Literature Review:
Magnesium Inclusion in Phosphate Binders

Magnesium Physiology and Effects of its Inclusion in Phosphate Binders

GI absorption of diet-derived phosphate may be lowered and controlled by cations such as calcium and magnesium.

$$M^{+2} + [Phosphate] \rightarrow M(Phosphate)_i$$

(Ions in solution) (Precipitate)

Use of calcium alone (as calcium acetate or calcium carbonate, for example) is known to be effective for phosphate binding. However, long-term use has been associated with risk of vascular calcification.

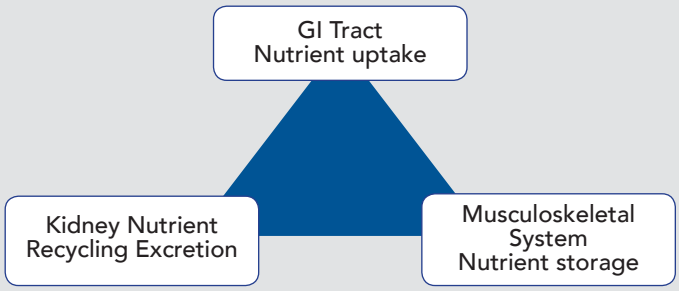
Use of magnesium alone (as magnesium hydroxide or magnesium oxide) has been studied. However, further development was slowed as a result of concerns about hypermagnesemia and diarrhea.

Since both physiological metals bind phosphate, what may be observed if they are used in combination?

WE KNOW A GREAT DEAL ABOUT THE PHYSIOLOGICAL ACTIONS OF CALCIUM.

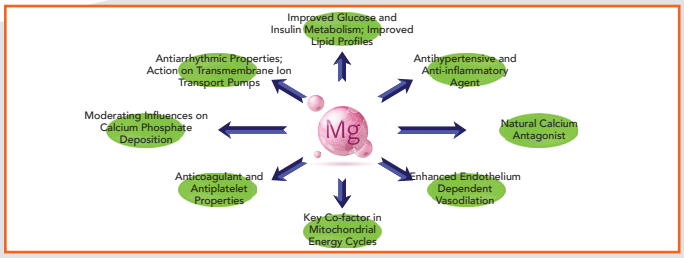
Let's Highlight Physiological Activities Associated with Magnesium.

Magnesium is the fourth most abundant cation in the body (after Ca, K, and Na). Skeletal muscles, heart, teeth, bones, and many other organs require magnesium to sustain their physiologic functions.



Maintenance of normal serum levels of magnesium depends on the delicate interplay between net absorption in the gut, uptake and release from the musculoskeletal system, and net excretion in the kidney. About 80% of dietary magnesium is absorbed paracellularly. Active transport accounts for about 20% of magnesium absorption.

Magnesium is the second most abundant intracellular cation. It activates more than 600 enzymes, is a key co-factor in over 300 enzymatic reactions, and influences the body in a variety of ways.



- o Magnesium plays a key role in supporting the effectiveness and clinical benefits of vitamin D. The activities of 3 major vitamin D-converting enzymes (including 1alpha-hydroxylase and 24-hydroxylase in the kidneys) are magnesium dependent, as are the activities of vitamin D-binding proteins.
- o Magnesium plays a critical role in activating and regulating human NAD-dependent isocitrate dehydrogenases located in the cytosol, mitochondria, and peroxisomes.
- o Magnesium plays a role in erythrocyte stabilization and function, supporting normal red cell lifespan.

Reference values for serum magnesium concentration vary.

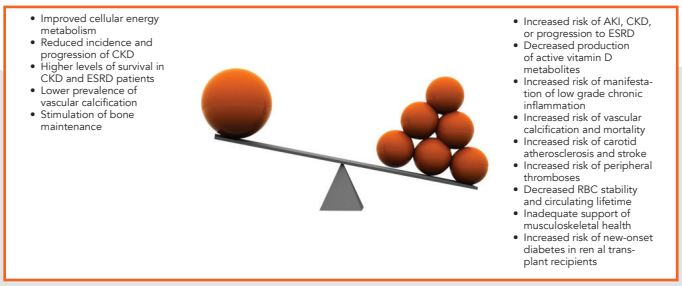
- o 0.7 – 1.0 mmol/L (based on 1974 NHANES I cohort);
- o 0.5 – 1.05 mmol/L (Source 2);
- o 0.7 – 1.05 mmol/L (Source 3);
- o 0.7 – 1.1 mmol/L (Source 4);
- o 0.76 – 1.15 mmol/L (Source 5).

Symptoms of hypermagnesemia are typically observed when serum magnesium exceeds 2.0

Kidney function affects serum levels of magnesium. Patients with moderate CKD maintain serum magnesium levels within normal limits (0.5 – 1.0 mmol/L). However, skeletal or intracellular magnesium content of soft tissues may be depleted, a condition termed chronic latent magnesium deficit. When compensatory physiological changes fail (from KDIGO Stage 4 on), patients with advanced chronic kidney disease often have high serum magnesium concentrations (> 1.0 mmol/L).

Serum magnesium concentrations in patients undergoing hemodialysis often correlate with dialysate magnesium concentrations. In an effort to avoid potential adverse events associated with hypermagnesemia, the standard of care in the United States for dialysate magnesium concentration has been 0.375 – 0.5 mmol/L. However, at these concentrations, most patients exhibit an intra-dialytic decline in serum magnesium concentrations. Likewise, a study evaluating chronic HD patients who were receiving dialysate at these concentrations found a hypomagnesemia incidence of 39%. However, many of the patients in this second study were using proton pump inhibitors.

With respect to serum magnesium levels, observational cohort studies have shown an association between low serum magnesium concentrations and an increased incidence of cardiovascular and all-cause mortality for patients on hemodialysis as compared to patients having serum magnesium concentrations high in the normal range.



CALCIUM/MAGNESIUM PHOSPHATE BINDERS

Since 2004, European nephrologists have recognized that multi-year treatment of hyperphosphatemia with an oral tablet made up of a combination of 110 mg calcium (as calcium acetate) and 60 mg of magnesium (as magnesium carbonate) (hereafter, Ca/Mg) rapidly and significantly lowered serum phosphate without increasing serum calcium or raising serum magnesium levels beyond the normal range.1 In fact, the European Medicines Agency authorized clinical use of Ca/Mg in 2008, even before completion of controlled clinical trials that verified the value of Ca/Mg therapy.

Of greater potential impact on CKD care is the published conclusion that Ca/Mg is not inferior to sevelamer, a preferred current standard of care for hyperphosphatemia in many dialysis centers. Two large European clinical studies – one randomized and controlled, the other a study in clinical practice – have confirmed the unique value of Ca/Mg treatment vs. sevelamer (Table) in controlling serum phosphate and Fibroblast Growth Factor 23 (FGF-23), two biomarkers where increases are strongly associated with renal disease progression, morbidity and mortality. Of note, Ca/Mg's effectiveness in broader clinical practice was consistent with the results observed in a randomized controlled clinical trial.

Several other features of the Ca/Mg combination were not studied in either clinical trial but are of especial significance for pediatric patients. For over a decade, cardiologists have recognized that magnesium is a key cardiovascular regulator, which helps maintain electrical, metabolic, and vascular homeostasis. Adequate concentrations of magnesium improve insulin sensitivity, hyperglycemia, diabetes mellitus, ATP production, and dyslipidemia. Increased magnesium also increases nitric oxide, improves endothelial dysfunction, and induces both direct and indirect vasodilation. Thus, published literature suggests that serum magnesium concentrations high in the normal range such as those associated with Ca/Mg treatment may provide ancillary benefits that were not specifically monitored in published clinical studies.

Outcomes of the controlled randomized, single blind, multicentre CALMAG trial including 255 patients from five European countries

Reported Outcome	Ca/Mg vs. Sevelamer	Ref
Lowered serum phosphate into K/DOQI target range after 24 weeks	Both treatments	14
• Detailed analysis of rate of lowering serum phosphate over time	Ca/Mg more effective (p = 0.0042)	14
• Predefined target ranges of serum phosphate achieved	Ca/Mg group reached target more quickly; time to target reduced by as much as 84 days compared to sevelamer	14
Number of tablets required to reach target range	Lower in Ca/Mg group	14
Improved global KDIGO outcomes	Significantly increased (p = 0.0067) in Ca/Mg group	14
Ionized serum calcium	Did not differ between groups	14
Serum magnesium	Small (0.2597 mmol/L, P < 0.0001) but asymptomatic increase in Ca/Mg group	14
Serum levels of FGF-23	Significantly reduced with no difference between groups at week 25	15
Serum levels of iFGF-23	Comparably lowered	15
Relationship between serum FGF-23 and serum phosphate	Strongly correlated at all time points in both groups	15
Bone turnover parameters (AP, BAP, P1NP, OPG, ß-CTX, TRAP-5b)	No change in Ca/Mg group, Increased significantly in sevelamer group	15
Number of study dropouts	18 in Ca/Mg group vs. 34 in sevelamer group	14
These reports support further investigation of the phosphate-binding properties of liquid concentrates containing both calcium and magnesium salts.		

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