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Monitoring of ionized magnesium in hemodialysis patients: A useful tool to allow a personalized prescription of dialysate composition

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ABSTRACT

Background and aims:

The dialysate magnesium (Mg) concentration is a major determinant of Mg balance in hemodialysis. This study aimed to assess the systemic variations of total (tMg) and ionized Mg (iMg) during a dialysis session using acetate or citrate fluids and 0.5 or 0.75 mM Mg.

Materials and methods:

134 patients in maintenance hemodialysis were assigned to a dialysis session with 4 different dialysates: acetate fluid with 0.5 mM Mg (1) or 0.75 mM Mg (2), citrate fluid with 0.5 mM Mg (3) or 0.75 mM Mg (4). Ionized form was measured by direct ion-selective electrode.

Results:

A Mg loss was observed in both acetate (0.12 and 0.08 mmol/L) and citrate (0.13 and 0.14 mmol/L for tMg and iMg, respectively) fluid groups containing 0.5 mM Mg. The use of acetate and citrate dialysates with 0.75 mM Mg led to a significant median intra-dialytic increase of 0.15 and 0.08 mmol/L for tMg, respectively. A significant augmentation in iMg concentration with acetate (0.11 mmol/L) but not with citrate dialysate (0.02 mmol/L) was observed.

Conclusion:

While a dialysate Mg concentration at 0.5 mM leads to a negative balance, increasing the concentration to 0.75 mM significantly raises post-dialysis circulating Mg. Monitoring of iMg should allow a personalized prescription in dialysate Mg.

1. Introduction

Mg is a divalent cation mainly stored in bone (60%), muscle and red blood cells (30 to 40%). Plasma Mg only accounts for 1% of the Mg pool with a concentration ranging from 0,75 to 0,95 mmol/L in healthy subjects with normal renal function. This level results from an appropriate balance between intestinal Mg absorption and renal excretion. In the serum/plasma Mg is found in 3 different forms: protein-bound (20%), a complexed form (15 %) and an ionized (iMg) form (65 to 75%) [1–3]. The kidney function plays a key role in Mg balance since tubular reabsorption accounts for 95% of the filtered form. The renal handling

of Mg is a highly adaptive mechanism that mainly depends on the plasma concentration, but which is exceeded when glomerular filtration rate is <30 mL/min/m² [4].

In chronic kidney disease (CKD), the concentration of magnesium (Mg) is the result of dietary intake, Mg supplementation, medications (proton pump inhibitor use, anti-acids, phosphate binders), residual renal function or per-dialytic losses [4–5]. Hypomagnesemia has been associated with per-dialytic complications (myocardial contractility disorders, arrhythmias, hemodynamic instability) or chronic complications (hypertension, vascular calcifications, muscle weakness, tetany) [6–8]. A recent meta-analysis of 13 observational studies [9] in hemodialysis (HD) patients evidenced that low serum Mg was associated (hazard ratios (HRs) and 95% confidence intervals (CIs)) with higher all-cause (HR 1.58 [95% CI: 1.31–1.91]) and cardiovascular (HR 3.08 [95% CI: 1.27–7.50]) mortality. Manifestations of moderate and severe hypermagnesemia are related to neuromuscular toxicity causing cardiac conduction defects, hypotension and paralysis [6–7]. In addition, as a potent activator of calcium-sensing receptor, Mg may have an important regulatory role in PTH secretion. Hypermagnesemia suppresses PTH secretion especially at low-normal serum calcium levels, whereas this effect may become weaker at high and low serum calcium levels [10].

However, severe hypomagnesemia can also paradoxically suppress PTH production at any given calcium level [11] leading to relevant hypocalcemia.

At the CKD 5 dialysis stage, dialysate Mg concentration is a major determinant of Mg balance [4–7]. Therefore, dialysate Mg prescription represents one of the treatment strategies to regulate Mg homeostasis in dialysis patients. Previous studies, assessing the dialysate Mg and the dialytic balance in HD patients [4], mostly addressed acetate fluids with 0.25, 0.5 or 0.75 mM Mg. More recently, Safranek et al [12] showed a relationship between citrate exposure and kinetic behavior of serum Mg concentrations between a traditional dialysis solution containing acetate and a citrate enriched dialysis solution with a fixed concentration of magnesium (0.5 mM). In addition, dialysis modalities have changed over time using high-flux membranes, hemodiafiltration using high convection volume, citrate dialysate as well as the use of proton pump inhibitors, oral supplementation and diet. Assessing Mg status is challenging. Total plasma Mg is routinely measured in the central laboratory to assess magnesium status. As almost 99% of the total body Mg is intracellular with a great part located in red blood cells, the intraerythrocyte Mg concentrations [13] may provide a more accurate assessment of the pool. But it is not readily available. The ionized form of Mg, which represents the biologically active form of Mg within the body, is measurable by ion selective electrode on a blood gas analyzer [14]. In addition, iMg is the only form that can be ultrafiltered. In dialysis patients, significant discrepancies of the proportion of ionized to total magnesium have been reported because of acid-base status, binding to undialyzed anionic compounds, bone mineral disease and hypoalbuminemia [4]. To the best of our knowledge, no study previously compared the four conditions, citrate vs acetate fluids and 0.5 vs 0.75 mmol/L Mg in the same chronic dialysis population using both tMg and iMg determination.

It appears that the effect of a dialysis session with Mg-enriched citrate dialysis solution on both iMg and tMg fractions have not been evaluated specially in high-performance dialysis. The aim of the present study is therefore twofold. Firstly, we evaluated Mg status in chronic dialysis patients according to tMg and iMg reference range as well as the impact of acid-base status, anionic compounds, and albumin/ protein on iMg concentration. Secondly, we assessed the systemic variations of iMg in parallel to those of iCa before and after a single dialysis session using acetate or citrate fluids and 0.5 or 0.75 mmol/L of Mg.

2. Materials and methods

2.1. Study design and settings

This observational cross-sectional study was carried out in two dialysis facilities of Montpellier, France (a hospital-based facility [Lapeyronie University Hospital] and a public non-profit association [Aide pour l'Installation à Domicile de l'Épuration extra Rénale]). A total of 134 stable CKD patients on regular dialysis treatment for at least 6 months with no residual renal function were included.

All maintenance dialysis patients received either high-flux HD (n = 10) or on-line hemodiafiltration (HDF) (n = 124) treatments with ultrapure bicarbonate-buffered dialysate three times a week (12 h per week). Four different kinds of dialysate were tested during a single midweek dialysis session as part of the routine patient follow-up and quality assurance process. The first dialysate was acetate fluid (3 mM) with 1.5 mmol/L of Ca and 0.5 mmol/L of Mg, used as the reference dialysis fluid (n = 72 dialysis sessions). The second dialysate was acetate buffer containing 1.5 mmol/L of Ca and 0.75 mmol/L of Mg (n = 65 dialysis sessions). The third was citrate dialysis fluid (0.8 mM citrate and 0.3 mM acetate) containing 1.65 mmol/L of Ca and 0.5 mmol/L of Mg (n = 78 dialysis sessions). The fourth dialysate was citrate buffer containing 1.65 mmol/L of Ca and 0.75 mmol/L of Mg (n = 75 dialysis sessions).

The study protocol complied with the Declaration of Helsinki and was registered at clinicaltrials.gov (NCT05337436). The Institutional Review Board of Montpellier University Hospital approved the study protocol (IRB-MTP_2022_01_202100918) and waived the need for signed consent for participants.

2.2. Data collection

Medical records were reviewed for demographic and clinical data. Pre- and post-dialysis heparin blood samples were drawn, tested for iMg and iCa on whole blood and then centrifuged (2000 g for 10 min) for routine parameter measurements on a Cobas 8000 instrument using e802, c702 and c502 modules (Roche Diagnostics, Meylan, France). Total

Mg (tMg) and Ca (tCa) were analyzed by colorimetric methods, NM-BAPTA [15] and xylidyl blue complex assays, respectively. The CVs, calculated from Roche internal quality control over a 12 month-period were 1.5% for tMg (means 0.81 and 1.34 mmol/L) and 1.4% for tCa (means 2.24 and 3.34 mmol/L). The anion gap was calculated as follows: anion gap = (sodium mEq/L + potassium mEq/L) – (bicarbonate mEq/L + chloride mEq/L). Based on previously published data [1,16] and manufacturer's recommendations, a range of 0.70–1.00 mmol/L and 2.20–2.52 mmol/L for tMg and tCa respectively was used as the reference interval.

pH, ionized Mg and Ca were measured using direct ion-selective electrode on Nova Stat Profile Prime Plus® (Nova Biomedical, Waltham, MA, USA) blood gas analyzer [14]. Prior to the study, imprecision was assessed using the Clinical and Laboratory Standard Institute (CLSI) EP15-A3 protocol (one run per day, five replicates per run for five days, n = 25 replicates per sample) [17] by repeat analysis of 2 levels of Nova aqueous quality control samples (STAT Profile Prime Plus Ampuled chemistry levels 4,5). The within-laboratory coefficients of variation (CV) were 2% for iMg (means 0.57 and 1.09 mmol/L) and 1% for iCa (means 1.09 and 1.56 mmol/L). The iMg and iCa manufacturer's reference ranges were 0.45–0.60 mmol/L and 1.09–1.3 mmol/L, respectively [18]. The intra-individual variabilities of serum/plasma tMg and whole blood iMg were 2.9% [19] and 2.0% [20] respectively. 2.3. *Statistical analysis* Data were expressed as median [interquartile range] for continuous variables and proportions for categorical variables. The agreement between Mg classifications as low, normal or high using tMg and iMg was assessed through 290 pre-dialysis pairs (tMg, iMg) from 134 dialysis patients using the percent agreement and the weighted Cohen's κ -test coefficient with values ≤ 0.2 as indicating no agreement and 0.21–0.39 as minimal, 0.40–0.59 as weak, 0.60–0.79 as moderate, 0.80–0.90 as strong and above 0.90 as almost perfect agreement [21]. The same analysis was performed for Ca classifications using tCa et iCa. The impact of pH, anion gap protein and albumin among discordant Mg or Ca classifications was evaluated by Student's *t*-test. The comparisons of variables between pre-dialysis and post-dialysis were performed using the by paired Student's *t*-test. The comparisons of variables between the four groups of patients, based on dialysis fluid composition, were performed using the Kruskal-Wallis test. When comparisons were statistically significant, two-by-two comparisons were carried out using the post hoc Dunn's pairwise tests with Bonferroni correction. Statistical analysis was carried out with the XLSTAT® software for Windows, version 2016.06.35661 (NY, USA) and the statistical significance was set at $p < 0.05$.

Table 1

Characteristics of each dialysis session: dialysate composition, hemodialysis status and dialysis efficiency. Values were described by using median [interquartile range] for quantitative variables.

	Acetate Dialysate 0.5 Mg	Acetate Dialysate 0.75 Mg	Citrate Dialysate 0.5 Mg	Citrate Dialysate 0.75 Mg
Nb sessions	72	65	78	75
Dialysate Composition				
Acetate (mmol/L)	3	3	0.3	0.3
Citrate (mmol/L)	0	0	0.8	0.8
Calcium (mmol/L)	1.5	1.5	1.65	1.65
Magnesium (mmol/L)	0.5	0.75	0.5	0.75
high flux Hemodialysis on line Haemodiafiltration	5	3	5	7
High flux dialyzers used				
Polysulfone	55	16	48	45
Polyethersulfone	11	35	21	18
Polyester-polymer alloy	4	1	5	7
Polyacrylonitrile	2	2	4	3
Polyphenylene	0	11	0	2
Pre-HD systolic blood pressure (mmHg)	129 [114-147]	121 [110-142]	130 [115-156]	131 [115-152]
Pre-HD diastolic blood pressure (mmHg)	66 [49-77]	62 [51-79]	65 [56-79]	66 [53-77]
Pulse rate (beats per minute)	75 [67-80]	73 [66-81]	74 [67-81]	73 [63-81]
Intradialytic weight change (pre-post) (kg)	-2.2 [-2.7--1.5]	-1.7 [-2.2--1.3]	-2.1 [-2.8--1.6]	-2.3 [-2.8--1.4]
Urea (Kt/V) _{sp, Dougrinis}	1.57 [1.4-1.73]	1.57 [1.35-1.79]	1.55 [1.35-1.76]	1.52 [1.31-1.77]

Table 2

Characteristics of each dialysis session: Pre-Dialysis biological variables. Values were described by using median [interquartile range].

	Acetate Dialysate 0.5 Mg	Acetate Dialysate 0.75 Mg	Citrate Dialysate 0.5 Mg	Citrate Dialysate 0.75 Mg
Nb sessions	72	65	78	75
Protein (g/L)	68.5 [64-71]	67 [62-72]	68 [63-71]	66 [62-70]
Albumin (g/L)	37.3 [34.7-39.1]	37.8 [35.5-41]	38.8 [35.8-40.6]	38.6 [35.2-40.4]
Sodium (mmol/L)	138 [136-139]	137 [135-139]	137 [135-139]	138 [135-139]
Potassium (mmol/L)	4.8 [4.4-5.2]	4.8 [4.2-5.2]	4.7 [4.2-5.2]	4.8 [4.1-5.2]
Chlore (mmol/L)	98 [96-101]	99 [96-102]	98 [97-101]	99 [96-101]
Bicarbonate (mmol/L)	22 [21-23]	22 [20-23]	21 [20-23]	22 [20-23]
Anion Gap (mmol/L)	21 [20-23]	21.5 [19-23]	21 [19-23]	21 [19-23]
Calcium (mmol/L)	2.22 [2.13-2.29]	2.24 [2.15-2.35]	2.20 [2.09-2.30]	2.19 [2.07-2.31]
Phosphate (mmol/L)	1.47 [1.14-1.73]	1.15 [0.93-1.56]	1.37 [0.97-1.69]	1.24 [0.88-1.54]
Magnesium (mmol/L)	0.91 [0.82-0.97]	0.88 [0.79-0.97]	0.85 [0.79-0.97]	0.90 [0.80-1.00]
pH (units)	7.39 [7.37-7.44]	7.41 [7.38-7.46]	7.40 [7.37-7.44]	7.40 [7.37-7.44]

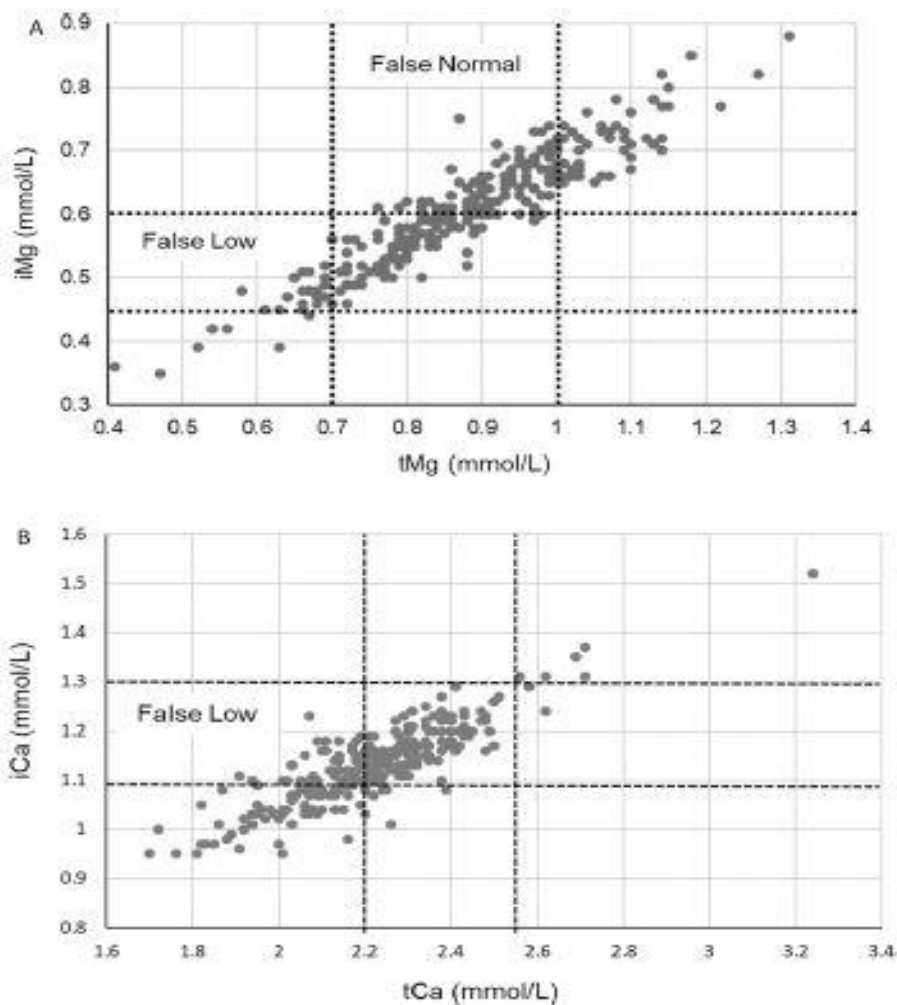


Fig. 1. Correlation between pre-dialysis levels of A) total magnesium (tMg) and ionized magnesium (iMg); B) total calcium (tCa) and ionized calcium (iCa). The horizontal and vertical dotted lines represent the reference interval for each parameter. Patients were categorized as low, normal or high based on total forms (horizontal axis) and ionized forms (vertical axis).

3. Results

3.1. Characteristics of the population

The group consisted of 52 women and 82 men with a median age of 70.9 (IQR, 63.2–78.5) years. Mean kt/v was 1.55 ± 0.32 . Characteristics of each dialysis session are described in Table 1 for dialysate composition, hemodialysis status, dialysis efficiency and in Table 2 for biological variables.

3.2. Agreement between Mg classifications using tMg and iMg reference ranges

The percent agreement between the reference interval using tMg and iMg was 56.9 [IC95%, 51.0–62.6]. The weighted kappa coefficient was 0.31 [IC95%, 0.24–0.39] indicating a minimal agreement to assess Mg status. Based on the discordance observed between ionized and total plasma Mg, two groups of patients were identified: the “false normal” group (36.2%) characterized by high ionized and normal total forms and the “false low” group (6.9%) characterized by normal ionized and low total forms (Fig. 1A). A significantly lower anion gap ($p = 0.004$) was found in patients with high iMg and normal tMg compared to the control group with both normal tMg and iMg (Table 3). The pH was not different between both groups. The group with normal iMg and low tMg demonstrated a significantly lower albumin level compared to the control group.

By comparison, the percent agreement between the reference interval using tCa and iCa was 75.9 [IC95%, 70.5–80.6] and the weighted kappa coefficient was 0.54 [IC95%, 0.46–0.63] indicating a weak agreement. Based on the discordance observed between ionized and total plasma Ca, most of the patients were classified in the “false low” group (20.7%) characterized by normal ionized and low total forms

3.3. Dialytic balance of magnesium during the session

All dialysis sessions led to significant changes in the divalent total or ionized cations ($p < 0.001$) (Table 4) except for iMg when citrate dialysate with 0.75 mmol/L of Mg was used ($p = 0.07$). All dialysate compositions showed a significant tCa and iCa load during the session. Acetate and citrate dialysates with 0.5 mmol/L of Mg led to a significant Mg loss, including both total (-0.12 and \square 0.13 mmol/L, respectively) and ionized (-0.08 and \square 0.14 mmol/L, respectively) Mg (Table 5). By contrast, the use of acetate and citrate dialysates with 0.75 mmol/L of Mg led to a positive balance with a significant median intra-dialytic augmentation of 0.15 and 0.08 mmol/L for tMg, respectively. This increase in tMg was associated with a significant augmentation in iMg concentration with acetate dialysate (0.11 mmol/L) whereas iMg remained unchanged when using citrate fluid. The Mg changes during the session depends on pre-dialysis levels. The “cut-off” values corresponding to a neutral balance were determined (Fig. 2). When pre-dialysis level was below this concentration, an uptake was observed during the session. The “cut-off” value with a citrate-enriched dialysis solution was lower than that of a traditional dialysis solution containing acetate for a fixed concentration of magnesium (0.5 or 0.75 mmol/L). Based on tMg, dialysate fluids with 0.5 Mg led to an uptake in 11.1% and 11.5% of patients for acetate and citrate, respectively. Using Mg-enriched dialysis solution, a positive balance was observed for 93.8% and 72.0% of the patients for acetate and citrate, respectively. Based on iMg, dialysate fluids with 0.5 Mg led to an uptake in 5.6% and 2.6% of patients for acetate and citrate, respectively. Using Mg-

enriched dialysis solution, a positive balance was observed for 95.4% and 56.0% of the patients for acetate and citrate, respectively (Supplementary Figs. 1 and 2).

Significant differences in divalent cation changes among the four dialysate fluids were observed for tMg, iMg and iCa but not for tCa (Table 5). Significant differences in pairwise comparisons were found for iMg and tMg ($p < 0.0083$ after Bonferroni correction) between dialysates highlighting the negative balance of Mg using dialysate concentration with 0.5mmol/L of Mg. Interestingly, the tMg and iMg negative balances were similar between the two acids at 0.5 mM. (Fig.3A). Regarding iCa, significant differences in pairwise comparisons were found between acetate- and citrate-based dialysates highlighting a higher iCa load with acetate use (Fig. 3B).

Table 3
Factors associated with discordant interpretation using ionized and total forms of divalent cations. Values were expressed as median [interquartile range].

	"False normal" High ionized and normal total forms	"Control" Both normal ionized and total forms	
Magnesium status			
N	105	111	
pH	7.39 [7.37-7.43]	7.41 [7.37-7.44]	$p = 0.08$
Anion gap (mmol/L)	20.3 [19.0-22.4]	21.8 [20.0-23.9]	$p = 0.004$
Protein (g/L)	63.0 [63-70]	67.0 [62.-71.0]	$p = 0.94$
Albumin (g/L)	37.9 [35.5-40.6]	38.6 [36.2-40.5]	$p = 0.88$
	"False low" Normal ionized and Low total forms	"Control" Both normal ionized and total forms	
Magnesium status			
N	20	111	
pH	7.42 [7.30-7.46]	7.41 [7.37-7.44]	$p = 0.12$
Anion gap (mmol/L)	20.4 [19.2-23.1]	21.8 [20.0-23.9]	$p = 0.21$
Protein (g/L)	65.5 [62.8-68.0]	67.0 [62.-71.0]	$p = 0.28$
Albumin (g/L)	36.9 [34.9-38.3]	38.6 [36.2-40.5]	$p = 0.04$
Calcium status			
N	60	145	
pH	7.37 [7.34-7.40]	7.41 [7.38-7.46]	$p < 0.0001$
Anion gap (mmol/L)	20.4 [17.7-22.1]	20.9 [19.2-22.6]	$p = 0.03$
Protein (g/L)	64.0 [59.0-69.0]	68.0 [65.0-72.0]	$p < 0.0001$
Albumin (g/L)	36.4 [34.0-38.6]	38.3 [35.9-40.5]	$p < 0.0001$

(Fig. 1B). This group demonstrated significantly ($p < 0.001$) lower protein albumin and pH values compared to the control group with both normal tCa and iCa (Table 3).

Table 4

Pre- and Post- dialysis levels of plasma Magnesium (tMg and iMg) and Calcium (tCa and iCa) in the four groups defined by dialysate composition. Values were expressed as median [interquartile range].

	Acetate 0.5 Mg = 0.5 mmol/L Ca = 1.50 mmol/L N = 72	Acetate 0.75 Mg = 0.75 mmol/L Ca = 1.50 mmol/L N = 65	Citrate 0.5 Mg = 0.5 mmol/L Ca = 1.65 mmol/L N = 73	Citrate 0.75 Mg = 0.75 mmol/L Ca = 1.65 mmol/L N = 75
Total Magnesium (mmol/L)				
<i>Pre</i>	0.91 [0.82-0.97]	0.88 [0.79-0.97]	0.85 [0.79-0.97]	0.90 [0.80-1.00]
<i>Post</i>	0.79* [0.76-0.82]	1.04* [1.00-1.08]	0.73* [0.70-0.76]	0.99* [0.94-1.03]
<i>p</i>	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001
Ionized Magnesium (mmol/L)				
<i>Pre</i>	0.65 [0.58-0.68]	0.60 [0.53-0.65]	0.61 [0.56-0.67]	0.60 [0.54-0.66]
<i>Post</i>	0.54* [0.52-0.59]	0.71* [0.67-0.73]	0.48* [0.45-0.50]	0.63 [0.59-0.66]
<i>p</i>	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> = 0.07
Total Calcium (mmol/L)				
<i>Pre</i>	2.22 [2.13-2.29]	2.24 [2.15-2.35]	2.20 [2.09-2.30]	2.19 [2.07-2.31]
<i>Post</i>	2.52* [2.43-2.59]	2.53* [2.46-2.64]	2.57* [2.51-2.63]	2.55* [2.47-2.64]
<i>p</i>	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001
Ionized Calcium (mmol/L)				
<i>Pre</i>	1.15 [1.09-1.17]	1.13 [1.1-1.18]	1.13 [1.08-1.17]	1.12 [1.08-1.17]
<i>Post</i>	1.25* [1.21-1.29]	1.25* [1.21-1.29]	1.17* [1.12-1.20]	1.19* [1.14-1.24]
<i>p</i>	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> < 0.001

4. Discussion

Our results support the known discordant interpretation between ionized and total values to assess magnesium status in dialysis patients but with a general shift toward higher values when using iMg. In addition, our findings confirmed a Mg loss (both ionized and total forms) using dialysate concentration with 0.5 mmol/L of Mg. We found that enrichment of acetate fluid with 0.75 mM of Mg resulted in a significant iMg load depending on predialysis levels while citrate fluid with 0.75 mM resulted in a neutral balance for iMg. These two findings suggest a personalization of dialysis fluid according to iMg.

4.1. Discordance between pre-dialysis total and ionized values of divalent cations

It has been clearly established that tCa concentration depends on protein-bound calcium (approximately 45%), which is sensitive to blood pH, albumin (the major factor), and total protein levels [22].

Table 5
Impact of the dialysate composition on plasma Magnesium (tMg and iMg) and Calcium (tCa and iCa) changes during the dialysis session.

	Acetate 0.5 Mg = 0.5 mmol/L Ca = 1.50 mmol/L N = 72	Acetate 0.75 Mg = 0.75 mmol/L Ca = 1.50 mmol/L N = 65	Citrate 0.5 Mg = 0.5 mmol/L Ca = 1.65 mmol/L N = 78	Citrate 0.75 Mg = 0.75 mmol/L Ca = 1.65 mmol/L N = 75	p
tMg Delta Pre/Post	-0.12 [-0.18 - -0.03]	0.15 [0.11-0.24]	-0.13 [-0.20 - -0.05]	0.08 [-0.01-0.19]	<0.0001
iMg Delta Pre/Post	-0.08 [-0.13 - -0.05]	0.11 [0.03-0.15]	-0.14 [-0.17 - -0.08]	0.02 [-0.03-0.06]	<0.0001
tCa Delta Pre/Post	0.32 [0.20-0.43]	0.32 [0.20-0.41]	0.37 [0.27-0.47]	0.36 [0.26-0.47]	0.087
iCa Delta Pre/Post	0.12 [0.07-0.15]	0.12 [0.06-0.16]	0.04 [-0.01-0.08]	0.08 [0.02-0.11]	<0.0001

Accordingly, the majority of the observed calcium discrepancies in our study was a subgroup of patients with normal iCa and low tCa for which both significantly lower protein and albumin levels were found. However, data for Mg are less conclusive. In the present work, the use of iMg, the biologically active form, tended to reclassify dialysis patients in the normal (74%) and in the increased (49%) Mg categories by comparison with the tMg.

Several studies have examined the ionized fraction of tMg in dialysis patients compared to healthy controls [4]. Some studies found a similar fraction [23,24] whereas others did not [25,26]. It has been suggested that hypoalbuminemia and metabolic acidosis could lead to a higher iMg fraction while a reduced ionized fraction could be due to the presence of anionic compounds that complex Mg. In line with this, the anion gap was recently evaluated as a determinant of the ionized fraction of divalent cations in hemodialysis patients [27]. Unlike calcium, few patients in our study had normal iMg associated with low tMg and only low albumin levels had an impact on tMg concentrations. Such results were not found in a recent study of 236 patients with de novo atrial fibrillation including patients from the emergency department (n = 131) and intensive care units (n = 105) [18]. In our study, dialysis patients with normal tMg and high iMg represent the majority of discordant results. Due to the change in divalent cations binding to plasma proteins, ionized concentrations decrease as the pH increases. However, this effect is not as pronounced for iMg concentration (0.12 mmol/L per

pH unit) compared to that of iCa (0.36 mmol/L per pH unit) [28]. In line with these experimental data and in accordance with the results obtained in patients with de novo atrial fibrillation [18], we did not observe an impact of pH on the ionized fraction of Mg in patients with normal tMg values. Consistent with previous findings [27], the anion gap, here, was significantly lower in patients with high iMg values and normal tMg.

Lack of assay harmonization and between-run calibration have been put forward to explain the apparent discrepancy observed in patient classification in the literature [24]. Standardization of the automated tMg measurements using dye binding or enzymatic assays seems to be effective regarding traceability of the calibration to both higher order reference materials and reference measurement procedures [1]. By contrast, the determination of iMg needs a specific ion selective electrode which can suffer from a lack of assay standardization as seen for iCa [29]. An earlier evaluation of three available analyzers from three different manufacturers (AVL Medical Instruments AG, KONE Instruments and Nova Biomedical) showed significant differences regarding iMg concentration which therefore limits result comparison in clinical practice. The authors recommended improving the specificity of electrodes as well as standardization of calibrators and control materials [30]. It should be noted that the only commercially available analyzer at present is from Nova Biomedical. Some authors addressed the need to redefine reference ranges to assess Mg status [1,2,18] using tMg or iMg in view of the clinical manifestations. The lack of standardization of diagnostic reference intervals of iMg and the ongoing uncertainty on the reference intervals could hamper the interpretation of the data. The distribution observed in our study differs from that previously described in 118 hemodialysis patients [27] where the authors identified a discordant subgroup of patients (56%) with high tMg and normal iMg but is comparable to that previously observed in intensive care unit settings [31,32]. Both comparators used the same analyzer to measure iMg and the same reference interval to interpret agreement between classification. In 2023, Ansu Baidoo et al. [33] published a systematic review and meta-analysis to estimate a reference range for iMg. The estimated reference ranges for healthy adults were 0.40–0.68 mmol/L for iMg and 0.72–1.0 mmol/L for tMg based on a total of 53 studies. The agreement increased to 79.3% between tMg and iMg using these two reference intervals in our study. Based on the observed discordances, the “false normal” group (6.9% vs 36.2%) characterized by high ionized and normal total forms was present in a smaller proportion and the “false low” group (9.3% vs 6.9%) characterized by normal ionized and low total forms was present in the same proportion. A third group emerged, the “false high” group (4.5%) characterized by normal ionized and high total forms.

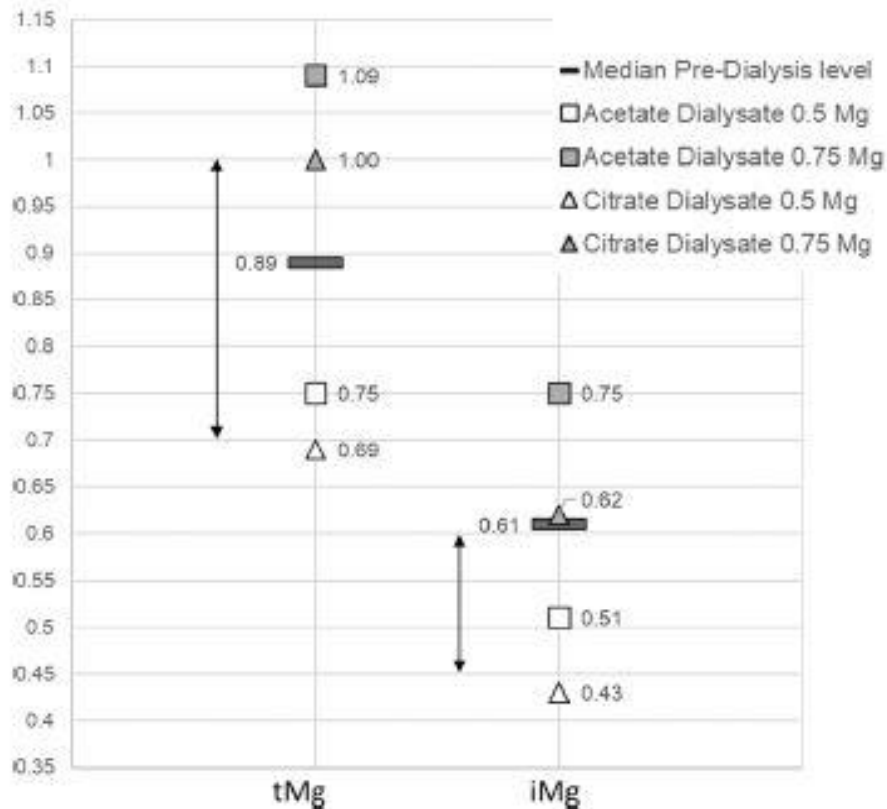


Fig. 2. Cut-off values of tMg (left panel) and iMg (right panel) associated with a neutral balance with the 4 tested dialysate fluids. The up down arrow represents the reference interval. Values are expressed in mmol/L.

4.2. Dialytic balance of calcium and magnesium during the session

The 2017 KDIGO guidelines related to CKD-Mineral and Bone Disorder suggest the use of a dialysate calcium concentration between 1.25 and 1.50 mmol/L [34]. Dialytic calcium balance is partly dependent on iCa diffusion gradient between blood and dialysate compartments with a neutral balance using a dialysate concentration of 1.25 mmol/l and a calcium load using a dialysate concentration of 1.5 mmol/l [35]. In our study, the calcium balance (delta between pre- and post- dialysis values) was slightly positive with all 4 dialysates with no difference between groups using tCa. These results confirm previous findings which suggest that a higher calcium content has to be used with citrate dialysis compared with standard dialysis [12,36]. Indeed, the complexes formed between citrate and divalent cations influence the ionized fraction available for diffusion in the dialysis fluid. It has been reported that supplementation of the citrate dialysate with 0.25 mmol/L of calcium corrected the difference in post-dialysis calcium concentration between acetate and citrate modalities [37]. In our study, using an increased Ca concentration of 0.15 mmol/L in the citrate dialysate resulted in a similar balance of tCa. However, the iCa load appeared significantly lower with citrate fluid (about 0.05 mmol/L) than with acetate fluid (about 0.12 mmol/L). Differences could be

explained by the ion selective electrode sensitivity to the different calcium forms. Indeed, it has been shown that citrate plasma levels during citrate HD reach a maximum at 2 h to become then stable, while they progressively increase during citrate HDF with values at 4 h significantly higher than in citrate HD [38]. As a result, at the end of the dialysis session, the 3 forms of Ca are measured, particularly the Ca-citrate complex, using colorimetric method but not with the ion selective electrode.

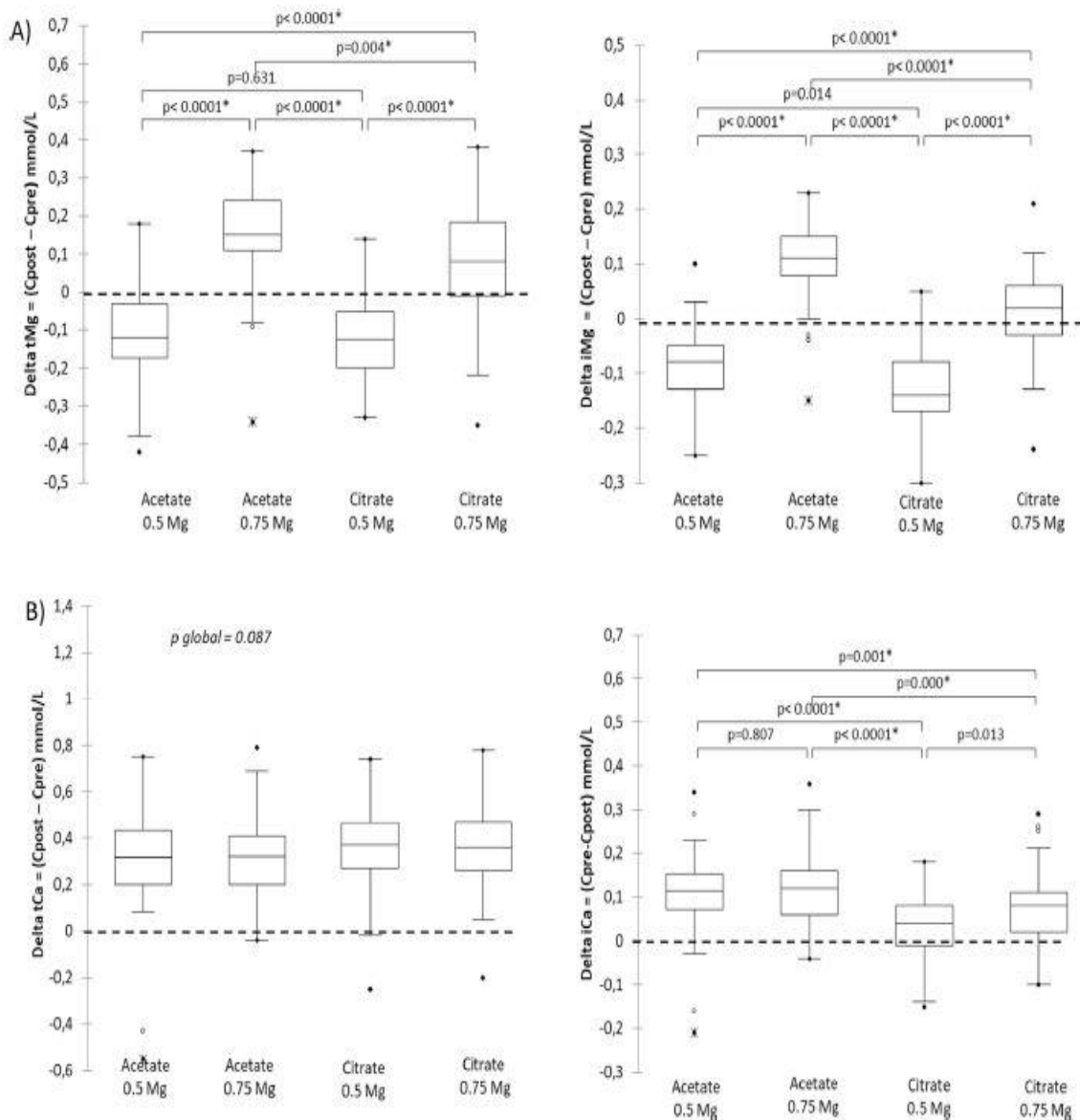


Fig. 3. Dialytic balance of A) Magnesium; B) Calcium with the 4 tested dialysate fluids. Statistical significance $p < 0.0083$ after Bonferroni correction.

However, less attention has been paid to Mg. Cunningham et al. in 2012 [4] reviewed studies on serum/ionized Mg with different Mg dialysate concentrations and reported three studies evaluating the influence of HD treatment on total and ionized Mg fractions. The two dialysate concentrations (0.5 and 0.75 mmol/L) led to a decrease of both tMg and iMg, whereas in our study, a significant positive balance of 20% for both tMg and iMg with acetate dialysate Mg

concentration at 0.75 mmol/L was found. Mean pre-dialysis tMg (ranging from 0.97 to 1.19 mmol/L) and iMg (ranging from 0.62 to 0.71 mmol/L) concentrations in these studies were higher than in ours where median tMg and iMg ranged from 0.85 to 0.90 and 0.65 to 0.60 mmol/L, respectively. This could partly explain the observed discrepancy since the pre-dialysis level influences Mg diffusion during the session. The modification of dialysis solution with substitution of part of acetate by citrate influences changes of iMg during dialysis [12,36]. We confirmed the results obtained by Safranek et al [12] using acetate and citrate dialysis solutions with a fixed concentration of Mg at 0.5 mmol/L and found predialysis “cut-off” concentrations lower with citrate than with acetate dialysis solution of 0.68 (vs 0.75) and 0.43 (vs 0.51) mmol/L for tMg and iMg respectively (Fig. 2). We extend previous results in this domain by showing that increased Mg concentration in the citrate dialysate led to a significant slightly positive balance of 10% for tMg and a neutral balance of 4% for iMg. This latter discrepancy between the two forms of Mg could be explained, once again, by the diffusion of citrate in the blood at the end of the dialysis session [38].

A higher concentration of dialysate Mg appears to have beneficial effects on endothelial cell function and vascular tone in HD patients [7]. Schmaderer et al [39] investigated the impact of higher dialysate magnesium concentration on 3-year mortality in a pilot observational case-control study in patients on maintenance hemodialysis treated with low (0.50 mmol/L) or high (0.75 mmol/L) Mg in the dialysate. In this study, the high dialysate magnesium was associated with a more beneficial cardiovascular survival rate. However, conflicting results emerged from short-term prospective randomized interventional studies. A 28-day parallel group randomized controlled clinical trial conducted by Bressendorf et al [40] showed that increasing dialysate magnesium from 0.5 to 1 mmol/L decreased calcification propensity in subjects undergoing maintenance hemodialysis. A randomized 4-week crossover study conducted by Del Giorno et al [41] showed that increasing dialysate Mg from 0.5 to 0.75 mmol/L improved vascular stiffness of subjects undergoing maintenance hemodialysis. A 2-week randomized crossover study of low (0.5 mmol/L) versus high (1 mmol/L) dialysate Mg conducted by Jefferies et al [42] failed to demonstrate an improvement of intradialytic hemodynamics or myocardial stunning. Nevertheless, the authors found a significant correlation between Mg changes during the session and changes in global longitudinal strain. Decreasing Mg changes was significantly associated with high Mg dialysate concentration. In line with this, the ongoing Magnesium in chronic haemodialysis (MAGIC-HD) study, a randomized double-blinded standard of care-controlled trial will evaluate the feasibility of sequential Mg increase (from 0.5 to 1 mmol/L) in the dialysate [43].

This study acknowledges some limitations. Firstly, our conclusions are limited by the relatively small size of the population. The factors associated with discordant interpretation using ionized and total forms of divalent cations could be affected by deviation from normality of serum albumin concentration in particular. In addition, as the number of sessions is depicted, individual outliers could skew the data. Secondly, this single-center study was

carried out in the South of France and may not be generalizable to other countries with different lifestyles including diet.

In conclusion, our results showed that the use of a dialysate containing 0.75 mmol/L of Mg results in a positive balance for the patient and supports the individualization of dialysate Mg concentrations to modulate plasma concentrations in dialysis patients. Increasing Mg level in citrate dialysis fluids to 0.75 mmol/l appears necessary and could improve clinical outcomes. The monitoring of iMg should be relevant to personalize the prescription of Mg in acetate dialysate fluid according to predialysis level in order to avoid changes in Mg during the session associated with overall longitudinal strain [42]. It has been shown that total intraerythrocyte Mg was comparable in chronic HD using the same dialysate Mg (either 0.5 mmol/L or 1 mmol/L) for at least 3 months [13], indicating the absence of risk of hypermagnesemia manifestations. In addition, the monitoring of iMg could help to better define hypomagnesemia in the context of hypoalbuminemia, to unmask hypermagnesemia in patients with normal tMg.

CRediT authorship contribution statement

Anne-Sophie Bargnoux: Data curation, Formal analysis, Writing – original draft. **Marion Morena:** Data curation, Formal analysis, Writing – original draft. **Annie Rodriguez:** Data curation, Formal analysis, Resources. **Caroline Courtais-Coulon:** Data curation, Formal analysis. **Anne-Marie Dupuy:** Writing – review & editing. **Nils Kuster:** Conceptualization. **Lotfi Chalabi:** Conceptualization, Resources, Supervision. **Jean-Paul Cristol:** Conceptualization, Methodology, Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request. *Acknowledgements* The authors acknowledge Nova Biomedical for providing reagents for this study.

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