

# Low dietary magnesium increases supraventricular ectopy<sup>1-4</sup>

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## ABSTRACT

**Background:** Magnesium has been suggested to be beneficial in counteracting all phases of the processes that lead to ischemic heart disease, including terminal events such as arrhythmia and sudden death.

**Objective:** We tested the hypothesis that an intake of magnesium considerably below the recommended dietary allowance can produce chemical and physiologic evidence of depletion.

**Design:** Twenty-two postmenopausal women were maintained in a metabolic unit and ate a diet of conventional foods containing less than one-half of or more than the recommended dietary allowance for magnesium (320 mg/d). Dietary assignments were random and double blind in a crossover design. Magnesium concentrations were measured by spectroscopy and ion-specific electrolyte analysis, and Holter electrocardiograms lasting  $\approx 21$  h were recorded.

**Results:** Magnesium concentrations in erythrocytes, serum (total and ultrafilterable), and urine were significantly lower when dietary magnesium was lower. Holter monitors showed a significant increase in both supraventricular and supraventricular plus ventricular beats when the dietary magnesium concentration was low. Hypomagnesemia, hypocalcemia, and hypokalemia were not found.

**Conclusions:** The magnesium requirement was defined with the use of biochemical and electrophysiologic criteria. The recommended dietary allowance of 320 mg/d seems correct; 130 mg is too little. Persons who live in soft water areas, who use diuretics, or who are predisposed to magnesium loss or ectopic beats may require more dietary magnesium than would others. *Am J Clin Nutr* 2002;75:550-4.

**KEY WORDS** Dietary requirements, ectopy, Holter monitor, soft water, magnesium, postmenopausal women, ischemic heart disease, arrhythmia, ectopic beats

## INTRODUCTION

Magnesium has been suggested to be beneficial in counteracting all phases of the harmful processes that lead to death from ischemic heart disease. For example, Selye (1, 2) mentioned magnesium as being protective against experimental cardiopathies. Seelig and Heggtveit (3) summarized some plausible mechanisms by which magnesium protects against cardiopathies. Hellerstein et al (4) found that a low-magnesium diet sometimes contributed to the production of aortic lipidosis in rats fed an atherogenic diet. Elin and Hosseini (5) suggested that magne-

sium may protect Seventh-day Adventists who eat nuts regularly from coronary heart disease. Chipperfield and Chipperfield (6) found less magnesium in the uninfarcted heart muscle of persons who died suddenly than in the heart muscle of healthy control subjects. Their data were related to the "water factor": ie, the risk of ischemic heart disease is higher where the drinking water is soft and lower where the drinking water is hard (7, 8). There is a high correlation between the magnesium content of water and the hardness of the water ( $r = 0.90$ ) (9, 10). Other studies showed that intravenous magnesium seems beneficial in reducing the risk of arrhythmias immediately after myocardial infarction (11-15). More recent research on the possible benefits of magnesium in ischemic heart disease was directed toward cardiac electrophysiology (16-19) and the balance between supply and demand of the myocardium for oxygen (20).

According to Shils (21), magnesium deficiency in animals and people is accompanied by a variety of undesirable changes in neuromuscular function such as muscle fasciculations and spasm, tremor, tetany, and convulsions. Chvostek and Trousseau signs sometimes are present. Generally, these changes are associated with hypomagnesemia, which also can be associated with hypocalcemia and hypokalemia. Serum magnesium concentration may not be a good indicator of systemic magnesium depletion (21-23); indeed, there are no reliable noninvasive techniques for determining magnesium status (24). Hypomagnesemia can increase the risk of supraventricular and ventricular arrhythmias, including ventricular tachycardia and ventricular fibrillation (25).

The recommended dietary allowance (RDA) for magnesium for women has been increased from 280 to 320 mg/d (and to >400 mg/d for men) (24, 26). These values are based on balance data and usual intakes of the US population. Magnesium intakes of women often are below the RDA (27). Committees

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**TABLE 1**  
Composition of the diet<sup>1</sup>

Menus	Weight
	g
Day 1	
Breakfast	
Orange drink mix <sup>2</sup>	25
Canadian bacon croissant	100
Shredded Cheddar cheese	30
Lunch	
Carbonated citrus drink <sup>3</sup>	240
Ham and broccoli casserole	135
Cottage cheese, 2% fat	80
Cherry crisp	75
Dinner	
Lemonade	275
Chicken and rice casserole	286
Lettuce salad	60
Ranch dressing	25
Sugar cookie	30
Vanilla frosting	15
Snack	
Cheesecake	70
Mandarin oranges	30
Day 2	
Breakfast	
Cranapple drink	135
Ham and cheese omelet	115
English muffin	30
Margarine	5
Lunch	
Carbonated citrus drink	250
Pepperoni pizza	145
Lettuce salad	60
French dressing	20
Sugar cookie	30
Dinner	
Lemonade	275
Beef stew	246
Cottage cheese, 2% fat	80
Peach slices	40
Angel cake	45
Vanilla frosting	15
Snack	
Strawberry Jell-O <sup>4</sup>	120
Strawberries	40
Vanilla wafers	30
Day 3	
Breakfast	
Orange drink mix	25
Cornflakes	30
Nondairy creamer	120
Sugar	5
Croissant	30
Strawberry jelly	15
Lunch	
Carbonated citrus drink	240
Beef soft-shell taco	172
Sour cream	15
Taco sauce	15
Peach cobbler	78
Dinner	
Lemonade	225
Chicken burger	140

(Continued)

**TABLE 1 (Continued)**

Hamburger bun	40
Lettuce leaf	10
Mayonnaise	5
Tomato soup	120
Vanilla wafers	25
Snack	
Lemon pudding	100
Whipped topping <sup>5</sup>	10

<sup>1</sup>Weights include demineralized water used in recipes. The daily diet was calculated to contain 255 g carbohydrate, 78 g fat, and 74 g protein per 8.4 MJ (2000 kcal). Supplements of manganese and zinc (as sulfates), iron and potassium (as gluconates), and vitamin D<sub>3</sub> were added daily to ensure dietary adequacy.

<sup>2</sup>Dry mix, demineralized water added (Tang; Kraft Foods, Inc, Rye Brook, NY).

<sup>3</sup>7-Up; Dr Pepper/Seven Up, Inc, Plano, TX.

<sup>4</sup>Kraft Foods, Inc.

<sup>5</sup>Cool Whip; Kraft Foods, Inc.

that set RDAs generally err on the side of generosity (24), introducing a safety factor over requirements so that recommendations are adequate for practically all healthy persons.

We are engaged in long-standing research on measurements of mineral requirements to develop dietary recommendations to prevent disease, promote health, and allow optimal function throughout life. Thus, it is necessary to compare responses to lower and higher nutrient intakes. We tested the hypothesis that an intake of magnesium considerably below the RDA can produce both chemical and physiologic evidence of depletion. It seemed prudent and desirable to include frequent measurements of neuromuscular and cardiovascular functions in an experiment with 2 intakes of magnesium so that both safety and science could be served. This work is the only measurement of the magnesium requirement of healthy persons; it was planned and most data were collected before the recent RDA revision.

## SUBJECTS AND METHODS

Twenty-nine healthy, postmenopausal women aged 47–78 y ( $\bar{x} \pm \text{SD}$ : 64.7  $\pm$  8.4 y) were admitted to the study after medical, psychological, and nutritional evaluations established that they had no underlying disease and were emotionally suited for the project. They were informed in detail of the nature of the research and associated risks. Protocols were approved by the Institutional Review Boards of the University of North Dakota and the US Department of Agriculture and followed the guidelines of the US Department of Health and Human Services and the Helsinki Declaration of 1975 as revised in 1983.

The women were maintained in a metabolic unit in groups of 15 and 14 and were under close supervision for  $\approx$ 6 mo. Because dietary magnesium and copper are highly correlated (28), a diet designed to be low in magnesium also will be low in copper. Preliminary estimates made before the study began showed that the study diet (Table 1) was low in copper and magnesium, <1 and 100 mg/d, respectively, per 8.4 MJ. During a 10-d equilibration period, the diet was supplemented with 1.0 mg Cu and 200 mg Mg daily. During this period the women were assigned to 2 dietary groups in a random, double-blind, crossover design. According to group assignment, the women were then given the study diet either without a magnesium supplement (placebo) or

**TABLE 2**  
Magnesium measurements<sup>1</sup>

	Lower-magnesium diet	Higher-magnesium diet	Normal range
Serum (mmol/L)	0.83 ± 0.007	0.86 ± 0.007 <sup>2</sup>	0.66–1.23
Erythrocyte (μmol/g Hb)	6.01 ± 0.058	6.21 ± 0.058 <sup>3</sup>	3.6–6.1
Ultrafilterable (mmol/L)	0.57 ± 0.003	0.59 ± 0.003 <sup>4</sup>	0.45–0.66
Urine (mmol/d)	2.88 ± 0.12	5.68 ± 0.12 <sup>5</sup>	3.0–5.0

<sup>1</sup> $\bar{x} \pm \text{SEM}$ ;  $n = 22$ . Chemical analysis showed mean magnesium intakes of 130 or 411 mg/d. Hb, hemoglobin.

<sup>2-5</sup>Significantly different from lower-magnesium diet (repeated-measures ANOVA): <sup>2</sup> $P < 0.005$ , <sup>3</sup> $P < 0.025$ , <sup>4</sup> $P < 0.030$ , <sup>5</sup> $P < 0.0001$ .

with a magnesium supplement for 81 d. Then, women receiving the unsupplemented diet received the supplemented diet and vice versa for 81 more days. Diets of one-half of the women were supplemented with 1 mg/d Cu and the rest with 3 mg/d Cu throughout the 162 d, with no crossover. Magnesium was supplemented as magnesium gluconate capsules (Willner Chemists, Inc, New York) in divided doses with meals, and copper was added as copper sulfate in juice. Placebo capsules contained lactose (Gallipot, Inc, St Paul).

Diets were weighed carefully and were eaten completely (without any extra foods) in a 3-d rotation. The dietary intake of each subject was based on energy needs, as calculated by the Harris and Benedict equation (29), plus an additional 50% of basal energy expenditure for normal activity. During the study, energy intakes were adjusted to maintain body weight to within ±2% of admission weight by adjusting the amount of the basal diet in 837-kJ (200-kcal) increments.

Copper and magnesium in 6-d composites of diets were measured by inductively coupled argon plasma emission spectroscopy (ICAP; Perkin-Elmer, Norwalk, CT) after wet digestion of aliquots of freeze-dried material with nitric and perchloric acids (30). Urinary copper, magnesium, and calcium were determined by ICAP analysis of a diluted urine aliquot; values for the last 3 balance periods for each diet were averaged.

Blood was drawn into plastic syringes from an antecubital vein, which had been made visible by temporary use of a tourniquet, after the subjects had fasted for 10 h. Aliquots were processed within 90 min of the time the blood was drawn. Serum magnesium and calcium concentrations were determined by flame atomic absorption spectrophotometry after dilution 50-fold with an acidic lanthanum chloride diluent (31). Potassium, ionized calcium, and ionized magnesium were determined in heparinized plasma by using a NOVA CRT 8+ electrolyte analyzer (Nova Biomedical, Waltham, NJ). Serum ultrafilterable magnesium samples were prepared by using an Amicon MPS-1 filter system (Amicon, Inc, Beverly, MA) and a procedure described by D'Costa and Cheng (32). The magnesium content of the ultrafiltrate was determined by ICAP analysis (30). Parathyroid hormone in serum was determined by radioimmunoassay (Inctar, Stillwater, MN). Blood values are the mean of 2 values measured within 2 wk of the end of each dietary period.

Holter electrocardiograms were recorded with increasing frequency near the end of each dietary period (Del Mar Avionics, Irvine, CA). Data from the last 3 recordings evaluated by computerized scoring at the end of each dietary period were analyzed by repeated-measures analysis of variance after square root transformation (33). Chvostek and Trousseau signs were sought by, respectively, gently tapping the subject's cheek superficially over the facial nerve for 1–2 s and examining the subject's hand

after her arm was encased in a sphygmomanometer cuff inflated to 10 mm Hg higher than systolic blood pressure for 2 min.

Although the intakes of copper were greater than the highest intake proved insufficient for women (34), all cardiograms were examined for ventricular premature discharges and heart block because these changes have been detected in copper depletion studies (35, 36). If ventricular discharges were found to be 4-fold higher than the higher number found on 2 recordings during the equilibration period, copper supplements were given to women consuming 1 mg Cu/d because Velebit et al (37) found this increase to be evidence of aggravation of arrhythmias. Institutional review boards and volunteers had been promised copper supplements under these circumstances.

Statistical analysis was by repeated-measures analysis of variance (33).

## RESULTS

Replicate analysis of a total diet standard reference material (Total Diet SRM#1548; National Institute of Standards and Technology, Gaithersburg, MD) ( $n = 6$ ) yielded values of  $2.6 \pm 0.14$  and  $550 \pm 16 \mu\text{g/g}$  ( $\bar{x} \pm \text{SD}$ ) compared with certified values of 2.3–2.9 and 540–572  $\mu\text{g/g}$  for copper and magnesium, respectively, and concurrent analysis of a diet pool ( $n = 11$ ) yielded values of  $0.76 \pm 0.06 \mu\text{g/g}$  and  $0.26 \pm 0.02 \text{ mg/g}$  compared with the expected ranges of 0.63–0.83  $\mu\text{g/g}$  and 0.23–0.30 mg/g for copper and magnesium, respectively. Direct chemical analysis determined that the women's mean, daily dietary magnesium intakes were 130 mg with the deficient diet and 411 mg with the supplemented diet.

Twenty-two women completed the 172-d study and contributed to the means mentioned in the text and tables. Three women resigned and 4 in the group receiving the lower amount of dietary copper were supplemented with extra dietary copper because of new cardiographic findings resembling those found in studies of copper depletion. One woman had a right bundle branch block, 1 woman had a few episodes of ventricular ectopy and atrioventricular dissociation, and 2 women had a >4-fold increase in ventricular discharges (to a maximum of 30 and 238 per 21 h). No one else in the study exhibited either heart block or a 4-fold increase in ventricular discharges. Neither feeding sequence nor copper effects were significant ( $P > 0.1$ ).

Because the results were unaffected by dietary copper and by the sequence of the different intakes of magnesium, according to analysis of variance, data are presented only as to the intake of magnesium. Serum magnesium concentrations were significantly lower when the amount of magnesium in the diet was lower (Table 2) (3.5%), as were concentrations of erythrocyte magnesium (3.3%) and ultrafilterable magnesium in serum (4.2%). Inferences about erythrocyte magnesium were unaffected when

**TABLE 3**Ectopy<sup>1</sup>

	Lower-magnesium diet	Higher-magnesium diet
	% of beats	
Supraventricular beats	0.074 (0.034–0.128)	0.042 (0.014–0.085) <sup>2</sup>
Ventricular beats	0.125 (0.038–0.262)	0.073 (0.012–0.184)
Sum of above	0.274 (0.139–0.453)	0.160 (0.063–0.303) <sup>3</sup>

<sup>1</sup>Mean; range in parentheses based on the means  $\pm$  one pooled SD before data were back-transformed from square roots to percentage beats.  $n = 22$ .

<sup>2,3</sup>Significantly different from lower-magnesium diet (repeated-measures ANOVA): <sup>2</sup> $P < 0.020$ , <sup>3</sup> $P < 0.015$ .

the results were expressed per unit of cells or packed cells instead of per unit of hemoglobin. Urinary magnesium concentrations were 49% lower when the amount of magnesium in the diet was lower. No significant changes were noted in potassium, ionized calcium, or ionized magnesium concentrations in plasma or in serum calcium or parathyroid hormone. Neither Chvostek nor Trousseau sign was positive in any of 25 weekly examinations. Daily loss of magnesium via feces and urine exceeded dietary intake by 3.9 mmol (94 mg) ( $P = 0.0001$ ) when the amount of dietary magnesium was low (data not shown).

Holter electrocardiograms were recorded for a mean of  $20.7 \pm 0.87$  h and  $84990 \pm 10595$  heartbeats. Data on ectopy are summarized in **Table 3**. Supraventricular beats were more frequent when dietary magnesium was low. Although the increase in ventricular ectopy was not significant, the sum of supraventricular plus ventricular beats was significantly higher when dietary magnesium was low. One woman had one episode of 4 consecutive ventricular beats. No other ventricular tachycardia or ventricular fibrillation was detected during 130 recordings.

## DISCUSSION

The diet used in this study was both ordinary and apparently adequate. Its inadequacy in magnesium was shown by biochemical and physiologic changes. Restriction of magnesium intake resulted in decreased urinary loss, as reported by Shils (21), who mentions low urinary magnesium as an early sign of depletion. The mean loss in depletion was slightly lower than the minimal daily loss assumed to be normal (38, 39). Magnesium concentrations decreased in serum and erythrocytes, but the hypomagnesemia, hypocalcemia, and hypokalemia Shils reported were not found in our study, probably because the intake of magnesium here was considerably higher than in his studies. Parathyroid hormone concentrations did not increase, probably because serum calcium and ionized calcium concentrations did not decrease; perhaps the decrease in serum magnesium concentration counteracted changes in calcium too subtle to be detected.

Women in this study consumed a diet low in magnesium for 81 d. Decreases in magnesium indexes showed that the women were being depleted of magnesium. A longer experiment or a diet lower in magnesium might have produced greater changes, with values in Table 2 moving into the deficiency range.

Although none of the mean blood values in Table 2 were below respective normal ranges, 130 mg Mg/d was sufficiently low to modify magnesium homeostasis. Because 99% of magnesium in the body is intracellular (21, 24), assessment of magnesium status is difficult (21–23). The decrease in erythrocyte

magnesium concentrations may reflect intracellular magnesium in myocardial cells.


A magnesium-dependent ATPase controls sodium and potassium transport across cell membranes (40). Impairment of this pump as a result of a low intake of dietary magnesium may have altered membrane potential and myocardial irritability. Magnesium is central to a variety of cellular mechanisms that control activity of muscle and nerve cells (41). Cardiac muscle seems to have been more sensitive to this intake than was skeletal muscle, as shown by the absence of Chvostek and Trousseau signs in the present study.

The frequency of supraventricular beats was higher with lower amounts of dietary magnesium. Perhaps if a larger group of women were exposed to these diets, the rate of ventricular ectopy also would increase significantly. Although the standard settings of the instrument reflected widely used clinical criteria, the criteria discriminating between the 2 types of ectopy are somewhat arbitrary. Because of this uncertainty, we calculated the combined frequency of ectopy. Results were unaffected by dietary copper. Magnesium depletion was verified by both chemical and physiologic criteria.

An intake of magnesium of less than one-half of the RDA changed cardiac rhythm. The daily dietary magnesium requirement of these middle-aged women exceeded 130 mg/d; 411 mg daily was sufficient. A criterion based on cardiac electrophysiology confirmed the correctness of the RDA. Whether extra dietary magnesium will decrease idiopathic ectopy is worth testing.

Some women may habitually eat a diet similar to that in this experiment for long periods. According to Pennington (27), magnesium intakes of women in the United States generally do not meet the 1989 RDA of 280 mg; some groups average <75% of this amount, or 210 mg/d. If magnesium intakes are positively skewed similarly to those of copper (42), substantial numbers of women must eat 130 mg daily with some regularity. This amount is  $\approx 40\%$  of the revised RDA of 320 mg (26).

The increase in the number of ectopic beats in this experiment was both small,  $\approx 100$ /d, and undesirable. Extra systoles are common in healthy persons (43) and generally are of unknown origin. Whether a diet low in magnesium contributes to this phenomenon is unknown; however, a diet low in magnesium probably will not benefit persons with valvular disease or cardiac hypertrophy or persons who consume toxins such as alcohol or caffeine, which predispose to this arrhythmia. These persons may require more dietary magnesium than average. Leddingham and Raine (25) suggest that magnesium depletion may occur with the use of diuretics, especially in subjects whose dietary intake is low and who live in soft water areas. Shils (21) listed several clinical conditions contributing to magnesium depletion via decreased absorption or increased loss or with endocrine disorder. Perhaps patients with enteropathies from atrophy, gluten, inflammation, infection, radiation, or surgery; renal dysfunction from nephrotoxic drugs or tubular diseases; endocrine disorders such as diabetes mellitus, hyperaldosteronism, or hyperthyroidism; or familial disorders such as Bartter syndrome or renal wasting syndrome will be more at risk from a diet low in magnesium than others.

In summary, an apparently adequate, ordinary diet low in magnesium disrupted magnesium homeostasis. An increase in myocardial irritability was detected with Holter electrocardiography. 

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