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Plasma Magnesium and the Risk of Ischemic Stroke among Women

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Abstract

Background and Purpose—Lower plasma magnesium levels may be associated with higher blood pressure and endothelial dysfunction, but sparse prospective data are available for stroke.

Methods—Among 32,826 participants in the Nurses' Health Study who provided blood samples in 1989–1990, incident ischemic strokes were identified and confirmed by medical records through 2006. We conducted a nested case-control analysis of 459 cases, matched 1:1 to controls on age, race/ethnicity, smoking status, date of blood draw, fasting status, menopausal status and hormone use. We used conditional logistic regression models to estimate the multivariable adjusted association of plasma magnesium and the risk of ischemic stroke and ischemic stroke subtypes.

Results—Median magnesium levels did not differ between ischemic stroke cases and controls (median=0.86 mmol/l for both; p-value=0.14). Conditional on matching factors, women in the lowest magnesium quintile had a relative risk (RR) of 1.34 (95% confidence interval [CI]: 0.86–2.10, p trend=0.13) for total ischemic stroke, compared to women in the highest quintile. Additional adjustment for risk factors and confounders did not substantially alter the risk estimates for total ischemic stroke. Women with magnesium levels <0.82 mmol/l, had significantly greater risk of total ischemic stroke (multivariable RR=1.57; 95% CI: 1.09–2.27, p=0.01), and thrombotic stroke (multivariable RR=1.66; 95% CI: 1.03–2.65, p=0.03) compared to women with magnesium levels ≥0.82 mmol/l. No significant effect modification was observed by age, body mass index, hypertension or diabetes.

Conclusions—Lower plasma magnesium levels may contribute to higher risk of ischemic stroke among women.

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Keywords

Plasma Magnesium; Ischemic Stroke

Introduction

Plasma levels of magnesium have been inversely associated with risk factors for stroke, such as hypertension[1, 2] and diabetes[3, 4]. Plasma magnesium has also been inversely associated with the risk of cardiovascular outcomes including coronary heart disease[5, 6] and atrial fibrillation[7]. Lower magnesium levels may lead to stroke by initiating an inflammatory cascade which triggers oxidative responses in endothelial cells leading to vasoconstriction and thrombus formation[8], or through effects on hypertension, diabetes and atrial fibrillation.

The relationship between serum magnesium and the risk of ischemic stroke has been examined in only one prospective cohort study[9]. Low serum magnesium levels were associated with a higher risk of ischemic stroke among men and women in the Atherosclerosis Risk in Communities (ARIC) Study, men and women in the highest plasma magnesium quartile had a 25% (95% CI, 5–41%) reduced risk of ischemic stroke in models adjusted for age, sex and race; however, adjustment for hypertension and diabetes, which may possibly be biological mediators of the effects of magnesium, eliminated an association[9]. To provide further evidence on this relationship, we prospectively examined the association between plasma magnesium and the risk of ischemic stroke and ischemic stroke subtypes (thrombotic and embolic strokes) among women in the Nurses' Health Study (NHS).

Methods

Study population

The NHS is a prospective cohort study which began in 1976, when 121,700 female registered nurses aged 30 – 55 years at enrollment, completed questionnaires about their lifestyle factors and medical history. Follow-up questionnaires are sent to these women biennially to update this information. Between 1989 and 1990, 32,826 women in this study cohort provided blood samples; of these, 18,743 provided a second blood sample between 2000 and 2001. The women who provided a blood sample did not differ appreciably from those who did not.[10] Blood samples archived in continuously monitored liquid nitrogen freezers at −80 degrees Celsius.

We carried out a nested case-control study of ischemic stroke among the 32,826 women who provided a blood sample. Cases and controls were both required to be free of cancer or prior cardiovascular disease at the time of blood collection. Incident ischemic stroke cases were matched 1:1 to controls who remained free of stroke prior to the case date, with matching by age (± 2 years), race/ethnicity (white/African-American/Asian/Hispanic/other/unknown), smoking (never, past and current), date of blood draw, fasting status, menopausal status and hormone use (yes/no). This study was approved by the institutional review board at Brigham and Women's Hospital and informed consent was obtained from all participants.

Ascertainment of Plasma Magnesium

Matched ischemic stroke case-control pairs were shipped to the laboratory in the same batch. Magnesium was measured by colorimetric assay on an Hitachi 917 analyzer (Roche Diagnostics, Indianapolis, IN). The coefficient of variation for plasma magnesium was 4% and the intraclass correlation between two blood samples collected from the same women was 0.63 for samples obtained 2 to 3 years apart and 0.39 for samples obtained 10 years apart. Total cholesterol (CV of 4%), LDL and HDL cholesterol (CV of 4%), C-reactive protein (CV of 2%), and glycosylated hemoglobin (CV of 4%), were measured in the Clinical and Epidemiological Research Laboratory at Children's Hospital (Boston, MA) for all cases and controls.

Ascertainment of Stroke

Women who reported a nonfatal stroke on a follow-up questionnaire were asked for permission to review their medical records. Medical records were reviewed by physicians blinded to the exposure status. Fatal strokes were initially ascertained by reports from relatives or postal authorities and a search of the National Death Index and were then documented by medical records and death certificates.

Strokes were confirmed according to the criteria of the National Survey of Stroke which requires a constellation of neurological deficits of sudden or rapid onset lasting ≥24 hours or until death. Strokes were regarded as incident if they occurred after the date of return of the 1980 questionnaire but before June 2006. Strokes were classified as ischemic stroke due to thrombotic or embolic occlusion of a cerebral artery with imaging data from computed tomography (CT) or magnetic resonance imaging (MRI); 97% of the cases had a CT or MRI. Thrombotic strokes were defined as infarction involving the cortical artery regions in the cerebrum and the cerebellum (cortex and subcortical areas) or the focal, small and deep areas such as the internal capsule, corona radiate, basal ganglia and brainstem, without involvement of cortex. Strokes were defined as embolic if evidence of an embolic source was present in the medical record and if imaging studies and/or neurology consult supported the diagnosis[11]. In the setting of incomplete evidence or competing etiologies where type could not be assigned, the strokes were considered unclassified ischemic stroke.

Statistical Analyses

A total of 459 confirmed ischemic stroke cases (303 thrombotic, 129 embolic and 27 unclassified ischemic strokes) and 459 controls had magnesium levels available for analyses. Quintiles of plasma magnesium were created based on the distribution of plasma magnesium among the controls, and assigned cases to each quintile based on their plasma magnesium levels. Magnesium levels were also dichotomized (<0.82 mmol/l versus ≥0.82 mmol/l) to approximate clinically low levels, and compare the lowest quintile to all other quintiles. The means and proportions of baseline characteristics, cardiovascular risk factors, and biomarkers across quintiles of plasma magnesium were calculated among the cases and controls; we conducted tests of significance to compare the means and proportions between cases and controls, using Mantel-Haenszel and Fisher's exact tests.

Multivariable conditional logistic regression was used to examine the association between plasma magnesium and the risk of ischemic stroke and ischemic stroke subtypes (thrombotic and embolic strokes). Three multivariable models were created, model 1 was conditional on matching factors only: age, race/ethnicity, smoking, date of blood draw, fasting status, menopausal status and hormone use; model 2 was adjusted for lifestyle risk factors: alcohol, body mass index (BMI), physical activity, aspirin and thiazide diuretic use; model 3 was further adjusted for potential mediators: HbA1c, history of diabetes, hypertension, coronary heart disease and total/high density lipoprotein cholesterol (total/HDL cholesterol). For each model, we derived relative risks (RR's) and 95% confidence intervals (CI's). Effect modification by age, BMI, hypertension and diabetes was tested and significance of interactions was assessed using the likelihood ratio tests. Sensitivity analyses were conducted to calculate adjusted RRs and 95% CIs for measurement error correction in plasma magnesium, using samples collected approximately 10 years apart. We also examined the possibly non-linear relation between plasma magnesium and ischemic stroke with likelihood ratio tests, comparing the model with only the linear term to the model with the linear and cubic spline terms. All analyses were conducted with SAS for UNIX statistical software (version 9.2; SAS Institute).

Results

Among the 459 women who developed an ischemic stroke, the mean age at baseline in 1990 was 60.8 years, while the mean age at stroke diagnosis was 71 years. The differences between cases and controls in cardiovascular disease (CVD) risk factors for ischemic stroke are shown in Table 1. Women in the lowest quintile of plasma magnesium were more likely to consume more alcohol, be current smokers, use thiazide diuretics, postmenopausal hormone therapy, have hypertension and diabetes, compared to women in the highest quintile (Table 2). The median magnesium levels in the lowest and highest quintiles, based on the distribution in the controls, were 0.78 mmol/l and 0.95 mmol/l respectively. The median magnesium levels did not differ between the ischemic stroke cases and controls (0.86 mmol/l in each, p-value 0.14) in univariate analyses.

In models conditional on matching factors (Table 3), there was no significant association between plasma magnesium and the risk of total ischemic stroke. The RR and 95% CI for the lowest quintile compared to the highest quintile was 1.34 (0.86 – 2.10), p-trend 0.13. This risk was similar after adjusting for other lifestyle risk factors (RR 1.24 [0.78 – 1.98], p-trend 0.29) including alcohol intake, BMI, physical activity, aspirin and thiazide diuretics use. When further adjusted for HbA1c, history of diabetes, history of hypertension, coronary heart disease, total/HDL cholesterol, the risk estimates remained similar (RR 1.34 [0.82 – 2.17], p-trend 0.19). Next, we examined the association of plasma magnesium with thrombotic and embolic strokes, the RR and 95% CI for the lowest vs highest quintile was 1.63 (0.89 – 2.98), p-trend 0.09 for thrombotic stroke and 1.12 (0.39 – 3.19), p-trend 0.72 for embolic stroke, in the fully adjusted models.

When magnesium levels were dichotomized comparing the lowest quintile to all other categories, the RR and 95% CI for magnesium levels <0.82 mmol/l compared to those ≥0.82 mmol/l was 1.64 (1.17 – 2.31), conditional on matching factors only (Table 4). When we

adjusted for confounding by other lifestyle risk factors, this risk estimate was not substantially altered. In the fully adjusted model (model 3), the RR and 95% CI for total stroke was 1.57 (1.09 – 2.27). The estimates were similar for thrombotic stroke, 1.66 (1.03 – 2.65).

Additional analyses correcting for measurement error did not yield substantially different results. Potential effect modification of the association between plasma magnesium and risk of ischemic stroke by age, BMI, hypertension and diabetes was examined in stratified analysis. No significant effect modification was observed by any of these variables ($p > 0.05$) but power may be limited.

Discussion

In this prospective study, plasma magnesium levels were not associated with the risk of ischemic stroke in women across the full distribution of plasma magnesium. However, women with magnesium levels <0.82 mmol/l had a 57% (95% CI: 9% – 127%) higher risk of ischemic stroke and this association remained unchanged after controlling for other factors associated with magnesium levels and stroke risk.

Several cross-sectional and retrospective case-control studies have observed that serum magnesium levels are lower in individuals with acute stroke compared to healthy controls[12–14]. However, in these studies, magnesium was not measured prior to the stroke diagnosis and thus hypomagnesaemia may have been a consequence rather than a cause of stroke in these patients. Nonetheless, magnesium may influence stroke severity and outcome; individuals with lower magnesium levels had worse post-stroke prognosis[13, 15]. Early data from a small randomized clinical trial suggested a benefit of intravenous magnesium on acute stroke prognosis and outcome[16], but results from the Intravenous Magnesium Efficacy in Stroke (IMAGES) trial[17] as well as preliminary results from the FAST-MAG trial presented at the 2014 American Stroke Association's International Stroke Conference failed to show any clinical benefit of intravenous magnesium infusion on stroke outcomes in the acute stroke setting.

To the best of our knowledge, only one other prospective study has examined magnesium levels and risk of ischemic stroke. In the Atherosclerosis Risk in Communities (ARIC) study based on 577 ischemic stroke cases in men and women with 16 years of follow up, serum magnesium levels were inversely associated with ischemic stroke incidence. However, adjustment for hypertension and diabetes attenuated risk ratios to non-significant levels (RR comparing high to low serum magnesium quartiles, 1.04; 95% CI, 0.82 – 1.32, $p = 0.99$), suggesting that these factors may have mediated the association. In our study, we found increased risk of ischemic stroke among women with lower magnesium levels, even after controlling for hypertension and diabetes. The difference between our findings and those of ARIC may be explained by differences in the populations. The ARIC study included white and black men and women who had a mean age of 54 years at baseline, while our study population consisted of only female nurses who were predominantly white with a mean age of approximately 60 years at baseline.

Further, our data are generally in accordance with the findings on dietary magnesium, although the correlation between dietary and plasma levels is poor ($r = 0.02$)[5]. In a meta-analysis of 7 prospective studies, dietary magnesium intake was inversely associated with the risk of stroke, an increase in intake of 100 mg/day was associated with a 9% significant reduction in risk of ischemic stroke[18]. Magnesium-rich foods such as green leafy vegetables[19, 20], whole grains[21, 22] and coffee[23] have also been associated with reduced risk of ischemic stroke in the Nurses' Health Study and other cohorts.

The best method of ascertaining magnesium status remains unclear. Plasma magnesium accounts for only 1% of whole body magnesium concentration[24] but has been shown to be fairly strongly correlated with intracellular free magnesium levels ($r = 0.54$)[25]. As magnesium is under tight homeostatic control, dietary magnesium may be a poor estimate of biologically active magnesium; thus, plasma magnesium may be a better exposure to estimate the true association between magnesium and stroke.

Several potential mechanisms may mediate a reduced risk of ischemic stroke by magnesium. Hypertension and diabetes, known risk factors for stroke, were inversely associated with plasma levels of magnesium[2]. In experimental studies, increased plasma magnesium levels appeared to reduce blood pressure by blocking calcium channels, thus attenuating agonist induced vasoconstriction, decreasing vascular resistance and increasing the capacitance function of cerebral arteries[26–29]. High magnesium levels have been shown to have beneficial effects on insulin resistance, glucose metabolism and risk of type 2 diabetes[30]. A small randomized clinical trial showed that magnesium supplementation (500 mg magnesium citrate daily for 4 weeks) was associated with reduced insulin concentrations[31].

In addition, magnesium has been shown to inhibit arterial thrombus formation in animal studies[32, 33] thus low plasma magnesium levels may be associated with the risk of thrombus formation in humans. In previous studies, serum magnesium levels were inversely associated with von Willebrand factor levels[9], and von Willebrand factor levels were positively associated with the incidence of ischemic stroke[34]. Although low levels of serum magnesium have been associated with higher risk of atrial fibrillation[7, 35] which is a potent risk factor for embolic stroke[36], our study was underpowered to evaluate the hypothesis of an anti-arrhythmic effect of magnesium as a potential pathway for reducing the risk of ischemic stroke.

This study has several strengths including its nested case control design, prospectively collected blood samples, and careful stroke outcome assessment based on medical records. However, the study is limited by using a single assessment of plasma magnesium at baseline to examine the relationship between plasma magnesium and ischemic stroke and there may be substantial variation in levels over time; only a modest intraclass correlation between 2 plasma sample measurements approximately 10 years apart was observed ($r = 0.39$). Furthermore, we studied a population of women who were predominantly Caucasian; therefore our results may not be generalizable to men or other racial and ethnic groups.

In conclusion, the results of this study suggest that low plasma magnesium may be associated with increased risk of ischemic stroke. If confirmed, our findings may have significant public health impact as magnesium deficiency is potentially modifiable.

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Table 1

Baseline Characteristics By Case Control Status in 1990

	Cases (n=459)	Controls (n=459)
Age* (years)	60.8 (6.0)	60.7 (6.0)
Median magnesium (mmol/l)	0.86	0.86
BMI (kg/m^2)	25.9 (5.1)	25.4 (4.8)
Race*		
- White, %	96.0	97.0
- African-American, %	1.3	1.0
- Asian, %	1.0	0.7
- Hispanic, %	1.3	1.0
- Other, %	0.4	0.3
Smoking*		
- Never, %	42.0	42.0
- Past, %	41.0	42.0
- Current, %	18.0	17.0
Alcohol (g/day)	5.9 (10.8)	5.3 (10.3)
Physical Activity (METs/week)	15.1 (19.6)	16.2 (18.5)
History of Heart Disease, %	5.0	6.0
History of High Cholesterol, %	48.0	46.0
History of High Blood Pressure, %	48.0	34.0
History of diabetes, %	12.0	6.0
HbA1c ≥ 6, %	17.0	11.0
Aspirin		
- non-users, %	53.0	49.0
- 1–5 tab/wk, %	25.0	31.0
- ≥ 6 tab/wk, %	22.0	19.0
CRP ≥ 28.5 nmol/l, %	39.0	34.0
Postmenopausal Hormone Therapy use*, %	48.0	47.0
Thiazide diuretics, %	24.0	17.0

Values are means (except where indicated) ± SD or percentages and are standardized to the age distribution of this study population.

*Indicates matching factors.

Table 2

Baseline Characteristics By Magnesium Quintiles in 1990

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Range (mmol/l)	**0.7 – <0.82**	**0.82 – <0.86**	**0.86 – <0.90**	**0.90 – <0.95**	**0.95 –1.15**
Cases/Controls	**106/71**	**77/86**	**96/113**	**76/96**	**104/93**
Age* (years)	61.4 (5.6)	61.1 (5.8)	60.0 (6.3)	60.3 (5.7)	61.1 (6.1)
Magnesium (mmol/l)	0.74 (0)	0.82 (0)	0.86 (0)	0.92 (0)	0.99 (0)
BMI (kg/m^2)	25.9 (5.4)	25.7 (5.3)	25.5 (5.0)	25.8 (4.4)	25.5 (4.5)
Race*					
- White, %	98.3	96.0	96.1	97.0	97.0
- African-American, %	0	0.6	1.9	1.0	1.5
- Asian, %	0.6	1.2	0.5	1.0	0.5
- Hispanic, %	0.6	1.8	1.0	1.0	1.0
- Other, %	0.5	0.4	0.5	0	0
Smoking*					
- Never, %	41.0	38.0	43.0	42.0	39.0
- Past, %	38.0	42.0	43.0	41.0	45.0
- Current, %	21.0	21.0	14.0	17.0	15.0
Alcohol (g/day)	7.8 (12.9)	5.6 (9.9)	4.3 (9.6)	5.7 (11.0)	5.4 (10.1)
Physical Activity (METs/week)	15.1 (19.8)	15.1 (16.9)	17.1 (20.2)	14.0 (16.0)	16.9 (21.5)
History of Heart Disease, %	5.0	6.0	5.0	4.0	7.0
History of High Cholesterol, %	50.0	46.0	44.0	46.0	51.0
History of High Blood Pressure, %	52.0	45.0	34.0	37.0	39.0
History of diabetes, %	13.0	11.0	9.0	5.0	9.0
HbA1c ≥ 6, %	16.0	18.0	11.0	13.0	12.0
Aspirin					
- Non-users, %	50.0	50.0	51.0	53.0	55.0
- 1–5 tab/wk, %	25.0	28.0	31.0	27.0	29.0
- ≥ 6 tab/wk, %	25.0	22.0	18.0	20.0	16.0
CRP ≥ 28.5 nmol/l, %	45.0	37.0	37.0	36.0	28.0

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Range (mmol/l)	**0.7 – <0.82**	**0.82 – <0.86**	**0.86 – <0.90**	**0.90 – <0.95**	**0.95 –1.15**
Cases/Controls	**106/71**	**77/86**	**96/113**	**76/96**	**104/93**
Postmenopausal Hormone Therapy use*, %	56.0	55.0	52.0	41.0	33.0
Thiazide diuretics, %	32.0	24.0	17.0	14.0	17.0

Values are means ± SD or percentages and are standardized to the age distribution of this study population.

*matching factors.

Table 3

Plasma magnesium quintiles in relation to total ischemic stroke, thrombotic and embolic strokes (RR [95% CI])

Plasma Magnesium, mmol/l						
	Quintile 1	**Quintile 2**	**Quintile 3**	**Quintile 4**	**Quintile 5**	**p-trend**
Range	0.7 – < 0.82	0.82 – < 0.86	0.86 – < 0.90	0.90 – < 0.95	0.95 – 1.15	
Total Ischemic Stroke						
Cases/Controls	106/71	77/86	96/113	76/96	104/93	
Model 1	1.34 (0.86–2.10)	0.85 (0.55–1.32)	0.75 (0.49–1.15)	0.73 (0.48–1.10)	1.00	0.13
Model 2	1.24 (0.78–1.98)	0.81 (0.51–1.28)	0.75 (0.48–1.15)	0.72 (0.47–1.10)	1.00	0.29
Model 3	1.34 (0.82–2.17)	0.86 (0.53–1.38)	0.83 (0.53–1.31)	0.75 (0.48–1.16)	1.00	0.19
Thrombotic Stroke						
Cases/Controls	62/44	60/56	60/72	57/67	64/64	
Model 1	1.46 (0.84–2.53)	0.11 (0.65–1.90)	0.84 (0.50–1.43)	0.88 (0.54–1.42)	1.00	0.11
Model 2	1.46 (0.83–2.58)	1.03 (0.59–1.81)	0.82 (0.47–1.43)	0.83 (0.50–1.37)	1.00	0.15
Model 3	1.63 (0.89–2.98)	1.09 (0.61–1.95)	0.94 (0.53–1.68)	0.86 (0.51–1.45)	1.00	0.09
Embolic Stroke						
Cases/Controls	37/24	15/24	29/36	17/23	31/22	
Model 1	1.09 (0.46–2.60)	0.50 (0.21–1.21)	0.58 (0.27–1.24)	0.55 (0.24–1.29)	1.00	0.80
Model 2	0.90 (0.34–2.38)	0.47 (0.18–1.25)	0.64 (0.26–1.56)	0.42 (0.16–1.11)	1.00	0.94
Model 3	1.12 (0.39–3.19)	0.54 (0.20–1.48)	0.74 (0.29–1.90)	0.44 (0.16–1.20)	1.00	0.72

*Quintiles of magnesium based on distribution in controls

Model 1: Matching factors only (on age, race/ethnicity, smoking, date of blood draw, fasting status, menopausal status and hormone use)

Model 2: Model 1 + alcohol, BMI, physical activity, aspirin, thiazide diuretics

Model 3: Model 2 + HbA1c, History of diabetes, hypertension, CHD and total/HDL cholesterol

Table 4

Dichotomized magnesium levels in relation to total ischemic stroke, thrombotic and embolic strokes (RR [95% CI])

	Low magnesium	High magnesium	P-value
Magnesium levels	**< 0.82 mmol/l**	**≥ 0.82 mmol/l**	
Total Stroke			
Cases/Controls	106/71	354/389	
Model 1	1.64 (1.17 – 2.31)	1.00	<0.01
Model 2	1.55 (1.08 – 2.21)	1.00	0.01
Model 3	1.57 (1.09 – 2.27)	1.00	0.01
Thrombotic Stroke			
Cases/Controls	62/44	241/259	
Model 1	1.51 (0.99 – 2.32)	1.00	0.05
Model 2	1.56 (1.00 – 2.45)	1.00	0.05
Model 3	1.66 (1.03 – 2.65)	1.00	0.03
Embolic Stroke			
Cases/Controls	37/24	92/105	
Model 1	1.87 (0.99 – 3.49)	1.00	0.05
Model 2	1.56 (0.76 – 3.21)	1.00	0.22
Model 3	1.76 (0.83 – 3.72)	1.00	0.14

Model 1: Matching factors only (on age, race/ethnicity, smoking, date of blood draw, fasting status, menopausal status and hormone use)

Model 2: Model 1 + alcohol, BMI, physical activity, aspirin, thiazide diuretics

Model 3: Model 2 + HbA1c, History of diabetes, hypertension, CHD and total/HDL cholesterol