



Received: 01 November 2016  
Accepted: 28 February 2017  
First Published: 06 March 2017

\*Corresponding author: Claudius Küchle, Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany  
E-mail: [claudius.kuechle@mri.tum.de](mailto:claudius.kuechle@mri.tum.de)

Reviewing editor:  
Udo Schumacher, University Medical Center Hamburg-Eppendorf, Germany

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## NEPHROLOGY & UROLOGY | RESEARCH ARTICLE

# Correcting low magnesium levels in hemodialysis by higher dialysate magnesium

Claudius Küchle<sup>1\*</sup>, Yana Suttman<sup>1</sup>, Anna-Lena Reichelt<sup>1</sup>, Julia Apfelböck<sup>1</sup>, Volker Zoller<sup>1</sup> and Uwe Heemann<sup>1</sup>

**Abstract:** Albeit low magnesium levels are a known mortality factor in dialysis patients, low (0.5 mmol/l Mg) dialysate magnesium is routinely used. The apprehension that hypermagnesemia will be induced by higher dialysate magnesium prevents its use. How high patients' magnesium levels actually are is mostly unknown, since magnesium levels are not even routinely measured. Thus, we determined the predialytic magnesium levels in 205 outpatients, dialysed with a magnesium concentration of 0.5 mmol/l and found them lower compared to age matched non dialysis patients. In another group of 54 patients we demonstrated that dialysis itself causes a significant loss of magnesium. We tested different magnesium substitutions and found higher dialysate magnesium levels of 0.75 mmol/l convenient to handle. To study the safety of such dialysate magnesium levels, we utilized a dialysate magnesium of 0.75 mmol/l in 34 patients over 30 months and heeded for complications due to hypermagnesemia. Before substitution, magnesium levels were in the low range of 0.53 mmol/l. The elevated magnesium dialysate increased serum levels to 0.63 mmol/l and was not associated to any apparent side effects or significant changes in calcium, phosphate or iPTH levels. In summary, a higher dialysate magnesium concentration is safe and averts the loss of magnesium during dialysis.

### ABOUT THE AUTHORS

Improvement of renal replacement therapy is archived by generations of devoted physicians and their ever new understanding of pathophysiology. This leads to continuous inventions in dialysis technique and to improvement of skills and medication.

But sometimes we gain some progress by just reading the basic literature: Low magnesium levels are known to be a strong negative predicting factor in patients on dialysis, and they tend to fall through the years. So, as we showed higher magnesium levels to be easily attained, our next step will compare the differences in smooth muscle cell ossification and atherosclerosis in greater groups of patients on different dialysate magnesium concentrations.

By this means, we hope to convince our colleagues to use higher dialysate magnesium level in order to decrease the cardiovascular risk of our dialysis patients.

### PUBLIC INTEREST STATEMENT

Since the 1980th magnesium is known to reduce arteriosclerosis in healthy and renal diseased patients. Yet, as all electrolytes in patients with end stage renal disease it might render a uremic toxin, capable of toxic effects. Thus dialysis was once intended to remove the substance and a low dialysate magnesium was chosen. Unfortunately the amount of nutritional magnesium intake in western countries is decreasing since years, so do magnesium levels in dialysis patients. Now for some bad news: low magnesium is irrefutably associated with a high mortality in dialysis patients. So we asked basic questions: how are the magnesium levels in ambulatory dialysis patients? And as we found them low, how to safely overcome this. We proved that higher magnesium dialysate levels resulted in stable, unchanging high magnesium levels. So higher magnesium dialysate levels are safe and higher patients' magnesium levels easy to attain. But you have to measure!

**Subjects: Nephrology; Dialysis; Physiology**

**Keywords: hypomagnesaemia; substitution; haemodialysis**

### 1. Background

Cardiovascular diseases are the leading cause of morbidity and mortality in chronic kidney disease patients (Goodman et al., 2000). Low magnesium levels are a strong negative predicting factor in patients on dialysis, leading to smooth muscle cell ossification and atherosclerosis (João Matias et al., 2014; Reffelmann et al., 2011; Sakaguchi et al., 2014). The correlation between high levels of serum magnesium and lower mortality in end stage renal disease (ESRD) has also been evidenced (Ishimura, Okuno, Yamakawa, et al., 2007). Nevertheless, deficiency of serum ionized magnesium in patients on hemodialysis is seen since 1993 (Markell et al., 2003). Additionally, although the normal total serum magnesium in adults ranges from 0.70 to 1.10 mmol/l, numerous observations have demonstrated that serum magnesium in ESRD patients above these level are associated with even better survival (de Roij van Zijdewijn et al., 2015; Ishimura et al., 2007). Serum magnesium in ESRD patients is affected by the dialysate magnesium concentration, which standardly is 0.5 mmol/l and inevitably induces a post dialytic hypomagnesaemia. It is doubtful whether this deficit can be regained by nutrition. On the other hand, the substitution of magnesium in renal insufficiency is considered to be hazardous, due to impaired renal excretion and the risk of accumulation. So we evaluated the present low magnesium dialysate concentration in a cohort of ESRD patients, investigated the magnesium losses during dialysis with heparin or citrate as anticoagulants and studied the impact of a higher normalized magnesium concentrate of 0.75 mmol/l on the blood magnesium levels in ESRD patients.

### 2. Subjects and methods

We chose to measure ionized magnesium level as it represents the biological active form of magnesium, and, even more important, in dialysis patients significant shifts of the proportion of ionized to total Magnesium are known, so total magnesium measurements in dialysis patients tend to underestimate magnesium deficits (Altura and Altura, 1991–1992; Huijgen et al., 1998). As ionized magnesium is not readily measured, we measured total magnesium in our experiment on long term substitution. We did so in order to make sure that extremely high magnesium levels would reliably show up in total magnesium measurements.

Measurements of ionized magnesium were performed with a magnesiometer (type CRT 8, Nova Biomedical, Waltham MA). In the case of outpatients, measurement of total magnesium concentration was impossible. To just give a rough approximation we estimated this value using the formula: total Mg =  $(\text{Mg}^{2+} \times 100)/61$ , which we calculated from the proportion of our measured paired total and ionized values. This calculated value has not been used for any further statistical analysis.

Magnesium in dialysate was increased to 0.75 mmol/l by using commercial available admixture provided by Fresenius Medical Care, Bad Homburg, Germany.

All parts of this study were approved by the ethical committee of the Technische Universität München.

As aforementioned we performed our analyses in three steps:

- (1) In step one we measured magnesium levels in 205 outpatients undergoing intermittent haemodialysis in eight dialysis centres located in Munich and surrounding area with standard dialysate magnesium concentration of 0.5 mmol/l. Patients were eligible if they were chronic hemodialysis patients, longer than 3 months on dialysis, aged  $\geq 18$  years and had regular hemodialysis 3 times per week. Exclusion criteria were systemic infection, malignoma and pregnancy. Peak weekly magnesium levels were determined before the start of the dialysis after the longest interval off dialysis. All patients received a chronic heparin or low molecular weight heparin dialysis. Demographic and clinical characteristics are given in Table 1.

**Table 1. Demographic and clinical characteristics**

<b>Demographics</b>	<b>N = 205</b>
Age (years), mean ± SD	66.04 ± 15.6
Sex m/f, n (%)	133 (64.8)/72 (35.2)
<i>Magnesium</i>	
Total Mg (mmol/l), est.	0.95
Ionised Mg (mmol/l), mean ± SD	0.58 ± 0.08
<i>Cardiovascular risk factors</i>	
Arterial hypertension, n (%)	183 (89.2)
Diabetes mellitus, n (%)	78 (38.0)
Coronary heart disease, n (%)	47 (22.9)
Peripheral arterial disease, n (%)	27 (13.2)
Hyperparathyroidism, n (%)	174 (84.9)
Hypercholesterolemia, n (%)	117 (57.0)
Current smokers, n (%)	36 (17.6)
<i>Dialysis data</i>	
Dialysis salvage (months), mean ± SD	61.27 ± 67.08
Time on dialysis (h), mean ± SD	4.47 ± 0.83
Ultrafiltration volume (liter), mean ± SD	1.88 ± 1.21
<i>Hemodynamics</i>	
pSBP (mmHg), mean ± SD	123.81 ± 16.62
pMAP (mmHg), mean ± SD	97.19 ± 13.38
pDBP (mmHg), mean ± SD	74.67 ± 12.48

Notes: SD: standard deviation, m/f: male/female, pSBP: peripheral systolic blood pressure, pMAP: peripheral mean arterial pressure, pDBP: peripheral diastolic blood pressure.

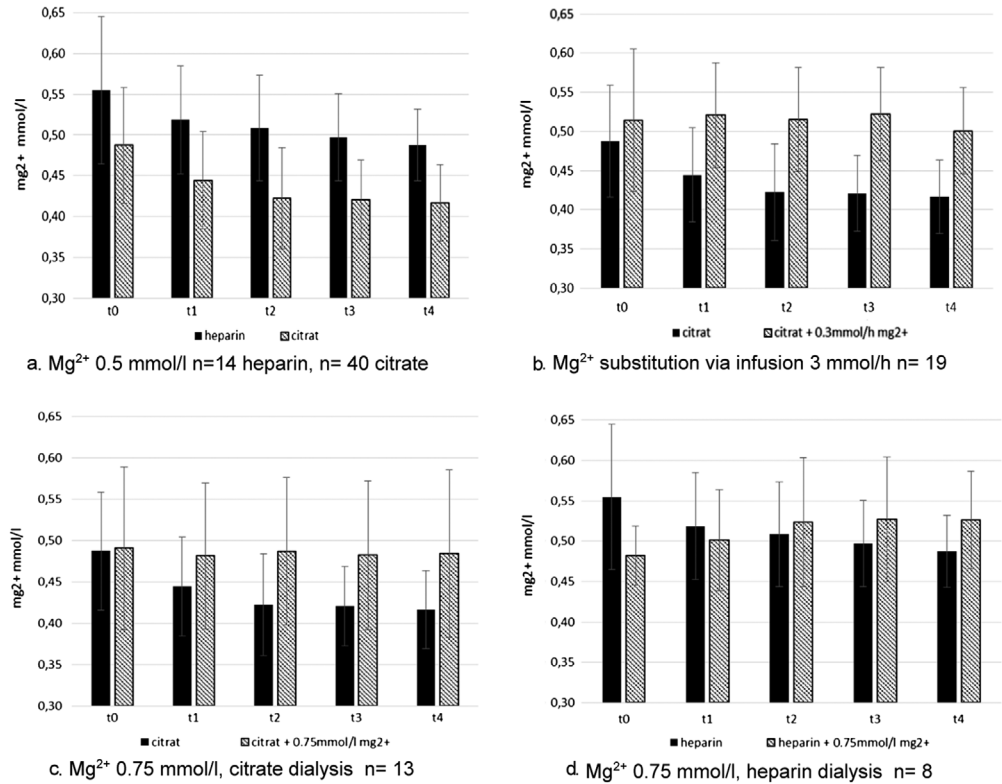
- (2) In a second step we measured the ionized magnesium levels at different times during single intermittent haemodialysis with different anticoagulation (citrate or heparin) in 54 patients. So we aimed to describe the direct impact of the dialysis procedure on the serum magnesium. These measurements were conducted at our university dialysis department, applying the same inclusion criteria as mentioned before. We then tested the effectivity and practicability of different types of magnesium substitution via infusion or via dialysate enrichment (Figure 1).
- (3) After detecting low magnesium levels in the outpatients tested (see results), we started substituting magnesium in the university department chronic dialysis patients ( $n = 34$ ; same including criteria as mentioned before), by increasing the dialysate levels to 0.75 mmol/l, which was found to be most convenient. 26 patients received chronic heparin dialysis and 8 were anticoagulated with citrate. The mean age was  $57.8 \pm 17.8$ , 68% of the patients were male. The mean predialytic ionized magnesium before substitution, was low in all patients ( $0.53 \pm 0.12$  mmol/l ( $0.87 \pm 0.17$  mmol/l total Mg) (Figure 2).

Magnesium was measured every three months as a part of our routine quarterly blood check, before anticoagulation was begun to avoid interference with heparin or citrate (Altura et al., 1994). Nausea, flushing, headache, lethargy and drowsiness, hypocalcaemia, hypotension and bradycardia, were defined as potential hypermagnesaemia side effects. All patients were asked three times a week on the ward round about having such symptoms and were ECG monitored.

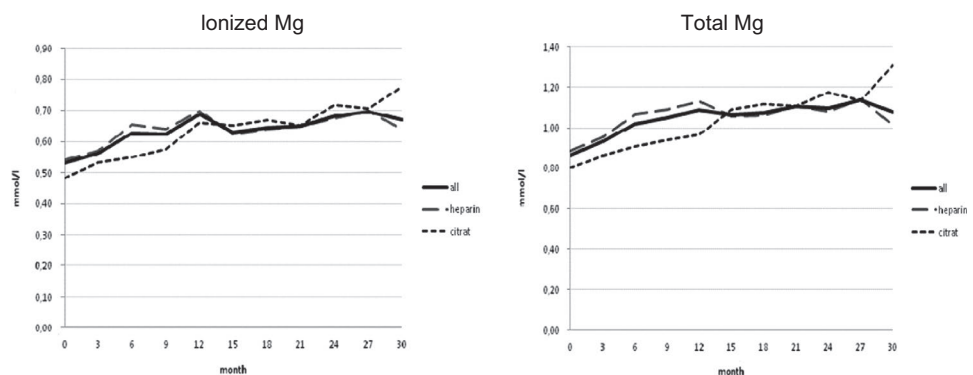
Statistical methods: SPSS 20.0 software ([www.spss.com](http://www.spss.com)) was used for all statistical tests. Quantitative data were presented using the mean and standard deviation, values are expressed as mean ± SD. Comparison of quantitative data between groups was made using t-test and Friedman

**Figure 1. Intradialytic levels of ionised serum Magnesium.**

Note: t = hours after start.



**Figure 2. Long term course of ionized and total Magnesium levels, 0.75 mmol/l magnesium dialysate.**



Wilcoxon test for different time points through the follow up

ionized Mg <sup>2+</sup>	month 0 to 3	month 3 to 6	month 0 to 6	month 6 to 30
all				
p	.025	.001	.001	.278
heparin				
p	.064	.001	.004	.656
citrate				
p	.109	.734	.043	.180

total Mg	month 0 to 3	month 3 to 6	month 0 to 6	month 6 to 30
all				
p	.004	.009	.001	.552
heparin				
p	.023	.009	.006	.859
citrate				
p	.042	.674	.046	.180

test for independent samples. Paired samples were analysed by t-test for pair samples. Comparison between groups with non-normally distributed variables was performed using Wilcoxon signed-rank test. For all comparisons a  $p < 0.05$  was considered statistically significant.

### 3. Results

#### 1. Magnesium levels in ESRD outpatients treated with 0.5 mmol/dl magnesium:

All outpatients ( $n = 205$ ), treated with standard magnesium dialysate of 0.5 mmol/l, had low normal predialytic ionized magnesium levels ( $0.58 \pm 0.08$  mmol/l (0.95 mmol/l estimated total Mg)). None of the patients had elevated levels. The normal range for ionized magnesium was defined as  $0.61 \pm 0.6$  mmol/l, established from a group of 50 outpatients with an eGFR of  $> 60$  ml/min and a medium age of  $60 \pm 17.1$ y.

#### 2.1. Effect of heparin and citrate anticoagulation on magnesium clearance during dialysis:

At the start of the dialyses sessions all patients ( $n = 54$ ) had low normal magnesium levels, without a significant difference between heparin ( $n = 14$ ) ( $0.565 \pm 0.11$  mmol/l) and citrate anticoagulation ( $n = 40$ ) ( $0.487 \pm 0.072$  mmol/l). Throughout the dialysis with 0.5 mmol/l magnesium, there was a significant decrease in the ionized magnesium in both groups (heparin  $p = 0.001$ , citrate  $p < 0.001$ ), but in the patients with citrate anticoagulation the intradialytic magnesium loss was higher, as compared to those with heparin (Figure 1(a)).

#### 2.2. Effect of substitution of magnesium:

Patients dialysed with 0.75 mmol/l magnesium dialysate did not lost magnesium throughout the dialyses. While we observed a slight, although insignificant increase in the ionized magnesium levels in the heparin group, it remained stable in the citrate group. While the total magnesium significantly increased in the heparin group ( $p = 0.006$ ), it did not in the citrate group (ns.  $p = 0.445$ ), (Figure 1). The results for magnesium substitution via infusion 3 mmol/h are shown in Figure 1(b).

#### 3. Long-term effects of dialysis using 0.75 mmol/l magnesium:

We included 34 chronic dialyses patients, who all until then, were dialysed with a 0.5 mmol/l magnesium concentrate. 8 of them were anticoagulated with citrate and 28 with heparin. Within the next two years 8 patients moved and were lost of follow up, 6 died, 7 were transplanted and one changed to peritoneal dialysis, so we ended up with 11 heparin and 3 citrate patients after 30 months.

The mean predialytic ionized magnesium before substitution was  $0.53 \pm 0.12$  mmol/l ( $0.87 \pm 0.17$  mmol/l total magnesium). Serum magnesium levels, both ionized and total, increased significantly within 6 months of treatment ( $0.63 \pm 0.14$  mmol/l,  $1.02 \pm 0.22$  mmol/l,  $p = 0.01$  for both). In the next 18 months the levels stabilized, without further significant increase or decrease, on average to  $0.66 \pm 0.02$  mmol/l (total  $1.09 \pm 0.04$  mmol/l), which is still within the presumed normal range, and did not significantly deviate from each other (mean value difference ionized  $p = 0.278$ , total  $p = 0.552$ ) (Figure 2). All magnesium values after six months substitution were significantly higher than the zero-point values, specified as the last value using 0.5 mmol/l magnesium dialysate. The ionized and total levels equably changed.

During follow up we detected neither clinical signs of hypermagnesiemia, nor toxic levels of magnesium in any of the patients. After 30 months ionized calcium showed a slight tendency of increase, iPTH decreased and phosphate levels minimal increased. None of the mentioned changes reached statistical significance at any time.

### 4. Discussion

The correlation between high levels of serum magnesium and lower mortality in end stage renal disease (ESRD) is evident (Ishimura et al., 2007; Markell et al., 1993). As shown amongst others by Ishimura et al. (2007); Lacson, Wang, Ma, and Passlick-Deetjen, (2015) and de Roij van Zuidewijn et al. (2015), exaggerated serum magnesium levels in ESRD patients are associated with an even better survival. This leads to the finding that high magnesium level yet compensates for cardiovascular

risk of high phosphate levels in a Japanese cohort study (Sakaguchi et al., 2014). The effect can be partly explained by the finding that low magnesium levels lead to smooth muscle cell ossification and development of atherosclerosis (João Matias et al., 2014; Reffelmann et al., 2011; Sakaguchi et al., 2014).

Notable, the common dialysate ionized magnesium concentration is low (0.5 mmol/l). This was once chosen on the assumption that ESRD patients tend to cumulate alimentary and drug derived magnesium and thus, are at risk of intoxication. Nevertheless, deficiencies of serum ionized magnesium in dialysis patients are noticed since 1993 (Markell et al., 1993). Consistently with the decreasing intake of magnesium, decreasing magnesium levels in European dialysis patients have recently been shown (de Roij van Zuijdewijn et al., 2015).

Our hypothesis was that a low magnesium concentration in the dialysis fluid, aggravated by the decreasing dietary magnesium intake, might be a crucial pathway to induce an “iatrogenic” hypomagnesaemia. Using low magnesium dialysates we could thus increase the cardiovascular risk and mortality of our dialysis patients.

To address this, we measured the predialytic ionized magnesium concentrations in domestic haemodialysis patients dialysed with 0.5 mmol/l magnesium, we investigated the intradialytic dynamics of magnesium and investigated whether a long term magnesium substitution via dialysis is suitable to safely deliver adequate, meaning high magnesium levels (de Roij van Zuijdewijn et al., 2015; Ishimura et al., 2007).

We found that the standard magnesium dialysate of 0.5 mmol/l leads to low magnesium levels even at the beginning of the dialysis sessions, presumably because the intradialytic loss of magnesium is not regained while off dialysis. The magnesium loss was stronger (although this reached no significance) in patients on citrate anticoagulation, most probably due to the known binding of magnesium to citrate (Altura et al., 1994). Concluding that the dialysate magnesium concentration of 0.5 mmol/l is inadequately low, we tested two methods for safe magnesium substitution: by increasing the dialysate magnesium concentration to 0.75 mmol/l or by giving a 0.3 mmol/h magnesium infusion throughout the dialysis session (Figure 1). Both methods are efficient, however the substitution via higher magnesium dialysate concentrations was easier and more practicable.

Although the dialytic procedure plays the most important role in the regulation of the serum magnesium, as the end-dialyses serum magnesium parallels the dialysate magnesium content, magnesium concentration in ESRD patients are influenced by many other factors such as nutrition, remaining urine production or the drug intake. The nutritive magnesium intake has to be discussed as an alternative to a magnesium substitution on the dialysis. The last big nutrition study in Germany showed that over 40% of the mean German population had an alimentary magnesium deficiency (Heseker et al., 1994). Therefore, as we found, a chronic dialysis patient is not able to intake an adequately amount of magnesium with his ESRD diet. An oral supplemental magnesium substitution is due to the individual differences in the enteral metabolism and the remaining renal function complicated and hazardous, as it might indeed lead to accumulation up to toxic magnesium levels (Navarro-González, Mora-Fernández, & García-Pérez, 2009).

We proved that with the substitution of ionized magnesium using higher concentrated dialysate solution (0.75 mmol/l), we are able to increase the serum magnesium concentrations to stable high normal levels in all patients, without causing any notable side effects. The most significant increase takes place in the first six months after beginning the treatment. This is well in accordance with findings of Filiopoulos, Hadjiyannakos, and Vlassopoulos (2016), who followed patients over 4 months. With our 30 months survey, we could demonstrate stable levels of magnesium thus providing solid evidence for safety. This observation is significantly true for both heparin and citrate dialysis, although our citrate dialysis data base is on our opinion too small to be of statistical use. Worth mentioning, we found no statistically significant changes in calcium, phosphate or parathormone levels after 30 months.

## 5. Conclusion

Low levels of magnesium are associated with high morbidity and mortality in patients on dialysis. Despite this knowledge, we find low magnesium levels in our ESRD patients. Dialysis itself with its traditionally low magnesium levels of 0.5 mmol/l, nowadays contributes to this finding. Regarding our results, we recommend at least measuring serum magnesium to detect low levels. With paralleling ionized and total levels in ESRD (Figure 2) it might be adequate to measure total magnesium for a rough approximation and follow up. But, with the established shifts of the proportion of ionized to total magnesium in dialysis patients, the real frequency and degree of hypomagnesiemia might be underestimated.

Finding magnesium levels low, we quite simply propose using a higher dialysate magnesium concentration of 0.75 mmol/l. The method is now proven to safely increase the magnesium level. Concerning the ability of high magnesium levels to compensate for cardiovascular risk of high phosphate levels, we assume that this is useful information, facilitating further investigations of magnesium substitution on survival in dialysis patients.

### Funding

This work was supported by the German Research Foundation (DFG) and the Technical University of Munich (TUM) in the framework of the Open Access Publishing Program.

### Author contributions

Claudius Küchle and Yana Suttman developed the concept, wrote the manuscript and were equally contributing to this work. Anna-Lena Reichelt, Yana Suttman and Uwe Heemann analysed the data. All authors participated in clinical conduct, data collection and analysis. All authors have read and approved the submission. The work was part of the doctoral thesis of Julia Apfelböck and Volker Zoller.

### Competing Interests

The authors declare no competing interest.

### Author details

Claudius Küchle<sup>1</sup>  
E-mail: [claudius.kuechle@mri.tum.de](mailto:claudius.kuechle@mri.tum.de)  
ORCID ID: <http://orcid.org/0000-0001-7178-4269>  
Yana Suttman<sup>1</sup>  
E-mail: [Yana.suttman@gmail.com](mailto:Yana.suttman@gmail.com)  
ORCID ID: <http://orcid.org/0000-0002-9697-3565>  
Anna-Lena Reichelt<sup>1</sup>  
E-mail: [Anna-lena.Reichelt@mri.tum.de](mailto:Anna-lena.Reichelt@mri.tum.de)  
Julia Apfelböck<sup>1</sup>  
E-mail: [julia.apfelboeck@t-online.de](mailto:julia.apfelboeck@t-online.de)  
Volker Zoller<sup>1</sup>  
E-mail: [volkermzoller@gmail.com](mailto:volkermzoller@gmail.com)  
Uwe Heemann<sup>1</sup>  
E-mail: [uwe.heemann@lrz.tum.de](mailto:uwe.heemann@lrz.tum.de)

<sup>1</sup> Department of Nephrology, Klinikum rechts der Isar, Technische Universität München, Ismaninger Straße 22, 81675 München, Germany.

### Citation information

Cite this article as: Correcting low magnesium levels in hemodialysis by higher dialysate magnesium, Claudius Küchle, Yana Suttman, Anna-Lena Reichelt, Julia Apfelböck, Volker Zoller & Uwe Heemann, *Cogent Medicine* (2017), 4: 1302544.

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