Brief Critical Reviews

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Magnesium Supplementation and Osteoporosis

Among other things, magnesium regulates active calcium transport. As a result, there has been a growing interest in the role of magnesium (Mg) in bone metabolism. A group of menopausal women were given magnesium hydroxide to assess the effects of magnesium on bone density. At the end of the 2-year study, magnesium therapy appears to have prevented fractures and resulted in a significant increase in bone density.

The incidence and morbidity associated with osteoporosis is increasing worldwide. If current trends continue, there will be an estimated 500,000 fractures of the hip per year in the United States by the end of the century.[1] Despite a commensurate increase in scientific attention, a clear understanding of the pathophysiology of the various forms of osteoporosis has not yet been reached. Women with postmenopausal osteoporosis have significantly decreased levels of the nutrition markers transferrin, prealbumin, retinol-binding protein, and fibronectin compared to age-matched controls, providing evidence that osteoporosis is associated with a nutritional deficiency.[2]

Of the many nutrients important to maintain healthy bone, calcium has received the most attention. Cumming[3] used meta-analysis to test the strength of the published literature on calcium and bone mass in adult women. Forty-nine separate studies were published between 1986 and 1989 that met the inclusion requirements of (1) adult women with reported bone mass measurements (2) assignment of calcium supplement by the investigators and (3) a control group in intervention studies. Cross-sectional studies showed a small positive correlation between calcium intake and bone mass with the summary mean correlation coefficient being greater for premenopausal women (0.18) than for postmenopausal women (0.04). Although longitudinal studies provided diverse results, women with mean age in the 50s showed an overall improvement of 0.8% bone mass per year with calcium intervention. Based on this result, the author speculated that up to half of the women who take calcium supplements might prevent the usual 2% loss in bone per year that occurs with aging, and that high calcium intake could benefit women in their early postmenopausal years.[3] An additional intervention study has shown that calcium supplementation at a dose of 1000 mg/day significantly slowed appendicular bone loss in normal postmenopausal women.[4]

Although decreased bone mass is the hallmark of osteoporosis, qualitative changes in bone matrix are also present, which could result in fragile or brittle bones that are more susceptible to fracture.[5] Because brittle bones cannot be detected by routine bone mineral density measurements,[6] brittleness has not been well characterized in osteoporotic bone. There is growing evidence that magnesium may be an important factor in the qualitative changes of the bone matrix that determine bone fragility.

The importance of magnesium in skeletal metabolism and calcium regulation has been previously reviewed.[7–9] Magnesium is present in bone in macromineral quantities, comprising 0.5–1% of bone ash. Magnesium influences both matrix and mineral metabolism in bone, and magnesium depletion causes cessation of bone growth, decreased osteoblastic and osteoclastic activity, osteopenia, and bone fragility.[10] Magnesium prevents bone fragility by destabilizing hydroxyapatite crystals, and acts synergistically with ATP to stabilize amorphous calcium phosphate and prevent hydroxyapatite formation.[10] As the magnesium content of apatite decreases, the crystal size increases.[11] Thus, bone mineral with decreased magnesium content results in larger and more perfect bone mineral crystals, which may be more brittle than more amorphous crystals. Trabecular bone from osteoporotic women has a reduced magnesium content and larger bone crystal formation than controls.[12–14] Magnesium depletion, as determined by an increased retention of an intravenous magnesium load, may be observed in people with osteoporosis.[12–14] Some reports have found decreased magnesium content in the trabecular bone of osteoporotic subjects[15,16] but increased or normal magnesium levels in cortical bone samples.[17–19]

Adequate serum magnesium levels are necessary for proper calcium metabolism since hypomagnesemia can result in hypocalcemia,[20] peripheral resistance to the effects of vitamin D,[21] and resis-

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Table 1. Trabecular Bone Density in the Subject Subgroups and Controls

	Mean	SD	*n*	Range	95th CI for the Mean	*p*-value
Responders						
BD1	1.08	0.04	22	1.02–1.18	1.063–1.097	
BD2	1.11	0.04	22	1.02–1.20	1.093–1.127	<0.001
BD3	1.12	0.02	6	1.10–1.15	1.104–1.136	<0.02
Stationary						
BD1	1.12	0.03	5	1.07–1.15	1.094–1.146	
BD2	1.11	0.03	5	1.07–1.15	1.084–1.136	NS
BD3	1.09	0.03	3	1.07–1.12	1.056–1.124	NS
Nonresponders						
BD1	1.10	0.04	4	1.07–1.15	1.061–1.139	
BD2	1.07	0.04	4	1.02–1.12	1.031–1.109	0.01
BD3	1.08	—	1	—	—	
Controls						
BD1	1.15	0.03	23	1.08–1.19	1.138–1.162	<0.001
BD2	1.14	0.03	23	1.07–1.19	1.128–1.52	

Reference value for trabecular bone density: ≤1.19 g/cm^3. BD1 = initial measurement, BD2 = after 1 year, BD3 = after 2 years. NS: nonsignificant. *p* = probability of statistical difference by Student's paired *t*-test.

tance to parathyroid hormone (PTH).[22] Thus, adequate calcium intake may not ensure proper bone health if magnesium status is abnormal.

There is other circumstantial evidence that also points to a link between magnesium and osteoporosis. For example, dietary intake studies consistently show intakes of magnesium to be below the Recommended Dietary Allowances (RDAs) in many age groups,[23–25] so that large numbers of individuals may be at risk for magnesium deficiency. Conditions such as alcoholism, which are associated with magnesium wasting and chronic magnesium deficiency, are often associated with an increased prevalence of osteoporosis.[26] Magnesium-deficient rats manifest reduced bone formation and osteoclastic bone resorption.[27] Interestingly, estrogen replacement therapy, which is the most effective means of preventing Type I osteoporosis in women,[28] also results in increased bone and soft tissue magnesium levels.[29]

With this degree of supporting evidence, it is curious that magnesium supplementation has not been examined more frequently in studies of osteoporosis. Abraham and Grewal[30] did administer magnesium to postmenopausal women with good results, but it is difficult to draw conclusions as the subjects also received estrogen as well as numerous other dietary supplements.

Stendig-Lindberg et al.[31] reported the effect of oral magnesium supplementation in a 2-year controlled trial of women with documented osteoporosis. Thirty-one postmenopausal, osteoporitic women were enrolled in a prospective, 2-year controlled therapeutic trial and were treated with magnesium supplements (magnesium hydroxide tablets). The bone density of the ultradistal radius was measured via Comptom bone densitometry and was initially below the normal reference range minimum of 1.19 g/cm^3. All subjects had complained of chronic back pain, 55% had radiographic evidence of osteoporosis, 13% had pre-existing compression fractures, 97% had osteoarthritis of the spinal cord, and 55% had some degree of spinal deformity. Twenty-three age-matched, symptom-free, postmenopausal, osteoporotic women (bone density <1.19 g/cm^3) served as untreated controls. Treatment started with 250 mg daily, and dosages were then increased or decreased depending on individual tolerance levels to a maximum of 750 mg magnesium daily for the first 6 months. From 6 to 24 months, all subjects consumed 250 mg as a maintenance amount. Calculated dietary Mg intake during the study was estimated to be between 200 and 300 mg/day.

There were no reported side effects of the treatment, although only 32% of the subjects (n = 10) completed the entire 2-year trial. The mean trabecular bone density in treated patients showed a significant percent increase after the first year of treatment, with no change in density between the first and second year (Table 1). Seventy-one percent (responders, n = 22) of the treatment group responded with an increase in percent bone density after 1 year of treatment. In another 16% of the treatment group (stationary, n = 5), there was no change in bone density after this period, while four subjects (nonresponders) showed decreased bone density and were subsequently found to have endocrine disor-

ders. In the control group, there was a negative percent difference in bone density between baseline and 1 year. Magnesium supplementation significantly increased blood and urinary magnesium.

Critical evaluation of this study reveals several deficiencies. The average bone density of all the treatment groups was lower than that of the controls. The effect of intervention could be more effectively determined if the population of women were initially randomized by baseline bone density measurements. Study subjects were self-selected as they presented with complaints of back pain and may not be representative of the general population of women with postmenopausal osteoporosis. The initial group sizes were small, and the extremely small numbers that remained in the second year make interpretation of the results past the first 12 months problematic. Reproductive histories were not included. As bone loss is greater in the first 10 years after menopause and then decreases without intervention, it is important to know how recently the study subjects had undergone menopause. The methodology used by these researchers to measure bone density of the distal radius is comparable to other measures at this site, but the authors have not demonstrated that distal radius bone density reflects pelvic or spinal column densities. The finding that magnesium supplementation actually caused increased bone density rather than a stabilization of existing bone density is noteworthy. This has not been a finding of either calcium or estrogen intervention trials. It is possible that the first-year changes were a bone-remodeling transient and not a permanent effect.[32] Despite these drawbacks however, the authors' conclusion that magnesium therapy in postmenopausal women warrants further study certainly appears valid.

Three conclusions can be drawn from the work of Stendig-Lindberg et al. First, continued research to elucidate magnesium's role in bone metabolism and calcium–magnesium interactions is necessary. Second, magnesium intake should be measured when conducting studies investigating the importance of nutrients on the prevention or treatment of osteoporosis. And third, additional clinical therapeutic trails should be performed that vigorously evaluate magnesium as a potential treatment for postmenopausal osteoporosis.

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Hepatic Amino Acid Transport Primary to the Urea Cycle in Regulation of Biologic Neutrality

A biologic determination appears to be made as to whether the nitrogenous portion of food amino acids reaches the kidney for excretion as ammonium ion, or whether it is sent to the liver to form urea. It now becomes likely that this determination occurs primarily by hydrogen ion inhibition of at least one transport system by which the liver receives amino acids, and not by regulation applied directly to the liver-ornithine cycle.

During the last decade physiologists have argued that the liver may be more important than the kidneys in maintaining acid-base homeostasis. Figure 1 illustrates the question of whether the hepatic urea cycle is slowed during acidosis by its inhibition of the entry of bicarbonate and ammonium ions into the ornithine cycle (site 1) or by inhibition of amino acid transport across hepatocyte plasma membranes (site 2).[1] This in vivo testing was stimulated by earlier results of Boon and Meijer.[2] They showed that lowering the pH of a physiologic mixture of amino acids in isolated rat hepatocytes inhibited urea formation, by slowing production of the ammonium ion rather than by inhibiting its entry into the ornithine cycle.

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In vivo support of their hypothesis has now been obtained in adult rats[1] maintained at body temperature of 37°C under prolonged pentobarbital anesthesia. Acute metabolic acidosis or alkalosis was induced by infusion of either HCl or $NaHCO_3$ at 0.15 M in amounts of approximately 1.8 mmol in 3 hours. The abdomen was opened and blood samples were taken sequentially from portal vein, hepatic vein, and in some animals, from the aorta for pH determination. The liver was removed and frozen in liquid nitrogen. Plasma was separated, and amino acids were measured on a chromatographic amino acid analyzer. The liver samples were pulverized in liquid nitrogen, the protein precipitated with sulfosalicylic acid, and the amino acids and ammonia determined on aliquot portions. Protein and DNA content per g/liver were also determined. Urinary urea and ammonia were determined after perchloric acid deproteinization.

Mean portal blood pH values were 7.13 in acidosis and 7.66 in alkalosis. Urinary ammonia excretions in mmol/hour were 201 ± 42 in acidosis and 23 ± 9 in alkalosis; urea excretion rates were correspondingly 434 ± 52 and 680 ± 94. As indicated by hepatic vein/portal vein differences, the hepatic uptake of alanine, quantitatively dominant in degradation by the liver, was 15% in acidosis and 52% in alkalosis. Extractions of glycine and several other amino acids were significantly lower in acidosis than in alkalosis, and the total amino acid extraction was 55% lower in acidosis than in alkalosis. For these reasons, the concentration of amino acids leaving the liver in the hepatic vein were higher in