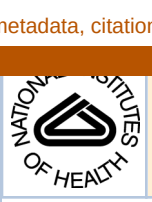

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Association of Dietary Magnesium Intake With Radiographic Knee Osteoarthritis: the Johnston County Osteoarthritis Project

Bo Qin, BSc[1], **Xiaoyan Shi, PhD**[2], **Peter S. Samai, MPH**[3], **Jordan B. Renner, MD**[4,5], **Joanne M. Jordan, MD, MPH**[3,5,6,7], and **Ka He, MD, ScD**[1,3]

[1]Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

[2]Advanced Analytics Division, SAS Institute Inc., Cary, NC

[3]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

[4]Department of Radiology, University of North Carolina at Chapel Hill, Chapel Hill, NC

[5]Thurston Arthritis Research Center, University of North Carolina at Chapel Hill, Chapel Hill, NC

[6]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

[7]Department of Orthopedics, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Purpose—To examine the cross-sectional association between dietary magnesium (Mg) intake and the radiographic knee osteoarthritis (OA) among African-American and Caucasian men and women.

Methods—The presence of radiographic knee OA was examined among participants from the Johnston County Osteoarthritis Project (JoCo OA) and was defined as Kellgren-Lawrence (K-L) grade of at least 2 in at least one knee. The Block Food Frequency Questionnaire (FFQ) was used to assess Mg intake. Effect modifiers were explored by testing interactions of Mg intake and selected factors based on previous literature. The multivariable logistic regression model with standard energy adjustment method was used to estimate the relation of Mg intake and radiographic knee OA.

Results—The prevalence of knee OA was 36.27% among 2112 participants. The relation of Mg intake and radiographic knee OA was found to be modified by race (*P* for interaction = 0.03). An inverse threshold association was observed among Caucasians. Comparing to those in the lowest quintile, the relative odds of radiographic knee OA was cut by half for participants in the second quintile of Mg intake (OR: 0.52; 95% CI 0.34–0.79); further Mg intake did not provide further benefits (*P* for trend = 0.51). A statistically significant association was not observed among African Americans.

Corresponding author: Dr. Ka He, Department of Nutrition, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 2221 McGavran-Greenberg, Campus Box: 7461, Chapel Hill, NC 27599, USA, Phone: 919-843-2476, Fax: 919-966-7216, kahe@unc.edu.

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Conclusion—A modest inverse threshold association was found between dietary Mg intake and knee OA in Caucasians but not in African Americans. Further studies are needed to confirm the results and to elucidate the possible mechanisms of action for the racial modification.

Introduction

Osteoarthritis (OA) is the most common type of joint disorder in the United States (1). OA can lead to difficulties in locomotor activities, and it is the principle reason for total knee replacement (2). Although the etiology of OA is not completely clear yet, several lines of evidence support the role of inflammation in OA pathogenesis (3–5). Previous studies found higher levels of C-reactive protein (CRP) and other inflammatory markers in people with OA compared with those without OA (3). Elevated levels of CRP were associated with early knee OA risk and the increased progression of OA (4). Also, a body of evidence suggests the key roles of proinflammatory cytokines IL-1 and TNF-α in the pathogenesis of human OA (5).

Magnesium (Mg) is one of the most important micronutrients for human health and is strongly associated with immune responses (6). In animals fed a Mg-depleted diet, inflammatory cytokine production was stimulated and an elevated level of proinflammatory cytokines observed (7–9). In human studies, individuals with low intake of Mg were more likely to have elevated CRP levels (10, 11).

Data directly relating Mg to OA are limited. One female twins study showed that there was a significant reduction in serum Mg levels among co-twins with OA (12). Also, low serum Mg was observed in women living in OA-endemic areas (13). In addition, studies have been published on Mg and some chronic diseases linked to inflammation. For example, patients with rheumatoid arthritis have been found to have inadequate Mg intake (14–16). Dietary Mg deficiency was associated with atherosclerosis, hypertension, osteoporosis, diabetes mellitus, colon and breast cancers which were suggested by several epidemiological studies (17). The mechanism of low Mg in relation to these health conditions was believed to be through promotion of inflammatory responses. Since low Mg might incite inflammatory responses that may play a central role in OA, it was hypothesized that Mg intake would be inversely associated with knee OA. In addition, previous findings on the presence of racial differences in the population inflammatory level suggests that there might be a racial difference in the relation between Mg intake and knee OA (18). Therefore, a cross-sectional analysis was conducted to test these hypotheses using available data from African-American and Caucasian men and women enrolled in the Johnston County Osteoarthritis Project (JoCo OA).

Materials and Methods

Study Population

The JoCo OA is a population-based study of OA in African American and Caucasians, aged ≥ 45 years, who were residents of one of the 6 townships of Johnston County for at least one year at the time of recruitment from 1990-98 and who were capable of completing the study protocol. Participants were recruited without regard to arthritis symptoms. The details of this study cohort and design have been described elsewhere (19). In brief, this project sampled potential participants from 6 townships in Johnston County and did not find significant difference between respondents and non-respondents in age, sex, ethnic group, education level, or presence of knee pain. From 1999 to 2003, a total of 1934 participants completed a survey including dietary intake measurement and radiographic knee OA assessment. A second recruitment was conducted from 2003 to 2004 to deliberately enrich the sample for African Americans and younger individuals using a similar protocol as before. 1146

individuals were enrolled and assessed. As described before (20), the newly recruited participants were younger (mean age 59.3 years in newly enrolled *vs* 65.8 years in the first recruitment) and more likely to be African American (40% *vs* 28%). These two recruitments established the study cohort that comprised of 3080 participants. The present analysis excluded participants with radiographic evidence of an inflammatory arthropathy of the knee (n=6) due to its distinct cytokine patterns from OA (21), and participants who had missing data on diet (n=921) or OA (n=59). A total of 2112 participants remained in the analyses. This study was approved by the Institutional Review Boards of the University of North Carolina at Chapel Hill and the Centers for Disease Control and Prevention. All participants gave written informed consent at the time of recruitment.

Diet Assessment

Dietary information was collected by a computer-based 68-item modified version of the National Cancer Institute (NCI) Block food frequency questionnaire (FFQ) to inquire about the average consumption of foods and drinks over the past 10 years. Participants were asked how often they consumed each food in the past 10 years and the portion size of the food. Questions included up to nine possible responses from never to 2 or more per day for food and from never to 6 or more per day for drinks. Respondents were asked to indicate if their usual serving size was medium portion size specified by the questionnaire for each food item, or one-half of the medium size, or 1.5 times of that size. The NCI Block FFQ has been well validated and adopted by previous epidemiological studies of Mg (22, 23). Information on multivitamin or Mg supplement use was also collected through the NCI Block FFQ. Nutrient intakes including Mg intake were calculated using the NCI DIETSYS software (24).

Radiographic Knee OA

All participants underwent bilateral anteroposterior radiography of the knee with weight-bearing. A single radiologist, without knowledge of participants' clinical status, read all radiographs by using the Kellgren-Lawrence (K-L) radiographic atlas. OA was divided into five categories according to K-L grades: 0 = absence of OA; 1 = doubtful of OA; 2 = minimal OA; 3 = moderate OA; 4 = severe joint OA (25). Radiographic knee OA was defined as K-L grade of at least 2 in at least one knee. As previously described (19), inter-rater reliability assessed with another trained radiologist and intra-rater reliability between radiographic readings of two separate times were high (κ=0.86 and 0.89 respectively).

Statistical Analysis

In this cross-sectional analysis, the means and standard deviations were calculated for the continuous variables (age, BMI, years of education and total energy intake) and the percentages for the categorical variables (gender, smoking status and alcohol drinking) across quintiles of Mg intake for both African Americans and Caucasians. Effect modifiers were explored by testing interactions of Mg intake and selected factors based on previous literature and statistical significance inferred by $P < 0.10$. Multivariable logistic regression with standard energy adjustment method was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for knee OA according to quintiles of Mg intake with the lowest quintile as the reference group. Median Mg intake value of each quintile was used for creating a continuous variable to test for trend. The analyses were separately conducted for Caucasian and African American. The model simultaneously adjusted for age, gender, body mass index (BMI), smoking status, alcohol drinking, education and total energy intake. Second- to fourth-order polynomial terms for continuous Mg variable were tested to assess potential nonlinear associations.

The current study conducted sensitivity analyses to test the robustness of the results by including additional dietary variables i.e. dietary fiber, calcium and potassium in the models. In addition, to explore the effects of supplementation, this study analyzed the data with adjustment for supplement use and by excluding supplement users separately. The effects of NSAID use and aspirin use in particular was also evaluated by additionally adjusting for the use of NSAID or aspirin, and by conducting sensitivity analysis on non NSAID users or non aspirin users respectively. A two-side *P* value less than 0.05 was considered significant except for the interaction *P* value whose cutoff was set at 0.10.

Results

Baseline characteristics of the study population according to quintiles of total Mg intake stratified by race are shown in Table 1. For both African Americans and Caucasians, compared with individuals in the lowest quintile of Mg intake, those in the highest quintile were more likely to be male and to be a smoker, have higher education levels, higher alcohol consumption and total energy intake. For African Americans, those in the highest quintile of Mg intake tended to be younger, while for the Caucasians they tended to be older, compared with the lowest quintile of Mg intake.

The overall prevalence of knee OA in the current study was 36.27%. The associations of Mg intake and knee OA were significantly modified by race (*P* for interaction = 0.03). After stratifying the data, a modest inverse threshold association between Mg intake and knee OA was observed in Caucasians adjusted by gender, BMI, smoking status, alcohol drinking, education and total energy intake (Table 2). The multivariable-adjusted ORs (95% CI) of radiographic knee OA across quintiles of Mg intake were 1, 0.52 (95% CI 0.34–0.79), 0.75 (95% CI 0.49–1.15), 0.60 (95% CI 0.38–0.95), 0.65 (95% CI 0.42–1.02); *P* for trend = 0.51. This observed threshold association was confirmed by fitting a fourth-order model (*P* = 0.03). No any significant association was found among African Americans.

Because dietary fiber, calcium, and potassium are likely to be correlated with the dietary Mg intake, sensitivity analysis was performed by testing each of them based on the multivariable adjusted model. None of these nutrients appreciably altered the result with or without adjusting for it or modified the observed associations.

Approximately, 35% participants used supplements in this cohort. To eliminate the possible confounding by supplement use, we further adjusted supplement use in the multivariable-adjusted model and analyzed data in supplement non-users only. The relation of Mg intake and radiographic knee OA remained. We additionally adjusted NSAID use and aspirin use in the model respectively and conducted sensitivity analysis on NSAID non-users or aspirin non-users, and the results remained (data not shown).

Discussion

In population-based cohort, a modest inverse threshold association between Mg intake and knee OA was found among Caucasians independent of major lifestyle variables. Such a relation was not observed in African Americans.

The results of the present study in Caucasians are in accordance with previous findings in serum Mg levels and OA. One previous twin study reported that there was a significant reduction in serum Mg levels among OA twins by discordant twin pair analysis of 66 monozygotic and 163 dizygotic twins (12). Another study found low serum Mg concentration in women living in an OA-endemic area (13), which indicates a possible inverse association between Mg intake and OA. To the best of our knowledge, studies directly relating Mg intake and OA have not been reported.

Although the magnitude is relatively small, the observed inverse association of Mg intake and knee OA in Caucasians is biologically plausible. Mg deficiency has long been considered to result in an inflammatory response (26), which is currently recognized as etiological to OA formation and progression. Several studies such as Women's Health Study and Nurses' Health Study where the majority of the study participants were Whites suggested that Mg intake or its serum level was inversely associated with human plasma CRP levels (10, 11, 27–29). Also, elevated CRP level was found in early OA patients compared with healthy individuals and was associated with greater OA progression (4). In addition, proinflammatory cytokines especially IL-1 and TNF-α were found to mediate OA pathogenesis. One animal study suggested that Mg deficiency was related to an up-regulated gene expression of IL-1 receptor and TNF receptor in rat thymocytes (30). Moreover, Mg has been recognized to initiate innate immune response by stimulating macrophages and promotes a pro-angiogenesis environment, which is believed to be intimately integrated in the progression of OA (3, 31, 32). The deficiency of this divalent cation may also impair the chondrocyte-matric interactions in the pathogenesis of OA through inhibition of the expression and activity of integrins (33).

A number of chronic diseases are involved in conditions associated with low-grade inflammation, such as obesity (34), insulin resistance and type 2 diabetes (35–37), hypertension (38), and coronary heart disease (39). Various studies suggested that these health conditions were associated with low Mg intake or low serum Mg level. For instance, a study found that serum Mg levels were lower in obese subjects than in lean individuals, and were correlated with elevated concentrations of inflammatory indicators (40). In addition, studies reported that Mg intake or serum Mg levels were inversely related to the risk of type 2 diabetes (41, 42), hypertension (41, 43), cardiovascular disease (41, 44, 45), and metabolic syndrome (10). These findings on Mg and the risks of low-grade inflammation-related diseases are consistent with the results in Caucasians showing an inverse threshold association between Mg intake and the knee OA, which is considered as an inflammation-related disease.

A similar inverse relation was not observed among African Americans as in Caucasians. Although the mechanism for the racial modification found in this study is not clear, there are several possible explanations. First, approximately 30% participants are African American in this cohort. Consequently, the numbers of prevalent cases of OA in African American participants were relatively small so that the results among African Americans might be explained by chance. Second, studies suggest that African Americans tend to have higher background levels of inflammation and oxidative stress than Caucasians. Therefore African Americans may be more prone to inflammatory diseases, which is in consistent with the result of the current study in that the prevalence of OA in Blacks was 41% while in Whites 34% (18). Studies also indicate that serum concentrations of antioxidants such as vitamin E and α-carotene were lower in African Americans than in Caucasians (46, 47). In the face of increased inflammation and lower levels of antioxidants in African Americans, it may be that the potential anti-inflammatory effects of Mg intake is not sufficient to substantially reduce the odds of OA among African Americans. Third, since the median level of the first quintile of Mg intake (130 mg/d) was nearly 50% of the estimated average requirement (EAR) (265 mg/d for female and 350 mg/d for male) (48), it might mask a possible threshold association existed in African Americans because of the relatively high reference level. In addition, African Americans may have a poorer quality of diet as compared with Caucasians (49–51). Possible racial differences in diet quality may partially account for the observed racial modification on the relation between Mg and knee OA. Finally, the possibilities cannot be completely ruled out that the observed racial difference is, at least in part, due to unknown or unmeasured confounders such as socioeconomic status, although

the multivariable model in this study accounted for different education levels, a reasonably proxy for this.

Some limitations need to be highlighted. The nature of the cross-sectional analysis does not allow us to establish the temporal association and causal inference between Mg intake and radiographic knee OA. It is therefore premature to discuss using Mg as a therapeutic tool in OA. However, since this study may be the first one investigating the relation between Mg intake and knee OA, the cross-sectional nature does not compromise the value of the study. Findings from this analysis can help generate hypothesis for future research. Besides, since Mg intake was assessed by FFQ, some degree of measurement error was inevitable. However, the NCI Block FFQ has been well validated and has been widely used in previous epidemiological studies of Mg intake (22, 23). Nevertheless, any measurement error in the current study is likely to be non-differential, and the information collected should enable ranking participants and calculate the relative risks.

The strengths of this study include the single experienced bone and joint radiologist assessing all of the radiographs, which generated accurate and consistent measurement of knee OA. Also, the consistent results in several sensitivity analyses suggest that the findings from the current study are robust. In addition, the findings of the current study are less likely to be confounded by supplement use since the results were found to be similar even among supplement non-users.

The increasing recognition that nutrition is involved in joint health and the potential benefits of dietary manipulation on patients with joint disorders call for more research on nutritional factors that either prevent or benefit the treatment of the joint disease (33). This study provides the first epidemiological evidence of a relation between Mg intake and knee OA. A modest inverse threshold association between Mg intake and knee OA risk was observed among Caucasians. Certainly further studies are needed to confirm the findings from the present study and to elucidate the potential mechanisms of action, particularly for the racial difference.

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Significance & Innovation

- Osteoarthritis (OA) may have an inflammatory pathogenesis and magnesium (Mg) an anti-inflammatory property, but data directly relating Mg intake to OA are lacking.
- This study provides the first epidemiological evidence of a relation between Mg intake and radiographic knee OA.
- Mg intake has a modest inverse threshold association with knee OA among Caucasians but not in African Americans.
- This study offers great value in hypothesis generation in studying the relation of dietary factors and OA.

Table 1

Baseline characteristics by quintiles of dietary magnesium by race, Johnston County Osteoarthritis Project

Characteristics	African Americans (n=665)						Caucasians (n=1447)					
	1	2	3	4	5	*P**	1	2	3	4	5	*P**
Mg intake†, mg/d	129.8	182.7	234.8	304.7	469.7	--	135.8	185.3	234.4	307.2	523.9	--
Age, y	64.4 (11.1)	61.7 (10.6)	60.5 (10.6)	61.2 (10.7)	61.3 (11.2)	0.01	64.2 (10.4)	65.4 (10.4)	65.3 (10.5)	62.9 (10.0)	64.8 (10.0)	0.02
BMI, kg/m^2	30.9 (6.6)	31.2 (7.6)	31.3 (8.0)	30.8 (8.1)	31.1 (5.6)	0.96	28.4 (5.2)	28.7 (5.6)	28.3 (5.5)	28.7 (6.0)	28.3 (5.9)	0.74
Female, %	83.5	76.4	67.2	59.7	62.0	<0.001	73.8	70.2	67.7	55.9	59.8	<0.001
Smoking status, %												
Never	66.7	66.5	53.7	43.7	55.7	0.006	68.1	50.4	62.7	52.0	53.4	<0.001
Former	17.2	18.7	26.8	30.2	25.3	--	18.9	30.7	27.1	29.7	35.2	--
Current	16.1	14.8	19.5	26.2	19.0	--	13.0	18.9	10.2	18.2	11.4	--
Alcohol drinking, %	12.0	7.8	18.9	21.1	14.7	0.03	6.9	15.1	14.6	24.9	23.1	<0.001
Education‡, y	11.0 (4.1)	11.8 (3.7)	12.4 (3.7)	11.8 (3.8)	12.5 (3.5)	0.008	12.0 (4.3)	13.2 (3.7)	13.7 (6.5)	14.1 (4.4)	14.4 (4.3)	<0.001
Total energy intake‡, kcal/d	1141 (341)	1573 (378)	1973 (469)	2442 (631)	2750 (1284)	<0.001	1099 (284)	1481 (360)	1812 (429)	2119 (626)	2046 (945)	<0.001

BMI, body mass index; Mg, Magnesium.

* *P* values are for test of difference across all quintiles of magnesium intake.

† Magnesium intake is median level of each quintile.

‡ Values are mean (standard deviation).

Table 2

Multivariable-adjusted relations of magnesium intake and knee OA*

	Quintiles of magnesium intake					*P* for trend
	1	**2**	**3**	**4**	**5**	
African American (n= 665)						
Mg intake, mg/d	129.80	182.44	234.77	303.98	469.74	--
# Participants	182	151	125	128	79	--
# Knee OA	71	64	50	57	33	--
Adjusted OR (95% CI)†	1.00 (Reference)	1.57 (0.92–2.68)	1.40 (0.76–2.58)	1.76 (0.89–3.47)	1.34 (0.60–2.98)	0.73
Caucasian (n= 1447)						
Mg intake, mg/d	135.77	186.35	234.36	306.62	523.87	--
# Participants	240	272	297	295	343	--
# Knee OA	93	79	110	90	119	--
Adjusted OR (95% CI)†	1.00 (Reference)	0.52 (0.34–0.79)	0.75 (0.49–1.15)	0.60 (0.38–0.95)	0.65 (0.42–1.02)	0.51

OA: osteoarthritis; Mg, Magnesium.

*Values are OR (95% CI).

†OR adjusted for age (y), gender, BMI (kg/m^2), smoking status (never smoker, past smoker, or current smoker), alcohol drinking (yes/no), education (in school years) and total energy intake (kcal/d).

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