ACKD Advances in Chronic Kidney Disease
A Journal of the National Kidney Foundation®
Vol 25, No 3, May 2018

EDITORIAL

Magnesium: An Important Orphan

Check for updates

All parentless, Little Orphan Annie, Norma Jean (Marilyn Monroe, *c*. 1946), John Lennon, and George Herman ("Babe") Ruth were orphans, who despite humble upbringings became great success in their own right. In this issue of *Advances in Chronic Kidney Disease*, David Leehey and colleagues provide a platform for the magnificence of magnesium, whereas I focus on several germane, clinical aspects of our most treasured "orphan."

INTRODUCTION

Magnesium has been termed the "orphan ion" because of its lack of specific endocrine control. However, this is not true because increases of aldosterone and parathyroid hormone activity, respectively, augment and lessen renal magnesium excretion. Nonetheless, among the bulk of nephrologists, magnesium has remained an orphan, primarily discussed as a treatment for unremitting, pre/eclamptic hypertension, or, as a nuisance, when elevated in patients with end-stage renal disease. Noteworthy is that nephrology's orphan ion participates in several hundred cellular biological processes daily, making it one of the most important minerals in humans, like iron. The popularity of magnesium and renal research regarding our orphan has surged since the description of paracellin-1,[1] the first magnesium-centric claudin. The mutation of paracellin-1 (claudin-16) is responsible for autosomal recessive familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC, MIM 248250). The purpose of this brief expose is to draw attention to a few major findings regarding this most important orphan ion.

MAGNESIUM AND MORTALITY

Despite the ubiquity of magnesium in dietary sources that we should eat, many of us fall short of our nutritional need. Dietary surveys reveal that the recommended daily allowance for magnesium is not met in Europe and the United States.[2] Magnesium deficiency may impose risk for individuals with the metabolic syndrome, diabetes, and hypertension. The recommended daily allowance for men is 420 mg and for women 320 mg. Ingestion of nuts, seeds, legumes, whole-grain cereals, leafy vegetables, and water will suffice. That daily requirements for magnesium are not met is disturbing given the epidemiological information regarding serum magnesium levels and the risk of death.

Kieboom and colleagues recently published their findings in 2016 from an analysis of the prospective, population-based Rotterdam Study.[3] From data on 9820 participants (mean age 65.1 years, 56.8% female) followed for a median of 8.7 years, the association of serum magnesium levels and mortality was inverse. A 0.1 mmol/L (0.24 mg/dL) increment of this ion associated with a lower coronary heart disease risk (hazard ratio, 0.82; 95% confidence interval: 0.70–0.96). Low serum magnesium concentrations ($n = 431$) below 0.80 mmol/L (1.95 mg/dL) were also associated with increased coronary risk and sudden cardiac death ($n = 217$; hazard ratio, 1.54; 95% confidence interval: 1.12–2.11). Others reported similar findings. The 2013 meta-regression analysis of 532,979 participants by Qu and colleagues found that magnesium levels were inversely associated with risk for total cardiovascular disease events.[4] Only levels between 0.72 and 0.9 mmol/L (1.75–2.19 mg/dL) were significantly associated with adverse events.

Does the inverse association between magnesium concentration and death risk apply to chronic kidney disease (CKD) patients? It seems to. Kanbay and colleagues' review targets this question directly. They posit that low magnesium levels nurture a pernicious environment for accelerated atherosclerosis, cardiac dysrhythmia, and chronic myocardial ischemia.[5] Furthermore, the group advocates the use of magnesium carbonate as an intestinal phosphate binder treatment. The replacement of classical magnesium hydroxide by the carbonate congener yields a substrate for hepatic bicarbonate generation that is additionally less diarrheagenic. Furthermore, there is less chance of inducing hypercalcemia using a magnesium-based phosphorus binder. In hemodialysis patients, a magnesium-free dialysate can be used with magnesium carbonate to maintain magnesium levels in the normal range. This strategy may also reduce parathyroid hormone levels with a coincident decrease of serum

© 2018 by the National Kidney Foundation, Inc. All rights reserved.
1548-5595/$36.00
https://doi.org/10.1053/j.ackd.2018.04.001

calcium and phosphorus concentrations.[6] Conceivably, the reduction of parathyroid hormone, an independent risk factor for mortality in hemodialysis patients, would be beneficial.

MAGNESIUM AND CALCIFICATION

Perhaps, the association of low magnesium levels in CKD patients[3,7,8] and increased cardiovascular mortality risk involves magnesium's ability to inhibit vascular calcification.[9] Vascular calcifications may appear in skin, muscles, blood vessels, and heart valves in advanced CKD. The process is complicated, and intensive, in vitro study provides a model. Vascular muscle cells transdifferentiate and assume a more osteoblast-like phenotype. The process is marked by new gene expressions of runt-related transcription factor 2 (*RUNX2*) and bone morphogenetic protein 2 (*BMP2*). Bone-specific alkaline phosphatase can now be secreted.

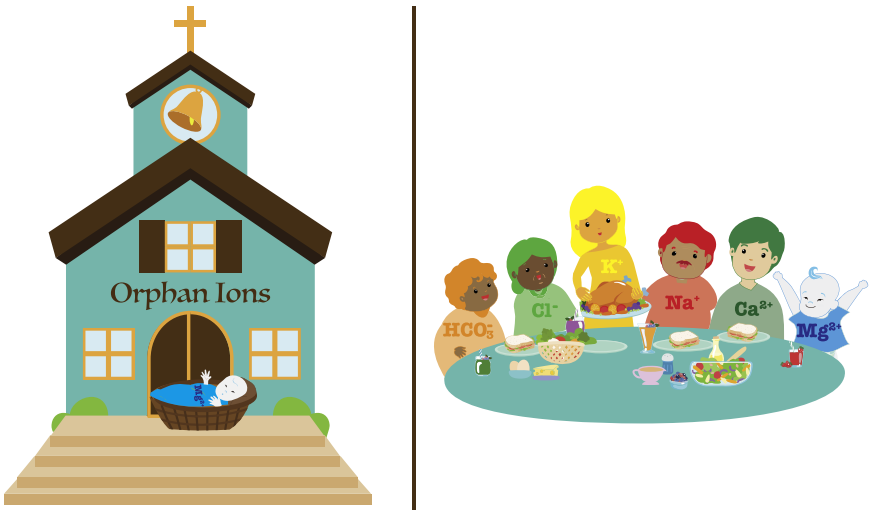
Consequently, the transdifferentiated vascular smooth muscle cells are no longer contractile, and can deposit mineral in the extracellular matrix. The deposition of calcium-phosphate nanocrystals is key, and the nanocrystals may participate in driving the process of transdifferentiation. Recall that the same process occurs in the progenitor sequence of idiopathic calcium oxalate lithiasis, i.e., Randall plaque formation.[9] Successive rounds of mineral deposition as nanocrystal in the surrounding matrix ultimately produce a metastatic calculus in soft tissue, a stiff vessel, or lithic heart valve. Extracellular magnesium ion can abrogate this calcification process via two mechanisms. First, magnesium ion directly suppresses transdifferentiation by reducing osteoblastic gene expression. Second, the nanocrystallization process is directly restrained by ionized, extracellular magnesium—simple chemistry at its best.[10] Interestingly, nanocrystallization is not inhibitable by selective chemical suppression of the vascular smooth muscle cells' magnesium channel, transient receptor potential cation channel subfamily M member 7 (TRPM7).[11]

Because advanced CKD patients are frequently exposed to proton pump inhibitors for a host of uremic gastrointestinal maladies, hypomagnesemia is likely more prevalent than suspected. No one needs reminding that this class of agents is among the most prescribed medications worldwide. Recently, chronic proton pump inhibitor use has been reported as a risk factor for incident CKD of the general US population, following analysis of data from the Atherosclerosis in Communities study with replication of findings using data from Geisinger Health.[12] Taken collectively, there is sufficient logic to maintain magnesium levels in advanced CKD patients and hemodialysis patients above the dangerous threshold levels associated with adverse cardiovascular outcomes. Prospective, randomized, controlled trials should only be conducted to determine the optimum level of serum magnesium concentration in CKD patients because an experimental group with lower-than-normal magnesium levels would be considered unethical by institutional review boards.

MAGNESIUM IN DIABETES

Diabetic patients have lower serum magnesium levels,[13] which have been associated with poor glycemic control. Corsonello and colleagues determined that serum, ionized magnesium levels in 30 diabetic subjects (0.39 ± 0.06 mmol/L) were nearly 0.2 mmol/L less than the levels of 20 healthy control subjects (0.58 ± 0.05 mmol/L; $P < 0.001$).[14] Hypertriglyceridemia and hemoglobin A1c levels were significantly and inversely associated with the ionized magnesium concentration. Although not proven in this study, the hypothesis would be that enhanced urinary magnesium losses accounted for the lower serum levels. The kidneys are capable of high-level magnesium conservation during magnesium deprivation with hypomagnesemia. Just 5% of the ultrafilterable load of magnesium, amounting to 80–100 mmol daily, is excreted in urine daily. However, in the presence of an osmotic diuresis imposed by supervention of the tubular maximum for glucose reabsorption in an individual with poor glycemic control, net magnesium losses would accrue.

This observation is particularly important because magnesium, which is nearly completely intracellular, is



Download English Version:

https://daneshyari.com/en/article/8769572

Download Persian Version:

https://daneshyari.com/article/8769572

Daneshyari.com