

Oral Magnesium Therapy Improves Endothelial Function in Patients With Coronary Artery Disease

Michael Shechter, MD, MA; Michael Sharir, MD; Maura J. Paul Labrador, MPH;
James Forrester, MD; Burton Silver, PhD; C. Noel Bairey Merz, MD

Background—Magnesium blocks many of the physiological actions of calcium. Nevertheless, the impact of magnesium supplementation on endothelial function and exercise tolerance in stable coronary artery disease (CAD) patients has not been assessed.

Methods and Results—In a randomized, double-blind, placebo-controlled trial, 50 stable CAD patients (41 men and 9 women, mean±SD age 67±11 years, age range 42 to 82 years) were randomized to receive either magnesium (n=25) (30 mmol/d Magosolv-Granulat; Asta Medica Company, Inc) or placebo (n=25) for 6 months. Before and after 6 months, endothelium-dependent brachial artery flow-mediated vasodilation (FMD) and endothelium-independent NTG-mediated vasodilation were assessed with high-resolution (10-MHz) ultrasound. Exercise stress testing was performed with use of the Bruce protocol. Intracellular magnesium concentrations ($[Mg^{2+}]_i$) were assessed from sublingual cells through x-ray dispersion (EXA) (normal mean±SD values 37.9±4.0 mEq/L). The magnesium therapy significantly increased postintervention ($[Mg^{2+}]_i$ versus placebo (36.2±5.0 versus 32.7±2.7 mEq/L, $P<0.02$). There was a significant correlation in the total population between baseline $[Mg^{2+}]_i$ and baseline FMD ($r=0.48$, $P<0.01$). The magnesium intervention resulted in a significant improvement in postintervention FMD (15.5±12.0%, $P=0.02$ compared with baseline), which was not evident with placebo (4.4±2.5%, $P=0.78$ compared with baseline). There was better exercise tolerance (9.3±2.0 versus 7.3±3.1 minutes, $P=0.05$) and less ischemic ST-segment changes (4 versus 10 patients, $P=0.05$) in the magnesium versus placebo groups, respectively.

Conclusions—Oral magnesium therapy in CAD patients is associated with significant improvement in brachial artery endothelial function and exercise tolerance, suggesting a potential mechanism by which magnesium could beneficially alter outcomes in CAD patients. (*Circulation*. 2000;102:2353-2358.)

Key Words: magnesium ■ lipoproteins ■ endothelium ■ coronary disease

Magnesium blocks many of the physiological actions of calcium.^{1,2} Epidemiological evidence that links magnesium deficiency to coronary artery disease (CAD) has been investigated for >3 decades.³⁻⁷ In the Atherosclerosis Risk in Communities (ARIC) Study,⁸ the relation of serum and dietary magnesium and CAD incidence during 4 to 7 years of follow-up was examined in a sample of 13 922 middle-aged adults free of baseline CAD from 4 US communities. After adjustment for traditional risk factors, the relative risk of CAD across quartiles of serum magnesium was 1.00, 0.92, 0.48, and 0.44 (P for trend=0.009), suggesting that low magnesium may be involved in the pathogenesis of CAD.

It is known that the vascular endothelium plays a key role in circulatory homeostasis through its ability to regulate the vascular milieu via the synthesis and release of biologically active substances, such as endothelium-derived relaxing factor (EDRF).^{9,10} The endothelium influences not only vascular

tone but also vascular remodeling, as well as hemostasis and thrombosis, through platelet, coagulant, and fibrin effects.^{11,12} In atherosclerotic arteries, these functions of the endothelium are impaired and potentiate an adverse pathophysiology through increased vasoconstriction (ie, paradoxical vasoconstriction)^{12,13} and thrombosis.¹² It has been suggested that by reducing cardiovascular risk factors, the modification or reversal of endothelial dysfunction may be of significant therapeutic benefit in the treatment of CAD.^{12,14}

The present study was designed to compare the effect of an oral magnesium intervention versus placebo on brachial artery endothelial function and exercise tolerance in patients with stable CAD.

Methods

Study Design and Population

The study design was a randomized, prospective, double-blind, placebo-controlled trial. Patients were recruited consecutively from a

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From the Preventive & Rehabilitative Cardiac Center and the Atherosclerosis Research Center, Cedars-Sinai Burns and Allen Research Institute, the Division of Cardiology, Department of Medicine, Cedars-Sinai Medical Center, and the University of California Los Angeles School of Medicine (M. Shechter, M. Sharir, M.J.P.L., J.F., C.N.B.M.); and IntraCellular Diagnostics, Inc (B.S.), Foster City, Calif.

Asta Medica Company, Inc (Vienna, Austria), manufacturer of the oral magnesium product used in the study, provided support for this work.

Correspondence to Michael Shechter, MD, MA, FACC, Preventive & Rehabilitative Cardiac Center, Cedars-Sinai Medical Center, 444 San Vicente Blvd, Suite 901, Los Angeles, CA 90048. E-mail shechtes@netvision.net.il

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supervised cardiac exercise and rehabilitation program at Cedars-Sinai Medical Center. Inclusion criteria included men and women aged >20 years, with CAD documented through prior myocardial infarction, CABG, or coronary angiography or angioplasty. Exclusion criteria included unstable angina, congestive heart failure of higher than New York Heart Association functional class III, chronic diarrhea, renal failure (serum creatinine >3 mg/dL), acute myocardial infarction within the preceding 3 months, hyperthyroidism/hypothyroidism, type 1 (insulin-dependent) diabetes mellitus, peripheral vascular disease, history of drug or alcohol abuse, chronic liver disease, or refusal to sign the informed consent. The study was approved by the institutional review board, and all participants gave written informed consent.

Study Protocol

The patients were randomized through a computerized randomization program (Rancode-Plus, Version 3.1; IDV Data Analysis) to receive either 15 mmol Magnosolv-Granulat PO BID (Asta Medica Company, Inc) or placebo for 6 months. Each pouch of Magnosolv-Granulat contains 15 mmol Mg^{2+} , 365 mg total magnesium (342 mg magnesium oxide, 670 mg carbonicum). The patients were instructed to continue taking their other regular medications and to maintain their usual diet during the study. Before and after 6 months, the patients underwent after an overnight fast, a physical examination, brachial reactivity testing, treadmill exercise testing, and blood tests for the measurement of lipids, blood cell count, electrolytes, and sublingual intracellular magnesium levels. Compliance of study medication was assessed at 1, 3, and 6 months on the basis of pill count.

Vascular Function Protocol

Endothelial function in the form of endothelium-dependent brachial artery flow-mediated vasodilation (FMD) was measured as previously described.^{15,16} Briefly, FMD was assessed in the right arm of the subject in the recumbent position in a temperature-controlled room (22°C) after a 10-minute equilibration period by a single ultrasonographer blinded to treatment assignment. With a 10-MHz linear array (CL 10-5; ATL) ultrasound (HDI 3000cv system; ATL), the brachial artery was longitudinally imaged ≈ 5 cm proximal to the antecubital crease, where the clearest image was obtained. When a reasonable image was obtained, the surface of the skin was marked, and the arm was kept in the same position throughout the study. The ultrasound probe was kept at the same position by the ultrasonographer during the entire study. ECG was monitored continuously, and blood pressure was monitored in the left arm every minute during the study.

Study Phases

Endothelium-Dependent FMD

After a 2-minute baseline period, a frozen longitudinal image of 3 cm of vessel without color flow was obtained and frozen for 5 seconds. The image was then unfrozen and switched to pulsed-wave Doppler for 5 seconds at a sweep speed at 50 mm/s. A pneumatic tourniquet placed around the forearm proximal to the target artery was inflated after the baseline phase to a pressure of 50 mm Hg above the subject's systolic blood pressure (or until no blood flow was detected through the brachial artery with the Doppler probe), and this pressure was held for 3 minutes. Increased flow was then induced with sudden cuff deflation. A continuous scan was performed at deflation and 60 and 90 seconds after cuff deflation with frozen and Doppler measurements recorded at similar intervals to the baseline phase.

Nitroglycerin-Induced

(Non-Endothelium-Dependent) Vasodilatation

At 13 minutes after cuff deflation, a second 2-minute baseline resting scan was recorded to confirm the vessel recovery. A sublingual nitroglycerin (NTG) tablet (0.4 mg Nitrostat; Parke-Davis) was then administered, and scanning was performed continuously for 5 minutes after the NTG.

Data Analysis

The ultrasound images were recorded on S-VHS videotape with an SLV-RS7 videocassette recorder (SONY). The diameter of the brachial artery was measured from the anterior to the posterior interface between the media and adventitia ("m line") at a fixed distance.¹⁷ The mean diameter was calculated from 4 cardiac cycles synchronized with the R-wave peaks on the ECG. All measurements were made at end diastole to avoid possible errors resulting from variable arterial compliance.¹⁸ Internal diameter was calculated with PC Prosound software (USC) with an Horita Data Translation Image Processing board (DT2862; 60 Hz). The diameter changes caused by endothelium-dependent flow-mediated vasodilatation (percent FMD) and endothelium-independent NTG-mediated vasodilation (percent NTG) were expressed as the percent changes relative to those at the initial resting scan. The intraobserver variability for repeated measurements is 0.0 ± 0.07 mm in our laboratory.

Treadmill Exercise Testing

After an overnight fast, a maximum symptom-limited exercise treadmill test (Bruce protocol¹⁹) was performed on all patients. We recorded blood pressure and heart rate at each exercise stage and at peak exercise, time to onset of angina, and 1-mm ST-segment depression; ST-segment depression at peak exercise; maximal ST-segment depression; presence of cardiac arrhythmias; metabolic equivalents (METs) and double-product (heart rate in bpm \times systolic blood pressure in mm Hg) achieved; and total exercise duration. Myocardial ischemia was defined as the presence of ≥ 0.1 -mV horizontal or downsloping ST-segment depression 80 ms after the J-point during exercise or recovery. Cardiac arrhythmias were defined as ventricular premature beats of Lown grade II or higher.

Intracellular Magnesium Measurement

Tissue magnesium concentration ($[Mg^{2+}]_i$) was measured in sublingual epithelial cells scraped from the mucosa adjacent to the frenulum and immediately fixed on a carbon slide with cytology fixative. The slides were examined with a scanning electron microscope (Philips), and suitable cells were identified. $[Mg^{2+}]_i$ was measured with radiographic analysis of individual epithelial cells (EXA; Intracellular Diagnostics, Inc) (normal values 37.9 ± 4.0 mEq/L). Reported values are the mean of 5 to 10 cells per patient; a specimen was rejected if variance exceeded 2%. Sublingual epithelial cell $[Mg^{2+}]_i$ correlates well with human atrial $[Mg^{2+}]_i$.²⁰ This method is used to assess total cellular magnesium and cannot differentiate free Mg^{2+} from bound species.²⁰

Lipid Determination

Fasting blood samples were analyzed for total cholesterol, HDL cholesterol (HDL-C), VLDL cholesterol, and triglyceride concentrations with an Hitachi 747 autoanalyzer. LDL cholesterol (LDL-C) was calculated with the Friedwald formula.²¹ No patients had a triglyceride level of ≥ 350 mg/dL (4 mmol/L).

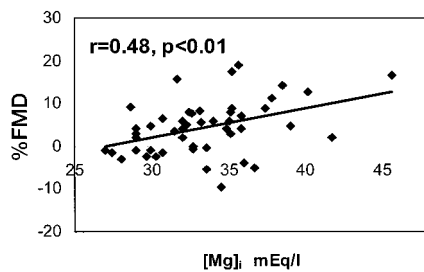


Figure 1. Correlation of percent change in baseline brachial artery flow-mediated vasodilation (%FMD) and baseline intracellular magnesium level ($[Mg^{2+}]_i$) in total study population ($n=50$), demonstrating a linear correlation.

Statistical Analysis

Group data are expressed as mean \pm SD. Differences between clinical characteristics and brachial artery vasodilator responses were evaluated and analyzed by unpaired t tests for 2-group comparisons and 1-way ANOVA for multiple group comparisons. Comparison of biochemical measurements was performed with the unpaired Student's t test and Wilcoxon signed-rank test. Log transformations were used to normalize data for regression analysis. Linear regression analysis was used to compare the continuous relation between brachial artery and LDL-C. Predictors of brachial artery vasodilator responses to reactive hyperemia were obtained through forward stepwise multilinear regression analysis. A P value of <0.05 was considered statistically significant.

Results

Patient Demographics

The study population was composed of 50 stable coronary patients (41 men and 9 women) with a mean age of 66 ± 11 years (range 42 to 83 years) and a body mass index of 26 ± 4 kg/m² (range 20 to 37 kg/m²). All patients had stable CAD documented with a previous myocardial infarction ($n=28$), CABG ($n=25$), or coronary angioplasty ($n=29$) (25 patients had multiple diagnoses). Eighty-eight percent of patients received aspirin, and two thirds were taking lipid-lowering agents; the remainder managed their hypercholesterolemia with a very low fat (vegetarian) diet. The overall group mean LDL-C was 91 ± 24 mg/dL (range 46 to 170 mg/dL). Overall compliance with the study medication was 89%. There were no significant changes in other medication use during the course of the study. There were no serious adverse effects.

Treatment Effect on $[Mg^{2+}]_i$

Of the 50 CAD patients, 36 (72%) had a baseline $[Mg^{2+}]_i$ below normal levels (37.9 ± 4.0 mEq/L), reflecting a magnesium-deficient state. There was no significant difference in baseline $[Mg^{2+}]_i$ between the magnesium and placebo groups (31.7 ± 3.3 versus 33.4 ± 4.8 mEq/L, $P=0.16$). There was a significant correlation in the total population between baseline $[Mg^{2+}]_i$ and baseline FMD ($r=0.48$, $P<0.01$) (Figure 1). Magnesium therapy significantly increased postintervention $[Mg^{2+}]_i$ versus placebo (36.2 ± 5.0 versus 32.7 ± 2.7 mEq/L, $P<0.02$).

Treatment Effect on FMD

At baseline, the total study population had an FMD of $4.4 \pm 2.5\%$ and an NTG-mediated vasodilation of $14.4 \pm 14.0\%$. There were no significant differences between the 2 groups at baseline FMD (Figure 2) or NTG-mediated dilation. There also were no significant differences between the 2 groups in baseline brachial artery diameter, age, body mass index, cardiac history, sex, cardiac medications, lipid-lowering therapy, exercise duration, ST-segment change, blood pressure, lipids, glucose, and $[Mg^{2+}]_i$ (Table 1).

The magnesium intervention resulted in a significant improvement in postintervention FMD ($15.5 \pm 12.0\%$, $P=0.02$ compared with baseline) that was not evident with placebo ($4.4 \pm 2.5\%$, $P=0.78$ compared with baseline) (Figure 2). At the end of the trial, Δ FMD (postintervention percent FMD minus baseline percent FMD divided by baseline percent FMD) was significantly higher in the magnesium than the placebo group ($25.2 \pm 13.0\%$ versus $-4.5 \pm 2.5\%$, $P<0.02$). In the total population, there was a significant correlation of change in $[Mg^{2+}]_i$ with change in FMD ($r=0.39$, $P<0.01$). There was no significant effect of treatment on NTG-induced vasodilation between magnesium and placebo groups ($13.9 \pm 11.1\%$ versus $14.4 \pm 14.0\%$, $P=0.82$).

Patients were then divided into groups with a mean of $\leq 34.6 \pm 4.1$ mEq/L $[Mg^{2+}]_i$ ($n=26$) and $>34.6 \pm 4.1$ mEq/L $[Mg^{2+}]_i$ ($n=24$) at study exit. Five patients (20%) from the placebo group and 19 patients (76%) from the magnesium group had a $[Mg^{2+}]_i$ above the mean. Percent change in FMD from baseline to postintervention was significantly higher in patients with greater than the mean $[Mg^{2+}]_i$ ($8.53 \pm 8.16\%$ versus $1.99 \pm 5.95\%$, $P<0.02$).

Treatment Effect on Exercise Performance

At baseline, there were no significant differences between the 2 groups in regard to exercise stress testing or the presence of exercise-induced ischemic ST-segment depression. At 6 months, there was a trend toward a better cardiac functional capacity measured with METs and significantly improved exercise duration in patients who received magnesium compared with the placebo patients (10.2 ± 2.0 versus 8.5 ± 3.6 METs, $P=0.08$, and 9.3 ± 2.0 versus 7.3 ± 3.1 minutes, $P=0.05$) (Table 2). Patients in the magnesium group also had less ischemic ST-segment changes (4 versus 10 patients, $P=0.05$) and fewer arrhythmias (0 versus 4 patients, $P=0.05$) during exercise testing compared with the placebo group.

Treatment Effect on Other Variables

After 6 months, there were no significant group differences in exit blood pressure, body mass index, glucose, total cholesterol, LDL-C, HDL-C, triglycerides, and use of cardiac medications.

Discussion

The results of the present study demonstrate that an oral magnesium intervention for 6 months resulted in significant improvement in brachial artery endothelial function in a population of stable CAD patients. These results are further supported by our $[Mg^{2+}]_i$ data that demonstrate a moderate correlation between $[Mg^{2+}]_i$ and brachial artery endothelial

TABLE 1. Baseline Characteristics of Study Population

Variable	Placebo (n=25)	Magnesium (n=25)	P
Male sex, n (%)	19 (76)	21 (84)	0.54
Age, y	66±12	68±10	0.54
BMI, kg/m ²	26±4	25±4	0.65
Prior MI, n (%)	17 (68)	12 (48)	0.12
Prior CABG, n (%)	16 (64)	10 (40)	0.08
Prior PTCA, n (%)	15 (60)	14 (56)	0.49
Diabetes mellitus, n (%)	5 (20)	3 (12)	0.35
Systemic hypertension, n (%)	12 (48)	10 (40)	0.38
Current smokers, n (%)	2 (8)	0 (0)	0.24
History of hypercholesterolemia, n (%)	15 (60)	18 (72)	0.27
Aspirin, n (%)	23 (92)	22 (88)	0.50
Hypoglycemic agents, n (%)	5 (20)	3 (12)	0.35
β-Blockers, n (%)	9 (36)	11 (44)	0.48
Calcium antagonists, n (%)	4 (16)	3 (12)	0.50
Long-acting nitrates, n (%)	3 (12)	0 (0)	0.11
ACE inhibitors, n (%)	5 (20)	6 (24)	0.49
Lipid-lowering agents, n (%)	15 (60)	18 (72)	0.27
Vitamins, n (%)	11 (44)	13 (52)	0.38
SBP supine, mm Hg	145±18	147±21	0.78
DBP supine, mm Hg	69±14	69±10	0.92
Exercise duration, min	7.2±2.8	7.3±3.0	0.63
METs achieved	8.5±2.7	8.4±2.8	0.52
ST-segment depression, n (%)	4 (16)	3 (12)	0.30

BMI indicates body mass index; DBP, diastolic blood pressure; MI, myocardial infarction; SBP, systolic blood pressure. Values are expressed as mean±SD.

function at baseline, as well as a significant increase in $[Mg^{2+}]_i$ in response to oral magnesium therapy that accompanied the improvement in brachial artery endothelial function. Our study also demonstrated a trend toward improved functional capacity (measured with METs) and significant improvement in exercise duration and ischemic ECG response in the oral magnesium intervention group. These latter results are concordant with our previous work that demonstrates a significant association between $[Mg^{2+}]_i$ and cardiac functional capacity in stable CAD patients.²²

The mechanisms to explain these beneficial effects of magnesium may be multiple. Higher $[Mg^{2+}]_i$ may improve intracellular ATP production and glucose use, because magnesium is a cofactor of ATP. Because magnesium is considered nature's physiological calcium blocker,^{1,2} it reduces the

release of calcium from and into the sarcoplasmic reticulum and protects the cells against calcium overload under conditions of ischemia. Magnesium reduces systemic and pulmonary vascular resistance, with a concomitant decrease in blood pressure and a slight increase in cardiac index.^{23–25} Elevation of extracellular magnesium levels reduces arteriolar tone and tension in a wide variety of arteries² and potentiates the dilatory action of some endogenous (adenosine, potassium, and some prostaglandins) and exogenous (isoproterenol and nitroprusside) vasodilators.² As a result, magnesium mildly reduces systolic blood pressure²⁵ and may provide afterload reduction and thus unload the ischemic ventricle.²³ Kugiyama et al²⁶ demonstrated that exercise-induced angina is suppressed by intravenous magnesium in patients with variant angina, potentially as a result of improvement of coronary artery spasm. These types of arteriolar effects may explain our results of a beneficial magnesium effect for FMD and exercise tolerance in our CAD patients.

Experimental models that involve the manipulation of $[Mg^{2+}]_i$ levels shed additional light on the role of magnesium in response to cellular stress and improvement of endothelial function. Dickens et al²⁷ challenged cell cultures of bovine endothelial cells with oxygen-derived free radicals under conditions of normal or deficient extracellular magnesium. The magnesium-deficient cells exhibited greater oxidative endothelial injury than the magnesium-replete cells, suggesting that tissues subjected to oxidative stress in the setting of

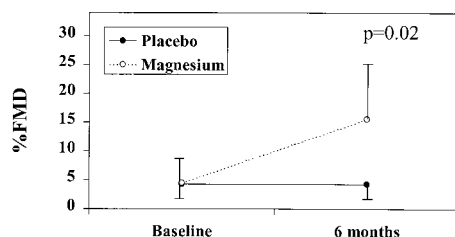


Figure 2. Percent change in endothelium-dependent brachial artery flow-mediated vasodilation (%FMD) from baseline in placebo (●) (n=25) and magnesium (○) (n=25) groups at baseline and after 6 months.

TABLE 2. Exercise Parameters at 6 mo

Variable	Placebo (n=25)	Magnesium (n=25)	P
Supine heart rate, bpm	65±15	59±8	0.14
Standing heart rate, bpm	70±18	63±9	0.15
SBP supine, mm Hg	140±19	143±20	0.64
DBP supine, mm Hg	68±7	69±10	0.92
Exercise duration, min	7.3±3.1	9.3±2.0	0.05
Heart rate at maximum exercise, bpm	129±20	128±23	0.90
METs achieved	8.5±3.6	10.2±2.8	0.08
Double-product, bpm×mm Hg	22 297±4 907	22 571±6 400	0.86
Exercise-induced chest pain, n (%)	5 (20)	4 (16)	0.30
ST-segment depression, n (%)	10 (40)	4 (16)	0.05
Cardiac arrhythmias, n (%)	4 (16)	0 (0)	0.05

Cardiac arrhythmias indicate ventricular premature beats of Lown grade II or higher; DBP, diastolic blood pressure; SBP, systolic blood pressure. Values are expressed as mean±SD.

magnesium deficiency sustain greater damage due to intracellular lipid peroxidation. Pearson et al²⁸ demonstrated that hypomagnesemia selectively impaired the release of NO from coronary endothelium via a canine model. Because NO is a potent endogenous nitrovasodilator and an inhibitor of platelet aggregation and adhesion, hypomagnesemia may promote vasoconstriction and coronary thrombosis in hypomagnesemic states. Previous work from our laboratory has demonstrated a beneficial reduction in platelet-dependent thrombosis measured ex vivo in CAD patients randomized to receive an oral magnesium supplement.²⁹

Most of our CAD patients had a baseline $[Mg^{2+}]_i$ below normal levels (37.9 ± 4.0 mEq/L), reflecting a magnesium-deficient state. Elderly patients, especially those with CAD and heart failure, can have low body magnesium levels, and the mechanisms responsible for this are likely multifactorial. Although 37% of patients with congestive heart failure who receive diuretic therapy with the loop and thiazide diuretics have hypomagnesemia,³⁰ only 5 patients (14%) in the present study were receiving loop diuretics. Evidence suggests that the occidental “American diet” is relatively deficient in magnesium, whereas the “Oriental diet,” which is characterized by a greater intake of fruits and vegetables, is rich in magnesium.³¹ It has also been observed that CAD patients absorb more magnesium during magnesium loading testing than do those without CAD, suggesting that CAD is associated with excessive magnesium loss and a relative magnesium-deficient state.³²

Evidence suggests that endothelial dysfunction may be the initiating event in the atherosclerotic process that subsequently leads to clinical CAD.^{11,33} Accordingly, there has been an ongoing, aggressive search for therapeutic choices suitable for reversal of endothelial dysfunction with the hope that such intervention, if instituted early in the course of the disease, might prevent or modify the subsequent risk of clinical disease and related cardiac events.^{12–14,34} Magnesium, which is an inexpensive, natural, and relatively safe element, has been shown in the present study to improve endothelial function and thus may be justified as an adjuvant therapy for CAD patients. Further studies, with larger populations, are needed to prove our findings.

Study Limitations

High-risk patients, such as patients with congestive heart failure on diuretic therapy or elderly patients with low $[Mg^{2+}]_i$, may benefit from magnesium treatment even more than low-risk patients without severe $[Mg^{2+}]_i$ depletion. We studied a relatively small number of stable CAD patients with near-optimal lipid values who were participating in a supervised cardiac exercise program. It is possible that the impact of the oral magnesium intervention on the brachial artery FMD and exercise tolerance was underestimated due to this low-risk population. Further studies with larger numbers of CAD patients who are at higher risk are indicated, given these results.

There is both biologic and measurement variability in the ultrasound assessment of brachial artery FMD. However, prior work has demonstrated the feasibility of this approach, if performed carefully, for the detection of change in relatively small sample sizes.^{35–37}

Perhaps the major limitation of the present study is the lack of data regarding the prognostic value of endothelial dysfunction and its subsequent improvement. Because of the lack of such data, it is difficult to project the clinical significance of these findings.

Conclusion

In conclusion, we demonstrated that an oral magnesium intervention for 6 months in CAD patients results in significant improvement in brachial artery endothelial function and exercise tolerance, suggesting a potential mechanism by which magnesium could beneficially alter outcomes in patients with CAD.

Acknowledgments

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