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LACK OF ASSOCIATION BETWEEN SERUM MAGNESIUM AND THE RISKS OF HYPERTENSION AND CARDIOVASCULAR DISEASE

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Abstract

Background—Experimental studies have linked hypomagnesemia with the development of vascular dysfunction, hypertension, and atherosclerosis. Prior clinical studies have yielded conflicting results, but were limited by the use of self-reported magnesium intake or short follow-up periods.

Methods—We examined the relationship between serum magnesium concentration and incident hypertension, cardiovascular disease, and mortality in 3,531 middle-aged adult participants in the Framingham Heart Study offspring cohort. Analyses were performed using Cox proportional hazards regressions, adjusted for traditional cardiovascular disease risk factors.

Results—Follow up was 8 years for new-onset hypertension (551 events) and 20 years for cardiovascular disease (554 events). There was no association between baseline serum magnesium and the development of hypertension (multivariable-adjusted hazards ratio per 0.15 mg/dl, 1.03, 95% confidence interval [CI], 0.92-1.15; p=0.61), cardiovascular disease (0.77, 95% CI, 0.44-1.37; p=0.49) or all-cause mortality (0.64, 95% CI, 0.32-1.26; p=0.42). Similar findings were observed in categorical analyses, in which serum magnesium was modeled in categories (<1.5, 1.5-2.2, >2.2 mg/dl) or in quartiles.

Conclusions—In conclusion, data from this large, community-based cohort do not support the hypothesis that low serum magnesium is a risk factor for developing hypertension or cardiovascular disease.

Keywords

Magnesium; hypomagnesemia; hypertension; cardiovascular disease; mortality

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Conflicts of Interest: None

INTRODUCTION

Magnesium deficiency is common, especially among women, the elderly, and minorities.[1-3] It has been postulated that hypomagnesemia contributes to the development of hypertension and cardiovascular disease (CVD). In experimental studies, magnesium has been shown to participate in the regulation of vascular tone,[4] endothelial function,[5-7] vascular inflammation,[8, 9] and glucose and lipid metabolism.[10-15] Magnesium deficiency raises blood pressure in animal models[16] whereas magnesium supplementation prevents the development of hypertension in these models.[17, 18] Furthermore, in mouse models, higher levels of dietary magnesium have been found to suppress atherogenesis.[19-21]

Prior clinical studies have linked low dietary or serum magnesium with hypertension, cardiovascular disease,[22-31] and all-cause and cardiovascular mortality,[28, 29] but others have failed to find an association.[32, 33] Limitations of prior studies include the use of self-reported risk factors, lack of adjudicated endpoints, relatively short follow-up, and, in many cases, lack of access to measured magnesium concentrations. Dietary magnesium data could be inexact or susceptible to reporting bias,[34] and magnesium intake may not consistently increase serum magnesium levels.[35] Serum total magnesium levels are a good marker of magnesium status, because they correlate with ionized magnesium[36, 37] and intracellular magnesium[37] and demonstrate low intra-individual and temporal variability.[38]

The availability of routine measures of serum magnesium in the Framingham Offspring Study provided an opportunity to examine the association of serum magnesium with incident hypertension, CVD events, and mortality in a large, well-characterized cohort with long-term follow-up and standardized adjudication of endpoints. We hypothesized that low serum magnesium is associated with the development of hypertension, CVD events, and mortality.

METHODS

Study sample

The Framingham Heart Study began recruitment of an offspring cohort in 1971 with the enrollment of 5,124 children of the original Framingham Heart Study participants. Study design and selection criteria for this study have been previously described.[39] Participants attending the second examination of the offspring cohort (n=3,863), which took place between 1979 and 1982, were eligible for the current investigation. We excluded participants lacking a serum magnesium measurement (n=176) or with prevalent CVD (n=156). In analyses of incident hypertension, we further excluded individuals with hypertension at baseline (n=772), or who did not attend the 4th off spring cohort examination (n=239). Thus, the final number of eligible participants was 3,531 for the CVD analyses, and 2,520 for the hypertension analyses.

The study protocol was approved by the institutional review board of Boston Medical Center, and all participants provided written informed consent.

Measurement of Risk Factors

Cardiovascular disease risk factors were measured at entrance into the study as well as at each follow-up examination. Participants underwent a complete medical history, anthropometry, and laboratory assessment of cardiovascular disease risk factors. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Blood pressures were measured twice by a physician after the subject had been sitting for 5 minutes, and the mean of the two blood pressures was used for study analysis. Hypertension was defined as systolic blood pressure of 140 mm Hg or greater, diastolic blood pressure of 90 mm Hg or greater, or use of any antihypertensive medication, including diuretics. Current smoking was defined as regular cigarette smoking in the year prior to the examination. Blood was obtained

from participants while they were fasting, and measurements were made of total and HDL cholesterol, triglycerides, hemoglobin A1c, glucose, albumin, hemoglobin, and electrolytes. Diabetes was defined as a fasting glucose level greater than or equal to 126 mg/dL or the use of oral hypoglycemic agents or insulin.

Measurement of serum magnesium, calcium, and potassium levels

All participants had serum magnesium and calcium concentrations measured using a standard colorimetric assay (Roche Diagnostics, Alameda, California) and serum potassium measured by flame-emission spectrophotometry.[40]

Hypertension and CVD endpoints

The analyses focused on three outcomes of interest: incident hypertension, new-onset CVD, and all-cause mortality. Hypertension was defined as above. For the endpoint of incident hypertension, we analyzed only participants without hypertension at the baseline examination (the 2nd offspring examination). Incident hypertension was defined as the presence of hypertension at the 4th offspring examination, which took place approximately 8 years later.

All participants were under surveillance for the development of CVD events. Suspected CVD events were adjudicated by a panel of 3 investigators upon review of hospital records, medical office notes, and Framingham clinic visit notes, using standardized criteria that have been described previously.[41] A CVD event was defined as angina pectoris, coronary insufficiency (prolonged angina with documented ECG changes), myocardial infarction, stroke or transient ischemic attack, heart failure, intermittent claudication, or death secondary to cardiovascular disease. Sudden cardiac death was defined as a coronary heart disease death that occurred within < 1 hour of the onset of symptoms and had no other probable cause of death after review of the medical record.

Statistical analysis

For analyses of incident hypertension, multivariable logistic regression models were constructed. Magnesium concentrations were analyzed as continuous variables and by quartile. The quartiles were as follows: Quartile 1, 1.4-1.77 mg/dL, Quartile 2, 1.77-1.88 mg/dL, Quartile 3, 1.88-1.98 mg/dL, and Quartile 4, 1.98-2.5 mg/dL. The outcome variable was the development of hypertension between offspring cohort examinations 2 and 4, with analyses restricted to the sub-sample of participants who did not have hypertension at examination 2. Multivariable models were constructed, first adjusting for age and sex, and then adjusting for age, sex, BMI, diabetes status, systolic blood pressure, total/HDL cholesterol ratio, smoking status, hemoglobin, albumin and estimated glomerular filtration rate (GFR). Because there was no evidence of effect modification by sex, analyses were performed using pooled sexes. In secondary analyses, we repeated the multivariable analyses including calcium and potassium as covariates. To examine whether the risk of hypertension was evident only at the extremes of serum magnesium concentration, we repeated the above analyses using pre-specified clinical cut-points for magnesium concentration: <1.5, 1.5 to 2.2 (referent), and > 2.2 mg/dl.

Cox proportional hazards models were used to examine the relations of baseline magnesium concentrations with time to incident CVD and mortality. Covariates in the multivariable models included age, sex, BMI, diabetes, systolic blood pressure, total/high density lipoprotein ratio, smoking status, hypertension treatment, hemoglobin, serum albumin and GFR. In secondary analyses, we examined the association between serum magnesium and risk of sudden cardiac death.

All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, N.C.). Two-tailed p-values <0.05 were considered statistically significant.

RESULTS

Characteristics of the study sample

Baseline characteristics are shown in Table I, for the samples used in the incident hypertension analyses (n=2,520) and the incident CVD and mortality analyses (n=3,531). There were 772 (22%) participants with prevalent hypertension at the baseline examination. The range of observed values for magnesium was 1.41-2.40 mg/dl in men and 1.15-2.46 mg/dl in women. The number of participants with a serum magnesium <1.5 mg/dl was 12 for the hypertension analyses and 24 for the CVD and death analyses. The number of participants with a serum magnesium >2.2 mg/dl was 56 for the hypertension analyses and 73 for the CVD and death analyses.

Magnesium levels and hypertension

Between the baseline and follow-up examination, a total of 551 (22%) participants developed hypertension. In age- and sex-adjusted logistic regression analyses, serum magnesium was not significantly associated with incident hypertension (adjusted OR per standard deviation [0.15 mg/dl] increment in serum magnesium, 0.96, 95% confidence interval [CI] 0.87-1.06; P=0.39) **(**Table II**)**. Results were similar after adjustment for baseline systolic and diastolic blood pressure and other risk factors for hypertension.

Magnesium levels and CVD

In both age- and sex-adjusted and multivariable-adjusted analyses, there was no significant association between serum magnesium and incident CVD events (Table II**)**. In multivariable analyses, there was no association between low (<1.5 mg/dl) or high (>2.2 mg/dl) magnesium levels and incident CVD (Table III).

Magnesium levels and mortality

Because serum magnesium could affect mortality without affecting incidence of CVD,[30, 31] we also examined all-cause mortality as an endpoint (Table II). We found no significant association between serum magnesium and risk of death in either continuous or categorical analyses.

Additional analyses

There was no association between serum magnesium and sudden cardiac death, although there were only 29 events (data not shown). Serum sodium was not significantly correlated with serum magnesium (p=0.40). There were modest correlations between serum magnesium and serum calcium (r=0.18, p<0.001) and potassium (r=0.062, p=0.002). Nonetheless, addition of calcium and potassium as covariates in the multivariable-adjusted analyses did not alter our results (data not shown).

Power estimates

We performed post hoc calculations to determine our statistical power to detect an association between hypomagnesemia (defined as levels in the lowest quartile) and incident events. At $\alpha = 0.05$, we had 80% power to detect odds ratios of 1.4 or higher for hypertension, and hazards ratios of 1.35 for CVD and 1.4 for mortality.

DISCUSSION

We found no association between serum magnesium levels and the subsequent development of hypertension, CVD, or all-cause mortality. The validity of these findings is supported by the use of a large, well-characterized epidemiologic cohort, routine adjudication for incident

hypertension and CVD, a large number of events, and standardized assessment of serum magnesium.

Our findings are in contrast to those of prior studies that have related magnesium status to cardiovascular outcomes.[22-27, 30, 42-45] Many of these studies were based on dietary measures, which may be influenced by residual confounding or recall bias. Individuals who report reduced magnesium intake may have other comorbidities that predispose them to hypertension and CVD. Also, diets rich in magnesium may contain other nutrients that influence the development of CVD or CVD risk factors, only some of which can be accounted for in observational studies.

Only a few studies have examined the relationship between serum magnesium and CVD events. An analysis from the Atherosclerosis Risk in Communities (ARIC) cohort showed a significant association between serum magnesium and coronary heart disease in women but not men.[30] Although the ARIC sample was large, the follow-up period was relatively short (4 to 7 years), raising the possibility that early findings with serum magnesium could be attenuated over time. In the National Health and Nutritional Examination Survey Epidemiologic Follow-up Study (NHEFS), there was no significant association between serum magnesium and incidence of CVD, although serum magnesium was inversely associated with all-cause mortality and mortality from ischemic heart disease.[29] Serum magnesium was also found to be associated with cardiovascular and all-cause mortality in a group of middle-aged men in the Paris Prospective Study 2.[28] In the NHEFS and Paris Prospective 2 studies, categorization of death was based upon death certificates and ICD-9 codes, with their attendant limitations.[41]

The lack of association between baseline concentrations of serum magnesium and incident hypertension is consistent with results from ARIC Study.[33] Although there are experimental data to support a role for magnesium in the pathogenesis of hypertension,[4] our findings indicate that hypomagnesemia does not predict the development of hypertension, at least not at concentrations normally seen in human subjects.

Several limitations of our investigation deserve comment. Magnesium is predominantly an intracellular cation. Thus, serum magnesium levels may not fully reflect total body magnesium stores.[37] However, serum magnesium concentration correlates well with intracellular magnesium and is also the laboratory measurement that is most commonly used in clinical practice. Due to the limited number of study participants with very high or low serum magnesium, it is impossible to draw conclusions about the risk associated with a serum magnesium that is far outside the normal range. However, the lack of such individuals in this sample reflects the characteristics of the general population. This study consists of middle-aged, ambulatory individuals. We cannot exclude the possibility that serum magnesium levels may be linked to hypertension or CVD in other populations, including those with a higher prevalence of magnesium deficiency. Dietary information was not available at this examination, so it was not possible to correlate dietary intake with serum magnesium. Single, as opposed to serial or continuous, blood pressure measurements were obtained as part of this study. Lastly, serum magnesium was only measured once, which does not account for natural variation that may occur in magnesium concentration over time.

Magnesium deficiency is now relatively common, especially among certain populations.[1-3] Studies of magnesium supplementation in humans have generally been restricted to individuals with known cardiac disease or hypertension, and have shown conflicting results.[35, 46-50] Our findings do not support a link between low magnesium concentration and hypertension or CVD in patients with serum magnesium levels that fall close to or within the normal range of laboratory values. Accordingly, there does not appear to be a role for routine assessment of serum magnesium in identifying individuals at elevated risk of hypertension or CVD.

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Table I

Baseline characteristics of study participants

	Hypertension Analyses		CVD/Mortality Analyses	
	Male N= 1134	**Female N= 1386**	**Male N= 1705**	**Female N= 1826**
Age, years	42.5±9.6	42.4±9.4	44.6±10.2	44.1±9.8
BMI, kg/m^2	26.4±3.5	24.1±4.2	26.9±3.7	24.7±4.8
Systolic BP, mmHg	119±9.8	113±11.6	126±15.3	118±16.5
Diastolic BP, mmHg	77±6.9	73±7.5	81±9.2	75±9.4
Hypertension medications, %	-	-	9.7	7.9
Total/HDL Cholesterol Ratio	4.9±1.6	3.8±1.2	5.1±1.6	3.9±1.3
Triglycerides, mg/dL	116.0±87.3	78.1±51.9	124.9±89.1	86.9±70.9
Creatinine, mg/dL	1.2±0.2	1.1±0.2	1.2±0.2	1.1±0.3
Albumin, g/dL	4.5±0.3	4.4±0.3	4.5±0.3	4.4±0.3
Hemoglobin, g/dL	15.5±1.0	13.6±1.0	15.5±1.0	13.7±1.1
Phosphorus, mg/dL	3.1±0.4	3.3±0.4	3.0±0.4	3.3±0.4
Calcium, mg/dL	9.6±0.4	9.6±0.4	9.6±0.4	9.6±0.4
Magnesium, mg/dL	1.9±0.1	1.9±0.2	1.9±0.2	1.9±0.2
Diabetes, %	4.1	1.4	6.3	2.9
Smoking, %	37.2	36.4	35.3	37.0

Values are displayed as means (± standard deviation) or frequency in percent.

Table II

Risk of development of HTN, CVD or death based upon serum concentration of magnesium

	HTN		CVD		DEATH	
	OR (95% CI)	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Mg as a continuous variable *						
• Age and sex adjusted	0.96 (0.87-1.06)	0.39	0.62 (0.36-1.08)	0.09	0.63 (0.33-1.21)	0.09
• Multivariable adjusted	1.03 (0.92-1.15)	0.61	0.77 (0.44-1.37)	0.49	0.64 (0.32-1.26)	0.42
Mg by quartile						
• Age and sex adjusted						
Quartile 1	Referent	--	Referent	--	Referent	--
Quartile 2	0.90 (0.68-1.18)	0.44	0.99 (0.79-1.24)	0.92	1.03 (0.78-1.35)	0.84
Quartile 3	0.87 (0.65-1.15)	0.32	0.82 (0.65-1.04)	0.10	0.89 (0.67-1.18)	0.42
Quartile 4	0.86 (0.65-1.14)	0.29	0.87 (0.69-1.10)	0.23	0.86 (0.65-1.15)	0.31
p value for trend	----	0.28	----	0.11	----	0.21
• Multivariable adjusted						
Quartile 1	Referent	--	Referent	--	Referent	--
Quartile 2	0.97 (0.72-1.31)	0.86	1.09 (0.86-1.37)	0.47	1.12 (0.85-1.48)	0.41
Quartile 3	0.96 (0.70-1.32)	0.81	0.88 (0.69-1.13)	0.31	0.97 (0.72-1.30)	0.81
Quartile 4	1.03 (0.75-1.41)	0.86	0.91 (0.72-1.17)	0.47	0.92 (0.68-1.24)	0.57
p value for trend	----	0.89	----	0.23	----	0.43

* Odds ratios and hazards ratios are per 0.15 units change in Mg

Table III

Risk of development of HTN, CVD or death based upon serum concentration of magnesium with magnesium as a categorical variable

	HTN		CVD		DEATH	
	OR (95% CI)	**p value**	**HR (95% CI)**	**p value**	**HR (95% CI)**	**p value**
Mg as a categorical variable						
• **Age and sex adjusted**						
Mg <1.5 mg/dl	1.20 (0.30-4.82)	0.79	1.99 (1.02-3.85)	0.04	2.06 (1.02-4.17)	0.04
Mg 1.5-2.2. mg/dl	Referent	----	Referent	----	Referent	----
Mg >2.2 mg/dl	1.16 (0.62-2.17)	0.64	1.16 (0.68-1.97)	0.59	0.94 (0.46-1.89)	0.85
• **Multivariable adjusted**						
Mg <1.5 mg/dl	0.65 (0.14-2.95)	0.58	1.19 (0.60-2.36)	0.62	1.21 (0.58-2.54)	0.61
Mg 1.5-2.2 mg/dl	Referent	----	Referent	----	Referent	----
Mg >2.2 mg/dl	1.43 (0.71-2.89)	0.31	1.10 (0.64-1.89)	0.74	0.82 (0.38-1.75)	0.60

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