Nutrition 58 (2019) 36–39

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Dietary intake of magnesium and the risk of epilepsy in middle-aged and older Finnish men: A 22-year follow-up study in a general population

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ARTICLE INFO

Article History:
Received 21 March 2018
Received in revised form 31 May 2018
Accepted 19 June 2018

Keywords:
Magnesium
Epilepsy
Seizure
C-reactive protein

ABSTRACT

Objectives: Magnesium may play an important role in the prevention or treatment of epilepsy. We aimed to examine the association between dietary intake of magnesium and the incidence of epilepsy in middle-aged Finnish men in a prospective setting. As a secondary analysis, we also considered a possible association between dietary intake of magnesium and inflammation in subjects with epilepsy.

Methods: The study included 2442 men, ages 42 to 60 y, from the prospective Kuopio Ischaemic Heart Disease Risk Factor Study who were free of epilepsy at baseline between 1984 and 1989. Dietary intake of magnesium was assessed with a 4-d food record. The hospital discharge diagnosis of epilepsy was used as an outcome variable.

Results: During the average follow-up period of 22.4 y, 74 men (3%) developed epilepsy. Those who followed the recommended dietary intake (>350 mg/d) of magnesium had a lower risk of epilepsy (hazard ratio [HR]: 0.52; confidence interval [CI], 0.28–0.99; $P = 0.045$) after multivariate adjustments. However, the risk was not significant after adjustment for C-reactive protein (CRP). We also found that CRP concentration was directly associated with the risk of epilepsy (HR: 1.24; CI, 1.00–1.54; $P = 0.048$). This association was attenuated after adjustment for dietary intake of magnesium and no longer significantly associated with the risk of epilepsy (HR: 1.22; CI, 0.99–1.52; $P = 0.07$).

Conclusions: A higher dietary intake of magnesium was associated with lower incident epilepsy, and this association was slightly mediated by CRP. Further studies are required to identify the potential mechanisms.

Introduction

Epilepsy is one of the most important neurologic diseases [1] that needs to be prevented or treated. Nutrition may play a role in the physiopathology of epilepsy, and nutrients such as polyunsaturated fatty acids have been used in the treatment of epilepsy [2]. Minerals may either exacerbate or attenuate the severity of epileptic seizures [3]. However, the role of magnesium in the management of epilepsy, especially in adults, has not been fairly considered in epidemiologic or clinical trial studies. Human studies have considered the role of magnesium in the control of seizure, mainly in infants, and found that magnesium supplementation decreases the frequency of seizures [4–6]. A review of 22 cases of drug-resistant seizures also found that magnesium supplementation is a useful adjunctive medication to treat drug-resistant epilepsy [7]. Animal studies have also provided evidence for the relationship between low levels of magnesium and the risk of seizures [8,9].

The anticonvulsant activities of magnesium can be explained by several possible mechanisms. Higher levels of inflammatory markers have been shown to play a role in the development of epilepsy [10], and a higher intake of magnesium seems to decrease the risk of inflammation [11]. Magnesium is also necessary for neuronal membrane fluidity [12] and the management of N-methyl-D-aspartate receptor (NMDA) [13]. In addition, magnesium plays a crucial role in the functions of neurotransmitter range, such as gamma-aminobutyric acid (GABA) [12] and the expression of brain-derived neurotrophic factor (BDNF) [14].

Blood magnesium may not be a good indicator of the total body content of magnesium because it is not a sensitive marker

Sources of support: This study was supported by grants from the Jalmari and Rauha Ahokas Foundation and the Centre for International Mobility Fellowship (TM-14-9374) to Teymoor Yary, and the University of Eastern Finland.

Conflicts of interest: The authors have no conflict of interest. The authors were fully responsible for the study design and the funding agencies had no role in the collection, analysis or interpretation of data neither in writing of the manuscript.

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https://doi.org/10.1016/j.nut.2018.06.019
0899-9007/

to show intracellular magnesium pooling and mild magnesium deficiency [15]. Dietary intake of magnesium might be a better criterion to find the relationship between magnesium and risk of a disease. There is not enough evidence in support of the association between dietary intake of magnesium and the risk of epilepsy in adults. Therefore, we aimed to examine the association between dietary intake of magnesium and the incidence of epilepsy in middle-aged Finnish men in a prospective setting. As a secondary analysis, we also considered a possible association between dietary intake of magnesium and inflammation in subjects with epilepsy.

Methods

Study population

The Kuopio Ischaemic Heart Disease Risk Factor study was originally designed to explore cardiovascular disease (CVD) risk factors, atherosclerosis, and related outcomes in a population-based, randomly selected sample of men from Eastern Finland [16]. The baseline of the study was carried out between 1984 and 1989. A total of 2682 men, ages 42 to 60 y at baseline, were recruited in two cohorts. The first cohort, which enrolled from 1984 to 1986, consisted of 1166 men ages 54 y, and the second cohort enrolled from 1986 to 1989 and included 1516 men ages 42 to 60 y.

The baseline examinations were monitored by the 4-y examination round (1991–1993) in which 1038 men from the second cohort (88% of eligible men) participated. All men from the second cohort were invited for the 11-y examination round (1998–2001), and 854 men (95% of eligible men) participated. All eligible participants from the first and second cohorts were invited to the 20-y examination round. The baseline characteristics of the entire study population have been described elsewhere [16]. The baseline of epilepsy cases, subjects with C-reactive protein (CRP) >10 mg/L, and missing data were excluded. A total of 2442 samples were analyzed for the prospective setting. The Kuopio Ischaemic Heart Disease Risk Factor study protocol was approved by the research ethics committee of the University of Kuopio, and informed written consent was obtained from all participants before enrolment in the study.

Assessment of epilepsy

International Classification of Diseases (ICD) 9 codes were used to identify prevalent cases of epilepsy or recurrent seizures (ICD9: 345.0–9) among the cohort at baseline and these cases were excluded. New cases of epilepsy in the cohort during the follow-up period were identified on the basis of ICD-10 codes for discharge diagnosis, as recorded in the National Hospital Discharge Register and obtained by computer linkage. The following codes were considered as epilepsy: Epilepsy (G40.1–9), status epilepticus (G41.1–9), localization-related (focal and partial) epilepsy and epileptic syndrome with simple partial seizure (G40.10–19), localization-related (focal and partial) epilepsy and epileptic syndrome with complex partial seizure (G40.2: G20-22), generalized idiopathic epilepsy and epileptic syndrome (G40.30–31), other generalized epilepsy and epileptic syndrome (G40.4), special specific syndrome (G50–52), grand mal seizures, unspecified (with or without petit mal; G40.6), petit mal, unspecified, without grand mal seizures (G40.7), other epilepsy (G40.80; G40.89), and epilepsy, unspecified (G40.9).

Assessment of nutrients intake

The baseline dietary intakes of magnesium, zinc, and other nutrients were assessed with a 4-d food recording, which is a good method to measure magnesium intake [1]). Nutrient intakes were calculated using the Nutrica software (The Social Insurance Institution of Finland, Turku, Finland), and the loss of vitamins during food preparation was taken into account. Nutrica contains a large database of 1300 food items and dishes and 30 nutrients, including dietary magnesium, zinc, fats, and vitamins.

Assessment of other variables

The background information of the study subjects, including marital status and education, was obtained from questionnaires as previously described [17] Smoking status (never, past, or current smoker), smoker type (cigarettes, cigars), and the amount smoked per day were evaluated using questionnaires. Alcohol consumption (g/wk) was calculated with a structured quantity-frequency method using the Nordic Alcohol Consumption Inventory for drinking behavior over the previous 12 months [18]. Dietary intake of nutrients and total energy intake were calculated on the basis of 4-d food records [19]. The 12-month Leisure-Time Physical Activity questionnaire was used to assess leisure-time physical activity [20], and is described in more detail elsewhere [21]. The questionnaire was checked with an interview by a trained nurse and the energy expenditure from the Leisure-Time Physical Activity questionnaire was expressed as kcal/d. The weight and height of subjects were measured by the study nurse, and body mass index (BMI) was calculated as the ratio of weight in kg to the square of height in meters. A positive CVD history was coded as follows: 1) All subjects had at least one physician-diagnosed conditions (mocardial infarction, angina pectoris, other coronary conditions, cardiomyopathy, cardiac insufficiency, or stroke); and 2) all subjects also used nitrates at least once per week, and had angina pectoris according to the World Health Organization's Rose Angina questionnaire, which is a validated instrument to assess symptoms of typical angina pectoris in the general population [22]. Diabetes was defined as a self-reported physician-set diagnosis of diabetes. Serum CRP was measured with an immunometric assay (Immulite High Sensitivity CRP Assay, DPC, Los Angeles, CA).

Statistical analysis

Associations between the baseline characteristics of the study subjects (fatty acids, age, smoking status, marital status, education, alcohol intake, leisure-time physical activity, BMI, dietary intake of total fat, and CVD history) and prevalent diabetes according to the recommended dietary intake (RDI) of magnesium were examined using an independent sample *t* test for continuous variables and χ^2 test for categorical variables. The association between dietary intake of magnesium at baseline and the incidence of epilepsy during the follow-up period was examined with a Cox regression hazard's model that was adjusted for all listed baseline variables. The RDI of magnesium and CRP concentration were entered separately into the models. Moderation was examined with the interaction between magnesium and CRP. The SPSS statistical software (version 22; SPSS Inc., Chicago, IL) was used to analyze the data, and two-tailed *P* values of <0.05 were considered of statistical significance.

Results

A total of 74 men received a hospital discharge diagnosis of epilepsy during the average of 22.4 y of follow-up period. Table 1 presents the baseline characteristics of the study participants by RDI of magnesium for Finnish adult populations. Epilepsy incidence, CRP concentration, alcohol consumption, and BMI were significantly higher among subjects who received magnesium below the RDI. However, subjects with magnesium below the RDI were more educated. Total energy intake and dietary intake of total fat were higher among subjects who received magnesium above the RDI.

Table 2 shows the association between dietary intake of magnesium and the incidence of epilepsy in several different statistical models. Subjects who followed the RDI of magnesium had a lower risk of epilepsy after multivariate adjustments (hazard ratio [HR]:

Table 1
Baseline characteristics of the study participants by recommended daily intake of magnesium in the Finnish population (n = 2452)

	Recommended daily intake of magnesium		
	<350 mg/d (n = 667)	>350 mg/d (n = 1775)	*P*
Epilepsy case, n (%)	32 (4.8)	42 (2.4)	0.002
C-reactive protein, mg/L	2.09 ± 1.95	1.75 ± 1.68	<0.001
Age, y	53.2 ± 5.4	53.0 ± 5.0	0.477
Married or living as a couple, n (%)	578 (86.7)	1553 (87.0)	0.275
Education, y	9.4 ± 4.0	8.4 ± 3.2	<0.001
Current smoker, n (%)	205 (30.7)	552 (30.9)	0.996
Alcohol consumption, g/wk	95 ± 159	65 ± 107	<0.001
Leisure-time physical activity, kcal/d	143 ± 167	140 ± 176	0.674
Body mass index, kg/m^2	27.2 ± 3.6	26.7 ± 3.5	0.001
Total energy intake, kcal/d	1905 ± 408	2645 ± 546	<0.001
Total fat, g/d	81.3 ± 23.3	113.0 ± 32.4	<0.001
Cardiovascular disease, n (%)	137 (20.5)	329 (18.4)	0.236
Diabetes, n (%)	40 (6.0)	96 (5.4)	0.551
History of mental illness,%	37 (5.5)	107 (6.0)	0.675

Table 2
Risk of epilepsy (n = 74) by recommended daily intake of magnesium (<350 vs >350 mg/d) for the Finnish population

	Recommended daily intake of magnesium		
	<350 mg/d(n = 635)	>350 mg/d(n = 1,743)	*P*
Events, n/incidence rate	32/4.8	42/2.4	
Model 1	1	0.47 (0.30–0.74)	0.001
Model 2	1	0.52 (0.28–0.99)	0.045
Model 3	1	0.54 (0.29–1.0)	0.058

Cox proportional hazard-regression models were used to obtain hazard ratios and 95% confidence intervals. Model 1: Age (y) and examination y. Model 2: Adjusted for Model 1 + smokers (never, previous, current), marital status (married or living as a couple, not married, separated or divorced, widowed), education (y), alcohol consumption (g/wk), dietary intake of total fat (g/d), leisure-time physical activity (kcal/d), body mass index (kg/m^2), history of cardiovascular disease (yes/no), history of diabetes (yes/no), history of mental illness (yes/no), and dietary intake of calcium (mg/d) and zinc (mg/d). Model 3: Adjusted for Model 2 + C-reactive protein (mg/L).

Table 3
Risk of epilepsy (n = 74) by standardized mean value of C-reactive protein

	Epilepsy		
	Hazard ratio	95 % Confidence interval	*P*
Model 1	1.24	1.03–1.51	0.027
Model 2	1.24	1.00–1.54	0.048
Model 3	1.22	0.99–1.52	0.066

Model 1: Age (y) and examination y. Model 2: Adjusted for Model 1 + smokers (never, previous, current), marital status (married or living as a couple, not married, separated or divorced, widowed), education (y), alcohol consumption (g/wk), dietary intake of total fat (g/d), leisure-time physical activity (kcal/d), body mass index (kg/m^2), history of cardiovascular disease (yes/no), history of diabetes (yes/no), history of mental illness (yes/no), and dietary intake of calcium (mg/d) and zinc (mg/d). Model 3: Adjusted for Model 2 + recommended daily intake of magnesium for the Finnish population.

0.52; confidence interval [CI], 0.28–0.99; $P = 0.045$). The model was also adjusted for CRP concentration and found that CRP was affected by the association (HR: 0.55; CI, 0.29–0.1.0; $P = 0.058$; Table 2).

CRP concentration was directly associated with the risk of epilepsy (HR: 1.24; CI, 1.00–1.54; $P = 0.048$; Table 3) after adjustment for several confounders. However, CRP concentration was no longer significantly associated with the risk of epilepsy after adjustment for dietary intake of magnesium (HR: 1.22; CI, 0.99–1.52; $P = 0.066$; Table 3).

Discussion

This study found that an inverse association between dietary intake of magnesium and risk of epilepsy among middle-aged Finnish men. This association remained significant after adjustments for a number of potential confounders, such as smoking status, age, alcohol consumption, physical activity, BMI, marital status, history of mental illness, history of CVD and diabetes, and dietary intake of fatty acids.

We also found a direct association between CRP concentration and the risk of epilepsy. Therefore, we considered the possible role and interaction between magnesium and CRP concentration in subjects with epilepsy, and found that the inverse association between magnesium and the risk of epilepsy was not strongly mediated by the inflammatory process. To the best of our knowledge, this is the first prospective study to consider the association between magnesium and CRP and the risk of epilepsy, and showed an inverse and significant association between magnesium intake and epilepsy risk.

Prospective or randomized controlled clinical trials have not been conducted yet on the relationship between magnesium and the risk of epilepsy or the frequency of seizures in adults. However, a randomized, open-label follow-up study compared the efficacy and tolerability of adrenocorticotropic hormone (ACTH) plus magnesium sulfate and ACTH alone for the treatment of infantile spasms [6]. A group of subjects who received ACTH + magnesium sulfate were 73.7% seizure-free at 12 wk compared with 47.4% of the control group (ACTH alone) [6].

Case report studies have also shown that oral magnesium supplementation can control seizures in infants with hypomagnesaemia [4,5]. In addition, animal studies have shown that low blood-magnesium concentration is associated with seizures [8,9]. In rats, a deficiency in dietary intake of magnesium was associated with a reduction in the thresholds and latencies of seizure. In contrast, the administration of 3-wk magnesium supplementation was shown to increase the thresholds and latencies of seizure [8]. Magnesium supplementation has also been shown to enhance the efficacy of the anticonvulsant properties of valproate in pentylenetetrazol-treated rats [9].

Inflammation may play a role in the pathophysiology of epilepsy [10], and both animal and humans studies have suggested that magnesium may decrease inflammatory markers [23,24]. In humans, a low intake of magnesium was associated with higher levels of CRP concentration [25]. In animals, incused magnesium deficiency was associated with higher levels of proinflammatory cytokines such tumor necrosis factor and interleukin 6 [24]. In the present study, a higher concentration of CRP was significantly associated with the risk of epilepsy, and a dietary intake of magnesium attenuated this association. However, the relationship between magnesium and the risk of epilepsy appears not appreciably mediated by CRP because magnesium was still able to predict the risk of epilepsy.

Other possible mechanisms such as NMDA receptor, BDNF, and neurotransmitters may further explain the association between magnesium and epilepsy. NMDA receptor antagonists have been shown to have anticonvulsant properties, and magnesium is a non-competitive NMDA receptor antagonist that is able to manage neurotransmission through blocking voltage-dependent NMDA receptors [9]. In addition, magnesium is needed to bind the majority of monoamines to their receptors [26]. Magnesium seems to be a co-factor for the synthesis of GABA [13], synaptic GABA has a potent anticonvulsant property, and GABA synthesis reduces the risk of seizures [26]. BDNF has a critical role in the modification of the structure and function of the central nervous system as well as neuroprotective effects [27]. Magnesium has been shown to significantly increase the expression of BDNF [14].

The strengths of our study include the population-based recruitment, prospectively collected data, extensive examinations for potential confounders, and long follow-up period with a large number of events. A single measurement of magnesium at baseline only and a lack of measurements of copper intake may be potential limitations of the present study. Also, we considered the association between magnesium and epilepsy in middle-aged and older men, so our findings may not be generalizable to younger populations or women. In addition, history of convulsion without hospitalization was not available.

Conclusions

In this prospective population-based follow-up study, a higher dietary intake of magnesium was associated with a lower risk of epilepsy among middle-aged and older men from Eastern Finland. In addition, our results suggest that the association between dietary intake of magnesium and the risk of epilepsy is not mediated by CRP.

Acknowledgments

The authors thank the personnel at the former Research Institute of Public Health and all study subjects for their valuable contribution to this study. We also thank Kimmo Ronkainen M.Sc. for data management and support for this study.

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