Original article

Hypomagnesemia in hemodialysis is associated with increased mortality risk: Its relationship with dialysis fluid☆

Rafael Pérez-García*, María Teresa Jaldo, Marta Puerta, Mayra Ortega, Elena Corchete, Patricia de Sequera, Juan Antonio Martin-Navarro, Marta Albalate, Roberto Alcázar

Servicio de Nefrología, Hospital Universitario Infanta Leonor, Madrid, Spain

ABSTRACT

Hypomagnesaemia in haemodialysis (HD) is associated with increased mortality risk: its relationship with dialysis fluid (DF).

Introduction: Low concentrations of magnesium (Mg) in blood have been linked to the development of diabetes, hypertension, arrhythmias, vascular calcifications and an increased risk of death in the general population and in haemodialysis patients. The composition of the dialysis fluid in terms of its magnesium concentration is one of the main determinants of magnesium in haemodialysis patients.

Objective: To study magnesium concentrations in haemodialysis patients, their predictive mortality rate and what factors are associated with hypomagnesaemia and mortality in haemodialysis.

Methods: Retrospective study of a cohort of prevalent haemodialysis patients followed up for two years. Serum magnesium was measured every six months. The analysis used the initial and average magnesium values for each patient, comparing patients with magnesium below the mean (2.1 mg/dl) with those with magnesium above the mean. During the follow-up, three types of dialysis fluid were used: type 1, magnesium 0.5 mmol/l; type 3, magnesium 0.37 mmol/l (both with acetate); and type 2, magnesium 0.5 mmol/l with citrate.

Results: We included 137 haemodialysis patients in the study, of which 72 were male and 65 were female, with a mean age of 67 (15) [26–95] years old. Of this group, 57 patients were diabetic, 70 were on online haemodiafiltration (OL-HDF) and 67 were on high-flow haemodialysis (HF-HD). The mean magnesium of the 93 patients with dialysis fluid type 1 was 2.18 (0.37) mg/dl. In the 27 patients with dialysis fluid type 3 it was 2.02 (0.42) mg/dl. And in the 17 with dialysis fluid type 2 it was 1.84 (0.24) mg/dl (p = 0.01). There was a pronounced direct relationship between Mg and P and albumin. After a mean follow-up of 16.6 (8.9) [3–24] months, 77 remained active, 24 had died and 36 had been transplanted or transferred. Patients with magnesium above than 2.1 mg/dl had a longer survival (p = 0.008). The survival of patients with the three types of dialysis fluid did not differ significantly (Log-Rank, p = 0.424). Corrected for blood magnesium, patients with dialysis fluid with

☆ Please cite this article as: Pérez-García R, Jaldo MT, Puerta M, Ortega M, Corchete E, de Sequera P, et al. La hipomagnesemia en hemodiálisis se asocia a mayor riesgo de mortalidad: su relación con el líquido de diálisis. Nefrologia. 2020;40:552–562.

* Corresponding author.
E-mail address: rperezgarica@senefro.org (R. Pérez-García).

citrate have better survival (p = 0.009). The COX regression analysis shows how age, serum albumin, magnesium, dialysis technique and type of dialysis fluid have an independent predictive mortality rate.

Conclusions: Low serum magnesium levels have a greater association with an increased risk of mortality compared to high levels. The type of dialysis fluid affects the magnesium concentration and the risk of death.

La hipomagnesemia en hemodiálisis se asocia a mayor riesgo de mortalidad: su relación con el líquido de diálisis

R E S U M E N

La hipomagnesemia en hemodiálisis (HD) se asocia a mayor riesgo de mortalidad: su relación con el líquido de diálisis (LD).

Introducción: Concentraciones bajas de magnesio (Mg) en sangre se han relacionado con el desarrollo de diabetes, hipertensión arterial, arritmias, calcificaciones vasculares y con mayor riesgo de muerte, en población general y en hemodiálisis. La composición del LD y su concentración de Mg es uno de los principales determinantes de la magnesemia en los pacientes en HD.

Objetivo: Estudiar las concentraciones de magnesio en los pacientes en HD, su valor predictivo de mortalidad y qué factores se asocian a la hipomagnesemia y mortalidad en HD.

Métodos: Estudio retrospectivo de una cohorte de pacientes prevalentes en HD seguidos 2 años. Cada 6 meses se determina el Mg sérico. En el análisis se utiliza el Mg inicial y el medio de cada paciente, comparando los pacientes con Mg por debajo de la media, 2,1 mg/dl, con los que están por encima. Durante el seguimiento se han utilizado 3 tipos de LD: tipo 1, magnesio de 0,5 mmol/l y tipo 3, Mg 0,37 mmol/l ambos con acetato y tipo 2, 0,5 mmol/l de Mg con citrato.

Resultados: Se han incluido en el estudio 137 pacientes en hemodiálisis, 72 hombres y 65 mujeres, con una edad media de 67(15) [26–95] años. 57 pacientes eran diabéticos y 70 pacientes estaban en hemodiafiltración en línea (HDF-OL) y 67 en hemodiálisis de alto flujo (HD-HF). El Mg medio de los 93 pacientes con LD tipo 1 era: 2,18(0,37)mg/dl, en 27 con el tipo 3: 2,02 (0,42)mg/dl y los 17 con tipo 2: 1,84 (0,24)mg/dl (p = 0,01). El Mg se relaciona de forma directa significativa con el P y con la albumina. Después de un seguimiento medio de 16,6(8,9)[3–24] meses, 77 seguían activos, 24 habían fallecido y 36 se habían trasplantado o trasladado. Los pacientes con un Mg superior a 2,1 mg/dl tienen una supervivencia mayor, p = 0,008. La supervivencia de los pacientes con los tres tipos de LD no difería significativamente, Log-Rank, p = 0,424. Corregido por la magnesemia, los pacientes con LD con citrato tienen mejor supervivencia, p = 0,009. En el análisis de regresión de COX se observa como la edad, albumina sérica, Mg, técnica de diálisis y tipo de LD tienen valor predictivo de mortalidad independiente.

Conclusiones: Los magnesios séricos bajos respecto a los altos se asocian a mayor riesgo de mortalidad. El tipo de LD influye en la concentración de Mg y en el riesgo de muerte.

Introduction

Low magnesium (Mg) concentrations in blood have been associated to the development of diabetes, high blood pressure, cardiac arrhythmias and even an increased risk of death in the general population[1–8] and Mg intake is inversely related to the incidence of metabolic syndrome.[9]

Extracellular Mg correspond to 1% of the total body Mg. A 99% is contained in the intracellular compartment. Normal values of serum are 0.71–1.05 mmol/l (1.7–2.5 mg/dl), which are distributed as a 33% bound to proteins, 62% as ionized Mg and a 5% as anions complexes.[10–12] Serum [Mg] levels is partially regulated, its functional reservoir is the bone.

The intake of Mg is associated with the intake of foods recommended in a healthy diet.[11,12] One third of the Mg

ingested would is absorbed.[13] The net intestinal absorption of Mg is 100 mg/day, which is balanced by a renal excretion of 100 mg/day, after a tubular reabsorption of 2300 mg/day. In renal failure, serum Mg tends to increase due to lower filtration, although the tubular reabsorption is decreased.[14]

In hemodialysis (HD) patients, without significant residual renal function, Mg elimination takes place during the dialysis sessions. Therefore, the serum Mg level will depend on the intake, which is generally decreased in the recommended diets[11,12] and the dialysance of Mg. The dialysance of Mg depends on the effectiveness of the HD procedure, the K and the concentration of Mg in the dialysate. Generally, dialysis is performed with a Mg concentration of 0.5 mmol/l (1.2 mg/dl), so that the magnesium level is usually maintained around 2.3 and 2.4 mg/dl, but with that Mg concentration maintained in the dialysis fluid there are patients with hypomagnesemia and also with hypermagnesemia. It is also necessary to take into account the use of medication containing Mg in the composition[15] or those that interfere with Mg absorption such as omeprazole.[12]

In HD patients, serum Mg concentrations are associated with mortality.[16–22] Cardiac arrhythmias are a very prevalent cause of death in HD patients. Hypomagnesemia is associated with increased QT and arrhythmias[23]; the simultaneous occurrence of changes in serum potassium and metabolic alkalosis may potentiate the arrhythmogenic effects of hypomagnesemia. Cardiovascular mortality is the most prevalent in HD patients. Vascular injury and calcifications are frequent in HD patients and are associated with a high risk of death. The magnitude of vascular calcifications in HD patients is inversely related to magnesium levels.[24] It has been shown that Mg supplementation reduces the thickening of the arterial wall.[25]

To interpret correctly the association between hypomagnesemia and mortality, it is essential to know the cause of hypomagnesemia. One possibility is that hypomagnesemia is associated to a low Mg intake, malabsorption or malnutrition. Another possibility is a negative Mg balance during hemodialysis that is not compensated by Mg intake.

For years we have been using dialysate with citrate instead of acetate as a stabilizer. For the same calcium concentration in the dialysate, the calcium balance in HD is lower with citrate than with acetate.[26–29] This is due to the increase in calcium associated with citrate that diffuses from the blood to the dialysis fluid. Something similar happens with Mg that could explain the decrease in magnesium levels with the use of citrate in the dialysis fluid.[30]

Objective

To evaluate the Mg concentration in the HD patients. Investigate the predictive value of Mg concentration on mortality on hemodialysis patients and what are the factors associated with both hypomagnesemia and mortality.

1 To determine the magnesium concentrations in HD patients and its value as a predictor of mortality.
2 Analyze if patients with citrate in the dialysis fluid have lower levels of Mg than with acetate.

3 Study what factors are associated with hypomagnesemia and mortality in HD.

Methods

Design

This is a retrospective study to assess survival in a cohort of prevalent HD patients from 2014, followed for 2 years until the end of 2016. Mortality during follow-up has been evaluated in relation to epidemiological parameters, comorbidities, hemodialysis procedure with special emphasis on the type of dialysis fluid and, laboratory parameters with special emphasis on Mg.

Patients

Inclusion criteria: prevalent HD patients from the Infanta Leonor University Hospital Unit during 2014. Patients were on Chronic HD, over 18 years of age and signed an informed consent to allow the use of their clinical and laboratory information.

Exclusion criteria: patients with follow-up of less than 3 months or with less than 3 sessions of HD per week with significant residual renal function.

Hemodialysis technique

The dialyzers used wereAK200us® and Artis® (Baxter) and ST5008 (Fresenius, FMC, Bad Homburg, Germany). All machines have ionic dialysance (Diascan® or OCM®). The machines were connected to the TSS® computer application, automatically uploading the data for each session. Ultra-pure Dialysis fluid was used with levels of colony-forming units/ml below 0.1 and endotoxin levels below 0.03 EU/ml (SEN Guides). Patients were dialyzed 3 days per week for minimum of 12 hours a week, except those with significant residual renal function. There were high permeability dialyzers with synthetic membranes and a surface between 1.8 and 2.1 m^2. Patients with adverse reactions to these membranes were dialyzed with cellulose triacetate. The blood flow was the maximum allowed by vascular access without a drop of arterial line pressure below

-220 mmHg. Dialysis techniques were: online hemodiafiltration (OL-HDF) and high-flow HD (HF-HD).

During follow-up, 5 formulas of dialysis fluid (LD) were used, which have been grouped into three types: type 1 (Mg of 0.5 mmol/ L) and type 3 (Mg 0.37 mmol/L) both with acetate and type 2 (Mg 0.5 mmol/L) with citrate. The full composition is specified in the Table 1.

Parameters evaluated

The following parameters were analyzed: age, sex, underlying disease, comorbidity, dialysis technique HDF-OL/ HD-HF and Kt.

Biochemical parameters: sodium (Na), potassium (K), magnesium (Mg), total calcium (Ca t) and ionized Calcium (Ca^{++}), phosphorus (P) and parathyroid hormone (PTH). The pH

Table 1 – Composition of the dialysis fluids used.												
Dialysis fluid	Formula	Reference	Na mmol/l	Ca mmol/l	Mg mmol/l	K mmol/l	Cl mmol /l	Citrate mmol/l	Acetate mmol/l	Bicarbonate mmol/l	Glucose mmol/l	Osmolarity mOsm/L
Type 1	Gambro® Acetate	G295	140	1.5	0.5	two	109	0	3	35	8.33	294
Type 1	FMC® Acetate	ACF 3A5	140	1.5	0.5	two	107	0	4	35	8.33	296
Type 2	Gambro® Citrate	CX 265 G	140	1.65	0.5	two	109.3	1	0	34	8.33	
Type 2	Citrasate®	303-C (A+B)	139.3	1.5	0.5	1.9	104.37	0.8	0.3	35	8.33	287.22
Type 3	Gambro® Acetate	G196	140	1.5	0.37	1.5	108	0	3	34	8.33	

The 5 formulas are grouped into 3 types of LD: type 1 (Mg of 0.5 mmol/L) and type 3 (Mg 0.37 mmol/L) both with acetate and type 2 (Mg 0.5 mmol/L) with citrate.
Ca: calcium; Cl: chloride; Glu: glucose; K: potassium; Mg: magnesium; Na: sodium.

was measured by potentiometry, the pCO2 by Sveringhaus electrode, the pO2 by amperometry and the Ca^{++} by ion selective electrode (ISE). Biochemical determinations were obtained with an autoanalyzer (ADVIA® 2400 Chemistry System, Bayer). PTH determinations were made by chemiluminescence, using the ADVIA CENTAUR system from Bayer.

The serum concentration of Mg was was measured every 6 months. The initial Mg and the mean of the determinations in each patient were used for analysis.

Information was collected on whether or not the patient was on proton pump inhibitors (PPIs).

Evolution

The patients were followed until the end of 2016. Information recorded included whether the patients was still active, had received a transplant, was lost to follow-up or died.

Statistics

Variables with normal distribution are expressed as the mean and the standard deviation. The only variable with a non-normal distribution was the C-reactive protein (CRP), Kolmogorov-Smirnov Z, and with Log transformation it was possible to transform it into normal distribution.

For statistical analyzes, the serum Mg concentration was considered the first predialysis serum Mg concentration determined in each patient upon inclusion in the study. The mean of the Mg determinations in each patient was also evaluated.

The variable predialysis serum Mg concentration has been categorized as low and high, using the mean value of the population, 2.1 mg/dl, as the cut-off point.

The differences of the analytical variables according to the types of dialysis fluid was analyzed by one-step analysis of variance after performing the Levene test.

Test of Pearson was used to analyze bivariate correlations between variables with normal distribution.

Kaplan–Meier survival curves have been calculated and the factors were compared using the log rank test (Mantel-Cox). Stepwise Cox regression has been used, to elucidate the variables that independently influence mortality.

A $p < 0.05$ has been considered significant. SPSS 15.0 (Chicago. Illinois. USA) has been used for statistical analysis.

Results

The study included 137 hemodialysis patients, 72 men and 65 women, with a mean age of 67(15) years, ranging from 26 to 95 years. The causes of CKD were: diabetes 32.8%, glomerulonephritis 16.1%; vascular disease 11.7%; tubulointerstitial nephropathy 7.3%; adult polycystic kidney disease 5.8%; other nephropathies 9.5% and a 16.8% of unknown etiology. At the time of the study, there were 57 patients with diabetes.

Table 2 provides the data on biochemical parameters at baseline. The mean initial Mg of the patients was 2.1 (0.39) mg/dl. Serum Mg was determined 578 times in the 137 patients, between 1 and 5 times per patient during follow-up. The overall mean Mg concentration was 2.07 (0.34) mg/dl, ranging among the patients from 1.2 and 3.75 mg / dl. In

Table 2 – Baseline biochemical data.

N = 137	Mean	Standar Deviation	Minimum	Maximum
Mg (mg/dl)	2.1059	0.38735	1.20	3.70
Ca t. (mg/dl)	8.5626	0.85173	6.20	11.10
Ca $^{++}$ (mmol/l)	1.1656	0.11579	0.72	2.17
P (mg/dl)	4.7316	1,46053	1.20	9.00
PTH (pg/ml)	442.3605	299.11870	36.00	1555.00
25-OH VitD (ng/ml)	20.9106	7.41629	6.50	37.90
Bicarbonate (mmol/l)	21.7543	3,28365	14.20	33.40
Albumin (g/dl)	3.0243	0.59597	1.20	4.00
CRP (mg/l)	2.9105	4.52759	0.10	22.86

The serum Mg concentration significantly correlates with serum levels of P and Albumin (Fig. 1).

patients the initial Mg does not differ significantly from the average Mg.

A 67.9% of the patients (n = 93), were dialyzed with a dialysis fluid (type 1) containing acetate and Mg 0.5 mmol/l; a 12.4% of patients (n = 17) were dialyzed, with dialysis fluid (type 2) containing citrate and Mg 0.5 mmol/l and a 19.7% (n = 27) were dialyzed with dialysis fluid (type 3) with acetate and Mg 0.37 mmol/l. The mean value of serum Mg concentration in the 93 patients dialyzed with type 1 of dialysis fluid was: 2.18 (0.37) mg/dl, in the 27 patients on type 3 the mean Mg was 2.02 (0.42) mg/dl and the 17 on type 2 the mean value of Mg was 1.84 (0.24) mg/dl (p = 0.01) (Table 3).

Patients on treatment with proton pump inhibitors (PPI), n = 102, (74%) show serum Mg no different from those who did not take it, n = 35, (26%).

After a mean follow-up of 16 [3–24] months,[8,9] 77 patients remain still active, 24 had died and 36 had been transplanted or transferred. Patients with a Mg greater than 2.1 mg/dl have a longer survival than those with a lower Mg (Fig. 2). Survival of patients with the three types of dialysis fluid did not differ significantly, Log-Rank, p = 0.424 (Fig. 3). If the effect of the type of dialysis fluid on mortality is corrected the level of Mg, patients with citrate, dialysis fluid type 2, have better survival than those dialyzed with acetate (Fig. 4).

Table 4 shows that age, albumin, Mg, dialysis technique and type of dialysis fluid have an independent predictive effect on mortality.

Discussion

Serum Mg concentrations and mortality on HD

The present study shows that hemodialysis patients with serum Mg concentrations greater than mean of the population have a better survival than patients with values of Mg below the mean. Similar result has been observed in previous studies.[16–22] In these studies, patients separated into two or three categories were compared according to the Mg concentrations. The patients with the best prognosis were those with high serum Mg concentration. In the work by Ishimura et al[16] the cut-off point for Mg concentration favoring survival was 2.77 mg/dl of Mg. In another study in non-diabetic patients, the cut-off point was 2.5 mg/dl,[20] which is higher than the value of 2.1 mg/dl obtained in our study. In the present study, the mean serum Mg concentration is lower than in others, probably due

to the use in some patients of dialysis fluid with low Mg or with citrate. After the analysis of our results, our patients have not been dialyzed with a low Mg concentration in the dialysis fluid and higher Mg has been requested for some patients with acetate and for all patients on citrate.

The better survival of patients with high Mg in HD has been associated with a better nutritional status, with higher concentrations of albumin, triglycerides, phosphorus and lower values of CRP[19] and with a lower degree of inflammation.[18,22,31] Yu et al.[22] observed that serum concentrations of albumin, urea, creatinine and uric acid were higher in patients with hypermagnesemia and the CRP and Lipoprotein A were lower.

In the work of Mizuiri et al[31] the independent predictive value of Mg concentration on mortality is lost if albumin is included in the analysis which would mean for the authors that its role would be held in the nutritional status of the patient. In our study, both Mg and Albumin concentration maintains its independent predictive value for mortality, suggesting some other beneficial effect of Mg apart from the nutritional status, such as vascular calcifications and cardiac arrhythmias.

Why do some HD patients maintain a higher serum Mg than others?

In some of the previous studies it was deduced that a better nutritional state is related to higher levels of Mg. The intake of Mg is associated with foods recommended in a healthy diet.[11,12] The intake of Mg is currently decreasing and may not be sufficient to maintain the magnesium levels required to prevent diseases.[11] The diet that is usually recommended for chronic kidney disease (CKD) patients, before or after initiation of regular HD is focused on K, P and proteins and not on Mg, and its content is often low. Adequate and sufficient intake will contribute to higher levels of Mg and better nutritional status.

In other studies, a higher concentration of serum Mg was due to treatment with MgO.[19] Treatment with P binders containing Mg could contribute to higher levels of Mg.[15,32] A reduced concentration of Mg is associated with treatment with PPI drugs.[33–35] In our case, it was not observed the association of low Mg with PPI drugs, probably because it is masked by the lower concentrations of Mg induced by some of the dialysis fluids.

		N	Mean	Standard deviation	Standard error	Confidence interval 95%		F	p
						Lower limit	Upper limit		
Mg	Acetate 0.5	93	2.1785	0.37441	0.03882	2.1014	2.2556		
	Citrate	17	1.8353	0.24480	0.05937	1.7094	1.9612		
	Low acetate	27	2.0231	0.42361	0.08308	1.8520	2.1942		
	Total	137	2.1059	0.38735	0.03321	2.0402	2.1716	6,937	**0.001**
Ca t	Acetate 0.5		8.5912	0.77827	0.08158	8.4291	8.7533		
	Citrate		8.3800	0.95109	0.24557	7.8533	8.9067		
	Low acetate		8.5680	1.05187	0.21037	8.1338	9.0022		
	Total		8.5626	0.85173	0.07442	8.4154	8.7098	0.393	0.676
Ca ++	Acetate 0.5		1.1813	0.12280	0.01287	1.1557	1.2069		
	Citrate		1.0871	0.02823	0.00685	1.0725	1.1016		
	Low acetate		1.1617	0.10602	0.02164	1.1169	1,2064		
	Total		1.1656	0.11579	0.01008	1.1457	1.1855	5,059	**0.008**
P	Acetate 0.5		4.6548	1.48254	0.15373	4.3495	4.9602		
	Citrate		4.5412	0.96505	0.23406	4.0450	5.0374		
	Low acetate		5.1308	1.61933	0.31758	4.4767	5.7848		
	Total		4.7316	1.46053	0.12524	4.4839	4.9793	2.815	0.063
PTH	Acetate 0.5		440.8200	343.63986	48.59802	343.1586	538.4814		
	Citrate		544.5625	223.08383	55.77096	425.6895	663.4355		
	Low acetate		364.4500	203.08813	45.41189	269.4018	459.4982		
	Total		442.3605	299.11870	32.25480	378.2293	506.4916	**6.937**	**0.001**
Bic	Acetate 0.5		21.9854	3.36721	0.35692	21.2761	22.6947		
	Citrate		20.3563	2.54741	0.63685	18.9988	21.7137		
	Low acetate		21.8292	3.28957	0.67148	20.4401	23.2182		
	Total		21.7543	3.28365	0.28911	21.1822	22.3263	0.393	0.676
Alb	Acetate 0.5		2.9441	0.61086	0.06334	2.8183	3.0699		
	Citrate		3.1529	0.53282	0.12923	2.8790	3.4269		
	Low acetate		3.2269	0.53408	0.10474	3.0112	3.4426		
	Total		3.0243	0.59597	0.05110	2.9232	3.1253	**5.059**	**0.008**

The 5 formulas are grouped into 3 types of LD: type 1 (acetate 0.5, Mg 0.5 mmol/l), type 3 (low acetate, Mg 0.37 mmol/l) and type 2 (citrate, Mg 0.5 mmol/l).
Albumin g/dl; Bicarbonate mmol/l; Ca $^{++}$ mmol/l; Total Ca (Ca t) mg/dl; Mg mg/dl; P mg/dl; PTH pg/ml.
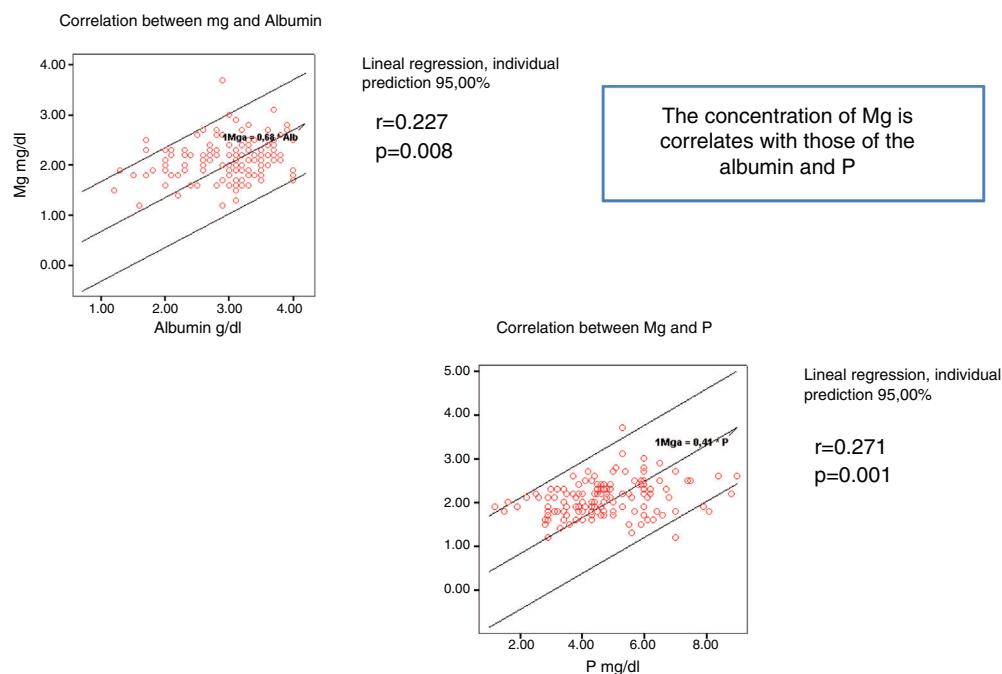In bold, statistically significant, p < 0.05.

Fig. 1 – **The concentration of Mg correlates with the concentration of albumin and P.**
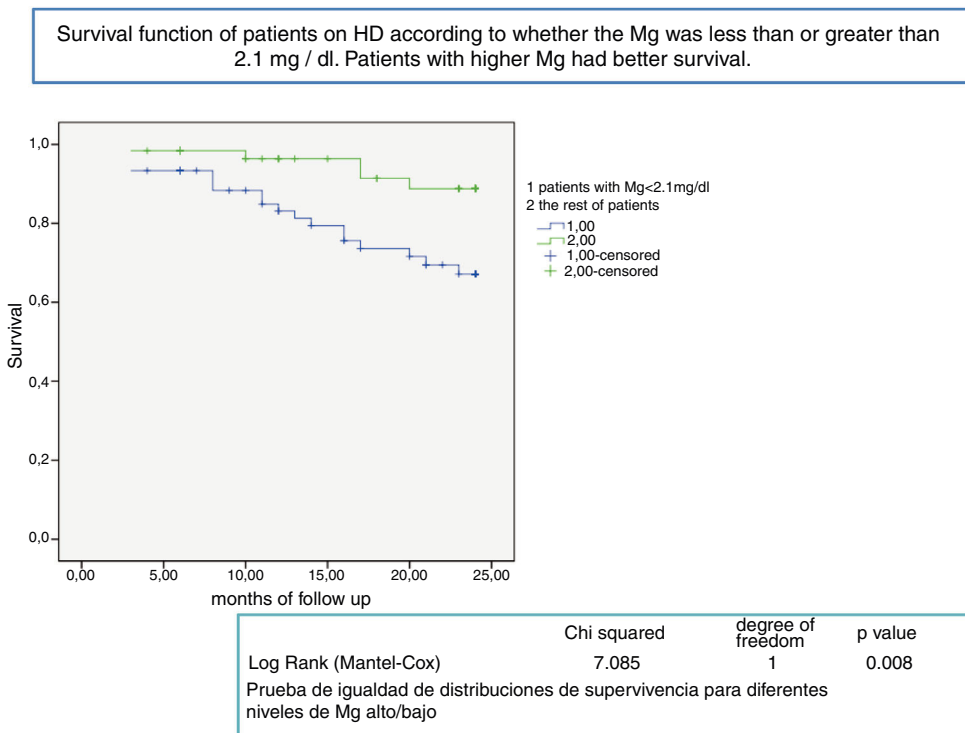
Fig. 2 – **Survival function of patients on HD according to whether the Mg was less than or greater than 2.1 mg/dl. Patients with higher Mg had better survival.**
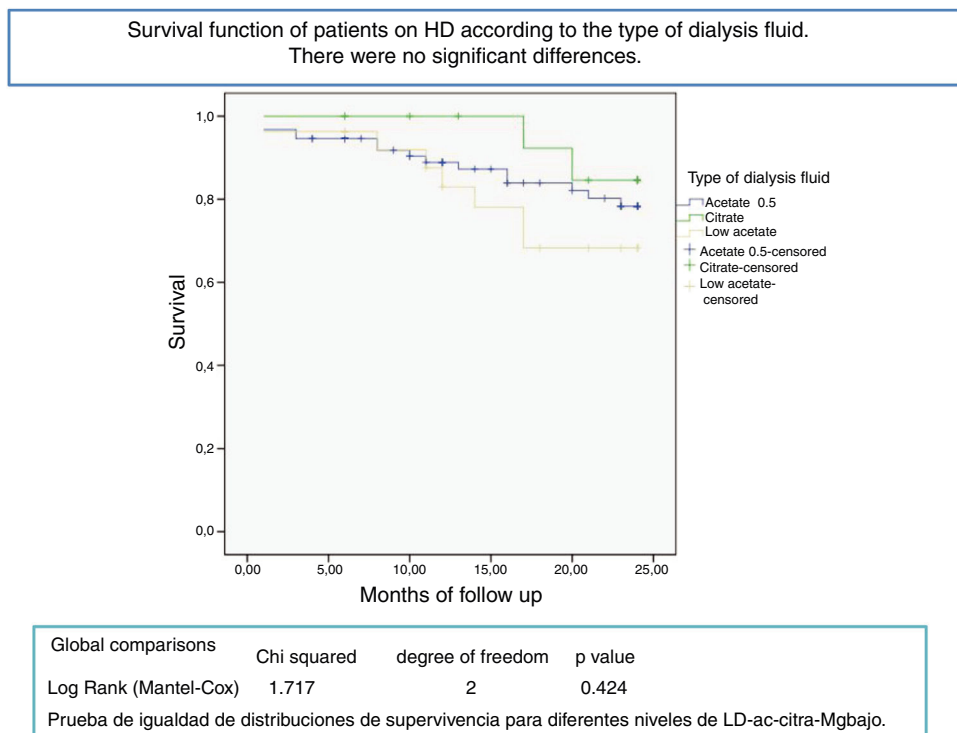

Fig. 3 – **Survival function of patients on HD according to the type of dialysis fluid. There were no significant differences.**
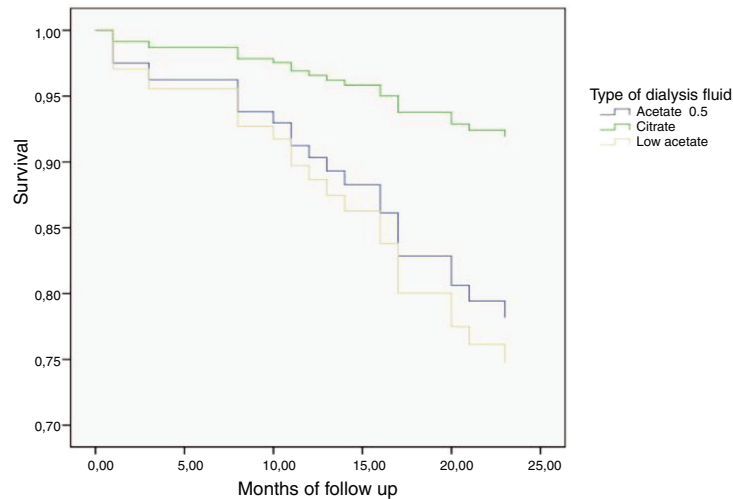
Fig. 4 – **Survival function with the three types of dialysis fluid corrected for serum Mg concentration. Is the positive effect of dialysis fluid without acetate offset by hypomagnesemia?**

Table 4 – COX survival analysis. Global score: gl 9, chi square 31.098; p = 0.00.									
	Mean	B	SE	Wald	df	p	Exp (B)	95.0% CI for Exp (B)	
								lower	higher
Age	67.274	0.058	0.021	7.564	1	**0.006**	1.059	1.017	1.103
Gender (M/F)	0.548	0.468	0.469	0.995	1	0.319	1.597	0.636	4.009
Diabetes (yes/no)	0.573	0.599	0.524	1.305	1	0.253	1.820	0.651	5.084
Mg mg/dl	2.117	-1.795	0.701	6.560	1	**0.010**	0.166	0.042	0.656
P mg/dl	4.673	0.311	0.178	3.045	1	0.081	1.364	0.962	1.934
Alb g/dl	3.001	-0.836	0.371	5.070	1	**0.024**	0.434	0.209	0.897
DF(type1,2,3)				4.616	2	0.099			
DF(type 1)	0.702	-0.176	0.493	0.128	1	0.720	0.838	0.319	2.201
DF (type 2)	0.113	-1.758	0.829	4.498	1	**0.034**	0.172	0.034	0.875
HDF-OL / HD technique	0.508	0.938	0.470	3.976	1	**0.046**	2.555	1,016	6,425

DF: dialysis fluid. In bold, statistically significant, p < 0.05.

As observed in our study in HD patients, the concentration of Mg in the dialysis fluids and the presence of acetate or citrate would be determinants of the serum Mg concentration. Others have shown that increasing Mg concentration in the dialysis fluid results in an elevation of serum Mg concentration [36].

In dialysis patients, the ionic Mg / total Mg ratio is decreased. That is, "normal" magnesium values in the general population may be indicative of true hypomagnesemia in HD patients [37]. This would be another argument to raise the content of magnesium in the Dialysis fluid. Alterations in the acid-base balance could influence the free fraction of magnesium.

Symptoms due to hypermagnesemia develop with concentration above 1.5 mmol/l (3.6 mg/dl); with values above 2.5 mmol/l there is areflexia and above 4.5 mmol/l respiratory or cardiac arrest may occur. These extremely high levels should be prevented, and generally caused by acute poisoning due to dialysate fluid contamination [38], or the massive intake of Epson's salt [39]. For the treatment of eclampsia, the therapeutic limits would be between 2.06 and 3.7 mmol/l.[40]

Effects of Mg that may influence the prognosis of the patient in HD

As in the general population, the association of serum Mg with mortality has also been described in patients with (CKD) not on dialysis.[41,42] Low serum Mg levels and low dietary magnesium intake would be associated with an increase in the incidence of CKD and its progression to advanced CKD.[42] This could be

due to the association of Mg with other factors that favor CKD progression and it may also be due to direct effects through endothelial dysfunction and vascular calcifications.

With respect to the HD treatment there are other factors that should be commented:

A relationship between the number of hypotensions and hypomagnesemia has been described.[43] Hypotension on dialysis is a determinant of morbidity and mortality.

In animal models it has been demonstrated the role of Mg on inflammation.[44] In HD patients there is an inverse relationship between CRP and Mg suggesting a role of low Mg on inflammation.[18] Thus, hypomagnesemia would be another of the factors involved in the chronic inflammatory status of HD patients.

In uremic rats, increasing Mg intake reduces mortality and reduce vascular calcifications.[45] The initiation of calcification by the complex Ca-PL-PO$_4$ is dependent on the Mg / Ca ratio present in the calcifying tissue.[46] Mg, by preventing the maturation of the calciprotein particles, would inhibit the calcification of the smooth muscle cells of the vessels induced by high P.[42] The risk of increased mortality associated with hyperphosphatemia would be attenuated by high Mg concentrations.[47] Serum Mg would be an independent predictor of the non-progression of vascular calcifications.[48] Increasing Mg in the dialysis fluid from 1.0 to 2.0 mEq / L decreases the rate of calcification in HD patients.[49]

Mg is capable of modulating PTH but with a lower potency than Ca. Hypermagnesemia could be associated with lower levels of PTH.[50] Mild hypermagnesemia would be associated with a lower risk of fractures in HD patients.[51] Mg has always been the great forgotten player of bone and mineral metabolism alterations.[52]

Changes in Mg along with modifications of K and Ca are associated with QT prolongation and the occurrence of cardiac arrhythmias.[53,54] Severe cardiac arrhythmias are a major cause of mortality in HD.

High concentrations of serum Mg would be related to a better response to erythropoietin (EPO).[55] The response index to erythropoietin is a prognostic marker.

Muscle function would be altered in HD patients with hypomagnesemia.[56]

All these effects of a low concentration of Mg could explain the relationship between Mg and mortality in HD patients.

Dialysis fluid (LD) and its influence on Mg and mortality in HD

The concentrations of Acetate in dialysis fluid commonly used in clinical practice, 3-4 mmol / l, increases the oxidative stress, the production of pro-inflammatory cytokines and synthesis of nitric oxide and may act as an adjunct to the other pro-inflammatory stimuli of uremic patients on HD.[57] The elimination of acetate from HD could improve survival of HD patients, at least in those older than 70 years.[58] Dialysis fluid with Citrate (CDF) do not produce this activation, so it could be an alternative in clinical practice. Citrate dialysis produces less acute post-dialysis alkalemia and modifies significantly serum levels of Ca, Mg and PTH.[30,59] CDF has a positive impact on hemodynamic tolerance.[30] Citrate in the dialysis fluid produces a negative balance of Ca and Mg[26–29] so it could induce hypomagnesemia in some patients.[39] The beneficial effect of a change of acetate by citrate could be counteracted by the development of hypomagnesemia. In the present work, the three types of dialysis fluids do not significantly influence mortality, but when the citrate dialysis fluid is associated with other variables and corrected for magnesium, it is associated with better survival. In the CDF, CX 265 G (Table 1) the concentration of Ca has been increased to 1.65 mmol/l to counteract the lower balance of Ca with citrate, the same should be done with Mg, which should at least be increased to 0.75 mmol/l. This would also be valid for some patients on dialysis fluid containing acetate; Schmaderer et al.[36] showed that by increasing the Mg concentration in the dialysis fluid to 0.75 mmol/l there is an improvement of cardiovascular mortality. The routine use of 0.5 mmol/l of Mg in dialysate with acetate would cause a slow decrease in serum Mg in most patients.[60]

Limitation of the study

Being a single center study the total number of patients recruited resulted to be low. This small number of patients prevented the inclusion of more variables in the regression model, although all patients being treated with the same guidelines reduces of this limitation.

Conclusions

Predialysis serum Mg concentrations above 2.1 mg/dl are associated with lower mortality than those with lower concentrations.

Dialysis fluids with Mg 0.37 mmol/l and acetate and with Mg 0.5 mmol/l and citrate are associated with low magnesium levels.

Dialysis fluids with citrate and Mg 0.5 mmol/l reduces the serum Mg concentration in the patient which neutralizes the possible beneficial effect of the dialysis fluid with citrate.

Hypothesis — future studies

It is postulated that the Mg content in the LD should be >0.5 mmol/l in some patients.

In the dialysis fluid with citrate, the Mg could be 0.75 mmol/l.

Hypothesis 1. An increase in the concentration of Mg above 0.5 mmol/l in the dialysis fluid with citrate could improve the clinical results.

Hypothesis 2. some patients with low Mg could benefit from a concentration greater than 0.5 mmol/L of Mg in the acetate dialysis fluid.

Conflict of interests

The authors declare that they have no conflict of interest.

REFERENCES

1. 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;48:927–40.

2. Pham PC, Pham PM, Pham SV, Miller JM, Pham PT. Hypomagnesemia in patients with type 2 diabetes. Clin J Am Soc Neph. 2007;2:366–73.

3. Larsson SC, Wolk A. Magnesium intake and risk of type 2 diabetes: a meta-analysis. J Intern Med. 2007;262:208–14.

4. Resnick LM, Oparil S, Chait A, Haynes RB, Kris-Etherton P, Stern JS, et al. Factors affecting blood pressure responses to diet: the Vanguard study. Am J Hypertens. 2000;13:956–65.

5. Touyz RM. Magnesium in clinical medicine. Front Biosci. 2004;9:1278–93.

6. Agus MS, Agus ZS. Cardiovascular actions of magnesium. Critical Care Clin. 2001;17:175–86.

7. Kaye P, O'Sullivan I. The role of magnesium in the emergency department. Emerg Med J. 2002;19:288–91.

8. Fairley JL, Zhang L, Glassford NJ, Bellomo R. Magnesium status and magnesium therapy in cardiac surgery: a systematic review and meta-analysis focusing on arrhythmia prevention. J Crit Care. 2017;42:69–77.

9. He K, Liu K, Daviglus ML, Morris SJ, Loria CM, Van Horn L, et al. Magnesium intake and incidence of metabolic syndrome among young adults. Circulation. 2006;113:1675–82.

10. Del Giorno R, Riva H, Donato G, Gabutti L. Ionized and total serum magnesium in hemodialysis: predictors and variability. A longitudinal cross-sectional study. Clin Exp Nephrol. 2018;22:620–8.

11. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium. An update on physiological, clinical and analytical aspects. Clin Chim Acta. 2000;294:1–26.

12. Vormann J. Magnesium: nutrition and metabolism. Mol Aspects Med. 2003;24:27–37.

13. Fine KD, Santa Ana CA, Porter JL, Fordtran JS. Intestinal absorption of magnesium from food and supplements. J Clin Invest. 1991;88:396–402.

14. Massry SG. Magnesium homeostasis in patients with renal failure. Contrib Nephrol. 1984;38:175–84.

15. de Francisco AL, Belmar L, Piñera C, Kislikova M, Seras M, Serrano M, et al. Effect of calcium acetate/magnesium carbonate in the treatment of hyperphosphataemia in dialysis patients in real clinical practice. One year follow up. Nefrologia. 2014;34(5):617–27.

16. Ishimura E, Okuno S, Yamakawa T, Inaba M, Nishizawa Y. Serum magnesium concentration is a significant predictor of mortality in maintenance hemodialysis patients. Magn Res. 2007;20(4):237–44.

17. Lacson E Jr, Wang W, Ma L, Passlick-Deetjen J. Serum magnesium and mortality in hemodialysis patients in the United States: a cohort study. Am J Kidney Dis. 2015;66(6):1056–66.

18. Selim GN, Spasovski G, Tozija L, Georgievska-Ismail L, Zafirova-Ivanovska B, Masin-Spasovska J, et al. Hypomagnesemia and cause-specific mortality in hemodialysis patients: 5-year follow-up analysis. Int J Artif Organs. 2017;40:542–9.

19. Tamura T, Unagami K, Okazaki M, Komatsu M, Nitta K. Serum magnesium levels and mortality in Japanese maintenance hemodialysis patients. Blood Purif. 2019;47 Suppl:1–7.

20. Shimohata H, Yamashita M, Ohgi K, Tsujimoto R, Maruyama H, Takayasu M, et al. The relationship between serum magnesium levels and mortality in non-diabetic hemodialysis patients: a 10-year follow-up study. Hemodial Int. 2019;23:369–74.

21. Wu L, Cai K, Luo Q, Wang L, Hong Y. Baseline serum magnesium level and its variability in maintenance hemodialysis patients: associations with mortality. Kidney Blood Press Res. 2019;44:222–32.

22. Yu L, Li H, Wang SX. Serum magnesium and mortality in maintenance hemodialysis patients. Blood Purif. 2017;43:31–6.

23. Gussak I, Gussak HM. Sudden cardiac death in nephrology: focus on acquired long QT syndrome. NDT. 2007;22:12–4.

24. Ishimura E, Okuno S, Kitatani K, Tsuchida T, Yamakawa T, Shioi A, et al. Significant association between the presence of peripheral vascular calcification and lower serum magnesium in hemodialysis patients. Clin Nephrol. 2007;68:222–7.

25. Turgut F, Kanbay M, Rusen Metin M, Uz E, Akcay A, Covic A. Magnesium supplementation helps to improve carotid intima media thickness in patients on hemodialysis F. Int Urol Nephrol. 2008;40:1075–82.

26. Perez-Garcia R, Albalate M, Sequera P, Ortega M. Calcium mass balance with citrate dialysate is lower than with acetate. Nefrologia. 2017;37:109–10.

27. Steckiph D, Bertucci A, Petraulo M, Baldini C, Calabrese G, Gonella M. Calcium mass balances in on-line hemodiafiltration using citrate-containing acetate-free and regular dialysis concentrates. In: Abstract ERA-EDTA Congress. 2013. p. 7.

28. Nilsson LG, Sternby J, Grundström G, Alquist M. Citrate dialysis fluid and calcium mass balance. In: Abstract ERA-EDTA Congress. 2013.

29. Grundström G, Christensson A, Alquist M, Nilsson LG, Segelmark M. Replacement of acetate with citrate in dialysis fluid: a randomized clinical trial of short term safety and fluid biocompatibility. BMC Nephrol. 2013;14:216–25.

30. de Sequera Ortiz P, Pérez-García R, Molina Nuñez M, Muñoz González RI, Álvarez Fernández G, Mérida Herrero E, et al. Prospective randomised multicentre study to demonstrate the benefits of haemodialysis without acetate (with citrate): ABC-treat Study. Acute effect of citrate. Nefrologia. 2019;39:424–33.

31. Mizuiri S, Nishizawa Y, Yamashita K, Naito T, Ono K, Tanji C, et al. Hypomagnesemia is not an independent risk factor for mortality in Japanese maintenance hemodialysis patients. Int Urol Nephrol. 2019;51:1043–52.

32. Tzanakis IP, Papadaki AN, Wei M, Kagia S, Spadidakis VV, Kallivretakis NE, et al. Magnesium carbonate for phosphate control in patients on hemodialysis. A randomized controlled trial. Int Urol Nephrol. 2008;40:193–201.

33. Nakashima A, Ohkido I, Yokoyama K, Mafune A, Urashima M, Yokoo T. Proton pump inhibitor use and magnesium concentrations in hemodialysis patients: a cross-sectional study. PLoS One. 2015, http://dx.doi.org/10.1371/journal.pone.0143656.

34. Ago R, Shindo T, Banshodani M, Shintaku S, Moriishi M, Masaki T, et al. Hypomagnesemia as a predictor of mortality in hemodialysis patients and the role of proton pump inhibitors: a cross-sectional, 1-year, retrospective cohort study. Hemodial Int. 2016;20:580–8.

35. de Francisco ALM, Varas J, Ramos R, Merello JI, Canaud B, Stuard S, et al. Proton pump inhibitor usage and the risk of mortality in hemodialysis patients. Kidney Int Rep. 2017;3:374–84.

36. Schmaderer C, Braunisch MC, Suttmann Y, Lorenz G, Pham D, Haller B, et al. Reduced mortality in maintenance haemodialysis patients on high versus low dialysate magnesium: a pilot study. Nutrients. 2017;9:926–35.

37. Sakaguchi Y, Hamano T, Kubota K, Oka T, Yamaguchi S, Matsumoto A, et al. Anion gap as a determinant of ionized

fraction of divalent cations in hemodialysis patients. Clin J Am Soc Nephrol. 2018;13:274–81.

38. Chakurkar VV, Gade PS, Godbole AV, Wadia FF, Lobo VA. Inadvertently high dialysate magnesium causing weakness and nausea in hemodialysis patients. Hemodial Int. 2019, http://dx.doi.org/10.1111/hdi.12763.

39. Shoaib Khan M, Zahid S, Ishaq M. Fatal hypermagnesemia: an acute ingestion of Epsom Salt in a patient with normal renal function. Caspian J Intern Med. 2018;9:413–5, http://dx.doi.org/10.22088/cjim.9.4.413.

40. Barbosa FT, Barbosa LT, Jucá MJ, Cunha RM. Applications of magnesium sulfate in obstetrics and anesthesia. Rev Bras Anestesiol. 2010;60:104–10.

41. Xiong J, He T, Wang M, Nie L, Zhang Y, Wang Y, et al. Serum magnesium, mortality, and cardiovascular disease in chronic kidney disease and end-stage renal disease patients: a systematic review and meta-analysis. J Nephrol. 2019;32:791–802.

42. Sakaguchi Y, Hamano T, Isaka Y. Magnesium and progression of chronic kidney disease: benefits beyond cardiovascular protection? Adv Chronic Kidney Dis. 2018;25:274–80.

43. Elsharkawy MM, Abla M, Youssef AM, Zayoon MY. Intradialytic changes of serum magnesium and their relation to hypotensive episodes in hemodialysis patients on different dialysates. Hemodial Int. 2006;10 Suppl 2:S16–23.

44. Mazur A, Maier JAM, Edmond Rock E, Gueux E, Nowacki c W, Rayssiguier Y. Magnesium and the inflammatory response: Potential physiopathological implications. Arch Biochem Biophys. 2007;458:48–56.

45. Diaz-Tocados JM, Peralta-Ramirez A, Rodrıguez-Ortiz ME, Raya AI, Lopez I, Pineda C, et al. Dietary magnesium supplementation prevents and reverses vascular and soft tissue calcifications in uremic rats. Kidney Int. 2017;92:1084–99.

46. Boskey AL, Posner AS. Effect of magnesium on lipid-induced calcification: an in vitro model for bone mineralization. Calcif Tissue Int. 1980;32:139–43.

47. Sakaguchi Y, Hamano T, Isaka Y. Effects of magnesium on the phosphate toxicity in chronic kidney disease: time for intervention studies. Nutrients. 2017;9:112–23, http://dx.doi.org/10.3390/nu9020112.

48. Tzanakis IP, Stamataki EE, Papadaki AN, Giannakis N, Damianakis NE, Oreopoulos DG. Magnesium retards the progress of the arterial calcifications in hemodialysis patients: a pilot study. Int Urol Nephrol. 2014;46:2199–205.

49. Bressendorff I, Hansen D, Schou M, Pasch A, Brandi L. The effect of increasing dialysate magnesium on serum calcification propensity in subjects with end stage kidney disease: a randomized, controlled clinical trial. Clin J Am Soc Nephrol. 2018;13:1373–80.

50. Navarro JF, Mora C, Jiménez A, Torres A, Macía M, García J. Relationship between serum magnesium and parathyroid hormone levels in hemodialysis patients. Am J Kidney Dis. 1999;34:43–8.

51. Sakaguchi Y, Hamano T, Wada A, Hoshino J, Masakane I. Magnesium and risk of hip fracture among patients undergoing hemodialysis. J Am Soc Nephrol. 2018;29:991–9.

52. Lorenzo V, Rodríguez Portillo M, Pérez-García R, Cannata JB. De la osteodistrofia renal a las alteraciones del metabolismo óseo y mineral asociado a la enfermedad renal crónica: evolución de un concepto. Nefrología. 2007;27:527–33.

53. Tumlin JA, Roy-Chaudhury P, Koplan BA, Costea AI, Kher V, Williamson D, et al. Relationship between dialytic parameters and reviewer confirmed arrhythmias in hemodialysis patients in the monitoring in dialysis study. BMC Nephrol. 2019;20:80–93.

54. Kim ED, Watt J, Tereshchenko LG, Jaar BG, Sozio SM, Kao WHL, et al. Associations of serum and dialysate electrolytes with QT interval and prolongation in incident hemodialysis: the Predictors of Arrhythmic and Cardiovascular Risk in End-Stage Renal Disease (PACE) study. BMC Nephrol. 2019;20:133–44.

55. Yu L, Song J, Lu X, Zu Y, Li H, Wang S. Association between serum magnesium and erythropoietin responsiveness in hemodialysis patients: a cross-sectional study. Kidney Blood Press Res. 2019;44:354–61.

56. Okazaki H, Ishimura E, Okuno S, Norimine K, Yamakawa K, Yamakawa T, et al. Significant positive relationship between serum magnesium and muscle quality in maintenance hemodialysis patients. Magnes Res. 2013;26:182–7.

57. Pérez-García R, Ramírez Chamond R, de Sequera Ortiz P, Albalate M, Puerta Carretero M, Ortega M, et al. Citrate dialysate does not induce oxidative stress or inflammation in vitro as compared to acetate dialysate. Nefrologia. 2017;37:630–7.

58. Mercadal L, Franck JE, Metzger M, Yuan W, Kolko A, Monnet E, et al. Improved survival associated with acetate-free haemodialysis in elderly: a registry-based study. Nephrol Dial Transplant. 2015;30:1560–8.

59. Šafránek R, Moučka P, Vávrová J, Palička V, Pavlíková L, Sulková SD. Changes of serum calcium, magnesium and parathyroid hormone induced by hemodialysis with citrate-enriched dialysis solution. Kidney Blood Press Res. 2015;40:13–21.

60. Leenders NHJ, van Ittersum FJ, Hoekstra T, Hoenderop JGJ, Vervloet MG. Routine hemodialysis induces a decline in plasma magnesium concentration in most patients: a prospective observational cohort study. Sci Rep. 2018;8:10256.