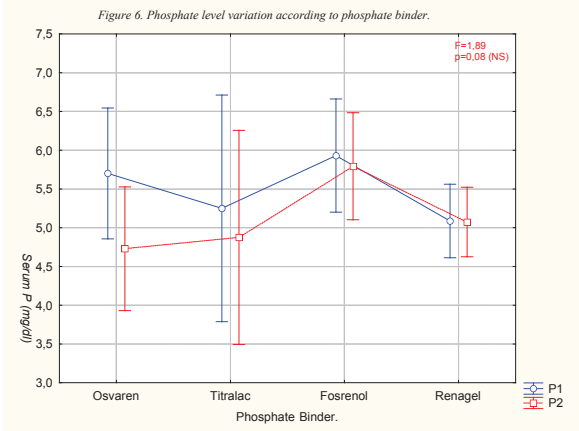

Figure 6: Phosphate level variation between individual phosphate binders showed no statistically significant difference suggesting that all phosphate binders used are equally effective.

significant decrease of serum magnesium level (n=12, t=3.45, p=0.005, Figure 4). Calcium level showed a slight, but not statistically significant, increase (n=12, t= -1.47, p=0.1 NS). On the other hand a considerable decrease of phosphate level was noted (n=12, t=2.8, p=0.01). Calcium-phosphate product showed a marginally significant decrease mainly due to phosphate decrease (n=12, t=2.0, p=0.06), iPTH level showed no significant alteration (n=12, t= -1.25, p=0.23, Table 2).

The effect of individual phosphate binders (PBND) upon the levels of calcium, phosphate and calcium-phosphate product, among the total cohort of patients, was tested by one way ANOVA (Table 4). The results showed no significant difference between the individual variables especially calcium (F=1.21, p=0.3 NS, Figure 5) and phosphate levels (F=1.8, p=0.08 NS, Figure 6). Moreover we tested the variation of calcium levels between Cal-Mag and Titralac and we found no statistically significant results (F=1.0, p=0.2 NS).

Finally we estimated the three-month cost for the individual phosphate binders which was as follow: OsvaRen=89.37 €, Titralac=17.1 €, Fosrenol=860.7 €, Renagel=678.24 €.

Discussion

Although our patients were dialyzed with a relatively low dialysate magnesium concentration (1 mEq/l = 0.5 mmol/dl) they exhibited a considerable increase in their serum magnesium. About 42 % of them exhibited serum magnesium level greater than 2.5 mg/dl. This finding suggests that ESRD patients are prone to hypermagnesaemia because of increased dietary magnesium intake and decreased magnesium excretion by diseased kidneys. The lower serum magnesium levels among patients with coronary artery disease is an interesting finding because there are very few reports addressing this issue among dialysis patients[12] and because it is of great importance taking into consideration the increased incidence of CAD among these patients. We do not say that there is a causative relationship between serum magnesium level and CAD but special attention should be paid under the light of previous findings among general population which showed that magnesium content of myocardium among persons dying from myocardial infarction is significantly lower than among persons dying from accidents and that magnesium content of myocardium was closely related with drinking water hardness[13]. The negative effect of chronic use of PPIs upon serum magnesium level is a recently recognized harm of these drugs and according to a recent review only 23 cases of documented hypomagnesaemia attributable to PPIs have been reported in literature[14]. According to our knowledge no report concerning the effect of PPIs upon serum magnesium level in haemodialysis patients published in literature until now. Although there is strong evidence that serum magnesium affects vascular calcification in haemodialysis patients[3,11,12] our data doesn't support this hypothesis but it is worthy to emphasize that, as mentioned above, no one of known variables which affect vascular calcification showed any significant effect upon this hazardous complication although iPTH, haemodialysis duration and magnesium level found to exhibit a weak relationship but not statistically significant. Although our study is underpowered this finding may suggest that vascular calcification is genetically determined and acquired disturbances of internal milieu simply accelerates the emergence of this phenomenon which is absolutely truth in ESRD patients with known derangement of calcium, phosphate and magnesium metabolism as well as PTH secretion. Recently an original article published by Hilaire CS et al suggest that certain mutations of NT5E gene encoding the production of CD73 protein which converts ATP to adenosine are responsible for the familial occurrence of extensive vascular calcifications of the lower extremities and joint calcifications among members of studied families[15]. Another topic which is controversial in literature is

the effect of serum magnesium upon PTH level[12]. Our data support a neutral effect of magnesium level upon iPTH level it is worthy to emphasize that multiple regression analysis between iPTH level and magnesium, calcium, phosphate and CaXP product revealed again a neutral effect of all tested variables upon iPTH level. We have to note that 22 of our patients received cinacalcet, because of increased iPTH levels, for more than six months and additional four patients underwent previous parathyroidectomy because of severe hyperparathyroidism but by excluding these patients from the statistical model we obtained again comparable results.

Administration of magnesium containing phosphate binders (CalMag) in twelve patients proved efficient in lowering serum phosphorus level but in expense of a significant increase in pre-dialysis serum magnesium level although no hazardous hypermagnesaemia was observed in our patients probably because we selected patients with low serum magnesium (<3.0 mg/dl). Substitution of dialysate with a lower magnesium concentration (0.75 mEq/L) achieved a significant decrease of pre-dialysis magnesium level comparable to that before CalMag administration. These findings suggest that magnesium containing phosphate binders are effective and safe in lowering phosphorus level in selected haemodialysis patients and that serum magnesium concentration is easily manipulated by dialysate magnesium concentration. Until large scale randomized controlled trials become available, using low magnesium concentration dialysate in order to avoid hypermagnesaemia and bone magnesium accumulation in haemodialysis patients seems reasonable but not definite answer can be given.

Comparing the efficacy of individual phosphate binders upon calcium, phosphate and CaXP product we did not find any significant difference upon serum level of phosphorus and calcium as well as upon CaXP product. A comparison of calcium levels between patients on CalMag or calcium carbonate did not reveal any significant result. These findings suggest that CalMag possesses similar efficacy compared to the usual phosphate binders in lowering phosphate levels without producing significant disturbances in calcium and calcium-phosphate product. More over calcium levels were comparable between CalMag and calcium carbonate phosphate binders. The three-month cost favours firstly the use of Titralac and secondly OsvaRen but we have to account more concern in choosing the proper phosphate binder among individual patients. Our findings support the use of CalMag in selected haemodialysis patients by taking into consideration a possibly beneficial effect of mildly increased serum magnesium level among these patients.

References

1. Stewart WK. The composition of dialysis fluid. In "Replacement of renal function". 3rd edition, edited by John F. Maher, Kluwer Academic Publishers. 1989, pp 199-217.
2. Wacker WEC, Parisi AF. Magnesium metabolism. N Engl J Med. 1968; 278: 658-663.
3. Meema HE, Oreopoulos DG, Rapoport A. Serum magnesium level and arterial calcification in end-stage renal disease. Kidney Int. 1987; 32: 388-394.
4. Ma J, Folsom AR, Melnick SL, Eckfeldt JH, Sharrett AR, Nabulsi AA, et al. Associations of serum and dietary magnesium with cardiovascular disease, hypertension, diabetes, insulin, and carotid arterial wall thickness: the ARIC study. Atherosclerosis Risk in Communities Study. J Clin Epidemiol. 1995; 48: 927-940.
5. O'Donovan R, Baldwin D, Hammer M, Moniz C, Parsons V. Substitution of aluminum salts by magnesium salts in control of dialysis hyperphosphataemia. Lancet. 1986; 1: 880-882.
6. Tzanakis IP, Papadaki AN, Wei M, Kagia S, Spadidakis VV, Kallivretakis NE, et al. Magnesium carbonate for phosphate control in patients on haemodialysis. A randomized controlled trial. Int Urol Nephrol. 2008; 40: 193-201.
7. de Francisco ALM, Leiding M, Covic AC, Ketteler M, Benedyk-Lorens E, Mircescu GM, et al. Evaluation of calcium acetate/magnesium carbonate as a phosphate binder compared with sevelamer hydrochloride in haemodialysis patients: a controlled randomized study (CALMAG study) assessing efficacy and tolerability. Nephrol Dial Transplant. 2010; 25: 3707-3717.
8. Gonella M, Calabrese G. Magnesium status in chronically haemodialyzed patients: the role of dialysate magnesium concentration. Magnes Res. 1989; 2: 259-265.
9. Katopodis KE, Koliousi EL, Andrikos EK, Pappas MV, Elisaf MS, Siamopoulos KC. Magnesium homeostasis in patients undergoing continuous ambulatory peritoneal dialysis: role of the dialysate magnesium concentration. Artif Organs. 2003; 27: 853-857.
10. Kyriazis J, Kalogeropoulou K, Bilirakis L, Smirnioudis N, Pikounis V, Stamatiadis D, et al. Dialysate magnesium level and blood pressure. Kidney Int. 2004; 66: 1221-1231.
11. Spiegel D. Magnesium in chronic kidney disease: unanswered questions. Blood Pur. 2011; 31: 172-176.
12. Tzanakis IP, Oreopoulos DG. Beneficial effects of magnesium in chronic renal failure: a foe no longer. Int Urol Nephrol. 2009; 41: 363-371.
13. Anderson TW, Neri LC, Schreiber GB, Talbot FDF, Zdrojewski A. Ischemic heart disease, water hardness and myocardial infarction. CME Journal. 1975; 113: 199-203.
14. MacKay JD, Bladon PT. Hypomagnesaemia due to proton-pump inhibitor therapy: a clinical case series. Q J Med. 2010; 103: 387-395.
15. St Hilaire C, Ziegler SG, Markello TC, Brusco A, Groden C, Gill F, et al. NT5E mutations and arterial calcifications. N Engl J Med. 2011; 364: 432-442.