Magnesium Balance in Chronic and End-Stage Kidney Disease

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This article explores the effects of CKD and end-stage kidney disease on magnesium balance. In CKD, there is decreased glomerular filtration of magnesium. Decreased tubular reabsorption can compensate to a degree, but once CKD stage 4 is reached there is a tendency toward hypermagnesemia. In dialysis, magnesium balance is dependent on the constituents of the dialysate that the blood is exposed to. The concentration of dialysate magnesium is just one of the factors that need to be considered. During transplantation, there are particular effects of immunosuppressants that can affect the magnesium balance and need to be considered by the clinician.

Key Words: Electrolytes, Magnesium, Kidney disease

INTRODUCTION

Magnesium is the eighth most abundant element within the earth's crust, the second most prevalent intracellular cation after potassium, is crucial for the functioning of ATP as well as the synthesis of both DNA and RNA, and is a cofactor in over 300 enzymatic reactions. Important links exist between this alkali earth metal and vascular calcification, cardiovascular disease, and CKD development.[1-3]

Magnesium balance is regulated via absorption from the gastrointestinal tract and elimination by the kidneys. The kidney excretion of magnesium depends on the glomerular filtration rate (GFR) that is then modulated by tubular reabsorption. As the GFR falls, the kidney's ability to excrete magnesium declines, and thus, there is a tendency for hypermagnesemia in CKD. However, there are other factors that contribute to magnesium balance in CKD, such as drugs (e.g. proton-pump inhibitors [PPIs], calcineurin inhibitors [CNIs]), vitamin D status, and the presence of diabetes. For patients on dialysis, magnesium excretion depends largely on the magnesium gradient across the dialysis membrane and other factors related to the patient and dialysate.

NORMAL MAGNESIUM BALANCE

To understand magnesium dysregulation in CKD, it is necessary briefly to touch on magnesium homeostasis in health. Extracellular magnesium accounts for 1% of total body magnesium with most of the remaining 99% sequestered in bones and muscles. Magnesium is absorbed in the gut and predominantly excreted by the kidneys. The fractional absorption of dietary magnesium is typically around 30%, and this can increase and decrease in response to both low and high magnesium diets, respectively.[4,5] Two transport mechanisms have been defined for intestinal magnesium absorption: paracellular and transcellular routes. Paracellular transport accounts for 80-90% of total absorption and is a passive process driven by the relatively high luminal concentration of magnesium and the electropositive transluminal gradient.[6] Transcellular magnesium relies on transport through the transient receptor potential channel melastatin member 6 (TRPM6) and TRPM7 channels.[6] Intestinal absorption may be influenced by vitamin D status[7,8] but this is controversial[9,10] and kidney TRPM6 expression per se does not appear to be influenced by vitamin D.[11]

The main excretory pathway for magnesium is kidney where the fractional excretion can change from nearly 0.5% in hypomagnesemia to greater than 70% in hypermagnesemia.[12] Magnesium is freely filtered (70-80% of magnesium is ultrafiltratable, the rest is protein bound) at the glomerulus, but under normal circumstances, approximately 95% is reabsorbed along the course of the kidney tubule. Bulk magnesium transport (up to 70%) occurs in the thick ascending limb with passive paracellular magnesium uptake. This process is driven by the luminal positive gradient driven by K^+ recycling via apical NKCC2 and ROMK transporters in thick ascending limb cells. The tight junction proteins claudin-16 and claudin-19 comprise the paracellular route for magnesium reabsorption driven by this gradient. Fine-tuning of magnesium reabsorption occurs in the distal convoluted tubule (DCT) and is an active process driven by TRPM6. The magnesium extruding transport protein on the basolateral cell membrane has yet to be identified. Regulation of kidney magnesium handling in the DCT is partly under control of parathyroid hormone (PTH) which increases tubular reabsorption of the cation.[13] Hypomagnesemia stimulates PTH synthesis and release via the calcium sensing receptor (CaSR) in the parathyroid glands, though with potency 2 to 3 times less than that of calcium.[14] However, in the DCT, the potency of magnesium and calcium as activators of the CaSR appears equal.[15] In the parathyroids, the CaSR exhibits a biphasic response in that very low levels of magnesium can reduce the sensitivity of the CaSR to calcium, as well as to magnesium itself, leading to decreased PTH release and profound hypocalcemia, a scenario that requires correction of the hypomagnesemia to restore the responsiveness of the CaSR to calcium and

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allow appropriate release of PTH.[16] PTH secretion is mediated by cyclic adenosine monophosphate. Cyclic adenosine monophosphate is dependent on magnesium for its production and this explains the unresponsiveness of the parathyroids in profound hypomagnesemia.[17] Other players involved in magnesium regulation in the DCT include epidermal growth factor and estrogen which activate transcription of TRPM6.[18,19]

ASSESSING MAGNESIUM STATUS

Although the usual starting point is measurement of blood magnesium concentration, this compartment only constitutes about 1% of the body's total stores. A person in negative magnesium balance will mobilize stores in muscle and bone to maintain serum levels. Thus, total magnesium stores have to be quite low before this is reflected by the serum concentration. Indeed, healthy volunteers on magnesium deficient diets did not deplete their serum levels after 92 days.[20] There is also evidence that those with serum levels in the low-normal range (0.75–0.80 mmol/L) may be functionally magnesium deficient as they display increased chronic disease risk akin to those with levels less than 0.75 mmol/L.[21-23]. Urinary excretion is modified within a few days of a change in gastrointestinal absorption.[20] Thus, the urinary excretion of magnesium probably reflects magnesium intake rather than the total body stores.

CLINICAL SUMMARY

- There is a tendency toward hypermagnesemia in CKD.
- Constituents of the diasylate are the main factors governing magnesium status in dialysis patients.
- In transplantation, calcineurin inhibitors can lead to hypomagnesemia.

Magnesium concentrations in tissues have been assessed as possible measures of total body stores. Erythrocytes, monocytes, sublingual epithelium, and hair cells have all been used for this purpose.[24-27] Magnesium content in sublingual cells correlates with the content in cardiac myocytes, suggesting that it is an acceptable marker for total body magnesium.[24] However, a study looking at replacing magnesium in CKD found that intracellular magnesium (as measured in sublingual epithelial cells) did not increase after 8 weeks of supplementation despite increased serum concentration and urinary fractional excretion of magnesium.[28] The rise in urinary magnesium in this study was not as high as the increased intestinal absorption. The patients were thus in positive magnesium balance and this presumably contributed to replacing body stores. Given the size of the intracellular compartment, 8 weeks was probably not long enough to see the supplemented diet resulting in increased epithelial cell magnesium.

Although there are problems with using serum magnesium as measure of magnesium balance, there are no other alternatives that are practical in routine clinical practice. Although it will take some time for serum magnesium to deplete, a low serum concentration will usually reflect chronic negative balance.

MAGNESIUM AND DISEASE

Magnesium has been linked to multiple diseases. In CKD, hypomagnesemia is associated with increased vascular calcification and mortality. The pathogenesis of vascular calcification in kidney disease is complicated and beyond the scope of this article. In brief, calcium phosphate can influence vascular smooth muscle cells (VSMCs) to become osteoblast like, promoting vascular calcification.[29] It has been shown that in vitro magnesium is able to prevent this process from occurring. In vitro studies have shown that magnesium inhibits osteogenic transformation and calcification of VSMCs, which is probably mediated via TRPM7 channels.[30] It also modulates the expression of several anticalcification proteins possibly via restoring microRNA signature at the site of calcification.[30,31] Magnesium can also activate the CaSR found in VSMCs, and this has also been shown to attenuate vascular calcification.[32] Hypomagnesemia can, therefore, lead to increased vascular calcification which will increase cardiovascular risk burden. Indeed studies have shown that low magnesium levels are associated with death in dialysis patients.[33]

A J-shaped curve describes the relationship between the serum magnesium and mortality. An observational study of over 65,000 patients found that a magnesium level above 2.3 mg/dL was a predictor of adverse outcomes.[34] A similar relationship is seen in dialysis patients, but in contrast to the previous study, the lowest level of risk is seen at levels of 2.7 mg/dL.[35] However, it is not clear whether hypermagnesemia is causal in relation to mortality as there are confounders (such as administration of magnesium supplements for hypomagnesemia). Untangling these will require prospective studies. Until this is known, it seems prudent to keep magnesium levels within range and to be aware of the adverse outcomes associated with both low and high magnesium concentrations.

MAGNESIUM BALANCE IN CHRONIC KIDNEY DISEASE

As glomerular filtration decreases in advancing CKD, increased fractional excretion of magnesium occurs to compensate for decreases in filtered magnesium. Nondiabetic patients with CKD (creatinine clearances of 30-115 mL/min/1.73 m^2) not on diuretics showed an inverse relationship between creatinine clearance and serum magnesium. This same relationship did not hold true for diabetic patients who tended to have lower magnesium levels (possibly due to decreased intestinal absorption due to autonomic neuropathy). In both groups, serum total and ionized magnesium remained in the normal range.[36] As CKD develops beyond stage 4, there is a tendency toward hypermagnesemia, and overt hypermagnesemia is frequently seen when creatinine clearance falls below 15 mL/min.[37] The degree of intestinal absorption becomes key in determining serum magnesium levels in these patients, in whom the ingestion of magnesium containing laxatives or antacids can lead to hypermagnesemia.[38] The use of phosphate binder sevelamer hydrochloride has also