RELATIONSHIP BETWEEN SERUM MAGNESIUM, PARATHYROID HORMONE, AND VASCULAR CALCIFICATION IN PATIENTS ON DIALYSIS: A LITERATURE REVIEW

Mingxin Wei,1,2 Khaled Esbaei,1,3 Joanne Bargman,1 and Dimitrios G. Oreopoulos1

Home Peritoneal Dialysis Unit,1 University Health Network and University of Toronto, Toronto, Ontario, Canada; Department of Nephrology,2 Guangxi People’s Hospital, Guangxi, P. R. China; Al-Fatah University,3 Tripoli Central Hospital, Tripoli, Libya

Secondary hyperparathyroidism is present in most patients with end-stage renal disease and has been linked to uremic bone disease, vascular calcification, and mortality. Current literature suggests an association between hypomagnesemia and cardiovascular disease in the general population. We reviewed all published studies on the relationship between serum magnesium and parathyroid hormone and the relationship between serum Mg and vascular calcification in dialysis patients. Of these, 10 of 12 studies of patients on hemodialysis and 4 of 5 studies of patients on peritoneal dialysis showed a significant inverse relationship between serum Mg and serum intact parathyroid hormone. Hyperparathyroidism develops in peritoneal dialysis patients dialyzed with a solution containing normal calcium (1.25 mmol/L) and low Mg (0.25 mmol/L), even though serum calcium is maintained at a normal level. Four of the hemodialysis studies and one of the peritoneal dialysis studies indicated that there is an inverse relationship between serum Mg and vascular calcification in these patients. Potential benefits have been attributed to magnesium carbonate as a phosphate binder and it may possibly be an effective, less toxic, less expensive phosphate binder. We believe that the role of Mg in secondary hyperparathyroidism and vascular calcification merits further investigation.

MAGNESIUM METABOLISM IN PATIENTS ON DIALYSIS

The kidneys play a prominent role in establishing serum Mg homeostasis, and patients with advanced chronic kidney disease often have an increased serum Mg concentration (13–17). Renal Mg excretion plays a dominant role in Mg homeostasis (18). Approximately 80% of serum Mg is ultrafilterable; 95% of the filtered load of Mg is reabsorbed by the kidney, and only 5% is excreted in the urine (19,20). Plasma Mg concentration is a major determinant of the renal handling of Mg. Under normal conditions, dietary Mg intake is a major determinant of serum and total body Mg levels. Gastrointestinal absorption can adapt to intake; therefore, under low Mg intake, a high proportion of Mg can be absorbed. In patients with renal failure, because they do not have alternative routes for Mg excretion (21), the role of digestive Mg absorption is controversial. There are no reports about Mg excretion through the gut. The presence of residual renal function in peritoneal dialysis (PD) patients does not influence the serum Mg level. In a study of 100 PD patients with weekly Kt/V of more than 2.1, Page et al. (22) found no significant correlation between residual renal function and serum Mg, but reported that serum Mg showed a positive correlation with protein catabolic rate \( (p < 0.001) \), indicating that protein intake influences serum Mg level.
Dialysis: Relationship Between Serum Mg and PTH in Patients on Dialysis

Over the years, there has been debate on the relationship between serum Mg and PTH in hemodialysis (HD) patients. Some studies (32,33) indicated that serum Mg level did not influence PTH in patients on regular HD. Other studies suggested a highly significant inverse correlation between serum Mg and PTH in HD patients (29,34–37). This suppressive effect of hypermagnesemia on PTH secretion was confirmed by later studies (38–43). Navarro et al. (17) found that, among 51 patients on CAPD for more than 6 months using a peritoneal fluid with Mg concentration 0.75 mmol/L, patients in the lower iPTH group (n = 31, serum iPTH <120 pg/mL) had a significantly higher serum Mg concentration than those in the higher iPTH group (n = 20, serum iPTH >120 pg/mL): serum Mg 1.16 ± 0.15 versus 0.91 ± 0.14 mmol/L (p < 0.001). When these 51 patients were divided into two groups according to their serum Mg level, those with serum Mg 0.60 – 1.01 mmol/L had a higher iPTH level than those with serum Mg >1.01 mmol/L: serum iPTH 190 ± 89 versus 69 ± 49 pg/mL (p < 0.001). Linear regression analysis showed a highly significant inverse correlation between serum Mg and iPTH (r = –0.70, p < 0.001). After controlling for the effect of other variables by partial correction analysis, there was still a significant negative relationship between serum Mg and iPTH (r = –0.57, p < 0.001). Based on these findings, one could speculate that an elevated serum Mg level may suppress PTH synthesis and/or secretion. Navarro et al. (15) reported similar results based on a study of 20 CAPD patients dialyzed with Mg concentration 0.75 mmol/L for more than 6 months previously: a significant negative relationship was found between serum Mg and iPTH (r = –0.63, p < 0.001). Saha et al. (16) described 26 patients who were on CAPD for 3 – 52 months: 13 patients using dialysate Mg concentration 0.75 mmol/L, 10 patients using dialysate Mg concentration 0.50 mmol/L, and 3 patients using dialysate Mg concentration 0.25 mmol/L. Again, these workers observed an inverse correlation between serum iPTH level and serum Mg level (r = –0.42, p < 0.05). Serum iPTH was slightly lower in patients dialyzed with Mg concentration 0.75 mmol/L compared to those with Mg concentration <0.75 mmol/L (p < 0.05). Cho et al. (44) studied 56 patients who were on CAPD for more than 6 months using dialysis fluid with Mg concentration 0.25 mmol/L, and found that 7 had serum iPTH level >300 pg/mL and 49 patients had serum iPTH level <300 pg/mL. Among all 56 patients, serum iPTH was not correlated with serum Mg level. However, in the 49 patients whose serum iPTH level was <300 pg/mL, there was a weak but statistically significant inverse correlation between serum iPTH level and serum Mg level (r = –0.295, p < 0.05). Those with serum iPTH <120 pg/mL (n = 30) had higher serum Mg level compared to those with serum iPTH 120 – 300 pg/mL (n = 19): serum Mg 1.01 ± 0.15 vs 0.91 ± 0.17 mmol/L (p < 0.05).

Recently, Katopodis et al. (23) studied 34 patients who had been on CAPD for at least 6 months. They divided them into two groups: group A (n = 19) patients were dialyzed with a fluid of 0.75 mmol/L Mg concentration, and group B (n = 15) patients with 0.50 mmol/L Mg concentration. Group A patients had a lower iPTH level compared to patients in group B but the difference was not statistically significant: serum iPTH 191.8 ± 261.2 versus 275.5 ± 229.2 pg/mL (p > 0.05). The reasons for the lack of significant difference in this study are not clear but may be related to factors such as the small number of patients studied, the variability of serum Mg concentrations, or to other poorly understood causes. Among all studies, only 2 of 12 HD studies and 1 of 5 PD studies showed no significant relationship between serum Mg and PTH. All these studies were retrospective, none was a double-blind randomized controlled trial, and therefore biases are unavoidable. Table 1 summarizes all these studies.

Furthermore, there is now evidence that hyperparathyroidism develops in PD patients dialyzed with low calcium (≤1.25 mmol/L) and low Mg (0.25 mmol/L) PD solution, even though their serum Ca is maintained at a normal level (45–50). One possible explanation for this is that the low Mg functions as a stimulus for PTH secretion independently of serum Ca concentration.
RELATIONSHIP BETWEEN SERUM Mg AND VASCULAR CALCIFICATIONS IN PATIENTS ON DIALYSIS

Traditional risk factors do not adequately explain the high prevalence of cardiovascular disease in patients on dialysis. High serum phosphorus concentration and increased Ca×P are associated with vascular and cardiac calcification and increased mortality (51–57). Recently, based on in vitro studies, Maier et al. (58) reported a direct role for low serum Mg in promoting endothelial dysfunction by generating a proinflammatory, prothrombotic, and proatherogenic environment that could facilitate the development of cardiovascular disease. The contribution of hypomagnesemia to vascular calcification has been well documented in animal models (59–67). Evidence that hypomagnesemia may play a significant role in the pathogenesis of cardiovascular disease in individuals without renal disease (11,12,68–71) suggests that we should not overlook the role of serum Mg in the development of vascular calcification in dialysis patients. Tzanakis et al. (72) studied intima-media thickness of both common carotids by B-mode ultrasound in 93 stable chronic HD patients and 182 age- and sex-matched healthy controls. They found that both serum Mg and intracellular Mg [estimated by determination of this ion in isolated peripheral lymphocytes and by atomic absorption (73)] showed a strong negative association with common carotid intima-media thickness (p = 0.001 and p = 0.003 respectively). Specifically, for each 0.5 mmol/L increase in serum Mg, a 0.35 mm reduction in the intima-media thickness of common carotids was observed (p = 0.1). The same authors reported that serum Mg might retard the development of arterial calcification found in HD patients (74). In this report, they studied 56 patients (34 males and 22 females) on HD for longer than 10 months, who had optimum Ca×P regulation not greater than 60 mg2/dL2, and followed up these patients for 8 years. They used M-mode, two-dimensional, and Doppler echocardiography to detect mitral annular calcification (MAC). All patients were receiving calcium and/or aluminum-containing phosphate binders with vitamin D derivatives but never Mg-containing binders. Mitral annular calcification was detected in 23/56 (41%) patients. They found that the biochemical profile of patients with MAC (with respect to Mg, Ca, P, Ca×P, and iPTH measurements) did not differ from that of patients without MAC, the only exception being serum Mg levels, which were significantly (p < 0.05) lower in patients with MAC. Multiple logistic regression analysis suggested that the levels of serum Mg could successfully predict MAC (overall accuracy 86%).

Izawa et al. (75) reported a patient in whom soft-tissue calcification improved after dialysis with a fluid with high Mg concentration. Meema et al. (76), from our center, described 44 CAPD patients who had been on CAPD for an average of 27 months (range 6 – 67 months) and who were followed up with sequential radiographic metabolic bone surveys. The patients were divided into two groups: group A (n = 22), in whom new peripheral arterial calcifications appeared or existing calcifications progressed, and group B (n = 20), in whom arterial calcifications either regressed or did not develop. In 2 patients, the arterial calcifications first progressed and then regressed. They found no differences between the two groups with respect to Ca, P, Ca×P, or PTH, but patients in group A had significantly lower serum Mg than patients in group B: 2.69 ± 0.52 and 3.02 ± 0.51 mg/dL respectively (p < 0.001). These authors suggested that serum Mg might retard the development or lead to the regression of arterial calcification in ESRD patients.

All these findings demonstrate a strong relationship between serum Mg level and calcification. Serum Mg may play an important protective role in the development and/or acceleration of arterial calcification in dialysis patients. However, it should be stressed that, although hypomagnesemia may be a risk factor for vascular calcification, this does not imply that hypermagnesemia has a protective effect. This can be shown only by prospective controlled studies of the relationship between serum Mg and calcification. A high Mg concentration resulted in regression of arterial calcification found in HD patients (74). In this report, they studied 56 patients (34 males and 22 females) on HD for longer than 10 months, who had optimum Ca×P regulation not greater than 60 mg2/dL2, and followed up these patients for 8 years. They used M-mode, two-dimensional, and Doppler echocardiography to detect mitral annular calcification (MAC). All patients were receiving calcium and/or aluminum-containing phosphate binders with vitamin D derivatives but never Mg-containing binders. Mitral annular calcification was detected in 23/56 (41%) patients. They found that the biochemical profile of patients with MAC (with respect to Mg, Ca, P, Ca×P, and iPTH measurements) did not differ from that of patients without MAC, the only exception being serum Mg levels, which were significantly (p < 0.05) lower in patients with MAC. Multiple logistic regression analysis suggested that the levels of serum Mg could successfully predict MAC (overall accuracy 86%).

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### TABLE 1

**Studies Reporting on the Relationship Between Serum Magnesium and Parathyroid Hormone in Patients on Dialysis**

<table>
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<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>(n)</th>
<th>r Value</th>
<th>p Value</th>
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<td>McGonigle RJ et al. (36)</td>
<td>1994</td>
<td>20</td>
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<tr>
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<td>1986</td>
<td>28</td>
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<tr>
<td>Kenny MA et al. (29)</td>
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<td>16</td>
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<td>Oe PL et al. (37)</td>
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<td>18</td>
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<tr>
<td>Navarro JF et al. (38)</td>
<td>1997</td>
<td>41</td>
<td>−0.60</td>
<td>&lt;0.001</td>
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<td>1998</td>
<td>14</td>
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<td>1999</td>
<td>110</td>
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<td>Peritoneal dialysis studies</td>
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<td></td>
<td></td>
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<td>Saha HH et al. (16)</td>
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<td>20</td>
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<td>51</td>
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<td>Cho MS et al. (44)</td>
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<td>56</td>
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<td>34</td>
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Mg and vascular calcification in dialysis patients. In planning such a study, one has to take into account that, because of the negative relationship between Mg and PTH, an elevated Mg level may be a factor in the development of relative hypoparathyroidism, with inadequately low levels of PTH. This situation may lead to a low bone turnover state, with all its consequences with delayed calcium and phosphorus deposition into the bone matrix and elevation of serum levels of calcium and phosphorus, thus increasing the risk of metastatic calcification. Table 2 summarizes the studies that have examined the relationship between serum Mg and vascular calcification in patients on dialysis.

MAGNESIUM CARBONATE AS A PHOSPHATE BINDER

Phosphate binders have been indispensable in the management of patients on dialysis. However, none of the existing phosphate-binding agents is truly satisfactory. Aluminum-containing agents are highly efficient but they have been abandoned because of their potential toxicity. Patients receiving long-term therapy with aluminum-based binders were at risk for encephalopathy and bone disease (associated with elevated aluminum levels in brain and bone), anemia, and myopathy (77–80). Recognition of these serious side effects prompted the search for aluminum-free phosphate binders. Calcium carbonate and calcium acetate bind phosphorus effectively but often induce hypercalcemia and a positive calcium balance, especially in patients with low-turnover bone disease. Elevated Ca×P (common with calcium-based binders) and positive calcium balance have been incriminated in the development of vascular, valvular, cardiac, and metastatic calcification (81–86) leading to increased morbidity and mortality (87). Furthermore, frequently, patients do not tolerate calcium-based binders and thus show poor adherence to them. The optimal choice would be an aluminum- and calcium-free phosphate binder, such as sevelamer or lanthanum carbonate, both of which are very expensive. Magnesium carbonate is another aluminum- and calcium-free phosphate binder.

O’Donovan et al. (33) reported on 28 patients on HD in whom oral aluminum hydroxide was discontinued and substituted with magnesium carbonate (elemental Mg 155–465 mg/day) as a phosphate binder. They were also switched from Mg 0.85 mmol/L to Mg-free dialysate. After 24 months of treatment on this regimen, serum phosphate was effectively controlled and predialysis aluminum concentration fell significantly. Predialysis Mg concentrations tended to fall toward the normal range and there was no evidence of increased secondary hyperparathyroidism. Patients tolerated the preparation well except for some initial mild diarrhea that ceased within weeks. Delmez et al. (88) conducted a 10-week, prospective, randomized crossover study on 15 HD patients who were on MgCO₃, at doses of 465 ± 52 mg/day elemental Mg, in combination with dialysate Mg concentration 0.25 mmol/L. With this regimen, these investigators were able to lower the CaCO₃ dose and use a higher calcitriol dose. Mean serum P levels with the MgCO₃/CaCO₃ combination were similar to those with CaCO₃ treatment alone: 5.7 ± 0.2 versus 5.2 ± 0.2 mg/dL, respectively. These authors reported no adverse gastrointestinal effects. Parsons et al. (89) studied 32 CAPD patients, who were dialyzed with Mg-free dialysate and used a mixture of CaCO₃ and MgCO₃ as a phosphate binder for over 1 year, with the simultaneous use of vitamin D analogs, and found that these patients achieved satisfactory control of hyperparathyroidism with normal calcium, Mg, and P concentrations (2.41, 0.97, and 1.36 mmol/L respectively). Other investigators have also shown that the use of magnesium-containing agents as phosphate binders could effectively control serum P and hyperparathyroidism (90–94), with serum Mg levels remaining in acceptable ranges, and except for mild and

<table>
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<tr>
<th>Author (Ref.)</th>
<th>Year</th>
<th>Patients (n)</th>
<th>p Value</th>
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<td>56</td>
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<td>M-mode, two-dimensional Doppler echocardiography</td>
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<td>Tzanakis I et al. (72)</td>
<td>2004</td>
<td>93</td>
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<td>Radiographic metabolic bone surveys</td>
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<td>Meema HE et al. (76)</td>
<td>1987</td>
<td>44</td>
<td>p&lt;0.001</td>
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transient diarrhea, no adverse effects were observed. All these studies indicate that, as a phosphate binder, MgCO₃ may be an effective alternative and less toxic compound than CaCO₃, with potential benefits on vascular calcification and control of hyperparathyroidism.

**CONCLUSION**

Secondary hyperparathyroidism and vascular calcifications are common in ESRD patients, and these changes are associated with poor quality of life and high mortality. There seems to be an inverse relationship between serum Mg and serum iPTH, and between serum Mg and vascular calcification, in dialysis patients. We propose that MgCO₃ may be a more effective, less toxic, and less expensive phosphate binder and hence an alternative to CaCO₃. The protective effect of elevated serum Mg on secondary hyperparathyroidism and vascular calcification should be investigated further in prospective studies.

**REFERENCES**


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