Magnesium therapy for nephrolithiasis

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Abstract. Purpose. Critically evaluate the experimental evidence and clinical trial outcomes as the basis for use of magnesium (Mg) supplements as therapy for calcium oxalate nephrolithiasis. Materials and methods. Literature search of MedLine and Web of Science through January 2005; articles cited in papers found by searches. Results. Magnesium inhibits calcium oxalate crystallization in human urine and model systems. Magnesium also inhibits absorption of dietary oxalate from the gut lumen. Three early trials of Mg oxide (MgO) and Mg hydroxide (Mg(OH)2) reported lower rates of recurrent stone formation. However in a double-blind, randomized, placebo-controlled trial with more carefully selected patients, there was no significant difference between recurrence rates with 650 or 1300 mg MgO daily and the placebo. Another trial reported 391 mg (21 meq) Mg daily as a mixed salt, Mg potassium citrate, reduced calcium stone recurrence by 90%, similar to potassium citrate, but with better gastrointestinal tolerance. The failure of MgO and Mg(OH)2 as sole therapy may be related to poor absorption and low rates of Mg deficiency in the patient populations tested. Conclusions. Clinical trial evidence does not justify the use of MgO or Mg(OH)2 as a sole therapy for calcium oxalate kidney stones in a general patient population. However, the addition of magnesium to potassium citrate therapy improves outcomes. Clinical trials should focus on patients who are likely to be Mg deficient.

Key words: magnesium, calcium, oxalate, nephrolithiasis

Mg acts as a competitor to calcium in oxalate binding. However, Mg oxalate (MgOx) is more soluble than calcium oxalate (CaOx), 0.07 g/100 mL versus 0.0007 g/100 mL respectively, so MgOx does not form stones at physiological urine concentrations. Because Mg competes with Ca in binding oxalate, both in the gut and urine, the ratio of Mg/Ca in the urine has been used as an estimate of stone risk. Because the absolute amount of oxalate to the total amount of these divalent cations is also important, the Mg/Ca ratio is less predictive of stone risk than when other urinary factors are included in the calculation of calcium oxalate saturation. For example, the relationship of Mg as an inhibitor of CaOx precipitability in 24 h urine is shown in the Tiselius Risk Index (TRI) equation [1]. A TRI of 1.0 equals the saturation level of CaOx:

\[ 1.9 \times [\text{Ox}] \times [\text{Ca}]^{0.84} \times [\text{Mg}]^{-0.12} \times [\text{Cit}]^{-0.22} \times [\text{Volume}]^{-1.03} \]

In actual urine, the TRI may exceed 1.0 without crystallization because it is in a metastable condition; also, inhibitory proteins are found in the urine [2]. In practice, Tiselius found the relative risk of stone recurrence in 8 years doubled only when the TRI exceeded 1.5 [3].

Another way of examining the effect of Mg on relative risk is to study crystallization of CaOx in model systems. Rodgers et al. [4] found that Mg in combination with citrate, another inhibitor, is more effective than either alone. Mg citrate slowed crystal growth rate, nucleation rate and supersaturation in his model system. A follow-up study [5] found Mg supplements alone had no effect, but Mg with citrate increased pH and lowered the relative saturation of brushite in urine.

A second way Mg may reduce the CaOx stone risk is through its effect on oxalate absorption. Even though MgOx is 100 times more soluble than CaOx, it...
is still relatively insoluble. Because of this property, Mg binds oxalate in the gut and reduces its absorption. Liebman and Costa [6] loaded healthy volunteers with 198 mg oxalate containing 18 mg C13-oxalate. Simultaneous consumption of 300 mg either elemental calcium as the carbonate salt or Mg as the oxide salt reduced oxalate absorption from 13.5% to 5.1% and 7.6% respectively. These results confirmed the 1986 report of Berg et al. [7] who used 500 g spinach as the oxalate load, which contained 2827 mg oxalate, and Mg as alkaline Mg carbonate. In rats, Mg deficiency causes nephrocalcinosis and stone formation [8] and Mg supplements reduced nephrolithiasis [9]. Thus, both theoretical considerations and animal studies support trials of Mg supplements as therapy for nephrolithiasis.

**Methods**


**Results**

In 1929 Hammarsten [10] showed that a deficiency of magnesium led to an increase in the urinary excretion of oxalate in humans, the process being reversed when magnesium was supplied. The extensive early studies on magnesium deficiency and the kidney were reviewed by Thomas and Durlach [11] in 1971. De Albuquerque and Tuma [12] reported the first human study in nephrolithiasis patients in 1962; which found that 3.7 mmol (150 mg) of Mg as MgO three times daily significantly reduced oxalate excretion and crystalluria in 9 persons with recurrent oxalate lithiasis. The first clinical trial in which stone recurrence was monitored was reported by Moore and Bunce [13], who gave 10.4 mmol Mg (420 mg) as MgO therapy to two patients with recurrent calcium stones and found no recurrence in one year of therapy. Melnick et al. [14] found in a larger trial with 33 patients that 17.9 mmol Mg (720 mg) as MgO divided into two daily doses, reduced the pretreatment rate of 1.41 to 0.36 stones per year post-treatment, a 75% reduction. No control group was included. In a similar trial with a control group, Johansson et al. [15] also found positive results of 4.4 mmol (400 mg) of Mg as Mg(OH)2 divided into two daily doses. Patients with no treatment had a 44% recurrence rate over 2-3 years compared to 12% in the Mg treatment group, a 73% reduction. However, the stone recurrence rate dropped in both groups: from 1.25 to 0.03 stones per year in the treatment group and from 0.5 to 0.22 in the no treatment group. In contrast, in a double-blind, randomized, placebo-controlled trial, Ettinger et al. [16] were not able to show a difference between 16.1 mmol or 32.2 mmol Mg as MgO daily and the placebo recurrence rates in 51 patients with a history of at least two stones. Recurrence rates over at least two years were reduced by 56-65% in all groups.

Adding magnesium to potassium citrate appears to change urine composition more favorably than using potassium citrate alone. Pak et al. [17] found that not only was urinary magnesium higher, but also pH and citrate. Although urinary oxalate was reduced from 829 to 716 μmol/l (about the 7% reduction expected), this decrease was not statistically significant, but contributed to the decrease in calcium oxalate activity and formation products. Kato et al. [18] reported similar findings using two supplements, potassium-sodium citrate plus 6.2 mmol (250 mg) MgO. Recently Ettinger et al. [19] confirmed the effectiveness of the use of magnesium potassium citrate in a randomized clinical trial. They found 12.7 mmol Mg (510 mg) daily of Mg potassium citrate reduced calcium stone recurrence over 30 months by 90%, similar to potassium citrate, but with better gastrointestinal tolerance.

**Discussion**

The failure of MgOx and Mg(OH)2 as sole therapy may be related to two factors. First is their poor absorption. MgO and Mg(OH)2 are the least bioavailable Mg salts [20]. The more soluble forms of Mg are chloride, gluconate, aspartate and citrate. Mg citrate doubled the Mg/Cr ratio 2-4 hours after oral loading, while MgO only increased the ratio by 3% [21].

Second, Mg deficiency is relatively rare in stone formers. Schwartz et al. [22] reported that only 11% of 24 h urinary Mg in stoneformers falls below 43 mg/d. Preminger et al. [23] reported that 4.3% of a series of 1116 patients had hypomagnesiuria, which they defined as having a urinary magnesium level of less than 50 mg/d. A large clinical laboratory (Litholink, Chicago IL) uses 44 mg/d as the lower limit for urinary Mg based on the 5th percentile of their normal population. In stoneformers over 18 y, 1494 of 31,300 urine collections (4.6%) fell below this cut point (J. Asplin, personal communication, January 6, 2004).

Even if a Mg salt is well absorbed and increases urinary Mg, most patients already have sufficient urinary Mg to decrease crystallization to its mini-
In figure 1, the effect of increasing Mg excretion on TRI is seen. For this figure, the assumption for curve A is that urinary calcium is constant at 6.39 mmol/d, citrate at 2.9 mmol/d, oxalate at 409 μmol/d and volume at 1.86 mL, the average urinary composition of stoneformers as reported by Ettinger et al. [18]. However, increasing daily Mg excretion from 1.5 mmol (37 mg) to 4.0 mmol (97 mg) may result in a clinically significant decrease in risk if a TRI cut-off of 1.5 is used as the critical value (dotted line); this level of change reduces the TRI from 1.54 to 1.30. From Fig. 1, it can be seen that a similar conclusion can be made for hyperoxaluric patients (curve A) and hypercalciuric patients (curve B). Overall, magnesium-deficient patients who excrete less than 50 mg/day are most likely to benefit from Mg supplements.

However, even a relatively insoluble Mg supplement will reduce oxalate absorption even if there is little increase in Mg excretion. As an example, if a Mg supplement reduced dietary Ox absorption by 6% with a daily consumption of 200 mg Ox as reported by Liebman and Costa [6], a 125 μmol/d (12 mg) drop, the TRI would decrease from 1.5 to 1.1 with Mg assumed to be constant at 5 mmol/d (121 mg) and other conditions as described above. Because both effects are fairly small, only a Mg supplement that both binds oxalate in the gut and increases urinary Mg excretion is likely to reduce the risk of stone recurrence. For example, if Mg supplementation both increased urinary Mg from 1.5 to 4.5 mmol/d and reduced oxalate from 475 to 350 μmoles/d, the TRI would decrease from 1.7 to 1.1.

Epidemiological evidence supports the probable effectiveness of increased magnesium in preventing symptomatic kidney stones. Taylor et al. [24] followed 45,619 men for 14 years, with dietary assessments every four years. After multivariate adjustment the relative risk for the highest quintile of magnesium intake (over 450 mg/d) compared to the lowest quintile (less than 314 mg/d) was 0.71.

Clinical trials of Mg supplements should include assessment of the Mg status of trial participants by urinary Mg/d, serum Mg and dietary Mg intakes. Dietary Mg is unlikely to be deficient if the diet includes green leafy vegetables and whole grains, as Mg is a major mineral in chlorophyll. Chocolate and nuts are good dietary sources of Mg, but also contain considerable amounts of oxalate which increases urinary oxalate [25, 26]. The trial design should require that the Mg supplement be taken with meals to maximize oxalate binding. Inclusion of both Mg deficient and Mg sufficient groups would help clarify which nephrolithiasis patients could benefit from Mg supplements.

References


