Magnesium in Chronic Kidney Disease: Unanswered Questions

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Abstract

Background: Magnesium ion is critical for life and is integrally involved in cellular function and a key component of normal bone mineral. In health, the kidneys, gastrointestinal tract and bone are responsible for maintaining serum magnesium concentrations in the normal range and magnesium balance. Most clinical disorders involving magnesium, other than chronic kidney disease (CKD), result in hypomagnesemia, either from gastrointestinal or kidney losses. CKD and particularly end-stage kidney disease is the only clinical condition where sustained hypermagnesemia may occur and net magnesium balance may be positive. Methods: This review will focus on normal magnesium homeostasis and review the literature in CKD with a particular focus on end-stage kidney disease and the potential role of magnesium as a phosphate binder and in cardiovascular and bone health. Results: A number of small to medium-size interventional trials have shown that magnesium-based compounds can serve as effective phosphate binders. Observational studies suggest that higher serum magnesium concentrations in dialysis patients may improve survival and may slow the progression of vascular calcification. While a few small prospective trials support these findings, no large or long-term studies are available. Conclusions: Magnesium balance remains poorly understood in patients with end-stage kidney disease. While observational and small randomized trials suggest that exogenous administration may be useful as a phosphate binder and may have protective cardiovascular effects in terms of both arrhythmias and vascular calcification, large randomized trials are needed to test these hypotheses.

Normal Magnesium Homeostasis

The gastrointestinal tract, the skeleton, and the kidneys are integrally involved in normal magnesium homeostasis. Gastrointestinal absorption is not highly regulated, and the kidneys play the primary role in maintaining balance. Bone plays an important role as a buffer, providing a large rapidly exchangeable pool to protect against acute changes in serum concentrations, although this has not been as well studied as in calcium regulation. Principal dietary sources of magnesium include green vegetables, seafood, meats, grains and nuts [1]. The understanding of normal magnesium physiology has been greatly increased by the discovery of mutations in specific magnesium transporters, most of which lead to de-
creased gastrointestinal magnesium absorption or kidney magnesium wasting [2, 3]. As a result, most clinical disorders of magnesium are due to magnesium deficiency and are predominately due to gastrointestinal or kidney losses. These disorders can be either hereditary or acquired. Chronic kidney disease (CKD), and especially end-stage kidney disease is the only clinical disorder that has the potential to cause sustained hypermagnesemia and net positive magnesium balance.

Serum magnesium concentrations can be reported as mEq/l, mM or mg/dl. One mEq/l = 0.5 mM and is approximately 1.2 mg/dl [1]. The magnesium concentration in health is closely maintained within a normal range that varies between laboratories, but is roughly 1.50–2.3 mEq/l (1.8–2.8 mg/dl). Only about 1–2% of total body magnesium is present in the extracellular fluid [4] of which about 20% is protein bound. The principal stores of the body’s 21–28 g (1,750–2,400 mEq) of magnesium are bone (67%) and muscle (20%). Due to the distribution of magnesium and the fact that intracellular magnesium may not be readily exchangeable, serum concentrations do not adequately reflect total body stores.

Magnum Balance in CKD

Stage 5 CKD patients on dialysis are generally felt to have elevated serum magnesium concentration and to be at risk for acute and chronic magnesium overload [5]. Gastrointestinal magnesium absorption is felt to be normal in patients with CKD, although one small study of 5 dialysis patients suggested it was decreased compared to normal controls, possibly due to low 1,25 dihydroxy-vitamin D levels [6]. The magnesium content of the dialysate is largely responsible for controlling magnesium balance in dialysis patients. Over the past 30 years, the dialysate magnesium concentration has changed very little, ranging from 0.35 to 0.75 mM in the bicarbonate dialysis era and from 0 to 0.75 mM in the acetate dialysis era [7]. Patients dialyzed against a magnesium concentration of 0.75 mM (1.5 mEq/l) demonstrated an increased postdialysis magnesium level of 2.32 mEq/l (2.78 mg/dl) compared to normal controls of 1.62 mEq/l (1.94 mg/dl) [8]. A study evaluating pre- and postdialysis serum magnesium concentrations found that patients dialyzed against a 0.75 mM magnesium dialysate had a decrease in their serum magnesium concentrations from 2.38 to 2.20 mEq/l, although both values were above normal controls of 1.36 mEq/l [9]. A more recent study using high-efficiency dialysis and magnesium dialysate concentrations of 0.75, 0.25 and 0 mM found that serum magnesium was unchanged on the 0.75 bath, decreased from 2.8 to 1.7 mEq/l (3.4–2.1 mg/dl) on the 0.25 bath, and decreased from 2.8 to 1.3 mEq/l (3.4–1.6 mg/dl) on the 0 mM bath. Net magnesium removal was calculated to be 56, 306, and 486 mg, respectively [10].

Overall, dialysis patients tend to have higher serum magnesium concentrations than controls. The serum concentrations are largely dependent on the dialysate composition unless the patient is ingesting excess magnesium. However, like all predominately intracellular ions, the serum magnesium concentration does not necessarily reflect total body balance.

Magnessium as a Phosphate Binder

Magnesium-based phosphate binders have been used since the mid-1980s and were initially introduced to replace aluminum-containing binders. Magnesium hydroxide use was complicated by diarrhea and mild hyperkalemia [11]. Magnesium carbonate (MgCO₃) proved more effective and resulted in fewer side effects. When substituted for aluminum hydroxide (Al(OH)₃), it provided equal control of phosphorus, without increases in serum magnesium. To achieve this goal, the investigators eliminated magnesium from the dialysate [12]. A combination of MgCO₃ and calcium carbonate (CaCO₃) was used in 32 peritoneal dialysis patients, again using a magnesium free dialysate, and demonstrated equal phosphorus control over 1 year compared with CaCO₃ or Al(OH)₃. In a crossover-designed hemodialysis study, MgCO₃ was added at a starting dose of 750 mg/day (214 mg elemental magnesium) and CaCO₃ was reduced by 50% [13]. The magnesium dose was uptitrated to achieve a phosphorus of <6 mg/dl. In this study, the dialysate magnesium was decreased from 0.75 (1.5 mEq/l) to 0.25 mM (0.5 mEq/l) during the period of magnesium administration. Overall, phosphorus was well controlled without an increase in serum magnesium concentrations. In a randomized trial of MgCO₃/CaCO₃ versus calcium acetate in hemodialysis patients on a standard 0.375 mM (0.75 mEq/l) magnesium bath, phosphorus was equally controlled, while the net calcium ingestion was significantly less in the MgCO₃-treated group [14]. The serum magnesium did increase in the magnesium-treated group, although it was well tolerated. In the largest study over 24 weeks, 204 patients completed a randomized trial of MgCO₃/C-acetate versus sevelamer hydrochloride. All patients were dialyzed against a 0.5 mM magnesium dialysate. Phosphorus con-
Magnesium and Cardiovascular Health

General Population
Cardiac arrhythmias are an important complication of magnesium depletion. Both extracellular and/or intracellular magnesium depletion has been implicated in a variety of cardiovascular disturbances including ventricular arrhythmias, especially in patients on digitalis. Magnesium depletion has been associated with a prolonged QTc interval [17], whereas magnesium supplementation has been shown to reduce the QTc intervals even in patients with normal serum magnesium levels [18]. Magnesium depletion also has been implicated in the pathogenesis of torsades de pointes, an arrhythmic disorder that occurs in the presence of QT prolongation. Because of its ability to shorten the QT interval in some studies, magnesium supplementation has been used with some success in treating torsades de pointes [19]. Magnesium has also been shown to attenuate the electrophysiologic effects of hyperkalemia [20] and to control ventricular arrhythmias, including those induced by digitalis [21]. However, the clinical utility of magnesium in preventing cardiac arrhythmias is controversial. Two meta-analyses found that prophylactic magnesium administration decreased the incidence of postcardiothoracic surgery atrial fibrillation [22, 23], although the dose of administered magnesium varied widely among trials.

There also appears to be a direct effect of magnesium on the regulation of vascular tone and possibly atherogenesis. A small trial evaluating endothelial function and nitroglycerin-mediated vasodilatation found that oral administration of magnesium for a 6-month period improved flow-mediated vasodilatation and exercise tolerance in patients with stable coronary artery disease [24]. Patients in the active treatment arm received 365 mg of elemental magnesium per day, and tissue levels, measured in sublingual epithelial cells, increased from below normal to within the normal range.

Chronic Kidney Disease
There are no data evaluating the effect of magnesium concentrations on cardiac arrhythmias in patients with end-stage kidney disease. Most literature in dialysis regarding magnesium relates to vascular reactivity and vascular calcification. Interest in magnesium in dialysis grew after several small retrospective studies showed that patients with higher serum magnesium concentrations had less progression of vascular calcification [25, 26]. A study in 44 peritoneal dialysis patients evaluated for progression of vascular calcification by fine detail radiographs of the hands and feet demonstrated that patients who did not progress had higher serum magnesium concentrations; 2.52 versus 2.24 mEq/l (3.0 ± 0.5 vs. 2.7 ± 0.5 mg/dl) than those who progressed [25]. There was no difference in calcium, phosphorus or PTH between groups. A study of 56 hemodialysis patients evaluated for valvular calcification by echocardiogram found that mitral annular calcification was more common in the subjects with serum magnesium concentrations <2.5 mEq/l (3 mg/dl) [26]. However, an observational study of 24 dialysis patients evaluated by repeat electron-beam computed tomography failed to show a difference in serum magnesium concentration in slow progressors versus rapid progressors [27]. The only prospective evaluation of vascular calcification in magnesium-supplemented dialysis patients was small and nonrandomized. Seven patients were treated with magnesium containing phosphate binders with a goal to elevate the serum magnesium concentration. Patients were evaluated by electron beam computed tomography at baseline, 6, 12 and 18 months for coronary artery and aortic calcification [28]. The authors found minimal progression over 18 months in these patients despite the presence of vascular calcification at study entry, a finding significantly different than reported in the literature for patients receiving calcium-based phosphate binders.

Two studies have evaluated carotid intima-media thickness and magnesium. An observational study of 93 hemodialysis patients showed an inverse correlation between both serum magnesium and intracellular magnesium and carotid intima-media thickness [29]. A short-term study (2 months) of magnesium-supplemented hemodialysis patients demonstrated a significant reduction in carotid intima-media thickness [30]. Finally, an observational study of 515 hemodialysis patients from Japan found an association of low magnesium and all-cause mortality even after adjustment for known confounders [31].

While these studies suggest a theoretical benefit for elevated magnesium levels in chronic dialysis patients at high risk for cardiac ischemia, arrhythmias, and death,
Magnesium in CKD

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References


