Magnesium-based interventions for normal kidney function and chronic kidney disease*

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Abstract. Magnesium (Mg) is one of the most important cations in the body, playing an essential role in biological systems as co-factor for more than 300 essential enzymatic reactions. In the general population, low levels of Mg are associated with a high risk of cardio-vascular disease (CVD). Despite the accumulating literature data, the effect of Mg administration on mortality in chronic kidney disease (CKD) patients has never been investigated as a primary end-point. We conducted a systematic search of studies assessing the benefits and harms of Mg in CKD (stages 1 to 5 and 5D), and considered all randomized controlled trials (RCTs) and quasi-RCTs evaluating Mg-based interventions in CKD. As a phosphate binder, Mg salts offer a plausible opportunity for doubly favorable effects via reduction of intestinal phosphate absorption and addition of potentially beneficial effects via increasing circulating Mg levels. Mg supplementation might have a favorable effect on vascular calcification, although evidence for this is very slight. Although longitudinal data describe an

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Magnesium (Mg) is the second most abundant intracellular cation and the 4th most abundant in the body [1]. The total Mg content in adults is ∼20 g compared with 1000 g of calcium [2, 3]. Sixty-five percent of the total Mg can be found in bones; the remaining Mg is located in the intracellular space (33%), with only a small amount in the extracellular space (2%), or in the intravascular compartment (<1%) [4]. The kidney is the key regulator of Mg balance: reabsorption occurs in the ascending limb of Henle’s loop, mainly via the paracellular route, while fine-tuning of Mg regulation occurs in the distal convoluted segment through transcellular TRPM5 ionic channels. Normal Mg plasma concentration is 1.6-2.6 mg/dL (0.65-1.05 mmol/L), and, similarly to calcium, it can be categorized into three fractions: ionized (55-70%), protein-bound (20-30%) and complexed with anions such as phosphate, bicarbonate, citrate or sulfate (5-15%) [5]. Despite its evident limitation in reflecting total body content, plasma concentration is the most widely used method to estimate Mg status [5].

Mg is crucial in biological systems as co-factor for more than 300 essential enzymatic reactions. It is a regulator of electrolyte passage through cellular membranes and as a basic “biological competitor” of calcium. In addition, Mg is a structural component of various tissues including mineralized bone. Maintenance of adequate intracellular Mg levels appears essential for life per se, considering that Mg is a fundamental co-factor for vital biochemical reactions, particularly those which depend upon ATP, and it is heavily involved in the Krebs cycle and glycolysis [6], and is also essential for the maintenance of RNA and DNA stability [7].

Hypo- and hypermagnesemia: clinical implications

Hypomagnesemia may present with various clinical and laboratory manifestations (table 1). The most important include arrhythmias, ECG changes, weakness, tremor, muscle fasciculation, seizures, depression, all associated in the most severe cases with hypokalemia and hypocalcemia [8]. Hypermagnesemia may present with malaise, articulation disorders, ataxia, nausea and vomiting. At higher concentrations, hypermagnesemia might lead to respiratory depression, areflexia and coma [5, 9]. The incidence of disturbed Mg levels is quite high among subjects at risk including frail patients, elderly, diabetic, and hospitalized patients, especially those admitted to intensive care units [5]. Furthermore, hypomagnesemia might be a side effect of a number of different medications, such as thiazide diuretics, proton-pump inhibitors, cisplatin, aminoglycoside antibiotics and calcineurin inhibitors [10]. In comparison to acquired hypomagnesemia, hereditary Mg-wasting disorders are relatively rare, comprising genetically determined disorders that affect, either primarily or secondarily, renal Mg handling. These inherited conditions affect different nephron segments and different cell types, and lead to variable but increasingly

<table>
<thead>
<tr>
<th>Table 1. Clinical signs and laboratory manifestations of magnesium deficiency</th>
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<tr>
<td>Neuromuscular manifestations</td>
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<td>Cardiovascular manifestations</td>
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<tr>
<td>Calcium metabolism abnormalities</td>
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</table>
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distinguishable phenotypic presentations. The most frequent, with an estimated prevalence of \( \sim 1:40,000 \) is Gitelman syndrome (GS), a disease caused by a recessive mutation in the gene encoding the thiazide-sensitive chloride co-transporter that is characterized by hypokalemic alkalosis, hypomagnesemia and hypocalciuria [10]. The same mutation leads to an alteration in \( \text{Na}^+ \) and \( \text{Cl}^- \) reabsorption in the distal convoluted tubule, which results in mildvolume contraction and subsequent hyperaldosteronism. Patients usually present during late childhood or adolescence with symptoms of muscle weakness; paresthesia and chronic fatigue are also frequent findings [11].

**Magnesium and cardiovascular disease (CVD)**

Mild hypomagnesemia predisposes to cardiac arrhythmias when it occurs in the setting of an acute ischemic event [12], congestive heart failure [13], or in the acutely ill patient [14]. This is not unexpected considering the important role of Mg in electrophysiology; Mg blocks calcium influx, reduces sinus node firing rate, prolongs AV conductance, and increases AV node refractoriness [15]. The 2010 ESC Guideline for the management of atrial fibrillation (AF) suggests that hypomagnesemia is an independent risk factor for postoperative AF [16]. This recommendation was supported by a meta-analysis of 20 randomized trials including 2,490 patients, which showed that prophylactic i.v. Mg administration decreased the proportion of patients developing postoperative AF from 28% in the control group to 18% in the treatment group [17]. Early studies reported a protective role of Mg on mortality after acute myocardial infarction [18], but more recent larger trials (ISIS-4 and MAGIC) could not confirm these results [19, 20]. Currently, cardiology guidelines recommend Mg therapy only in the setting of long QT syndrome (class IIa), digoxin intoxication-induced arrhythmias (class IIa), or for hypomagnesemia-related arrhythmias, but not as a routine indication in the management of acute myocardial infarction [21, 22].

High blood pressure has also been linked to hypomagnesemia [23]. However so far, clinical trials have failed to detect a significant antihypertensive effect of Mg supplementation alone [24], suggesting only that higher doses of antihypertensive drugs are required in patients with Mg deficiency [25]. Several recent clinical studies investigating the relationship between Mg metabolism and vascular pathobiology reported an association between low serum Mg and the carotid intima–media thickness [26] pulse wave velocity [27], or endothelial dysfunction [28]. Moreover, Mg intake was inversely associated with arterial calcification as noted in a recent cross-sectional cohort study which included 2,695 participants of the Framingham Heart Study, free from cardiovascular disease and who underwent multi-detector computed tomography of the heart and abdomen [29].

Overall, several lines of evidence point to an inverse association between daily dietary Mg intake and/or serum Mg levels and the risk of CVD in different patient populations, as summarized in a meta-analysis of 19 prospective cohort studies including 532,979 participants [30]. It needs to be acknowledged that despite convincing observational and associative data linking low Mg levels to a dismal cardiovascular risk profile and/or outcome, data are sparse regarding evidence-providing, prospective, randomized, controlled trials investigating the impact of Mg supplementation upon reduction of these cardiovascular risks and improved CV outcome [31].

**Magnesium and diabetes mellitus**

Hypomagnesemia is a common finding in patients with diabetes mellitus type 2 (T2DM) and might be linked to the development and/or severity of T2DM [32]. Furthermore, a lower Mg level is directly associated with a faster deterioration of renal function in T2DM patients [33]. Moreover, hypomagnesemia is associated with the long-term micro- and macrovascular complications of T2DM [32]. A recent meta-analysis including 13 prospective cohort studies with 536,318 participants and 24,516 cases of diabetes provided further evidence that low daily dietary Mg intake is inversely associated with the risk of T2DM in a dose–response manner [34]. The impact of Mg supplementation upon reduction of diabetes complications is currently unknown.

**Magnesium in chronic kidney disease**

Since the kidney is crucial in maintaining normal serum Mg concentrations in the narrow range of 1.6 to 2.6 mg/dL (0.65-1.05 mmol/L), serum
levels rise as renal function declines. While in moderate CKD (eGFR > 30 mL/min), the loss of renal function is generally compensated for by an increase in fractional Mg excretion; compensatory mechanisms become inadequate, and hypermagnesaemia develops as renal function deteriorates and approaches stage 5 CKD [35]. Calcium and vitamin D levels also influence intestinal Mg absorption. Thus, high intestinal calcium concentrations have been reported to decrease Mg absorption [36, 37], but these findings have not been confirmed by others [38]. Intestinal Mg is also absorbed independently of vitamin D and the intestinal vitamin D receptor [37, 39]. In individuals with stage 5 CKD treated with peritoneal dialysis or hemodialysis (stage 5D CKD), serum Mg concentrations become dependent on both residual kidney function and dialysate Mg concentration. Specifically, dialysate Mg concentrations of 0.75 mmol/L may cause slight increases in serum Mg [40]. More importantly, serum Mg concentrations in patients on dialysis are dictated by oral Mg intake, as shown by a cross-sectional study of hemodialysis (HD) patients who completed a dietary questionnaire: a strong positive correlation was noted between intake and Mg concentrations in patients on dialysis who completed a dietary questionnaire: a strong positive correlation was noted between intake and Mg serum concentration (r = 0.87, p < 0.01) [41].

Several lines of evidence suggest that low serum Mg level might be a novel risk factor for CKD itself, independent of traditional risk factors, including diabetes, hypertension, older age, and family history of CKD [42-44]. Data from experimental studies suggest that low Mg levels are associated with higher production of inflammatory and proatherogenic cytokines in endothelial cells [42], a pathway that might contribute to kidney function decline. Such an hypothesis was further supported by data from a large cohort (the Atherosclerosis Risk in Communities - ARIC study) that included 13,226 participants (aged 45–65) with a baseline eGFR of at least 60 mL/min/1.73 m2. Individuals with the lowest serum Mg levels (< 0.7 mmol/L) were approximately 1.6 times more likely to develop incident CKD, and 2.4 times more likely to develop ESRD than those with a normal serum level of Mg. Importantly, these associations were not confounded by previous diabetes or the use of diuretics for hypertension treatment, nor did they appear to be mediated by incident diabetes or hypertension.

Mg may play a particularly major role in the pathogenesis of vascular calcification in individuals with CKD [45, 46]. Hypomagnesaemia is associated with vascular and valvular calcification in experimental models [47-49], and in patients with stage 5 CKD [50, 51] – even after controlling for other known risk factors for vascular calcification, such as high serum phosphorus and parathyroid hormone (PTH) levels. A recently introduced nanoparticle-based in vitro test system, assessing the overall propensity of serum to calcify, analyzed the impact of serum Mg concentration on the serum mineralization properties [52]. The authors discovered that Mg had a pronounced anti-calcification effect when it was spiked into the assay in the presence of serum. However, this method, as an in vitro serum test, did not take into account the established contribution of cells, including vascular smooth muscle cells in promoting vascular calcification in vivo; therefore we cannot draw firm conclusion regarding the implication of Mg in the pathogenesis of vascular calcification.

**Magnesium and serum PTH levels**

The serum levels of PTH and Mg depend on each other in a complex manner [53]. PTH secretion by the parathyroid gland is physiologically controlled by serum ionized calcium levels, but Mg can exert similar effects [53] suppressing PTH secretion via the activation of the parathyroid calcium-sensing receptor (CaR), although Mg is two times less potent than Ca [54]. The suppressing effect of Mg upon PTH occurs mainly when a moderately low calcium concentration is present, while this effect is blunted by normal-to-high serum calcium concentrations [55]. Mg also modulates parathyroid gland function through up-regulation of the key cellular factors: CaR, vitamin D receptor (VDR), and fibroblast growth factor 23 (FGF23)/Klotho system [55]. These observations are supported by several studies in which serum Mg levels correlated negatively with PTH [56, 57]. In addition, chronic hypermagnesemia, potentially seen in dialysis patients, may lead to low serum PTH levels and might play a role in the pathogenesis of adynamic bone disease, which is associated with a higher mortality risk [58].

The inverse correlation between Mg and PTH noted in these studies provides only indirect evidence of the effect of Mg on PTH secretion. However, many variables other than serum Mg levels influence PTH levels. Many of the studies evaluating the relationship between PTH and Mg
are not well enough controlled to draw firm conclusions or suffer from other methodological flaws. Although not regarded as primary or secondary end-point, the effect of Mg on serum PTH level has been reported in nine interventional trials that studied Mg salts used as an intestinal phosphate binder for controlling hyperphosphatemia. In conclusion, these studies did not provide evidence demonstrating that the intervention exerts an effect on either group [59-67] (table 2). Clearly, this is an area that would benefit from further research to be able to elucidate the mechanisms by which Mg might influence serum PTH levels, particularly under conditions prevalent in patients with renal dysfunction.

**Magnesium as an intestinal phosphate binder in CKD**

Mg salts offer a plausible opportunity of doubly favorable effects via reduction of intestinal phosphate absorption and addition of potentially beneficial effects via increasing circulating Mg levels. Declining renal function is associated with a tendency for increasing serum phosphate levels. However, serum phosphate concentrations remain within normal limits due to excessive production of FGF23 and PTH, which lead to an increased urinary fractional excretion of phosphate. Many observational studies produced data showing a J-shaped relationship between serum phosphate levels and the risk of death, with both higher and lower phosphate concentrations being related to an increased risk of death [68]. Mg-containing phosphate binders may have certain intrinsic advantages: they do not contain aluminum and they allow calcium intake to be reduced or eliminated; they have been in use for many years and Mg-containing phosphate binders are relatively inexpensive compared with other calcium-free phosphate binders [69]. Finally, they tend to have laxative properties as opposed to other phosphate binders. Our systematic search, which collected data related to phosphate control at the end of treatment, identified eight randomized, controlled, prospective studies, and included a total of 563 patients (table 3). In one of them, the use of combined MgCO$_3$/CaCO$_3$ phosphate-binder treatment was compared with CaCO$_3$ monotherapy in a two-year, randomized, controlled, crossover trial in 29 HD patients; MgCO$_3$ used in conjunction with CaCO$_3$ allowed a reduction in the dose of calcium and yet achieve acceptable levels of Ca, P, and Mg [60]. Moreover, treatment with combined MgCO$_3$/CaCO$_3$phosphate binders was generally well tolerated, with mild and transient gastrointestinal symptoms [60].

A six-month, randomized, open-label study involving 46 hemodialysis (HD) patients investigated whether MgCO$_3$ was as effective as CaCO$_3$ (both agents were the only phosphate binders used in each group). The administration of MgCO$_3$ was an effective and inexpensive agent to control serum phosphate levels in HD patients and, in combination with a low dialysate Mg concentration, also avoided the risk of severe hypermagnesemia [63]. Another study published in 2009 investigated the safety and efficacy of fermaglute, a calcium-free iron and Mg-hydroxycarbonate binder, for treating hyperphosphatemia in HD patients [70]. Fermaglute showed promising efficacy in the treatment of hyperphosphatemia in chronic HD patients as compared with placebo in this initial phase II study [70]. However, the development of fermaglute is currently on hold due to suboptimal and adverse effect profiles in at least some clinical trials [71].

A large, well-designed, clinical trial published in 2010 compared the combination compound calcium acetate and MgCO$_3$ with sevelamer (CALMAG trial). In this randomized, controlled, parallel-group, investigator-blinded, multicenter study, 255 HD or hemodiafiltration patients were randomized to receive calcium acetate/MgCO$_3$ (n = 126) or sevelamer (n = 129) [72]. Ca acetate/MgCO$_3$ was not inferior to the comparator at controlling serum phosphate levels at week 25. There was no change in blood ionized calcium levels; there was minimal increase in total serum calcium and a small increase in serum Mg levels. It had a good tolerability profile and thus may represent an effective treatment of hyperphosphatemia [72]. In *post hoc* analysis of this study, CaMg and sevelamer-hydrochloride (HCl) lower serum levels of intact FGF23 comparably; regarding bone parameters, in contrast to sevelamer-HCl, CaMg had no influence on bone turnover markers [73].

**Critical review of the recent evidence linking Mg and vascular health in CKD**

Experimental data have shown that Mg is a potent inhibitor of vascular calcification (VC) [74-77]. Several mechanisms by which Mg inhibits the calcification process have been proposed. It
Table 2. Results of the RCTs reporting on the relationship between Mg-based therapy and serum PTH

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Primary outcome</th>
<th>Changes from baseline serum PTH (pg/mL)</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fournier et al., 1993</td>
<td>47</td>
<td>Mg oxide (co-intervention: iv alfacalcidol)</td>
<td>MgO (at a lower dose than in intervention group) ± CaCO₃</td>
<td>Prevention of radiologically evident hyperparathyroidism</td>
<td>NS NS 6</td>
</tr>
<tr>
<td>Delmez et al., 1996</td>
<td>30</td>
<td>1. MgCO₃ + CaCO₃ (co-intervention in phase 2 = calcitriol); 2. Lower Mg dialysate concentration</td>
<td>1. CaCO₃ (co-intervention in phase 2 = calcitriol); 2. Higher Mg dialysate concentration</td>
<td>To see if the chronic use of MgCO₃, in conjunction with 0.6 mg/dL Mg dialysate, would allow a reduction in the dose of CaCO₃ and yet achieve acceptable levels of Ca, P, and Mg.</td>
<td>NS NS 5</td>
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<tr>
<td>Kyriazis et al., 2004</td>
<td>16</td>
<td>Different dialysate Mg and Ca concentrations</td>
<td>Different dialysate Mg and Ca concentrations</td>
<td>NS NS NS 1</td>
<td></td>
</tr>
<tr>
<td>Spiegel et al., 2007</td>
<td>30</td>
<td>Combined MgCO₃ + CaCO₃</td>
<td>Ca acetate</td>
<td>Control of serum phosphorus, based on both level of serum phosphorus over time and the percentage of patients achieving the K/DOQI target of serum phosphorus, 5.5 mg/dL. Additional primary endpoints included serum magnesium and the average binder dose in terms of pill count during the efficacy phase: evaluation of blood pressure and serum iPTH and bicarbonate levels.</td>
<td>NS NS 3</td>
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<td>Number of patients</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Primary outcome</td>
<td>Changes from baseline serum PTH (pg/mL)</td>
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<td></td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>Tzanakis et al., 2008</td>
<td>51</td>
<td>MgCO₃</td>
<td>CaCO₃</td>
<td>NS</td>
<td>NS</td>
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<td></td>
<td></td>
<td>(co-intervention: lower dialysate Mg)</td>
<td>To evaluate the efficacy and safety of MgCO₃ as a phosphate-binder when given with a concurrent low dialysate Mg solution. The control of serum P.</td>
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<tr>
<td>Turgut et al., 2008</td>
<td>44</td>
<td>Mg citrate</td>
<td>Ca acetate</td>
<td>NS</td>
<td>NS</td>
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<td></td>
<td></td>
<td></td>
<td>Magnesium supplementation improves carotid intima media thickness (IMT) in HD patients.</td>
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<td>De Francisco et al., 2010</td>
<td>255</td>
<td>CaMg+Ca acetate (osvaren 435/235 mg)</td>
<td>The exploration of the efficacy of CaMg compared with sevelamer-HCl as an active control. The primary target variable = serum P at week 25.</td>
<td>-109.24 ± 229.903</td>
<td>-43.98 ± 171.438</td>
</tr>
<tr>
<td>Zwiech et al., 2011</td>
<td>40</td>
<td>MgCO₃</td>
<td>Sevelamer-HCl</td>
<td>NS</td>
<td>NS</td>
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<td></td>
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<td>To assess short-term Mg salt treatment efficacy in hemodialysys patients with hyperphosphatemia</td>
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<tr>
<td>Mortazavi et al., 2013</td>
<td>54</td>
<td>MgO</td>
<td>Placebo</td>
<td>NS</td>
<td>NS</td>
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<td></td>
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<td>To determine the efficacy of oral Mg (Mg) supplementation on endothelial function through evaluation of carotid intima-media thickness (cIMT), brachial artery flow-mediated dilatation (FMD), and C-reactive protein (CRP) among HD patients.</td>
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### Table 3. Results of the RCT reporting on the relationship between Mg based therapy and serum phosphate

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Study duration (months)</th>
<th>Primary end-point</th>
<th>Secondary end-point</th>
<th>Change-from-baseline serum P (mg/dL)</th>
<th>Change-from-baseline serum Mg (mg/dL)</th>
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<td></td>
<td>Intervention</td>
<td>Control</td>
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<tr>
<td>Fournier <em>et al.</em>, 1993</td>
<td>47</td>
<td>MgO (co-intervention: IV alfacalcidol)</td>
<td>MgO (in a lower dose than in intervention group) ± CaCO₃</td>
<td>6</td>
<td>Prevention of radiologically evident hyperparathyroidism</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Delmez <em>et al.</em>, 1996</td>
<td>15</td>
<td>1. MgCO₃ + CaCO₃ (co-intervention in phase 2 = calcitriol); 2. lower Mg dialysate concentration</td>
<td>CaCO₃ (co-intervention in phase 2 = calcitriol); higher Mg dialysate concentration</td>
<td>5</td>
<td>To evaluate if the chronic use of MgCO₃ in conjunction with 0.6 mg/dL Mg dialysate would allow a reduction in the dose of CaCO₃ and yet achieve acceptable levels of Ca, P, and Mg. To assess if the lower intake of CaCO₃ would result in less hypercalcemia, allowing the administration of a higher dose of iv calcitriol.</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Turgut <em>et al.</em>, 2008</td>
<td>44</td>
<td>Mg citrate</td>
<td>Ca acetate</td>
<td>2</td>
<td>Magnesium supplementation helps to improve carotid intima media thickness (IMT) in HD patients.</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Number of patients</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Study duration (months)</td>
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<td>51</td>
<td>MgCO₃ (co-intervention: lower dialysate Mg)</td>
<td>CaCO₃</td>
<td>6</td>
<td>To evaluate the efficacy and safety of MgCO₃ as a phosphate-binder when given concurrently with a low dialysate magnesium solution. The control of serum P.</td>
<td>Changes in serum Ca, Mg, Ca×P and PTH levels and changes in bowel movements</td>
<td>NS</td>
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<tr>
<td>McIntyre et al., 2009 (1)</td>
<td>63</td>
<td>1 mg of fermagate (Mg and ferric iron)</td>
<td>Placebo</td>
<td>1</td>
<td>To determine the efficacy (lowering of serum phosphate) of multiple oral doses of fermagate, compared with placebo, in the treatment of hyperphosphatemia in patients on stable hemodialysis.</td>
<td>Fermagate with placebo for its ability to lower cholesterol in patients on hemodialysis.</td>
<td>-1.414 ± 1.609</td>
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<tr>
<td>De Francisco et al., 2010</td>
<td>255</td>
<td>CaMg+ Ca acetate (osvaren 435/235 mg)</td>
<td>Sevelamer-HCl</td>
<td>6</td>
<td>The exploration of the efficacy of CaMg compared with sevelamer-HCl as an active control. The primary target variable = serum P at week 25.</td>
<td>NS</td>
<td>-2.352 ± 1.797</td>
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<tr>
<td>Number of patients</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Study duration (months)</td>
<td>Primary end-point</td>
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<td>To determine the efficacy of oral magnesium (Mg) supplementation on endothelial function through evaluation of carotid intima-media thickness (cIMT), brachial artery flow-mediated dilatation (FMD), and C-reactive protein (CRP) among hemodialysis (HD) patients.</td>
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<td>NS</td>
<td>NS</td>
<td>NS</td>
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</table>
appears that Mg is directly involved in the prevention of calcification because it plays a role as a natural, biological, calcium antagonist [5]. Additionally, it serves as a cofactor and/or modulator of Matrix Gla Protein (MGP) or pyrophosphatases, well known inhibitors of vascular calcification [78]. Furthermore, hypomagnesemia promotes endothelial inflammation via oxidation of HDL-cholesterol [79]. On the other hand, recent experimental in vitro data exclude a role for Mg in calcium phosphate hydroxyapatite crystal growth, composition or structure, the beneficial role of Mg in attenuating VC being linked more to an active cellular role [80].

Given the potential of high serum Mg to reduce VC as shown by various observational studies, some interventional studies addressed the use of Mg in CKD patients. Mg salts as phosphate binders may inhibit the development or progression of VC in clinical trials [81]. Of note, altered Mg levels were associated with diabetes [82], menopause [83] and CKD [84], three conditions that share a common phenotype of accelerated vascular ageing, characterized by Monckeberg calcification and impaired bone metabolism (ranging from adynamic bone disease in diabetes to high bone turnover in osteoporotic, menopausal women and certain subgroups of CKD patients).

Data from a pilot study conducted over a period of 18 months showed that long-term administration of oral Mg supplements in patients on intermittent HD therapy might retard arterial calcification progression as assessed by electron beam computed tomography [85, 86]. Another small, randomized interventional study in HD patients (n = 44), reported a beneficial effect of oral Mg supplementation over a two-month period on decreasing carotid intima–media thickness [64]. A double-blind, placebo-controlled, randomized trial examined the efficacy of oral Mg on endothelial function in HD patients and showed that, while Mg supplementation significantly decreased carotid intima–media thickness (cIMT), there were no significant effects on flow-mediated dilatation. Therefore, Mg might not directly improve endothelial function, but inhibit calcification instead, as reflected by the decrease in cIMT [67]. This study had some limitations related to the small sample size and the significant baseline imbalance in intima–media thickness between the groups. Although these results are promising, more, randomized, double-blind, controlled studies are needed to confirm the positive effect of Mg supplementation in reducing vascular calcification.

**Clinical evidence linking magnesium and survival in renal populations**

Longitudinal data describe an association between lower serum Mg levels and increased total and cardiovascular mortality in patients with stage 5D CKD [30]. In a prospective observational study (N = 515 patients), serum Mg concentration was a significant predictor of mortality in maintenance HD patients using a cutoff value of 2.77 mg/dL (1.14 mmol/L), representing the mean Mg value of all patients enrolled [50]. Recent data from Japan, noted a J-shaped association between serum Mg and the odds ratio of all-cause mortality in a huge cohort of 142,555 HD patients [58]. In an interesting subsequent analysis of this large database, the interaction between Mg and phosphate as risk factors for mortality was studied [58]. The striking finding from this analysis was that for those in the highest Mg tertile, hyperphosphatemia was not associated with an increased odds ratio for mortality, possibly pointing to some protective effect of Mg on phosphate toxicity. The previous finding of a J-shaped association between Mg concentration and mortality appeared absent for the highest phosphate group, where the risk progressively decreased with increasing magnesium.

**Critical review of the evidence available from randomized control studies**

Despite the fact that Mg is particularly attractive for future research, not only for its prognostic value but also as a potential therapeutic intervention, the effect of Mg administration on mortality in CKD patients has never been investigated as a primary end-point in an RCT.

Mortality data have been reported in four RCT studies, regardless of primary or secondary endpoint, without any difference between the intervention (i.e. administration the Mg salt as P binder or to determine the efficacy of oral Mg (Mg) supplementation on endothelial function) and the control group [59, 63, 67, 70]. There were only two studies assessing this outcome following Mg supplementation (two studies, 117 participants) and
found no significant effect of Mg supplementation on all-cause mortality [67, 70]. It is important to note that all of these studies were performed in HD patients, there being no RCTs with survival data performed in predialysis patients. Taken together, these studies are characterized by a very low incidence of death in both the interventional and control arms, precluding a firm conclusion regarding the effect of Mg on survival. Larger, randomized-controlled trials design to address the role of Mg in survival are required.

Conclusion

The potential importance of serum Mg levels or Mg supplementation regarding potential health benefits is far from being settled. However, the role of Mg in terms of the benefits and harms of higher or lower serum Mg levels continues to attract growing attention in research as shown by the increasing literature available on this topic. Currently, in clinical practice, Mg is often an ion “neglected” by many nephrologists because it has not been adequately studied in CKD. In the general population, low Mg serum levels and/or intake are associated with an increased risk of CVD, type II diabetes mellitus, and hypertension. In HD or peritoneal dialysis (PD), a patient’s serum Mg levels mainly depend on dialysate Mg concentrations, but other factors such as nutrition and medications also play an important role. As a calcimimetic, Mg acts on the parathyroid gland and seems to be associated with lower serum PTH levels. As many other variables influence bone and PTH, the role of Mg in CKD patients needs to be investigated in more depth, additional research that is well-designed and directly targeting the role of Mg is needed, because current data, although scarce and of limited quality, are very promising for clinical endpoints, particularly cardiovascular.

Disclosure


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