Effect of Magnesium Supplementation on the Fractional Intestinal Absorption of $^{45}CaCl_2$ in Women With a Low Erythrocyte Magnesium Concentration

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The cosupplementation of magnesium with calcium has been suggested to be beneficial in the prevention of osteoporosis. We investigated the effect of magnesium supplementation on parameters of bone resorption and fractional ^{45}Ca absorption. Twenty apparently healthy women with a mean age of 39.2 ± 9.2 years and an erythrocyte magnesium concentration less than 1.97 mmol/L were recruited into a controlled magnesium supplementation trial. During weeks 1 to 4, they received a daily control preparation, potassium/sodium citrate malate (PSCM). During weeks 5 to 8, the subjects received magnesium citrate malate (MCM) equivalent to 250 mg magnesium per day. During the fourth and eighth weeks, blood was collected for measurement of the serum intact parathyroid hormone (PTH) concentration and serum and erythrocyte magnesium concentration. Urine was collected for measurement of calcium, magnesium, creatinine, and deoxypyridinoline excretion. On the final day of each treatment period, 5 μCi $^{45}CaCl_2$ was administered orally, and the isotope was traced in the blood and urine over 7 hours. Urinary calcium, ^{45}Ca, and deoxypyridinoline excretion, as well as serum intact PTH levels, showed no statistically significant changes as a result of magnesium supplementation. However, urinary magnesium excretion increased by 31.1% ($P < .005$) while fractional ^{45}Ca absorption decreased by 23.5% ($P < .001$) as a result of magnesium supplementation. It is concluded that magnesium supplementation does not result in changes in bone resorption, while the fractional intestinal absorption of ^{45}Ca appears to decrease.

ALTHOUGH HYPOCALCEMIA is a well-recognized result of magnesium deficiency,[1] there is little information available concerning the effect of a subclinical magnesium deficiency on calcium absorption and metabolism. The absorption of calcium from the intestinal tract and the serum concentration of calcium are tightly regulated by the homeostatic actions of parathyroid hormone (PTH)[2,3] and calcitriol.[1,4] An adequate magnesium status is important in maintaining calcium homeostasis.[1-6] The severity of magnesium deficiency determines the regulatory response to it. If the deficiency is mild, PTH stimulates increased calcium and magnesium release from bone.[2] If the deficiency is severe, the secretion of PTH will be impaired.[2,7-9] The low PTH and low magnesium concentrations act together, decreasing calcium mobilization from bone, and thus hypocalcemia may develop.[3,7-11] In this case, the hypocalcemia is unresponsive to calcium or vitamin D supplementation,[7] but it is responsive to magnesium supplementation.[7,9-12] Furthermore, adequate levels of magnesium are postulated to be important for the biosynthesis of calcitriol in the kidneys[10] and for the end-organ action of PTH.[1,3,10] A poor magnesium status may contribute to suboptimal intestinal absorption of calcium, resulting in hypocalcemia.[11]

Magnesium supplementation has been advocated for the prophylactic treatment of osteoporosis,[5,6,13-16] and it has been reported that magnesium supplementation increases bone density.[1,6,13,17] Additionally, magnesium depletion may contribute to the development of osteoporosis.[6,13,17,18] The mechanisms by which magnesium may benefit the maintenance of a healthy skeleton are still unknown. It is possible that supplementation with magnesium, an important mineral constituent of bone,[5,6,11,16] has a direct advantageous effect on bone formation and density. An alternative possibility is that a suboptimal magnesium status impedes intestinal calcium absorption by the mechanisms already described. We hypothesized that magnesium supplementation increases calcium absorption, thus having a possible beneficial effect on bone density. Increased calcium bioavailability is a well-recognized cause of improved bone mineral density.[1,6,14,16,17]

We now report on the effect of magnesium supplementation on ^{45}Ca intestinal absorption in women with a low erythrocyte magnesium concentration. We also monitored urinary deoxypyridinoline excretion and serum intact PTH concentrations during the 8-week study. Our results indicate that magnesium supplementation does not improve calcium absorption, and in fact, it may even be detrimental to calcium status.

SUBJECTS AND METHODS

Screening

The subjects (N = 219) screened for this trial were females over age 21 years living in the greater Pretoria area. They were screened for erythrocyte magnesium concentration as described previously.[19,20] Individuals with an erythrocyte magnesium concentration less than 1.97 mmol/L (below the 15th percentile[19,20]) were invited to participate in a second screen. Exclusion criteria included a history of diabetes mellitus, renal, liver, bone, or gastrointestinal disease, or drug or alcohol abuse. Pregnant women were also excluded. Individuals who were using any of the following medications within 3 months of initiation of the trial were excluded: any diuretics, calcium-channel blockers, intravenous heparin, warfarin, vitamin K antagonists, and vitamin supplements containing vitamin D. All subjects were required to follow their normal diet and habitual life-style for 3 months preceding the trial and throughout the trial. During the second screen, potential trial participants were tested for normal liver function (serum alkaline phosphatase < 110 U/L, gamma-glutamyl transferase < 53 U/L, aspartate aminotransferase < 35 U/L, and alanine aminotransferase < 35 U/L), renal function (serum creatinine < 110 μmol/L), and PTH concentration (10 to 65 ng/L). The erythrocyte magnesium concentration was determined

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again, and only individuals in whom erythrocyte magnesium was less than 1.97 mmol/L were eligible for entry into the study. Twenty subjects were enrolled in the trial. Informed written consent was obtained from each study subject prior to trial entry. This clinical trial was approved by the Human Ethics Committee at the University of Pretoria and was performed according to the principles described in the Declaration of Helsinki.

Clinical Trial Protocol

The trial was 8 weeks in duration and composed of 6 visits. Inasmuch as the magnesium supplement chosen for the study was an organic complex (magnesium citrate malate [MCM]), we used citrate and malate with potassium and sodium as counter cations for the control preparation. During the first 4 weeks of the trial, the participants received potassium sodium citrate malate ([PSCM] available in sachets, each containing 2.30 g $KHCO_3$, 1.94 g $NaHCO_3$, 2.06 g citric acid, and 1.41 g malic acid). During the first week, the subjects received 1 sachet of PSCM in the evening on an empty stomach; this was increased to 2 sachets per day during the second to fourth weeks of PSCM supplementation. During the fourth week, the subjects visited the consulting rooms 3 times, ie, on Monday (visit 1), Friday (visit 2), and Saturday mornings (visit 3). Spot urine and blood samples were obtained from each subject during visits 1 and 2.

Before visit 3, the subjects were required to fast from 8 PM the previous evening. They were allowed to drink distilled water supplied by the laboratory. Participants also avoided dairy products for 3 days preceding visit 3.

On the morning of visit 3, venous blood samples with heparin as anticoagulant, as well as spot urine samples, were obtained from the subjects. Unused PSCM sachets were returned and counted to assess compliance. At 8 AM, the radiolabeled calcium load (5.0 µCi [0.2 mBq] $^{45}CaCl_2$ [5.0 mL] mixed in 2.0 mL 250-mmol/L $CaCl_2$ carrier solution, diluted to 250 mL deionized water) was administered orally. The drinking vessel was rinsed with deionized distilled water, and the water was again ingested. Heparinized blood (10 mL) was collected at 0, 15, 30, 45, 60, 90, 120, 180, 300, and 420 minutes after the ^{45}Ca load. Urine was collected from 8 to 11 AM, 11 AM to 1 PM, and 1 to 3 PM.

When the subjects completed visit 3, they received 50 sachets of MCM; each sachet contained the equivalent of 125 mg elemental magnesium complexed with citric acid (2.06 g) and malic acid (1.41 g). This supplement was used in a manner identical to that described for PSCM. During the fourth week of MCM supplementation, the subjects visited the consulting rooms 3 times (visits 4 to 6) and the same procedures described for visits 1 to 3, respectively, were performed.

Preparation of the Oral Radiolabeled Calcium Loads

The volume of ^{45}Ca solution mixed with carrier solution to obtain a 5.0-µCi dose was calculated from the stated activity at day 0 as supplied by Amersham (Amersham International, Amersham, UK) and the decay constant (0.0042 mBq/d). The calculated amount of ^{45}Ca solution was added to deionized water so that the final volume of ^{45}Ca was 5.0 mL. To this, 2.0 mL 250-mmol/L $CaCl_2$ carrier solution was added. The calcium solution was allowed to equilibrate for 36 hours in the dark at room temperature. The oral ^{45}Ca doses were made in duplicate, and 1 of the doses was administered to the study subject while the other was retained for scintillation counting.

Laboratory Analyses

Equal volumes of heparinized blood and hemolysis buffer (10% Triton ×-100 and 100 mmol/L Tris hydrochloride, pH 7.2) were mixed and used to determine the erythrocyte magnesium concentration by atomic absorption spectroscopy. The remainder of the heparinized blood was then centrifuged (10 minutes at 500 × *g*), and the plasma samples were stored at −70°C until the time of analysis. The erythrocyte magnesium concentration was calculated as reported previously.[21-23] Urinary magnesium and calcium concentrations were measured using acidified (with HCl(c) to pH 1) aliquots of spot urine samples. Urinary excretion data are expressed as micromoles of mineral per millimole of creatinine.

The hematocrit was determined using a Technicon H*1 autoanalyzer (Bayer Pip-Diagnostics Division, Newbury, UK). Serum intact PTH was measured using a 2-site immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA). Urinary deoxypyridinoline excretion was estimated from nonacidified urine samples. Equal volume of the spot urine samples collected during visits 1 to 3 and visits 4 to 6, respectively, were pooled, and the deoxypyridinoline concentration in the pooled urine samples was measured by the pyrilinks D kit (Metra Biosystems, Mountain View, CA).

^{45}Ca absorption was assessed by adding 1.5 mL plasma or urine to 8.5 mL scintillation cocktail. As a control for the total oral dose, a 100-µL aliquot of each subject's duplicate oral radiolabeled calcium cocktail was added to 8.5 mL scintillation cocktail (cocktail count). A vial containing only 8.5 mL scintillation fluid was also analyzed to assess background radiation. Samples were analyzed for 10 minutes using a Beckman (Fullerton, CA) LS 5800 scintillation counter. The count for the 100-µL aliquot was multiplied by 70 to obtain a full count for the entire 7.0-mL cocktail given to the subject.

Calculations and Statistics

Determination of fractional intestinal ^{45}Ca absorption. The fractional intestinal absorption of ^{45}Ca (f), adjusted for body mass, was calculated for each post–calcium load sample as follows[24]: $f = 0.15 \times BM \times (1{,}000/1.5) \times [(CPM_S\text{-}CPM_B)/(70 \times MCC)]$, where BM represents the body mass (kilograms) of the subject, CPM_S represents the CPM of the sample, CPM_B represents the CPM of the background (scintillation cocktail only), and MCC represents the mean cocktail count. The dose per liter of plasma was multiplied by 0.15 times the body weight to obtain an approximate value for the fraction of the oral dose circulating in the plasma and extracellular fluid.[24]

Total ^{45}Ca absorption was expressed as the area under the curve (AUC) of a plot of f versus time for each subject using $AUC = ½[(f_1 \times t_1) + (f_1 + f_2)(t_2 - t_1) + \ldots\ldots + (f_9 + f_{10})(t_{10} - t_9)]$, where t_1 represents 0 minutes, t_{10} represents 420 minutes, f_1 represents the fraction of the oral dose at t_1, and f_{10} represents the fraction of the oral dose at t_{10}.

Assessment of urinary ^{45}Ca excretion. The fractional urinary excretion of ^{45}Ca (fu) was determined using the equation $fu = \{[\text{urine volume (mL)} \times (CPM_{SU} - CPM_{BU})/1.5] \times 100\} \div \{MCC \times 70\}$, where CPM_{BU} and CPM_{SU} represent the CPM of the spot (basal) urine collection and the collected urine sample, respectively, while MCC represents the mean cocktail count. The basal urine sample had an fu value of zero. Total ^{45}Ca urinary excretion was then calculated using AUC analysis.

Statistics. The 2-tailed *t* test was used to assess the statistical significance of differences between AUC results for each supplementation period. For urinary deoxypyridinoline excretion, results were expressed as nanomoles of deoxypyridinoline per millimole of creatinine. Statistical significance was determined using the paired *t* test because equal aliquots of the deoxypyridinoline specimens were pooled before analysis. ANOVA was used to assess the statistical significance of changes in serum intact PTH, erythrocyte and plasma magnesium, and urinary calcium concentrations because 3 separate observations per treatment period were made for each of these analytes.

RESULTS

The mean age of the subjects was 39.2 ± 9.2 years, and the mean body mass was 64.4 ± 11.2 kg (mean ± SD). Compliance

Table 1. Parameters of Magnesium Status During PSCM (visits 1 to 3) and MCM (visits 4 to 6) Supplementation Periods

Parameter	PSCM	MCM	Statistical Significance (*P*)
E[Mg^{2+}] (mmol/L)	1.90 ± 0.18	1.93 ± 0.14	NS
PL[Mg^{2+}] (mmol/L)	0.75 ± 0.07	0.79 ± 0.06	<.001
U[Mg^{2+}] (μmol/mmol)*	257.96 ± 86.0	347.03 ± 139.76	.005

NOTE. Results are the mean ± SD. ANOVA was used since 3 observations were made on each subject during each of the 2 supplementation periods.

Abbreviations: NS, not significant; E[Mg^{2+}], PL[Mg^{2+}], and U[Mg^{2+}], erythrocyte, plasma, and urinary magnesium concentration, respectively.

*Expressed as μmol magnesium per mmol creatinine.

for supplement use was 99.3% ± 3.1% and 99.4% ± 3.8% for control and magnesium supplementation, respectively.

Table 1 shows the magnesium status of the subjects during each supplementation period. No statistically significant changes were noted for erythrocyte magnesium concentrations; however, magnesium supplementation resulted in statistically significant increases in the plasma magnesium concentration ($P < .001$) and urinary magnesium excretion ($P < .005$).

No statistically significant changes in the fasting serum intact PTH concentration, urinary deoxypyridinoline, urinary fractional ^{45}Ca (expressed as the AUC), or urinary calcium excretion were noted (Table 2). However, fractional ^{45}Ca absorption, expressed as the mean AUC, was 23.5% lower ($P < .001$) when the effect of magnesium supplementation was compared with the control preparation (Table 2 and Fig 1).

The mean radioactivity of the ^{45}Ca cocktails used with control and magnesium supplementation was 157,018 ± 1,519 per 100 μL and 155,932 ± 1,631 per 100 μL, respectively. This difference was not statistically significant.

DISCUSSION

The magnesium supplement chosen for this clinical trial has been shown to be bioavailable previously.[10] The difference between the MCM used in this trial and the formulation used previously is the calcium content. While our formulation contained less than 15 mg elemental calcium per 250-mg elemental magnesium dose, the formulation used by Ubbink et al[10] contained 500 mg elemental calcium per 250-mg elemental magnesium dose. However, Table 2 shows that the erythrocyte magnesium concentration remained unchanged as a result of magnesium supplementation. In contrast, the plasma magnesium concentration and urinary magnesium excretion increased as a result of magnesium supplementation. This confirms prior observations that erythrocyte magnesium concentrations do not respond to magnesium supplementation.[19,25,26] However, the plasma and urinary magnesium levels suggest that the magnesium status of the subjects improved significantly.

Table 2. Effect of Placebo (PSCM) and Magnesium (MCM) on Serum Intact PTH, Urinary Deoxypyridinoline and Calcium Excretion, and Fractional Intestinal $^{45}CaCl_2$ Absorption

Variable	Placebo (PSCM)	Magnesium (MCM)	Statistical Significance (*P*)
Serum iPTH (ng/L)	34.0 ± 12.4	33.0 ± 11.8	NS, ANOVA
Urinary Dpd (nmol/mmol)*	6.44 ± 1.64	6.75 ± 1.61	NS, paired *t* test
Urinary [Ca^{2+}] (mol/mmol)†	201.45 ± 94.0	237.97 ± 146.46	NS, ANOVA
Urinary $^{45}CaCl_2$ AUC (fu × time, min)	78.95 ± 46.71	76.30 ± 39.49	NS, 2-tailed *t* test
$^{45}CaCl_2$ AUC (f × time, min)	408.64 ± 66.12	312.46 ± 72.32	<.001, 2-tailed *t* test

NOTE. Results are the mean ± SD.

Abbreviations: NS, not significant; Dpd, deoxypyridinoline.

*Expressed as nmol deoxypyridinoline per mmol creatinine (in pooled specimens).

†Expressed as μmol calcium per mmol creatinine.

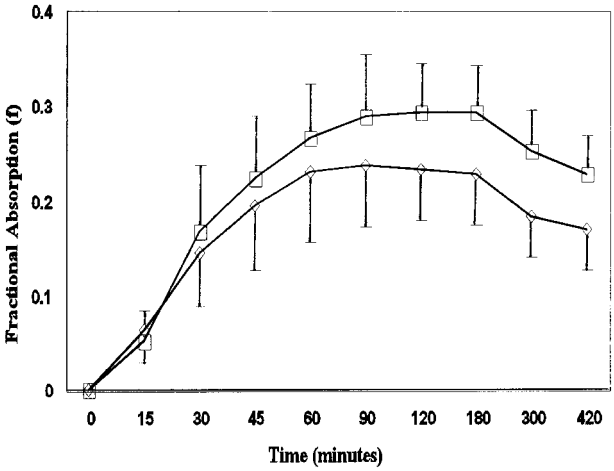

Fig 1. Fraction of $^{45}CaCl_2$ (% oral dose) in plasma over time after control (PSCM, □) and magnesium (MCM, ◇) supplementation. Error bars denote 1 SD.

The results of the ^{45}Ca loads indicate a statistically significant ($P < .001$) decrease in the intestinal absorption of ^{45}Ca as a result of MCM supplementation (Table 2). This was unexpected. In fact, we hypothesized that magnesium supplementation would correct any subclinical magnesium deficiency, and thus would allow for increased intestinal absorption of ^{45}Ca. The explanation for our results is uncertain. We excluded possible direct competition between calcium and magnesium absorption, since the last magnesium dose was taken 12 hours before the ^{45}Ca dose was given. The ileum is the predominant site of magnesium absorption,[27] while calcium is absorbed primarily in the duodenum.[28] Intestinal magnesium absorption is mediated by a saturable carrier and by passive diffusion.[29,30] The carrier mediates magnesium absorption when magnesium intake is normal or slightly elevated,[29,31] while passive diffusion occurs when magnesium intake is moderately or greatly increased.[29,31] Fine et al[29] found that increasing the dietary magnesium intake had no effect on calcium absorption, suggesting that magnesium does not inhibit active or passive calcium absorption.

Spencer et al[28] assessed the effect of magnesium supplementation on the fractional absorption of $^{47}CaCl_2$ during low (241 mg/d) and normal (812 mg/d) calcium intake. No change in the intestinal absorption of $^{47}CaCl_2$ was noted as a result of magnesium supplementation at either of the 2 levels of calcium

intake. The reason for the discrepancy between these data and our results is unclear. Spencer et al used only 5 subjects and did not integrate serum ^{47}Ca values over their study period. We suggest that plasma ^{45}Ca integrated over 7 hours, as in our study, is a more reliable indicator of calcium absorption.

A possible effect caused by different ^{45}Ca doses was ruled out by taking radioactive decay into account when preparing the doses. Indeed, no statistical difference between the ^{45}Ca loads during visits 3 and 6 was noted. Furthermore, the fractional intestinal absorption of ^{45}Ca (f value) was expressed as a fraction of the oral dose, thus excluding any dose-related effects.

Although we considered time-related effects as an unlikely explanation for our results, these should be considered because a randomized crossover study design was not used. The reasons for not using the latter study design include (1) uncertainty about the duration of the washout period required after magnesium supplementation and (2) the relatively short half-life of ^{45}Ca. Furthermore, the use of the radioisotope prohibited multiple calcium-load tests during control and magnesium supplementation periods. Future studies using stable calcium isotopes will be required to assess the effect of magnesium supplementation on calcium bioavailability.

Altered PTH concentrations do not explain the reduced fractional calcium absorption following magnesium supplementation, because serum intact PTH levels did not change significantly during the study period (Table 2). Vitamin D status also affects calcium absorption, but calcitriol concentrations were not measured in this study. However, it has been shown that magnesium deprivation is often associated with a low production of 1,25-dihydroxyvitamin D.[32] Thus, calcitriol synthesis and the fractional absorption of ^{45}Ca would be expected to increase with magnesium supplementation. However, our results contradict this.

We were unable to obtain evidence to support the notion that magnesium per se affects bone resorption. Urinary deoxypyridinoline and calcium excretion showed no statistically significant changes as a result of magnesium supplementation (Table 2). Urinary deoxypyridinoline excretion decreased in subjects supplemented with a combined magnesium/calcium supplement (magnesium citrate calcium malate),[10] and our current results suggest that this decline was due to the calcium content of the preparation used rather than the actions of magnesium. No statistically significant changes in the urinary excretion of calcium were observed as a result of MCM supplementation.

In conclusion, our results indicate that magnesium supplementation does not enhance the bioavailability of calcium from the intestinal tract in healthy subjects, but may result in less calcium absorption. The effect of magnesium supplements, which have become popular over-the-counter products, on long-term prophylactic calcium therapy requires further investigation.

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