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Hypermagnesemia is Associated with All-Cause Mortality in Patients with Chronic Kidney Disease

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Abstract

Introduction: Hypomagnesemia has been associated with cardiovascular events and hypermagnesemia with overall mortality in the general population. However, in chronic kidney disease (CKD) the evidence is not as robust. The objective of our study was to investigate the relationship between magnesium levels and cardiovascular morbidity and mortality, all-cause mortality and the progression to end-stage kidney disease in a CKD population.

Methods: Observational study of a cohort of 746 patients with CKD followed in a Nephrology outpatient unit. Baseline characteristics and analytical profile were collected at first visit, and patients were stratified according to their baseline magnesium levels into three categories: hypomagnesemia: <1.7 mg/dl, normal magnesium: 1.7-2.2 mg/dl and hypermagnesemia: >2.2 mg/dl. After a mean follow-up period of of 42.6 months, the following events were recorded: cardiovascular events, initiation of renal replacement therapy (RRT) and overall mortality of any cause or cardiovascular cause, and the relationship between magnesium levels and these outcomes was investigated.

Results: 746 patients were analyzed, with a mean age of 70 ± 13 years, 62.9% were males, 45.2% had CKD stage 3 and 35.9% stage 4 at the start of follow-up. Mean baseline magnesium levels were 2.09 ± 0.33 mg/dl, and there was a close correlation between magnesium levels and serum creatinine, estimated glomerular filtration rate, phosphorus and PTH values. Calcitriol was associated with higher magnesium levels while calcium supplements and proton pump inhibitors were associated with lower magnesium levels. After a mean follow-up of 42.6 ± 19.6 months, 341 (45.7%) patients reached an event (Cardiovascular event, RRT initiation or death). Both patients with hypomagnesemia (Mg<1.7 mg/dl) and hypermagnesemia (Mg>2.2 mg/dl) had a higher risk of cardiovascular events (LogRank 4.45, p=0.035, and LogRank 7.45, p=0.006 respectively). In the multivariate analysis, they lost their predictive power. Patients with hypermagnesemia had a higher risk of all-cause mortality (Log Rank 13.11, p<0.001), while there was no association with hypomagnesemia. In the adjusted multivariate analysis, hypermagnesemia maintained its predictive power for all-cause mortality (HR=1.524, CI=1.002-2.319, p=0.049). After performing a propensity score matching for magnesium levels, we achieved two comparable groups of 94 patients, finding again a higher all-cause mortality in the hypermagnesemia group (Log Rank 17.48, p<0.001), that persisted in the Cox model adjusted for Calcium, Phosphorus and PTH. No association was found between magnesium levels and initiation of RRT.

Conclusion: Magnesium values increase as CKD advances. Low magnesium levels predict cardiovascular events in patients with stage 3 and 4 CKD. On the other hand, patients with hypermagnesemia have a higher risk of all-cause mortality and cardiovascular events. Thus, with the available evidence to date, magnesium supplementation should be used with caution in these patients.

Keywords: Hypomagnesemia; Hypermagnesemia; Chronic kidney disease; End-stage kidney disease; Cardiovascular morbidity; Calcitriol

Introduction

Magnesium is the fourth most frequent cation in the human body and the second in the intracellular compartment [1]. It plays a role in the regulation of mitochondrial functions, inflammatory processes and immune defense, as well as the processes of allergy, growth and stress, and the control of neuronal activity, cardiac excitability, neuromuscular transmission, vasomotor tone and blood pressure [2]. Because of this, magnesium homeostasis, dependent on intestinal absorption and renal excretion, needs to be tightly regulated. In Chronic Kidney Disease (CKD) patients, magnesium levels are higher due to the decline in glomerular filtration and hence the decrease in the fraction of magnesium excretion.

Magnesium levels have an important impact on the cardiovascular system function [3]. In the last 20 years, a large number of observational studies have investigated this relationship, 19 of them being gathered in a meta-analysis published by Qu et al. which showed an inverse relationship between serum magnesium levels and the occurrence of cardiovascular events in the general population [4]. In addition, a study of the Atherosclerosis Risk in Communities (ARIC) cohort, which included more than 14000 participants, found an independent association between hypomagnesemia and the onset of heart failure, with a hazard ratio (HR) of 1.7 [5]. A Spanish study conducted in more than 7000 adults also found an inverse relationship between serum magnesium and cardiovascular, cancer and all-cause mortality [6]. In the same way, several observational studies have linked hypermagnesemia with an increase in overall mortality in hospitalized patients [7], patients admitted to critical units [8,9], and a meta-analysis found an association between hypermagnesemia and cardiovascular mortality in elderly patients [10].

However, in CKD patients the evidence of a relationship between magnesium levels and cardiovascular morbidity and mortality is not as robust. Several studies performed in hemodialysis patients found a relationship between cardiovascular mortality and lower magnesium levels, but some of them warn of a J-shaped association between magnesium and cardiovascular events or cardiovascular mortality [11,12]. In CKD patients not on dialysis, most of the studies have looked for surrogate endpoints.

Therefore, the existing data in patients with CKD who are not on dialysis is insufficient. We set out this study with the aim of investigating the relationship between magnesium levels and the progression to end-stage kidney disease (ESKD), cardiovascular morbidity and mortality and all-cause mortality in a population with CKD stage 3 and 4 followed in the Nephrology outpatient unit.

Methods

Observational study of a cohort of 746 patients with CKD followed in the Nephrology outpatient unit. Patients were consecutively included between December 2010 and December 2012, and followed up to December 2016. The inclusion criteria were: 1) age over 18 years, 2) CKD stages 3-4 (not on dialysis) defined according to the KDOQI guidelines [13] and 3) follow-up in the nephrology outpatient clinic for at least one year. The exclusion criteria were 1) hospitalization in the four months prior to the start of the study and 2) declining participation in the study. The following data was compiled at their first visit: Demographic variables (age, gender), etiology of CKD, history of cardiovascular (CV) disease [acute myocardial infarction (AMI), congestive heart failure (CHF), peripheral vascular disease (PVD), and cerebrovascular disease (CVD)], cardiovascular risk factors [diabetes mellitus (DM), dyslipidemia (defined by values according to ATP III guidelines or according to statin treatment)], antihypertensive medication and medication that can potentially affect magnesium levels [diuretics, proton pump inhibitors (PPI) and other antacids, corticosteroids, digoxin, laxatives, calcium supplements, vitamin D or calcimimetics], as well as other conditions with a potential relationship with magnesium levels [atrial fibrillation (AF)]. Baseline analytical variables were also collected: estimated glomerular filtration rate (eGFR) according to the formula Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), urine albumin/creatinine ratio (Alb/Cr), total CO2, parathyroid hormone (PTH), 25-hydroxy vitamin D, calcium, phosphorus and magnesium levels. The routine clinical and biochemical variables were analysed according to standardized methods and autoanalysers. The method used for plasma creatinine (Crp) was a latex-based turbidimetric immunoassay on a Hitachi analyser (Sigma Chemical Co., St. Louis, Missouri, USA), and the immunonephelometric method was used for measuring urinary excretion of albumin. The mean follow-up time was 42.6 ± 19.6 months. All patients were evaluated at least once a year during the follow-up period, during which cardiovascular events were collected. Cardiovascular events were defined as Acute Myocardial Infarction (AMI) (diagnosed by an electrocardiography and elevation of biomarkers of myocardial ischemia, and confirmed with cardiac catheterization), Congestive Heart Failure (CHF) (diagnosed by clinical parameters or reduction of the left ventricular ejection fraction <45%), ischemic or hemorrhagic cerebrovascular accidents (diagnosed with Computed Tomography), Peripheral Vascular Disease (PVD) (defined as stenosis of the main arteries of lower extremities confirmed by arteriography and/or need for amputation) and other ischemic events (mesenteric ischemia or ischemic neuritis). Initiation of renal replacement therapy (RRT) and overall mortality of any cause or cardiovascular cause were also recorded.

Statistical analysis

For statistical analysis, IBM SPSS, version 21.0 (IBM Corp, Armonk, New York, USA) for Windows XP has been used.

Patients were categorized into three tertiles according to their baseline magnesium levels as follows: Mg ≤ 1.70 mg/dl, Mg 1.71-2.19 mg/dl and Mg ≥ 2.20 mg/dl. Values have been expressed as mean ± standard deviation or median (interquartile range) depending on their distribution according to the Kolmogorov-Smirnov test. Chi-square test was used to compare the qualitative variables, and the t-student or Mann-Whitney test for the quantitative ones. To analyse cardiovascular survival, the Kaplan-Meier curves and the log-rank test were used. In order to assess the risk of a cardiovascular event in an adjusted manner, the Cox proportional risk model was used, where the variables that were associated with this risk in the Cox univariate analysis and the classic cardiovascular risk variables were included. We defined statistically significant differences as a two-tailed P value of less than 0.05. Finally, Propensity Score Matching was used to obtain two comparable groups for possible confounding variables and for survival analysis among the groups.

Results

Baseline characteristics

A total of 746 patients were analysed with an average age of 70 ± 13 years, 62.9% of whom were males. 341 patients (45.2%) had stage 3 CKD and 271 (35.9%) had stage 4 CKD. 41.3% of the patients had cardiovascular comorbidity. The baseline characteristics are summarized in **Table 1**. The different causes of CKD are shown in **Figure 1**.

Table 1: Baseline characteristics. Data presented as median (interquartile range), mean ± standard deviation, or percentage of the categorical variable. **Abbreviations:** eFGR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration Equation; PTH: Parathyroid Hormone; CKD: Chronic Kidney Disease; DM: Diabetes Mellitus; ADPKD: Autosomal Dominant Polycystic Kidney Disease; CHF: Congestive Heart Failure; IHD: Ischemic Heart Disease; PVD: Peripheral Vascular Disease; PPI: Proton Pump Inhibitors; AF: Atrial Fibrillation.

Baseline characteristics	
Age (years)	73 (63-80)
Sex (% male)	475 (63.7)
Serum creatinine (mg/dl)	2.07 (1.57-2.71)
eGFR CKD-EPI (ml/min/1,73 m^2)	28 (20-40)
Urine albumin/creatinine ratio	83 (0-500)
Serum Magnesium (mg/dl)	2,1 (1.9-2.3)
Serum Calcium (mg/dl)	9.3 (8.9-9.6)
Serum Phosphorus (mg/dl)	3.5 (3-4)
25-hydroxy vitamin D	16.3 (10.6-22.9)
PTH	125.0 (72.3-217.8)
CKD stage (%)	
Stage 3	341 (45.7)
Stage 4	405 (54.3)
CKD etiology (%)	
Vascular	180 (23.8)
DM	153 (20.3)
Glomerular	109 (14.4)
Interstitial	72 (9.5)
ADPKD	23 (3.0)
Not known/Other	218 (28.9)
Cardiovascular history (%)	312 (41.8)
CHF	167 (22.4)
IHD	164 (22)
PVD	98 (13.1)
Stroke	69 (9.2)
DM (%)	230 (308)
Hypertension (%)	587 (78.68)
AF (%)	91 (12.2)
Concomitant medication (%)	
Diuretics	420 (56.3)
PPI	334 (44.8)
Other antacids	14 (1.9)
Corticosteroids	12 (1.6)
Digoxin	14 (1.9)
Laxatives	5 (0.8)
Calcitriol	138 (18.5)
Vitamin D supplements	43 (5.8)
Calcium supplements	44 (5.9)
Phosphate binders	150 (20.2)
PTH analogues	3 (0.4)

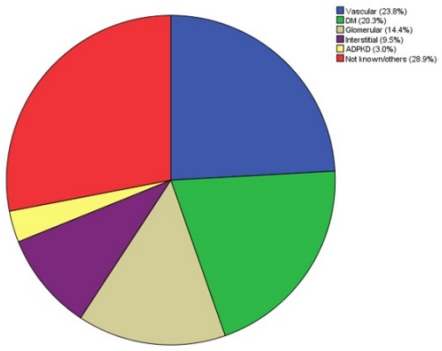

Figure 1: CKD etiology. **Abbreviations:** CKD=Chronic Kidney Disease; DM=Diabetes Mellitus; ADPKD=Autosomal Dominant Polycystic Kidney Disease.

Magnesium levels

The mean magnesium level was 2.09 ± 0.33 mg/dl. Kidney function was measured as serum creatinine and eGFR according to CKD-EPI, and both had a significant correlation with magnesium levels. Likewise, phosphorus and PTH values correlated with magnesium levels (**Table 2**).

We analysed the relationship between concomitant medication and magnesium levels, finding that only treatment with calcitriol was associated with higher magnesium levels (p=0.029), while treatment with calcium supplements and proton pump inhibitors (PPIs) were associated with lower magnesium levels (p=0.038 and 0.026 respectively) (**Table 3**). We did not find significant differences in magnesium levels between patients with atrial fibrillation (AF) and without it (2.08 ± 0.34 vs. 2.12 ± 0.26, p=0.238).

Table 2: Correlation between magnesium and: age and analytical variables. **Abbreviations:** eGFR: Estimated Glomerular Filtration Rate; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration Equation; PTH: Parathyroid Hormone.

Variable	R	P
Age	0.067	0.07
Serum creatinine	0.122	0.001
eGFR (CKD-EPI)	-0.133	<0.001
Urine albumin/creatinine ratio	-0.046	0.213
Calcium	0.012	0.745
Phosphorus	0.135	<0.001
PTH	0.087	0.02
25-hydroxy vitamin D	-0.021	0.586
Albumin	0.024	0.51

Table 3: Association between concomitant medication and magnesium levels. **Abbreviations:** PPI: Proton-Pump Inhibitors; PTH: Parathyroid Hormone.

Medication		Mean serum magnesium (mg/dl)	p
Diuretics	Yes	2.10 ± 0.32	0.197
	No	2.07 ± 0.33	
PPI	Yes	2.06 ± 0.31	0.026
	No	2.11 ± 0.34	
Other antacids	Yes	2.14 ± 0.29	0.503
	No	2.08 ± 0.33	
Corticosteroids	Yes	2.19 ± 0.27	0.546
	No	2.13 ± 0.27	
Digoxin	Yes	2.05 ± 0.25	0.681
	No	2.09 ± 0.33	
Laxatives	Yes	1.98 ± 0.34	0.601
	No	2.04 ± 0.28	
Calcitriol	Yes	2.15 ± 0.42	0.029
	No	2.07 ± 0.30	
Vitamin D supplements	Yes	2.01 ± 0.30	0.126
	No	2.09 ± 0.33	
Calcium supplements	Yes	1.99 ± 0.33	0.038
	No	2.09 ± 0.28	
Phosphate Binders	Yes	2.04 ± 0.17	0.775
	No	2.09 ±0.33	
PTH analogues	Yes	1.97 ± 0.32	0.528
	No	2.09 ± 0.33	

Events during follow up

After a mean follow-up of 42.6 ± 19.6 months, 341 (45.7%) patients reached an event (either CV event, RRT initiation or death). 104 patients died during follow-up, the most frequent cause being cardiovascular in 7.9% of the patients, followed by neoplastic causes (2.5%), infectious causes (1.5%) and conservative treatment (0.4%). 145 patients initiated RRT during follow-up (19.4%). Finally, 221 patients (29.6%) had a fatal or non-fatal CV event: 75 patients had ischemic heart disease, 26 had a stroke, 25 were diagnosed with PVD and 95 suffered from CHF.

Cardiovascular events during follow-up

Both patients with hypomagnesemia (Mg<1.7 mg/dl) and patients with hypermagnesemia (Mg>2.2 mg/dl) had a higher risk of cardiovascular events (Log Rank 4.45, p=0.035, and Log Rank 7.45, p=0.006 respectively) (**Figures 2 and 3**).

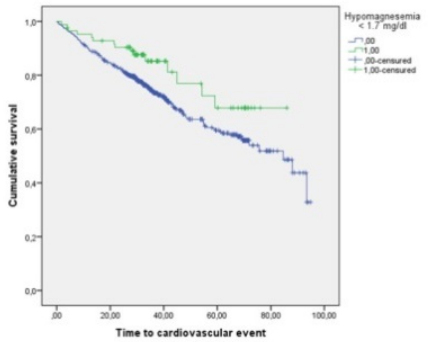

Figure 2: Time to cardiovascular event in patients with and without hypomagnesemia (< 1.7 mg/dl). Log Rank 4.45 (p=0.035).

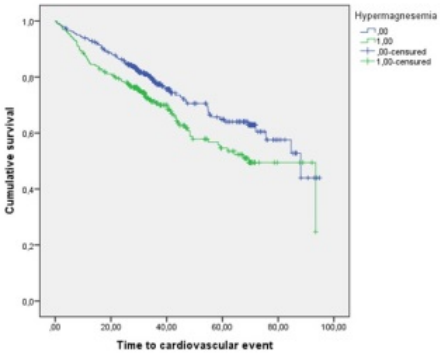

Figure 3: Time to cardiovascular event in patients with and without hypermagnesemia (> 2.2 mg/dl). Log Rank 7.45 (p=0.006).

In the Cox univariate analysis, age (p<0.001), cardiovascular comorbidity (p<0.001), diabetes mellitus (p<0.001), AF (=0.001), eGFR measured by CKD-EPI (p=0.035), phosphorus levels (p=0.048), hypomagnesemia (p=0.037) and hypermagnesemia (p=0.007) were associated with a higher probability of cardiovascular events. Calcium, vitamin D and PTH levels, as well as the albumin/creatinine ratio did not show a relationship with cardiovascular events. In the adjusted multivariate analysis for all the analytical variables (renal function, albuminuria and parameters of calcium-phosphorus metabolism), hypermagnesemia (HR=1.36, CI=1.03-1.79, p=0.032) as well as hypomagnesemia (HR=1.21, CI=1.01-1.58, p=0.047) maintained their predictive power for cardiovascular events. In the multivariate analysis adjusted for all the analytical and clinical variables, they lost their predictive power for cardiovascular events.

Mortality during follow-up

Patients with hypermagnesemia had a higher risk of all-cause mortality (Log Rank 13.11, p<0.001) (**Figures 4 and 5**), while there was no association between hypomagnesemia and all-cause mortality (p=0.743). In the Cox univariate analysis, age (p<0.001), cardiovascular history (p<0.001), DM (p<0.001), AF (p<0.001), eGFR measured by CKD-EPI (p=0.007), vitamin D levels (p=0.004) and hypermagnesemia (p<0.001) were associated with a higher probability of all-cause mortality. Calcium, phosphorus, PTH levels and albumin/creatinine were not associated with mortality. In the adjusted multivariate analysis for predictors of all-cause mortality, hypermagnesemia maintained its predictive power for all-cause mortality (HR=1.524, CI=1.002-2.319, p=0.049). We performed a propensity score matching for magnesium levels according to age, eGFR, albuminuria and previous ischemic heart disease, achieving two comparable groups of 94 patients each. In the survival analysis of both groups, we found again a higher mortality from any cause in the hypermagnesemia group (Log Rank 17.48, p<0.001). This association was maintained in the Cox model adjusted for Calcium, Phosphorus and PTH.

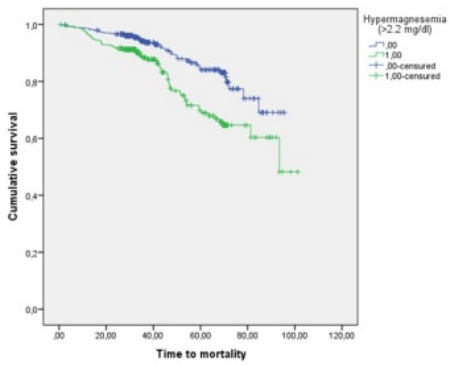

Figure 4: Time to death in patients with and without hypermagnesemia (>2.2 mg/dl). Log Rank 13.11, p<0.001.

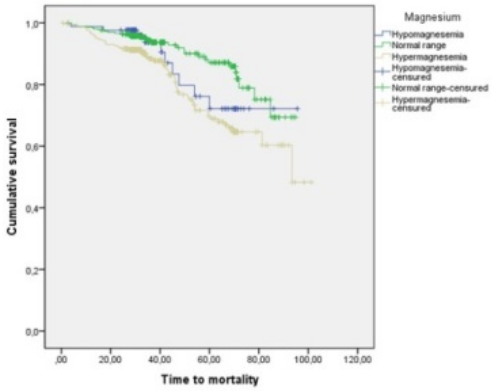

Figure 5: Time to death in patients with hypomagnesemia (<1.7 mg/dl), hypermagnesemia (>2.2 mg/dl) and magnesium in normal range (1.7-2.2 mg/dl). Log Rank 13.70, p=0.001.

Initiation of RRT during follow-up

Neither hypomagnesemia nor hypermagnesemia were associated with an increased risk of RRT.

Discussion

As a main finding, we found an increased risk of cardiovascular events in patients with both hypomagnesemia and hypermagnesemia, but it should also be noted that it is hypermagnesemia and not hypomagnesemia, which shows a greater association with all-cause mortality. This association is maintained in the model adjusted for all possible confounding variables, even after performing a propensity score matching.

The mean serum magnesium level in the population included in our study was 2.09 mg/dL. In the general population, the study with the largest number of patients carried out took place in the 1970s, in which 15820 patients were included and a mean serum magnesium level of 2 mg/dl was detected with 95% of the values lying between 1.8 and 2.2 mg/dl [14], thenceforth this range has been considered to be the normal range for magnesium values. Magnesium homeostasis, dependent on intestinal absorption and renal excretion, needs to be tightly regulated. The fractional absorption of magnesium is able to adapt to its intake, decreasing as the total amount available in the intestine increases [15]. In the same way, the fractional excretion of magnesium is able to adapt to its plasma levels, being closely determined by variable filtration ranges (up to 80% of plasma magnesium) and reabsorption (up to 95% of filtered magnesium) [16]. To date, a hormone that specifically regulates magnesium levels has not been identified yet [17]. In CKD there is a decrease in the magnesium excretion fraction. As kidney failure progresses, the urinary excretion of magnesium may be insufficient to maintain a balance with the intestinal absorption, and therefore magnesium intake becomes a fundamental determinant of serum magnesium [18]. In early stages, as long as creatinine clearance is above 30 ml/min, the drop in glomerular filtration is normally compensated by the increase in

the filtration fraction, achieving magnesium levels within the normal range. In more advanced stages, the compensatory mechanisms fail, and patients with CKD are more likely to have hypermagnesemia [3]. Drugs that contain magnesium, such as some phosphate binders; drugs that enhance the elimination of magnesium, such as diuretics; and the magnesium concentration in the dialysate in patients on renal replacement therapy have also an impact on the magnesium balance of these patients [19]. Therefore, in patients with CKD, as those included in our study, mean magnesium levels are higher, with an increase in mean magnesium levels as the stage of kidney disease progresses.

There is wide evidence of association of hypomagnesemia with cardiovascular events and mortality in observational studies in the general population [7-10]. In hemodialysis patients, several observational studies have found a relationship between cardiovascular mortality and lower magnesium levels [11,12,20-23]. A recently published meta-analysis concluded that there is an association between hypomagnesemia and cardiovascular and all-cause mortality in patients with CKD on dialysis and not on dialysis [24]. However, some of these studies warn of a J-shaped association between magnesium and cardiovascular events or cardiovascular mortality [11,12].

In patients with CKD who are not on dialysis, the magnesium levels used to define hypomagnesemia and hypermagnesemia are not homogeneous among different studies and the evidence is not as consistent. Some studies that included patients with CKD not on dialysis find an association with intermediate variables: a study including 283 patients with CKD, low magnesium levels were associated with the existence of endothelium-dependent vasodilation [25]. In another study that included 90 patients, hypomagnesemia was associated with worse lipid control [26], and an analysis of the PREVEND study found an increased risk of progression of CKD with lower levels of magnesium [27]. In a study with 1650 patients in whom an association was found between magnesium levels and both cardiovascular events and progression of kidney disease, the authors alerted about the possible interference of confounding factors [28]. In the recent Dallas Heart Study cohort [26], an association between hypomagnesemia and all-cause mortality in patients with CKD was detected, but not with cardiovascular mortality or cardiovascular events. However, only 36 patients included in the study had eGFR <60 ml/min/1.73 m^2. In the study by Van Laecke et al. [25], out of the 1650patients included, less than half of the patients had eGFR <60 ml/min/1.73 m^2, and the association between hypomagnesemia and both mortality and progression of kidney disease was lost in the adjusted model for all confounding variables. In a Spanish study published in 2013 [29], 70 patients with advanced CKD were included and an association between hypomagnesemia and cardiovascular events or mortality was not found. In another study published in 2016 by Hughes et al. that included 1306 patients, they found association with mortality at extreme magnesium levels [30].

In spite of the lack of evidence, several reviews suggest magnesium supplementation in patients with and without kidney disease, despite the limited evidence in clinical trials that were designed to measure intermediate endpoints only such as improvement of analytical levels [31,32]. Observational epidemiological studies in the general population where hypermagnesemia is associated with overall mortality are not taken into account [7-10], nor studies in hemodialysis that show a J-shaped association between magnesium levels and overall mortality [11,12].

Hypomagnesemia may increase cardiovascular risk due to its effect on vascular calcification. Several studies have suggested a protective effect of magnesium on vascular calcification through many mechanisms: inhibition of apatite crystal formation, antagonism of calcium entry into cells, restoration of the balance between the expression of promoters and inhibitors of calcification and activation of calcium receptors in smooth muscle fibers [33]. On the other hand, hypermagnesemia has effects on cellular electrical conduction and blood pressure, which could be reflected in the increase in mortality [34]. It alters the properties of different ion channels [35], which can lead to proarrhythmic conditions. In animal models, a competition between Mg and calcium ions in the receptors of cardiac myocytes has been observed, being able to cause deterioration of both ventricular contraction and relaxation [36]. In addition, hypermagnesemia seems to decrease the release of acetylcholine and sensitivity for its detection in muscle cells, which can lead to severe arrhythmias, bradycardia, prolongation of PR, QRS and QT, and complete atrioventricular block, situations which are associated with the risk of sudden death [37]. Taking into account that there is already an increased risk of arrhythmias in patients with CKD [38], this could explain the findings of our study.

The relationship between calcium-phosphorus metabolism and magnesium metabolism seems complex and has not been well established [39]. Although in some studies in dialysis patients an inverse relationship between magnesium and PTH levels had been reported [40,41], experimental studies in rats did not show any effect of magnesium on PTH in presence of normal calcium and phosphorus levels [42]. In our study, we found a positive correlation between magnesium and PTH levels, probably due to the existence of a positive correlation between magnesium and phosphorus, which could be related to the deterioration of kidney function. The increase in intestinal absorption of magnesium has been observed as an effect of vitamin D [43,44], which explains the differences in mean levels of magnesium that we found between patients treated with calcitriol and those without this treatment.

The main strength of our study is that it is the largest cohort of patients with stage 3 and 4 CKD in which magnesium levels and their consequences are studied. The main drawback lies in the cross-sectional nature of our study for the estimation of serum magnesium, although this is the same method chosen for serum magnesium estimation in most of the studies mentioned before.

Conclusion

Magnesium values increase as CKD advances. Serum magnesium is associated with age, kidney function, serum phosphorus levels and hyperparathyroidism, as well as with

treatment with calcitriol. Low magnesium levels predict cardiovascular events in patients with stage 3 and 4 CKD, but high magnesium levels predict cardiovascular events and all-cause mortality in this same population. The pathophysiological relationship has yet to be elucidated. Thus, with the available evidence to date, magnesium supplementation should be used with caution in these patients. Further observational and interventional studies are needed to better define the normal range values for serum magnesium and the associated cardiovascular risk in patients with CKD.

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