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Editorial

Whither Magnesium?

Magnesium is a chemical element with the atomic number 12, an atomic weight of 24, and the common oxidation number +2. Magnesium is an alkaline metal and the eighth most abundant element in the Earth's crust, where it constitutes about 2% by mass, and ninth in the Universe. Magnesium is easily built up in supernova stars by the sequential addition of three helium nuclei to carbon. Magnesium ion's high solubility in water helps ensure that it is the third most abundant element dissolved in seawater. Thus, magnesium seems ubiquitous and countless products contain magnesium. My wife swears by her GSR Magnesium IQ skis; I can offer no comment in that regard. A crude facsimile of magnesium is offered in Figure 1.

Magnesium is the second most prevalent intracellular cation and the fourth most abundant cation in the body. Magnesium is integral to the function of adenosine triphosphate and plays a role in a host of enzymatic reactions and transport processes, and in the synthesis of proteins, DNA and RNA. Oddly, magnesium gets relatively short shrift in terms of physician education. Disorders of magnesium metabolism made hardly 1.3 pages in my most recent edition of a commonly used Internal Medicine textbook [1]. The topic did a bit better in a textbook devoted solely to fluid and electrolyte metabolism [2]. The lay public seems a bit more aware. They generally know that grains, nuts, milk and green leafy vegetables provide magnesium. They are convinced that magnesium is 'good for you'. They know for instance that magnesium cures leg cramps, although the Cochrane Review folks are less convinced. Many people travel to the Dead Sea to get at it; presumably they absorb it through the skin, who knows?

One of my favourite clinical teachers, Robert Whang, scoured intensive care units of our hospitals checking the patients for magnesium deficiency [3]. In a survey of 1033 serum specimens for electrolyte analysis in an acute-care hospital, he and an associate found that 53% of the patients had magnesium levels <0.74 mmol/L, while the ordering physicians suspected and ordered magnesium levels specifically in only 10% of patients. Whang and Ryder concluded that in many patients, magnesium disturbances were not being detected. They recommended that routine magnesium measurements should be performed in acutely ill patients when electrolyte disturbances are suspected [4]. Whang was also interested in the relationship between magnesium and potassium, particularly intracellular potassium stores. He and an associate drew attention to the close interrelationship of magnesium, calcium and intracellular potassium. Clinically, magnesium deficiency is associated with hypocalcaemia, kaliuresis and hypokalaemia [5]. Decreased Na-K pump density in cells decreases ATPase activity; and increased cell membrane permeability related to intracellular potassium depletion are mechanisms that they implicate. Since the kidneys eliminate magnesium, nephrologists would be expected to know the most about it. The daily intake of magnesium is ~15 mmol of which approximately one third is absorbed. The circulating pool amounts to ~7.6 mmol and

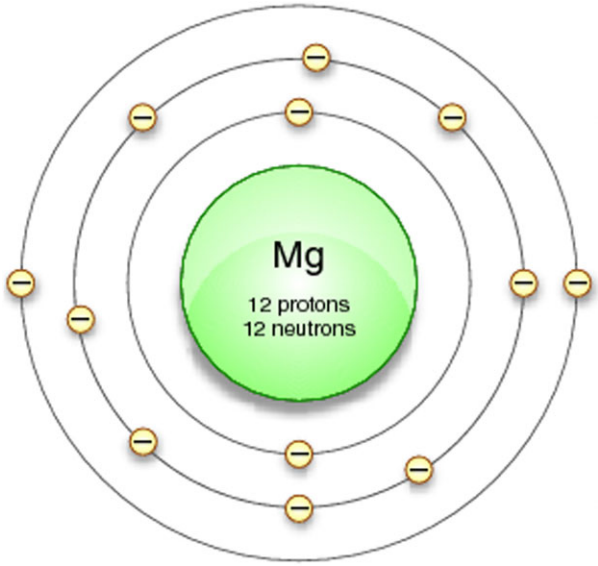

Fig. 1. The magnesium atom with its protons, neutrons, and electrons is displayed.

is in equilibrium with bone magnesium which is ~530 mmol, muscle magnesium ~270 mmol, other intracellular places ~190 mmol and erythrocytes ~5 mmol. Of the 5 mmol absorbed, the kidneys excrete 4 mmol and the rest is eliminated by other means. Robert Whang recognized that serum measurements, while practicable, were not adequate reflections of total body stores and took to measuring magnesium in mononuclear cells. Erythrocytes are apparently inexact reflectors.

Dialysis patients cannot eliminate magnesium via their kidneys. The dialysate is adjusted accordingly. Such patients should be prime candidates of interest regarding magnesium metabolism. The other cations have done pretty well, sodium in terms of volume regulation, potassium in terms of Nernst-Equation problems (like sudden cardiac death) and calcium in terms of bone disease. The relationship between serum magnesium concentrations and renal function is based on a (seminal) study from 40 years ago; the values were all over the map and were typically high. However, the authors did not report that the patients developed any symptoms related to their magnesium levels [6]. I was taught that magnesium, similar to potassium, was 'dangerous' in dialysis patients and could cause similar symptoms to hyperkalaemia. Forty years ago, before the advent of histamine receptor-2 blockers and proton-pump inhibitors, gastric disorders were treated with antacids and the favourite was Maalox®. The compound contains aluminum hydroxide and magnesium hydroxide to neutralize or reduce stomach acid. Dire were the consequences and limited was the future for any nephrology fellow who did not eliminate Maalox® from the treatment venue of any renal patient! Getting fired in those days was relatively

easy. Does hypermagnesaemia kill people? Perusal of the literature identified possible victims of acute poisoning, like ingesting water from the Dead Sea, but required values in excess of 10 mmol/L. Was that entire hullabaloo justified? I am no longer certain, because magnesium-containing phosphate binders could provide an attractive answer for multiple problems.

New exciting discoveries on the relevance of magnesium are being regularly reported. The magnesium ion is essential for all life as a cofactor for ATP, polyphosphates such as DNA and RNA and metabolic enzymes. Recently, Li *et al* [7] identified mutations in the magnesium transporter gene, MAGT1, in a novel X-linked human immunodeficiency syndrome characterized by CD4 lymphopenia, severe chronic viral infections and defective T-lymphocyte activation. They demonstrated that a rapid transient magnesium influx is induced by antigen-receptor stimulation in normal T cells and by growth-factor stimulation in non-lymphoid cells. MAGT1 deficiency abrogated the magnesium influx, which impaired responses to antigen receptor engagement, including defective activation of phospholipase Cγ1 and a markedly impaired calcium influx into T cells. These observations reveal a novel role for magnesium as an intracellular second messenger that couples cell-surface receptor activation to intracellular effectors. The findings identify MAGT1 as a possible target for novel therapies in immune disorders. More importantly, the findings usher in a specific role for magnesium trafficking in regulating immunity.

With this compendium, we would like to provide general nephrologists with a practicable overview of magnesium metabolism and what it means for their patients. We have gathered a group of basic scientists and experienced clinicians to deal with the issues involved. Importantly, substantial new knowledge has been accrued about magnesium and new avenues have been opened for patients. These avenues will demand rigorous, well-designed clinical studies, but our patients would expect no less. Willi Jahnen-Dechent and Markus Ketteler introduce us to magnesium and do not spare us from some important inorganic information about the element. Jeroen de Baaij, Joost Hoenderop and René Bindels discuss the amazing advances in molecular genetics concerning magnesium metabolism, including the channels responsible for magnesium transport. Helmut Geiger and Christoph Wanner discuss magnesium in the general population. Does magnesium metabolism contribute to arterial hypertension? My first brush with this topic was based on two landmark papers from the early 1980's [6,8]. These papers implicated magnesium deficiency in hypertension and blood vessel rarefication; what has happened since then? What do we know about magnesium in chronic kidney disease before dialysis and afterwards? John Cunningham, Mariano Rodríguez, and Piergiorgio Messa present what is known about this issue. Ziad Massy and Tilman Drüeke tackle the issue of magnesium and outcomes in CKD patients, focusing on vascular calcification. The exciting tenor of the discussions could be that magnesium interferes with vascular calcification and since most dialysis patients die from vascular disease, such a result would be of amazing significance. On the downside, there is nagging doubt (ignorance) about the effects of magnesium on chronic bone disease. Here is where most of the magnesium in the body 'is at'. Could additional magnesium access influence bone disease and how could we find out?

Alastair Hutchison and Martin Wilkie review the use of magnesium as a drug in chronic kidney disease patients. All of us who prescribed Maalox® knew that the compound was a great phosphate binder. Could a calcium acetate/magnesium carbonate binder solve some problems that we have with the other products? A randomized controlled trial has been performed to test the efficacy in terms of phosphate and parathyroid hormone control. And with this trial, we come full circle.

There are numerous missing variables and complex clinical research issues. Do phosphate binders prolong life of dialysis patients? I would not insist that this hypothesis be tested. Evidently, they do reduce fracture risk. Calcium-containing phosphate binders have been implicated in vascular calcifications. Could a magnesium-containing compound circumvent or even alleviate this problem? Would magnesium-containing phosphate binders make bone disease better or worse? What would be the interaction between a magnesium-containing phosphate binder and the calcium-sensing receptor? Magnesium has three stable isotopes: ^{24}Mg, ^{25}Mg and ^{26}Mg. About 79% of Mg is ^{24}Mg. Stable isotopes provide a non-radioactive opportunity for great clinical research. I see an opportunity for important clinical research on not only dialysis-related issues, but also regarding magnesium metabolism as a whole entity. Let us go for it, whole-heartedly. And, in the meantime, perhaps we could figure out what really causes those obnoxious leg cramps!

Respectfully,
Friedrich C. Luft
Charité Universitätsmedizin Berlin
Experimental and Clinical Research Center
Robert-Rössle Strasse 10
13125 Berlin, Germany

E-mail: luft@charite.de

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References

1. Goldman L, Auseillo D. *Cecil Textbook of Medicine*. Philadelphia, PA, U.S.A: Saunders Elsevier; 2004: 702–703
2. Narins R. *Clinical Disorders of Fluid and Electrolyte Metabolism*. MacGraw Hill, 1994: 1099–1115
3. Whang R. Magnesium deficiency: pathogenesis, prevalence, and clinical implications. *Am J Med* 1987; 82: 24–29
4. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia. Requested vs routine. *JAMA* 1990; 263: 3063–3064
5. Whang R, Whang DD. Update: mechanisms by which magnesium modulates intracellular potassium. *J Am Coll Nutr* 1990; 9: 84–85
6. Coburn JW, Popovtzer MM, Massry SG, Kleeman CR. The physicochemical state and renal handling of divalent ions in chronic renal failure. *Arch Intern Med* 1969; 124: 302–311
7. Li FY, Chaigne-Delalande B, Kanellopoulou C *et al.* Second messenger role for Mg2+ revealed by human T-cell immunodeficiency. *Nature* 2011; 475: 471–476
8. Altura BM, Altura BT, Gebrewold A, Ising H, Gunther T. Magnesium deficiency and hypertension: correlation between magnesium-deficient diets and microcirculatory changes in situ. *Science* 1984; 223: 1315–1317