Magnesium in Chronic Kidney Disease: Challenges and Opportunities

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Key Words

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Abstract

Cardiovascular disease is the leading cause of mortality and morbidity in patients with chronic kidney disease, which is partly explained by the fact that 40–70% of patients receiving dialysis have significant coronary artery disease. Recent clinical studies have shown that lower serum magnesium (Mg) levels are associated with vascular calcification and cardiovascular mortality among patients with end-stage renal disease (ESRD). On the other hand, hypermagnesemia inhibits parathyroid hormone secretion, which is considered an important independent risk factor for vascular calcification, left ventricular hypertrophy and mortality in ESRD patients. Finally, increasing evidence points towards a link between Mg and cardiovascular disease, even in subjects without chronic kidney disease. The purpose of this review was to critically review the current literature examining the effects of plasma Mg levels on cardiovascular disease and parathyroid hormone homeostasis in ESRD, and renal transplant patients.

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Introduction

Magnesium (Mg) is involved in many important enzymatic processes (such as neuromuscular excitation), electrolyte balance and skeletal metabolism. Mg also plays an important role in the regulation of vascular tone, heart rhythm and platelet-activated thrombosis [1, 2]. That it has major clinical importance is beyond doubt, as it helps to prevent insulin resistance, arrhythmias and osteoporosis. Mg deficiency has been reported to promote inflammation and it decreases the specific immune response (fig. 1) [3, 4]. Moreover, Mg supplementation may reduce mortality after myocardial ischemia-reperfusion injury [5].

Cardiovascular disease is the leading cause of mortality and morbidity in patients with chronic kidney disease (CKD). Forty to seventy percent of patients receiving dialysis have significant coronary artery disease [6]. Clinical and epidemiological studies have consistently suggested that vascular calcifications play an important role in the pathogenesis of cardiovascular disease and are a strong risk factor for increased morbidity and mortality in patients with end-stage renal disease (ESRD) [6, 7]. Recent clinical studies have shown that lower serum Mg lev-

Fig. 1. Possible mechanisms between Mg and cardiovascular disease in chronic kidney disease

els are associated with vascular calcification and cardiovascular mortality among patients with ESRD [8, 9]. On the other hand, hypermagnesemia inhibits parathyroid hormone (PTH) secretion, which is considered an independent important risk factor for vascular calcification, left ventricular hypertrophy and mortality in ESRD patients [10]. Finally, an increasing body of evidence points towards a link between Mg and cardiovascular disease, even in subjects without CKD. The purpose of this review is to critically review the current literature examining the effects of plasma Mg levels on cardiovascular disease and PTH homeostasis in ESRD and renal transplant patients.

Mg Physiology

Mg is the 2nd-most abundant intracellular divalent cation and functions as an allosteric modulator of several enzymes, or bridges structurally distinct molecules [11]. The total body store of Mg is approximately 25 g: 66% of this is in bone (not freely exchangeable), 33% is intracellular and 1% is extracellular. Extracellular Mg can be measured as total Mg, of which 55% is free or ionized and physiologically active, 15% is bound to anions and 30% is bound to albumin. No test for ionized Mg is available clinically. Normal serum Mg values range from 1.8 to 3.0

mg/dl (1.4–2.1 mEq/l) [12]. Mg homeostasis in humans primarily depends on the balance between intestinal uptake and renal excretion. Mg deficiency can result from reduced dietary intake, intestinal malabsorption or renal loss. The control of body Mg homeostasis primarily resides in the kidney tubules. Forty percent of Mg is absorbed in the proximal tubule via paracellular uptake in concert with salt/water uptake, 50% of Mg is absorbed in the thick ascending limb of Henle (primarily via paracellular uptake energized by the luminal Na/K/2Cl transporter), and 5% of Mg is absorbed in the distal tubule via active transport. Active reabsorption of Mg^{2+} takes place in the distal convoluted tubule and accounts for 10% of the total filtered load. Because the distal convoluted tubule is the last site of Mg^{2+} reabsorption, the final urinary secretion of Mg^{2+} is determined here. The epithelial Mg^{2+} channel, TRPM6 (transient receptor potential channel melastatin 6), is essential for the apical influx of Mg^{2+} in distal convoluted tubule cells. Renal tubular reabsorption is increased by extracellular volume contraction, hypomagnesemia and a high serum PTH level [13]. In the intestine, physiologic studies indicate 2 different transport systems for Mg acting in a parallel fashion: an active transcellular transport and a passive paracellular pathway at high intraluminal concentrations and, at low concentrations, by active transcellular uptake via the recently identified Mg^{2+} channel TRPM6, which is expressed

along the brush border membrane of the small intestine [14].

Mg has 3 important roles in that it: (1) is a biologic competitor of calcium, antagonizing it in binding cellular membranes and proteins; (2) functions as a cofactor in more than 300 essential enzymatic reactions; and (3) has a role in the regulation of the passages of electrolytes through the cellular membranes [15].

Mg Balance in ESRD Patients

Renal failure is the most common cause of hypermagnesemia, which is usually mild and asymptomatic even in ESRD patients. In CKD, until GFR falls to below 30 ml/min, urinary Mg excretion may be normal or even increased. As CKD progresses (<30 ml/min), urinary Mg excretion may be insufficient to balance intestinal Mg absorption, at which point dietary Mg intake then becomes a major determinant of serum and total body Mg levels [16]. However, administration of Mg-containing drugs (e.g. antacids and laxatives) and high Mg concentrations of dialysate may provoke severe, symptomatic or even fatal hypermagnesemia [12]. On the other hand, many factors are involved in controlling serum Mg in ESRD patients, and some conditions lead to a negative Mg balance in these patients, such as excessive intake of diuretics, reduced gastrointestinal uptake (due to acidosis, and poor nutrition and absorption) and a low Mg concentration of dialysate [17]. In patients with CKD on dialysis, bone Mg was increased by 66% in both cortical and trabecular bones, suggesting that dialysis patients have increased total body Mg stores. Patients in this study had been maintained for approximately 2 years on dialysis with a Mg concentration of 1.3 mEq/l (1.56 mg/dl), almost twice that of the current standard Mg dialysate concentration [18].

Vitamin D has an important role in absorption of Mg in the jejunum in ESRD and healthy subjects [19, 20]. Schmulen et al. [19] demonstrated that Mg absorption in the human jejunum is dependent on vitamin D, and they showed that 1- α ,25-dihydroxyvitamin D₃ therapy in patients with CKD is associated with an enhanced jejunal absorption of Mg.

Taken together, given the significance of the kidney for Mg homeostasis, it is predictable that Mg levels are mildly elevated in CKD patients, with evidence of total body accumulation over time. But what are the consequences, good and bad, of this?

Mg and Serum PTH

Mg is regulated mainly through renal excretion and to a lesser extent by hormones that affect its gastrointestinal absorption and bone metabolism, e.g. PTH, calcitonin, vitamin D and catecholamines [21]. Intestinal Mg absorption is passive only and directly related to dietary intake [13]. The relationship between Mg and PTH is complex. PTH increases serum Mg by increasing its gastrointestinal absorption, bone resorption and renal reabsorption. On the other hand, Mg is essential for synthesis, release and adequate tissue sensitivity to PTH. Hypermagnesemia, similar to hypercalcemia, inhibits PTH secretion [22]. Perfusion of isolated parathyroid glands of goats and sheep with varying concentrations of Mg showed that acute elevations of Mg levels inhibited PTH secretion [23]. Recent studies have also shown that hypermagnesemia inhibits PTH secretion in humans [24, 25]. Regarding the effect of Mg on PTH, a significant linear inverse correlation is present. A number of in vivo and in vitro studies have shown that Mg can modulate the secretion of PTH in a similar way to Ca [22]. However, in bovine species and humans, Mg is 2.5- to 3-fold less potent than Ca on a molar basis in suppressing PTH secretion. Thus, any suppressive effect of hypermagnesemia on PTH secretion could be completely and rapidly offset by the stimulation produced by hypocalcemia.

Secondary hyperparathyroidism is present in most patients with ESRD. Excess levels of serum PTH, hyperphosphatemia and high Ca $\times$ P product have been linked to uremic bone disease, vascular calcification and death [10]. Studies have reported increased vascular calcification in ESRD compared to the general population, with the predominant differences being earlier age of onset and greater distribution [6, 26]. Hyperphosphatemia, hypercalcemia and PTH have been reported to play a predominant role in the initiation and progression of vascular calcification in patients with ESRD [10, 27]. Turgut et al. [8] showed that PTH, which has a major role in the development of vascular calcification, was significantly decreased with Mg therapy.

The Beneficial Effect of Mg in the General Population

An inverse relationship between Mg and PTH has been described, and there is strong evidence suggesting that hypomagnesemia may play a significant role in the development of cardiovascular diseases in the general

population [28, 29]. Previous studies showed that low Mg status has an important role in the pathogenesis of cardiovascular disease [28], hypertension [30] and thrombosis [6] in subjects without kidney disease.

A cross-sectional study showed an inverse association between serum Mg and carotid intima-media thickness assessed by B-mode ultrasound in the general population [29]. Furthermore, The Honolulu Study provides further evidence that intake of dietary Mg is associated with a reduced risk of coronary heart disease in the general population [31]. Oral Mg therapy has been associated with significant improvement of endothelial function in patients with coronary artery disease [32] and with a decrease of plasma concentrations of triglycerides, VLDL and apo-B lipoprotein [33]. In addition, intravenous Mg is able to reduce infarct size by about 50% in models where both reperfusion injury and thrombosis occur [34].

Mg regulates arterial blood pressure via a reduction of total peripheral resistance despite a moderate increase in cardiac output [35], exerts an antithrombotic effect by inhibiting the upregulation of PAI-1 [36], stimulates nitric oxide synthesis, decreases inflammatory response [37] and facilitates the re-endothelialization of vascular injuries [38].

Despite of all these beneficial effects, Mg replacement or Mg containing agents like cathartics and antacids may cause severe or fatal hypermagnesemia even in patients without pre-existing renal dysfunction [39]. Potential harmful effects of elevated Mg include altered nerve conduction velocity, increased pruritus, and alterations to osseous metabolism and parathyroid gland function (mineralization defects, contribution to osteomalacic renal osteodystrophy and adynamic bone disease) [40]. Serum Mg levels greater than 10 mg/dl may also cause refractory hypotension [41], bradycardia, CNS depression, muscle weakness and paralysis with secondary respiratory failure [42], bowel hypomotility and hypocalcemia [43].

Further studies are still needed to assess more accurately the role of Mg in modulating the immune response in humans, but experimental findings in animal models suggest that inflammation is the missing link to explain the role of Mg in many pathological conditions. The safe serum Mg level range and the benefit of oral Mg supplementation for the prevention and treatment of hypertension, diabetes, CVD and atherosclerosis also warrant further study.

Mg in Peritoneal Dialysis Patients

There is now evidence that hyperparathyroidism, an independent risk factor for vascular calcification, develops in continuous ambulatory peritoneal dialysis (CAPD) patients dialyzed with low-calcium and low-Mg peritoneal dialysis solutions, even though their serum Ca is maintained at a normal level [44, 45]. One possible explanation for this is that low Mg functions as a stimulus for PTH secretion independently of serum Ca concentration. Table 1 summarizes data from clinical trials specifically addressing the effect of Mg on serum PTH level in peritoneal dialysis patients. In a study by Navarro et al. [60] among patients on CAPD, patients in the lower iPTH group have a significantly higher serum Mg concentration than those in the higher iPTH group. Linear regression analysis showed a highly significant inverse correlation between serum Mg and iPTH ($r = -0.70$, $p < 0.001$). Saha et al. [58] reported similar results based on a study of 26 CAPD patients dialyzed with 3 different Mg concentrations: 0.74, 0.50 and 0.25 mmol/l. They observed an inverse correlation between serum iPTH and Mg levels ($r = -0.42$, $p < 0.05$), with serum iPTH slightly lower in patients dialyzed with the highest Mg concentrations. In light of these studies, it can be speculated that a CAPD solution with high Mg might have a role in the prevention of development of vascular calcification by decreasing serum PTH level. This should, however, be subjected to a randomized controlled study. Finally, in a relatively small number of male patients undergoing CAPD ($n = 44$), serum Mg was reported to be significantly lower in patients with increased vascular calcification than in patients without vascular calcification [64].

Mg in Hemodialysis Patients

There is significant controversy on the relationship between serum Mg and PTH in hemodialysis (HD) patients. Some studies [48, 50] indicated that serum Mg level did not influence PTH in patients on regular HD. Other studies reported a highly significant inverse correlation between Mg and PTH in HD patients [46, 47, 49, 51, 52, 55–57, 65]. Table 1 summarizes data from clinical trials addressing the effect of Mg on serum PTH level in HD patients.

In dialysis patients, the dialytic procedure provides the primary role of Mg removal; therefore, the serum Mg concentration parallels the dialysate Mg content. Several studies using a lower Mg dialysate concentration (0.6 mg/

Table 1. Characteristics and results of the studies investigating the relationship between serum Mg and PTH in patients on HD and PD

Authors	Year	Study type	Clinical setting	Subjects n	Conclusion
<i>In HD</i>					
Pletka et al. [46]	1974	RS	NA	26	a significant inverse correlation between serum Mg and PTH levels
Parsons et al. [47]	1980	RS	lowering dialysate Mg in patients on HD	18	an inverse relation between serum Mg and PTH levels
Gonella et al. [48]	1981	RS	patients on HD with 3 different Mg concentrations in the dialysate	22	serum PTH levels were similar in all groups
McGonigle et al. [49]	1984	RS	patients on HD with increased Mg concentrations in the dialysate	20	a rise in serum Mg level reduces plasma PTH level
O'Donovan et al. [50]	1986	RS	patients on HD with decreased Mg concentrations in the dialysate	28	no evidence of increased secondary hyperparathyroidism
Kenny et al. [51]	1987	RS	Mg repletion in patients on HD with no Mg in the dialysate	16	a strong negative correlation between initial serum Mg and the percent change in serum PTH
Oe et al. [52]	1987	RS	Mg as a phosphate binder in patients on HD	18	oral Mg(OH) ₂ reduced the required Al(OH) ₃ dose and decreased PTH
Navarro et al. [22]	1997	RS	patients on HD were classified into 3 groups according to their PTH level	41	a negative linear correlation between serum PTH level and plasma Mg concentration
Bellucci et al. [53]	1998	RS		14	an inverse relation between serum Mg and PTH levels
Navarro et al. [54]	1999	RS	HD patients	110	serum Mg concentrations in dialysis patients are independently associated with PTH levels
Gohda et al. [55]	2002	RS	serum PTH and PTH genotypes in 86 HD patients and 80 control subjects	86	serum intact PTH levels were negatively correlated with serum Mg level
Guh et al. [56]	2002	RS	HD patients with 4 or more previously measured serum PTH	126	PTH levels were inversely correlated with serum Mg level
Baradaran and Nasri [57]	2006	CS	HD patients	41	an insignificant inverse correlation was found between the serum Mg levels and iPTH
<i>In PD</i>					
Saha et al. [58]	1997	RS	patients on PD with 3 different Mg concentrations in the dialysate	26	an inverse correlation was found between serum iPTH level and serum Mg level
Navarro et al. [59]	1998	RS	PD patients dialyzed with Mg concentration 0.75 mmol/l for more than 6 months	20	a significant negative relationship was found between serum Mg and PTH
Navarro et al. [60]	1999	RS	patients on PD for more than 6 months using a peritoneal fluid with Mg concentration 0.75 mmol/l	51	a significant negative relationship was found between serum Mg and PTH
Cho et al. [61]	2002	RS	patients on PD for more than 6 months	56	among the PD patients whose serum PTH level was <300 pg/ml, there was a significant inverse correlation between serum PTH level and serum Mg level
Katopodis et al. [62]	2003	RS	patients on PD with 2 different Mg concentrations in the dialysate	34	a negative but not significant relationship was found between serum Mg and PTH level
Takahashi et al. [63]	1994	RS	the utilization of Mg-free dialysate for 8 weeks on stable CAPD patients	5	Mg depletion stimulates PTH synthesis or secretion
RS = Retrospective study; CS = cross-sectional study; PD = peritoneal dialysis.					

dl) showed that blood Mg concentration ranged from 1.7 to 2.5 mg/dl [66]. Moreover, when the level of Mg in the dialysis fluid was reduced from 1.8 to 0.48 mg/dl, the mean serum Mg level decreased from 2.7 to 2.2 mg/dl. In these studies, the reduction in dialysate Mg was associated with a marked increase in serum PTH level [46, 67, 68]. Conversely, an increase in dialysate Mg concentration over 2 months produced a decrease in serum PTH, which was associated with a decrease in serum Ca and P levels [46].

Based on these findings, the weight of evidence suggests that increased serum Mg level provided by dialysis fluids with a higher Mg content may suppress PTH synthesis and/or secretion which is an independent risk factor for vascular calcification, left ventricular hypertrophy and mortality in HD patients.

Mg in Renal Transplantation

The use of immunosuppressive regimens including cyclosporine (CsA) and tacrolimus are associated with hypomagnesemia due to the suppressed reabsorption of Mg from renal tubules through the reduction of TRPM6 expression [69, 70]. This has raised the hypothesis that renal Mg wasting might be a contributory factor for CsA and tacrolimus toxicity. In animal studies, it has been shown that hypomagnesemia contributes to glomerular dysfunction and chronic renal fibrotic lesions. Furthermore, Mg supplementation for CsA-treated animals inhibits local inflammation by decreasing osteopontin and monocyte chemoattractant protein-1 expression, protects from renal fibrosis and tubular atrophy, and preserves renal function [71]. Yuan et al. [71] investigated the role of nitric oxide synthase on the effect of Mg supplementation to prevent chronic CsA nephrotoxicity. They showed that Mg supplementation improved the renal function and decreased CsA-induced renal histological lesions by correcting the abnormal activation of nitric oxide synthase [71]. In a retrospective study, Holzmacher et al. [72] demonstrated that low serum Mg levels were associated with a greater rate of decline in kidney allograft function and an increased rate of graft loss in renal transplant recipients with chronic CsA nephropathy. These results from animal and clinical studies suggest that hypomagnesemia may potentiate CsA-mediated nephropathy. In a prospective short-term pilot trial, Gupta et al. [68] investigated the effect of oral Mg supplementation on glucose tolerance and lipid profile in stable hypomagnesemic renal transplant patients. They found that correction of serum Mg in

nondiabetic renal-transplant patients is associated with reduced serum total cholesterol, LDL cholesterol and the total cholesterol/HDL cholesterol ratio [68]. The animal and clinical studies suggest that hypomagnesemia may potentiate CsA-mediated nephropathy.

The Effect of Mg on Athero- and Arteriosclerosis: Vascular Calcification and Carotid Intima-Media Thickness in ESRD

Cardiovascular mortality in dialysis patients is 10–20 times greater compared to the general population [73]. Atherosclerosis progresses more dynamically in HD patients than in the general population because of a high prevalence of traditional risk factors and exposure to additional nontraditional risk factors [74]. Table 2 summarizes data from clinical trials specifically addressing the effect of Mg on vascular calcification and carotid intima-media thickness in ESRD patients.

In HD patients, low Mg levels were reported to be associated with increased atherosclerosis of the common carotid artery. In a study by Tzanakis et al. [9], intima-media thickness of both common carotids was assessed by B-mode ultrasound in 93 stable chronic HD patients and in 182 age- and sex-matched healthy controls. HD patients had a significantly higher mean common carotid intima-media thickness than controls (0.87 ± 0.16 vs. 0.76 ± 0.13 mm, $p < 0.001$). Multivariate analysis revealed that in HD patients, both serum Mg and intracellular Mg were negatively associated with common carotid intima-media thickness ($p = 0.001$ and $p = 0.003$, respectively). Turgut et al. [8] also demonstrated an inverse association between serum Mg and carotid intima-media thickness in HD patients (fig. 2). They found that, while the mean serum calcium and phosphorus did not change significantly, carotid intima-media thickness and PTH improved significantly after Mg supplementation within 2 months. The authors suggested that the beneficial effect of Mg on carotid intima-media thickness might be due to the decreased serum PTH level. Furthermore, Mg-containing phosphate binders have been shown to be effective agents for controlling serum phosphorus and hyperparathyroidism in ESRD patients [76, 77].

Experimental studies have also demonstrated that hypomagnesemia is related to the development of ectopic calcification in animal models [80, 81]. It has also been shown that *in vitro* Mg is a potent inhibitor of the calcification process [82] and that experimental Mg deficiency appears to promote vascular calcification [83].

Fig. 2. The association of baseline serum Mg level and carotid intima-media thickness in HD patients.

Table 2. Characteristics and results of the studies investigating the relationship between serum Mg and vascular calcification, carotid intima-media thickness and MAC in patients on HD and PD

Authors	Year	Study type	Clinical setting	Subjects n	Conclusion
Ishimura et al. [75]	2007	PS	hand roentgenography of nondiabetic patients on HD	390	hypomagnesemia is associated with vascular calcification
Ng et al. [65]	2004	RS	bone biopsies from patients with renal osteodystrophy	153 biopsies	Mg suppresses PTH secretion
Nakagawa [76]	1997	RS	aortic calcification in patients on HD	28	treatment with Mg inhibited elevation of the calcium content of the aorta.
Meema et al. [64]	1987	RS	arterial calcifications in patients on PD	44	serum Mg was significantly lower in patients with increasing AC
Drachman et al. [77]	1986	RS	children on dialysis	18	serum Mg levels were similar in subjects with and without pulmonary calcification
Tzanakis et al. [9]	2004	RS	cIMT by B-mode ultrasound in stable chronic HD patients	93	Mg showed a negative association with cIMT
Tzanakis et al. [78]	1997	RS	echocardiography to detect MAC in HD patients	56	Mg levels were significantly lower in patients with MAC
Izawa et al. [79]	1974	CR	HD patient	1	soft tissue calcification improved after dialysis with a dialysate with high Mg concentration
Turgut et al. [8]	2008	PS	Mg supplementation to improve cIMT in HD patients	47	cIMT was significantly improved in patients treated with Mg

RS = Retrospective study; PS = prospective study; CR = case report; cIMT = carotid intima-media thickness; PD = peritoneal dialysis.

Hyperphosphatemia and abnormal PTH levels play a role in the initiation and progression of vascular calcification in ESRD patients [10, 27]. Ishimura et al. [75] found significantly lower serum Mg concentrations in HD patients with vascular calcifications than in those without calcification. In multivariate logistic regression analysis, a lower Mg concentration was a significant independent factor associated with the presence of vascular calcification after adjustment for other confounding factors, such as calcium and phosphate. Their analysis revealed that a 1-mg/dl decrease in serum Mg increased the risk for vascular calcification by 71.6% [75]. Additionally, in a longitudinal study, Meema et al. [64] speculated that hypermagnesemia may retard the progression of vascular calcification in ESRD patients. They evaluated 44 CAPD patients for the progression of vascular calcification measured by fine detail radiographs of the hands and feet. Patients were divided into those who demonstrated progression versus those who did not, and laboratory parameters were compared. There was no difference in calcium, phosphorus, PTH or alkaline phosphatase between the 2 groups. However, the serum Mg was significantly higher (3.02 ± 0.51 vs. 2.69 ± 0.52 mg/dl) in the group that did not show progression over an average time period of 27 months. The authors concluded that 'hypermagnesemia might be associated with retardation or improvement of arterial calcifications in peritoneal dialysis patients' [64]. Finally, Mitsopoulos et al. [84] investigated the effect of sevelamer on serum Mg in HD patients to assess the association of Mg levels with iPTH and lipid profiles. They found that HD patients receiving sevelamer have a significant increase in serum Mg. This increase in serum Mg is associated with a reduction in the iPTH level ($r = -0.40$, $p = 0.016$) [84]. It can be speculated that the rise in serum Mg levels might also contribute to the much debated superiority of sevelamer in suppressing vascular calcifications compared to other phosphate binders. Again, this should be tested clinically in a prospective way.

Mitral calcification is common in HD patients and severe secondary hyperparathyroidism, high $\text{Ca} \times \text{P}$ product, duration of dialysis and age are the proposed major predisposing factors shown in previous studies [85, 86]. Tzanakis et al. [78] reported a possible protective role of Mg against mitral valve calcification in such patients. They examined 56 HD patients with Doppler echocardiography to detect mitral annular calcification (MAC). The biochemical profile of patients with MAC with respect to Ca , $\text{Ca} \times \text{P}$, P and iPTH levels did not differ from that of the patients who did not have MAC; the only ex-

ception was that they reported significantly lower Mg levels in patients with MAC than in those without MAC. Patients with serum Mg levels below 3 mg/dl were twice as likely to have MAC, as compared to those with serum Mg levels above 3 mg/dl. Multiple regression analysis suggested that the levels of serum Mg could predict the presence of MAC successfully in 86% of the subjects, when controlling for age and the rest of the biochemical parameters at the same time.

Taken together, these studies suggest that Mg can be considered to be a potent 'natural PTH hormone antagonist' by decreasing synthesis/secretion of PTH and that higher serum Mg concentrations may play an important protective role in the development of vascular calcification, independent of serum calcium and phosphate, in ESRD patients. However, these trials were observational and, therefore, could not answer the important question of whether hypermagnesemia has a protective role in the progression of vascular calcification in ESRD. Further prospective randomized studies in large samples are needed to assess more accurately the role of Mg in atherosclerotic regression, vascular calcification and the relationship between Mg and PTH/bone metabolism, Mg levels and comorbidity, and Mg levels and patient survival in dialysis patients.

The Effect of Mg on Survival in ESRD Patients

There are only 2 studies which have tried to investigate the relationship between Mg and ESRD patient survival [87, 88]. Tzanakis et al. [87] found that lymphocyte Mg is an independent prognostic factor for improved survival ($p = 0.029$), while serum Mg had a similar but weaker relation ($p = 0.069$). Similarly, Ishimura et al. [88] investigated the prognostic value of serum Mg concentration for mortality in 515 patients on maintenance HD for a median follow-up time of 51 ± 17 months. They demonstrated that a lower serum Mg level was a significant predictor for mortality in HD patients, particularly for non-cardiovascular mortality [HR (per 1 mg/dl increase), 0.485 (95% CI: 0.241–0.975), $p = 0.0424$].

Other Relevant Cardiovascular Effects of Mg

Mg exerts a direct modulatory action on cardiac excitability and vascular smooth muscle contraction and relaxation [89]. Mg might also be involved with cardiac muscle contraction. Intradialytic changes of Mg could be

correlated with intradialytic hypotension in HD. Hypomagnesemia has been shown to contribute significantly to cardiac morbidity and mortality, particularly in states associated with myocardial ischemia [90]. Mg therapy, both for deficiency replacement and in higher pharmacologic doses, has been beneficial in improving cardiovascular hemodynamics and electrophysiologic functioning. In a study by Kyriazis et al. [91], a dialysis solution containing 0.25 mmol/l Mg and 1.25 mmol/l Ca was identified as a major cause of intradialytic hypotension due to an impairment of myocardial contractility. They showed that increasing the dialysate Mg level to 0.75 mmol/l could prevent the intradialytic hypotension frequently seen with the use of 1.25 mmol/l dialysate Ca and suggested that manipulating dialysate Mg levels independently or in concert with dialysate Ca levels might have important implications with regard to dialysis tolerance [91]. Mg deficiency-induced coronary vasospasm [92], defective energy metabolism [93] and excessive free radical generation [94] may be important variables acting in concert, or independently, to affect myocardial function. Plasma-ionized Mg also showed a negative correlation with QT dispersion, suggesting that Mg plays a role in maintaining myocardial electrical stability in HD patients.

Mg as a Phosphate Binder

Mg compounds have been tried as phosphate binders since the early aluminum binder era. Potential benefits have been attributed to Mg carbonate as a phosphate binder and it may possibly be an effective, less toxic and less expensive phosphate binder. O'Donovan et al. [50] switched 28 patients from aluminum hydroxide to Mg carbonate in combination with a Mg-free dialysate and compared the evolution with a control group. After 2 years, there were no differences in Ca, P and Mg levels between the groups, but the mean serum PTH concentration significantly decreased in patients receiving Mg carbonate.

Several studies using $\text{Mg}(\text{OH})_2$ (magnesium hydroxide) were complicated by diarrhea or mild hyperkalemia [52]. Parsons et al. [95] used a combination of equal proportions of MgCO_3 and CaCO_3 ('Dulwich mixture') in 32 CAPD patients treated with a Mg-free peritoneal dialysate for at least 1 year and demonstrated equal control of the serum phosphorus compared with calcium carbonate or $\text{Al}(\text{OH})_3$ without an increase in serum Mg. Delmez et al. [96] used a crossover-designed study in HD patients,

incorporating MgCO_3 and decreasing the CaCO_3 binder dose by 50%. The Mg dose was started at 750 mg/day (214 mg elemental Mg) and titrated weekly to achieve a target phosphorus of <6.0 mg/dl. The dialysate Mg was decreased from 1.8 mg/dl (1.5 mEq/l) to 0.6 mg/dl (0.5 mEq/l) in patients receiving MgCO_3 . Overall, equal control of serum phosphorus was maintained without an increase in serum Mg [96]. Fine et al. [97] also reported a significant reduction in dietary phosphorus absorption with increasing Mg intake. These authors concluded that, although calcium has a higher affinity for phosphorus than Mg on a milligram per milligram basis, the poorer gastrointestinal absorption of Mg relative to calcium leaves more elemental Mg available for phosphate binding [97]. A prospective, randomized (2:1), open-label trial was performed by Spiegel et al. [98] comparing Mg carbonate/calcium carbonate (20 patients) versus calcium acetate (10 patients) as a sole phosphate binder for 12 weeks. The dose of each binder was titrated to achieve the (then) Kidney Disease Outcomes Quality Initiative (K/DOQI) phosphate target of <5.5 mg/dl. Mg carbonate containing regimen provided equal control of serum phosphorus (70.6% of the Mg-containing and 62.5% of the calcium acetate group had their average serum phosphorus within the K-DOQI target during the efficacy phase), while significantly reducing daily elemental calcium ingestion from phosphate binders (908 ± 24 vs. $1,743 \pm 37$ mg/day, $p < 0.0001$). There were no differences between groups regarding serum iPTH or bicarbonate concentrations. The serum calcium level was significantly higher in patients taking calcium acetate. They concluded that MgCO_3 was generally well-tolerated, and was effective in controlling serum phosphorus while reducing elemental calcium ingestion [98]. Tzanakis et al. [99] evaluated the efficacy and safety of MgCO_3 as a phosphate binder. They found that MgCO_3 is an effective agent for serum phosphate control in HD patients and in combination with low-dialysate Mg concentration avoided the risk of severe hypermagnesemia. MgCO_3 was well tolerated as only 2 patients (8%) were removed from the study, 1 for diarrhea and the other for hypermagnesemia. In the CaCO_3 group in this trial, 5 patients (25%) complained of constipation, but none dropped out of the study [99]. The risk of severe hypermagnesemia is a major concern and both clinical and ECG disorders occur when serum $\text{Mg} > 4$ mg/dl [100]. Very few studies have reported on the prevalence of hypermagnesemia in dialysis patients and the number of the subjects who drop out of these studies due to side effects from Mg supplementation. Delmez et al. [96] did not report any adverse gastro-

intestinal effect within 10 weeks after starting MgCO_3 . In contrast, in Turgut et al.'s study [8], 1 patient (3%) was discontinued to the study due to diarrhea after Mg supplementation; 2 patients (8%) discontinued ingestion of MgCO_3 and dropped out because of persistent diarrhea (1 patient) and recurrent hypermagnesemia (1 patient; serum Mg >4 mg/dl) in Tzanakis et al.'s study [99]; and in Spiegel et al.'s study [98], 3 (15%) of the 20 patients on MgCO_3 withdrew because of diarrhea, while none of the patients experienced symptoms related to hypermagnesemia.

Mg can be administered to many patients without acute adverse side effects and can help reduce the total calcium intake when substituted for phosphate binders in patients with ESRD. There is increasing evidence that it is an effective phosphate binder and newer formulations using MgCO_3 cause less diarrhea than $\text{Mg}(\text{OH})_2$. However, the long-term effects on both the inhibition of vascular calcification or changes in bone morphology have not been adequately investigated. Clearly, much more clinical research is needed to fully understand the potential risks and benefits of Mg administration in ESRD.

Conclusion

Numerous studies now provide strong suggestive evidence for a protective role of Mg in vascular calcification, arrhythmias and atherosclerosis in ESRD patients. These studies also suggest that serum Mg concentrations in dialysis patients are independently associated with PTH levels. Thus, chronic mild hypermagnesemia may de-

crease PTH synthesis and/or secretion, and could be a very useful adjunctive therapy in alleviating complications of CKD-MBD. In this way it can offer viable alternatives to the combination of calcium as a phosphate binder and vitamin D therapy, a strategy that may lead to frequent hypercalcemic episodes, calcium accumulation and potentially harmful cardiovascular consequences [101].

Previous studies allow us to speculate on the possible salutary role of increasing plasma levels of Mg to facilitate the healing of vascular injuries and to prevent atherosclerosis, hypertension, arrhythmia and chronic myocardial ischemia. Mg-based compounds have the additional advantage of being much cheaper to use than some newer alternatives. Nevertheless, in an era of numerous negative studies in nephrology, the long-term effects on either the inhibition of vascular calcifications, reduction of ischemic disease, prevention of arrhythmias or changes in bone morphology have not been adequately investigated. We feel it is very important to repeat the 'Treat to Goal', RIND or CARE-2 study protocols, but with Mg instead of sevelamer in order to reach definitive conclusions.

The use of Mg (to spare calcium load) in conjunction with vitamin D therapy may be more effective and safer as a strategy for preserving skeletal health (but this has not been clinically proven) than the current practice of using calcium as the default oral phosphate binder. Mg, of course, is not necessarily a panacea, so serum levels should always be measured to avoid potential toxicity; however, the optimal serum level and the resulting tissue concentrations, especially in bone, remain poorly understood in the short and long terms.

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