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Low Serum Magnesium and the Development of Atrial Fibrillation in the Community: The Framingham Heart Study

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Abstract

Background—Low serum magnesium has been linked to increased risk of atrial fibrillation (AF) following cardiac surgery. It is unknown whether hypomagnesemia predisposes to AF in the community.

Methods and Results—We studied 3,530 participants (mean age, 44 years; 52% women) from the Framingham Offspring Study who attended a routine examination, and were free of AF and cardiovascular disease. We used Cox proportional hazard regression analysis to examine the association between serum magnesium at baseline and risk of incident AF. Analyses were adjusted for conventional AF risk factors, use of antihypertensive medications, and serum potassium. During up to 20 years of follow-up, 228 participants developed AF. Mean serum magnesium was 1.88 mg/dl. The age- and sex-adjusted incidence rate of AF was 9.4 per 1,000 person-years (95% confidence interval, 6.7 to 11.9) in the lowest quartile of serum magnesium (≤1.77 mg/dl), compared with 6.3 per 1,000 person-years (95% confidence interval, 4.1 to 8.4) in the highest quartile (≥1.99 mg/dl). In multivariable-adjusted models, individuals in the lowest quartile of serum magnesium were approximately 50% more likely to develop AF (adjusted hazard ratio, 1.52, 1.00 to 2.31; *P*=0.05), compared with those in the upper quartiles. Results were similar after excluding individuals on diuretics.

Conclusion—Low serum magnesium is moderately associated with the development of AF in individuals without cardiovascular disease. Because hypomagnesemia is common in the general population, a link with AF may have potential clinical implications. Further studies are warranted to confirm our findings and elucidate the underlying mechanisms.

Keywords

arrhythmia; epidemiology; atrial fibrillation; magnesium

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Hypomagnesemia has been linked to the pathogenesis of arrhythmias in experimental studies.[1] For instance, in rodents, magnesium deficiency potentiates the proarrhythmic effect of hypokalemia,[2] and high magnesium prevents the development of ventricular reperfusion arrhythmias.[3] In humans, low serum magnesium is associated with the development of atrial fibrillation (AF) after coronary artery bypass surgery.[4] Some, but not all, studies suggest that magnesium supplementation reduces the incidence of post-operative AF.[5–11]

Prior clinical studies examining the relation between serum magnesium and AF have focused on hospitalized, post-surgical patients. It is unknown whether low serum magnesium is associated with the development of AF in ambulatory individuals, particularly those without existing cardiovascular disease. Such a link could have public health implications, because low magnesium status is relatively common and potentially correctable. Thus, we examined the association between serum magnesium levels and future AF, using data from more than 2 decades of longitudinal follow-up in the Framingham Offspring Study.

METHODS

Study sample

The Framingham Heart Study was established in 1948. In 1971, 5,124 children (or their spouses) of the Original Framingham Heart Study participants were enrolled in the Framingham Offspring Study.[12] Participants attending the second examination of the Offspring cohort (n=3,863), which took place between 1979 and 1983, were eligible for the current investigation. We excluded participants lacking a serum magnesium measurement (n=176) or with prevalent cardiovascular disease (n=156) or AF (n=2). A total of 3,526 participants were eligible for the analysis. The study protocol was approved by the Boston University Medical Center Institutional Review Board, and all participants provided written informed consent.

Clinical assessment

Participants underwent a complete medical history, anthropometry and laboratory assessment of cardiovascular disease risk factors at entrance into the study and at each examination. Prevalent cardiovascular disease (myocardial infarction, unstable angina, heart failure, or stroke) was determined based upon blinded review of the medical history, hospital records and outpatient visit notes by 3 investigators. Blood pressure was measured twice by a physician after the participant had been sitting for 5 minutes, and the mean of the two blood pressures was used for analysis. Body mass index was calculated as weight in kilograms divided by the square of height in meters. Current smoking was defined as regular cigarette smoking in the year prior to the examination. Alcohol consumption was assessed by self-report of ounces per week. Moderate-heavy alcohol consumption was defined as ≥ 14 drinks/week for men and ≥ 7 drinks/week for women (1 drink = 13 grams of alcohol). Caffeine consumption was measured in cups of caffeinated coffee or tea per day. We classified a heart murmur as significant if at least 3 out of six intensity systolic or any diastolic murmur was present.

Blood was obtained from participants in the fasting state. Measurements were made of total and HDL cholesterol, glucose, albumin, hemoglobin, high-sensitivity C-reactive protein, and electrolytes. Medication use was by self-report. 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. Glomerular filtration rate was estimated from serum creatinine using the simplified Modification of Diet in Renal Disease equation.[13] All participants underwent a 12-lead

electrocardiogram, and the electrocardiographic PR interval was measured manually by a Framingham clinic physician.

Measurement of serum magnesium

All participants had serum magnesium measured using a standard colorimetric assay (Roche Diagnostics, Alameda, California). Potassium was measured using flame-emission spectrophotometry.[14]

Measurement of AF outcome

All participants were under routine surveillance for the development of AF. AF was diagnosed if atrial fibrillation or atrial flutter was present on an electrocardiogram obtained from a Framingham clinic visit, outpatient physician visit, inpatient hospitalization, or Holter monitor. All potential cases of AF were adjudicated by a Framingham Heart Study cardiologist.

Statistical analysis

Descriptive statistics were performed for key clinical risk factors using means and standard deviations for continuous variables and percentages for categorical variables. Pearson correlations were used to summarize the associations between continuous risk factors and serum magnesium. Mean serum magnesium levels were assessed in participants with and without dichotomous risk factors. Age- and sex-adjusted incidence rates were calculated by quartiles of serum magnesium.

We assessed the relation of clinical factors to serum magnesium with linear regression. Cox proportional hazard regression analysis was used to examine the relation of baseline serum magnesium concentrations with incident AF. Follow-up was censored at 20 years. The proportionality of hazards assumption was confirmed. Magnesium concentration, which was approximately normally distributed, was analyzed in quartiles. Because there was no evidence of effect modification by sex, sex-pooled models were constructed. Covariates in the multivariable models included age, sex, body mass index, diabetes, systolic blood pressure, total/high density lipoprotein ratio, smoking status, and anti-hypertensive treatment. We additionally adjusted for measures potentially associated with magnesium status: hemoglobin, serum albumin, estimated glomerular filtration rate and alcohol consumption. Caffeine consumption was not included in multivariable models because it has previously been found not to be associated with incident AF in this cohort.[15]

Cox proportional hazards regression was also used to examine the relation of baseline serum potassium and calcium and AF. In secondary analyses, models were estimated with and without adjustment for serum potassium, C-reactive protein, heart failure, significant heart murmur, and electrocardiographic PR interval. We also conducted Cox proportional hazard models excluding individuals who developed AF after a diagnosis of heart failure, cardiac surgery, or myocardial infarction, and those on diuretic therapy at baseline. In further analyses we tested for effect modification between moderate to heavy alcohol use and magnesium concentration and risk of AF. We conducted a series of sensitivity analyses examining various approaches to categorizing magnesium concentrations, including examining the lowest quartile vs. the upper 3 quartiles and the lowest decile vs. the upper 9 deciles. We also performed a spline analysis to assess the linearity of the association between serum magnesium and AF risk.

All analyses were performed using SAS 9.1.3 (SAS Institute, Cary, N.C.). Two-tailed $P < 0.05$ were considered statistically significant. The authors had full access to the data and

take responsibility for its integrity. All of the authors have read the article as written and agreed with submission in its current form.

RESULTS

Characteristics of the study sample are shown in Table 1. The baseline mean age of the sample was 44 years and the sample consisted of 52% women. The mean serum magnesium level was 1.88 mg/dl with a range of 1.41 to 2.40 mg/dl in men, and 1.86 mg/dl with a range of 1.15 to 2.46 mg/dl in women. The association of baseline factors with serum magnesium is shown in Table 2.

Over a mean follow-up time of 18.6 ± 3.7 years, 228 participants (5%) developed new-onset AF. The cumulative incidence of AF by quartile of serum magnesium is shown in Table 3. The age-and sex-adjusted incidence of AF was 9.4 per 1,000 person-years (95% confidence interval [CI], 6.7 to 11.9) in the lowest quartile of serum magnesium, compared with 6.3 per 1,000 person-years in the highest quartile (95% CI, 4.1 to 8.4).

Results of multivariable Cox proportional hazard regression analyses are shown in Table 4. In age- and sex-adjusted analyses, the risk of incident AF was highest in the lowest quartile of serum magnesium (hazard ratio compared with the highest quartile, 1.54, 95% CI, 1.06 to 2.22; *P*=0.02). No gradient in risk of AF was observed across the upper three quartiles of serum magnesium. A similar pattern was observed in the multivariable-adjusted analyses (Table 4).

Because the excess risk of AF appeared confined to individuals in the lowest magnesium quartile, we performed additional analyses with magnesium as a dichotomous variable. An increased risk of AF was noted in individuals in the lowest quartile (adjusted hazard ratio, 1.34, 95% CI, 1.01 to 1.77; *P*=0.05) or lowest decile (adjusted hazard ratio, 1.48, 95% CI, 1.02 to 2.14; *P*=0.04) of serum magnesium, compared with the remaining participants (Table 4). We also performed a spline analysis to further assess the shape of the relation between baseline magnesium and AF risk (Figure 1).

There was no association between serum potassium and AF in age- and sex-adjusted (HR per SD of serum potassium, 0.92, 95% CI, 0.81–1.04; p=0.18) or multivariable-adjusted (HR, 0.97; 95% CI, 0.85–1.10; p=0.62) models. Similarly, there was no association between serum calcium and AF in either age- and sex-adjusted (HR per SD of serum calcium, 0.96, 95% CI, 0.84–1.09; p=0.54) or multivariable-adjusted (HR, 0.93, 95% CI, 0.81–1.06; *P*=0.26) models.

The association of serum magnesium with AF persisted in models further adjusting for serum potassium concentration (multivariable-adjusted HR for the lowest quartile, 1.33, 95% CI, 1.00–1.77; *P*=0.05), and C-reactive protein (HR, 1.34, 95% CI, 1.00–1.80; *P*=0.05). In models adjusted for PR interval or heart murmur, the hazard ratios were minimally attenuated (HR after adjustment for PR interval, 1.32, 95% CI, 0.99–1.75; *P*=0.06; HR after adjustment for heart murmur, 1.27, 95% CI, 0.95–1.69; *P*=0.11). The hazard ratio was also similar in analyses excluding any case of AF that developed after the diagnosis of heart failure (N= 29), myocardial infarction (N=5), or cardiac surgery (N=29) (HR, 1.33, 95% CI, 0.95–1.85; *P*=0.09).

There was no association between moderate-to-heavy alcohol consumption and magnesium concentration (*P*=0.99). Furthermore, there was no interaction between moderate-to-heavy alcohol use and magnesium concentration on the risk of AF (interaction *P*=0.72).

DISCUSSION

In summary, low serum magnesium was associated with the development of AF in a longitudinal, community-based cohort. Although previous studies have reported an association between low serum magnesium and AF risk in the context of cardiac surgery,[4] the present study is the first, to our knowledge, to demonstrate this association in the broader community.

Magnesium has several effects on the cardiac conduction system. It is an essential cofactor for the Na-K ATP pump, which controls the movement of sodium and potassium across the cell membrane.[16] Disruption or alteration in the function of this pump in the setting of hypomagnesemia may impact myocardial excitability. Magnesium also may prolong the effective refractory period and alter the function of the inward rectifying potassium channel, although this has not been shown in all studies.[17–22] Magnesium infusion prolongs atrioventricular node conduction time,[23] whereas low serum magnesium concentration increases sinus node automaticity.[24] Clinical studies have shown that intravenous magnesium can augment rate control in AF, and facilitate maintenance of sinus rhythm.[25] In contrast, hypomagnesemia increases the dose of digoxin required for rate control,[26] and lowers the threshold for digoxin-related arrhythmias.[27] In small metabolic unit studies, restriction of dietary magnesium to less than one-half of the recommended daily allowance increased supraventricular ectopy[28] and risk of AF.[29] Another recent study reported an inverse relation between magnesium status and sudden cardiac death, potentially lending further support to the link between hypomagnesemia and cardiac arrhythmias.[30]

Magnesium and potassium deficiency frequently coexist,[31] and in experimental models, hypomagnesemia has been shown to potentiate the electrophysiologic effects of hypokalemia.[2] Because of the association between magnesium and potassium, we performed secondary analyses adjusting for serum potassium, and the magnesium-AF relation remained unchanged. Furthermore, baseline serum potassium was unrelated to incident AF in our data. Hence, it seems unlikely that potassium concentrations explain the serum magnesium - AF association.

Our analyses suggest that the association with serum magnesium and AF is not linear, but observes a threshold. The excess risk of AF appears primarily in those in the lowest quartile of serum magnesium.[4] Although residual confounding from chronic illnesses or malnutrition that predispose to both hypomagnesemia and AF cannot be excluded, several features of the present study attenuate this concern. First, our cohort consisted primarily of ambulatory, young to middle-aged adults with little comorbidity. Second, even the lower magnesium values observed in our study were not in the range found with malnutrition or severe deficiency. Third, if low serum magnesium was simply serving as a marker of chronic illness, then we would expect it to be associated with other adverse outcomes. However, we previously found that magnesium status was not associated with all-cause mortality or vascular risk in the Framingham Offspring cohort.[32] Thus, our findings with regard to the risk associated with low magnesium status appear specific for AF, a biologically-plausible endpoint in view of the experimental data and studies in the acute hospital setting.

Causality is difficult to infer from the data. Nonetheless, we believe our study has significant strengths, including the use of a large, well-characterized cohort, rigorous adjudication of AF and other cardiovascular outcomes, the long period of follow-up and standardized ascertainment of baseline magnesium concentrations in a single laboratory.

Several limitations deserve mention. Serum magnesium concentration may not fully reflect total body magnesium stores, although serum magnesium correlates well with intracellular magnesium levels.[33] Serum magnesium was only measured at one time point, and

magnesium levels fluctuate over time. Nonetheless, random misclassification of magnesium status would be expected to bias the results toward the null. Since AF can be paroxysmal and asymptomatic, it is possible that not all cases of AF were detected. We did not differentiate between types of AF (paroxysmal, persistent or permanent, AF or atrial flutter); hence, we cannot comment as to whether the relation between magnesium and AF varies by subtype.

Also, we were unable to examine the relation between dietary magnesium intake and AF, because dietary magnesium records were not available at the index examination. However, direct measurements of serum magnesium levels avoid reporting bias, which is a limitation of dietary recall studies.[34] Alcohol consumption may have been underestimated because it was obtained by self-report. In addition, we did not specifically ask about binge drinking, which could also influence serum magnesium concentrations. We did not assess sleep apnea at the index examination. Although sleep apnea is associated with incident AF,[35] its relation with magnesium status is unknown. Family history of AF was not available on a significant proportion of the sample. Thus, we did not include this variable as a covariate. We submit that it is unlikely that parental AF is a strong correlate of offspring magnesium status. Our study sample was largely of European ancestry, so the generalizability of our results to other races/ethnicities is uncertain.

We observed that low serum magnesium was associated with the development of AF. If confirmed, our observations may have important public health implications, because the prevalence of AF is increasing, and magnesium deficiency is common and potentially modifiable.[36, 37] Further studies are warranted to determine whether the association is present in other populations, and whether magnesium supplementation lowers AF risk.

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Clinical Perspective

Data from both experimental and human studies suggest that low magnesium may be linked to the development of arrhythmias. While hypomagnesemia has been associated with the development of atrial fibrillation (AF) after cardiac surgery, it is unknown whether serum magnesium is associated with the development of AF in healthy, ambulatory individuals. In a longitudinal, community-based study of 3,530 individuals without known cardiac disease, we identified an association between low serum magnesium and the development of AF over 20 years of follow-up. We found that those in the lowest quartile of serum magnesium were approximately 30% more likely to develop AF than those in the upper three quartiles. This association persisted despite adjustment for known AF risk factors and the interim development of heart failure, myocardial infarction, or cardiac surgery. Because magnesium deficiency is relatively common and easily treatable with dietary supplementation, a link with AF in the general population has potential clinical implications.

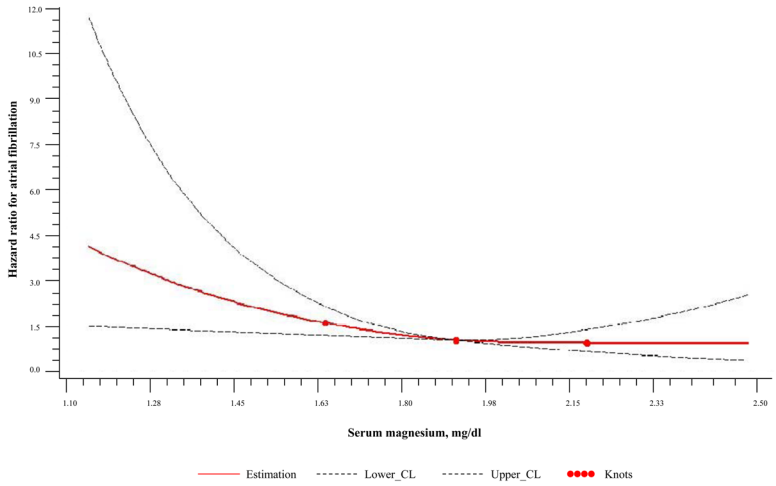

Figure 1.
Spline analysis.

Table 1

Characteristics of study participants.

	Quartile of Serum Magnesium			
	1 (N=936)	**2 (N=906)**	**3 (N=839)**	**4 (N=849)**
Age, years	45.0±10.2	44.0±10.0	44.0±9.9	44.4±9.9
Body mass index, kg/m^2	26.0±4.8	25.7±4.3	25.7±4.3	25.9±4.1
Systolic blood pressure, mm Hg	123±17	121±16	122±17	121±16
Diastolic blood pressure, mm Hg	78±10	78±10	78±10	78±10
Antihypertensive medications, %	12	7	8	8
Total/HDL cholesterol ratio	4.3±1.5	4.4±1.6	4.6±1.6	4.7±1.6
Creatinine, mg/dL	1.0±0.2	1.1±0.2	1.2±0.2	1.2±0.3
Albumin, g/dL	4.4±0.3	4.4±0.3	4.5±0.3	4.5±0.3
Hemoglobin, g/dL	14.4±1.4	14.5±1.3	14.7±1.4	14.8±1.3
Phosphorus, mg/dL	3.2±0.5	3.2±0.4	3.1±0.4	3.2±0.4
Calcium, mg/dL	9.5±0.4	9.6±0.4	9.6±0.4	9.7±0.4
Magnesium, mg/dL	1.7±0.1	1.8±0.03	1.9±0.03	2.1±0.1
Diabetes, %	8	4	2	3
Smoking, %	35	35	36	39
Potassium, mEq/L	4.6±0.5	4.7±0.5	4.7±0.5	4.7±0.5
C-reactive protein, mg/L	2.6±5.1	2.4±5.0	2.3±4.3	2.3±4.3
Alcohol consumption, drinks/week	7.6±11.4	8.6±12.5	7.9±10.0	8.8±12.1
Caffeine consumption, cups/day	3.6±3.0	3.8±2.7	4.0±2.8	3.8±2.7
Significant murmur, N(%)	1	0.4	0.2	0.4
Interim myocardial infarction, N(%)	2	2	1	1
Interim heart failure, N(%)	2	2	2	2
Interim cardiac surgery, N(%)	1	1	1	1

Clinical characteristics are expressed as mean±SD, or %

Table 2

Associations between baseline risk factors and serum magnesium concentration

Correlation of serum magnesium with baseline characteristics in the entire sample (N=3,530).		
	r	**P-value**
Age, years	−0.027	0.11
Body mass index, kg/m^2	−0.019	0.27
Systolic blood pressure, mm Hg	−0.053	0.002
Diastolic blood pressure, mm Hg	0.005	0.77
Total/HDL cholesterol ratio	0.093	0.0001
Creatinine, mg/dL	0.310	0.0001
Albumin, g/dL	0.167	0.0001
Hemoglobin, g/dL	0.097	0.0001
Phosphorus, mg/dL	0.011	0.51
Calcium, mg/dL	0.154	0.0001
Potassium, mEq/L	0.098	0.0001
Alcohol consumption, oz/week	0.022	0.19

Mean magnesium concentration in mg/dl according to the presence of selected risk factors.

	Risk Factor		**P-value**
	Present Mean (SD)	**Absent Mean (SD)**	
Male Sex	1.89 (0.15)	1.86 (0.16)	0.0001
Antihypertensive medications, %	1.83 (0.18)	1.88 (0.15)	0.0001
Diabetes, %	1.80 (0.19)	1.88 (0.16)	0.0001
Smoking, %	1.88 (0.16)	1.87 (0.16)	0.009
Chronic kidney disease *	1.93 (0.21)	1.87 (0.16)	0.005
Diuretic use	1.84 (0.19)	1.88 (0.15)	0.0001

* Chronic kidney disease defined as estimated glomerular filtration rate below the 5th percentile by sex.

Table 3

Age- and sex-adjusted incidence of AF, according to magnesium quartile

Quartile	Serum magnesium range, mg/dl	No. of Events	Person-years	Incidence rate (95% CI), per 1,000 person-years
Lowest	≤1.77	80	17,209	9.4 (6.7–11.9)
Second	1.78–1.88	53	16,933	6.9 (4.6–9.0)
Third	1.89–1.98	50	15,619	7.1 (4.8–9.3)
Highest	≥1.99	45	15,908	6.3 (4.1–8.4)

Table 4

Multivariable regression models

	Age-and Sex-Adjusted			Multivariable-Adjusted*		
	HR	**95% CI**	**P-value**	**HR**	**95% CI**	**P-value**
In entire sample (n=3530)						
Quartile 1	1.54	(1.06–2.22)	0.02	1.45	(0.99–2.12)	0.06
Quartile 2	1.11	(0.75–1.66)	0.60	1.11	(0.74–1.67)	0.61
Quartile 3	1.15	(0.77–1.72)	0.49	1.14	(0.76–1.71)	0.53
Quartile 4	1.00	Referent	-	1.00	Referent	-
In individuals not on diuretics (n=3239)						
Quartile 1	1.53	(1.02–2.27)	0.04	1.52	(1.00–2.31)	0.05
Quartile 2	1.02	(0.66–1.58)	0.92	1.09	(0.69–1.69)	0.72
Quartile 3	1.07	(0.69–1.66)	0.76	1.08	(0.69–1.69)	0.73
Quartile 4	1.00	Referent	-	1.00	Referent	-
With magnesium as a dichotomous variable (n=3530)						
Quartile 1	1.41	(1.07–1.86)	0.01	1.34	(1.01–1.77)	0.05
Quartiles 2–4	1.00	Referent	-	1.00	Referent	-
By decile (n=3530)						
Decile 1	1.69	(1.18–2.41)	0.004	1.48	(1.02–2.14)	0.04
Deciles 2–10	1.00	Referent		1.00	Referent	

*Multivariable models are adjusted for the following covariates: age, sex, body mass index, systolic blood pressure, diabetes, total/high density lipoprotein ratio, smoking status, anti-hypertensive treatment, hemoglobin, albumin, glomerular filtration rate, and alcohol consumption.