Original Research

Dietary Magnesium and C-reactive Protein Levels

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Objective: Current dietary guidelines recommend adequate intake of magnesium (310–420mg daily) in order to maintain health and lower the risk of cardiovascular disease. Recent evidence from animal and clinical studies suggests that magnesium may be associated with inflammatory processes. The objective of this study was to determine whether dietary magnesium consumption is associated with C-reactive protein (CRP), a marker of inflammation, in a nationally representative sample.

Methods: Analysis of adult ($\geq$17 years) participants in a cross-sectional nationally representative survey (National Health and Nutrition Examination Survey 1999–2000 [NHANES]) who were not taking magnesium or magnesium-containing supplements. The primary outcome measure was high sensitivity CRP (elevated $\geq$3.0mg/L).

Results: Among US adults, 68% consumed less than the recommended daily allowance (RDA) of magnesium, and 19% consumed less than 50% of the RDA. After controlling for demographic and cardiovascular risk factors, adults who consumed <RDA of magnesium were 1.48–1.75 times more likely to have elevated CRP than adults who consumed $\geq$RDA (Odds Ratio [OR] for intake <50% RDA = 1.75, 95% Confidence Interval [CI] 1.08–2.87). Adults who were over age 40 with a BMI >25 and who consumed <50% RDA for magnesium were 2.24 times more likely to have elevated CRP (95% CI 1.13–4.46) than adults $\geq$RDA.

Conclusions: Most Americans consume magnesium at levels below the RDA. Individuals with intakes below the RDA are more likely to have elevated CRP, which may contribute to cardiovascular disease risk.

C-reactive protein (CRP) is an important serum protein that reflects vascular inflammation, and is associated with increased risk of cardiovascular disease events [1,2]. Low grade inflammation and elevation of CRP has also been associated with obesity, high blood pressure and diabetes [3–6]. Because of these associations and the fact that cardiovascular disease is a leading cause of morbidity and mortality in the U.S. [7,8], the American Heart Association (AHA) recently published guidelines that define risk levels for CRP, and recommended further research be done, including investigation of possible nutritional causes of elevated CRP [2].

Interest in a possible relationship between magnesium and CRP has increased due to recently published studies documenting

an association between serum magnesium levels and cellular processes that affect vascular endothelial functions including production of inflammatory cytokines and oxidative stress [9–13], processes that also result in elevation of CRP. Further, decreased serum magnesium levels have been documented in people with obesity who also have elevated CRP [14]. Both magnesium and CRP have been associated with alterations in blood pressure [3,15–17]. Whether dietary magnesium intake is associated with CRP levels in the general population of adults has not been determined.

To investigate the possible relationship between dietary magnesium consumption and CRP we conducted a study using the 1999–2000 National Health and Nutrition Examination

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Survey (NHANES 99–00), a national study of the civilian, non-institutionalized population in the United States. Use of the NHANES database provides a nationally representative sample, the availability of high sensitivity C-reactive protein assays, and the ability to take into account demographic and other risk factors that may affect the relationship between magnesium and CRP [3–5,18].

METHODS

We derived our study sample from the participants in the National Health and Nutrition Examination Survey 1999–2000 (NHANES 99–00). The NHANES 99–00 is the most recent release of this nationally representative, complex, multi-stage, probability based survey of the civilian, non-institutionalized population of the US. The 12-month survey was conducted beginning April 1999 by the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention. This survey was designed to collect information about the health and diet of people in the United States. The NHANES 99–00 combined a home interview with health tests done in a Mobile Examination Center. The health tests consisted of both physical exam and laboratory components. The laboratory data files include findings from analyses of blood, urine, hair, air, tuberculosis skin test, and household dust specimens. Specimens were collected at the mobile examination centers or in the home. The NHANES design includes an over-sampling of minority persons. Because of this complex sampling design appropriate weighting factors (based on statistical stratification and population estimates) must be taken into account when calculating population-based frequency estimates. In the NHANES 99–00, 5773 adults age 17 or older were interviewed and examined. By race/ethnicity, this population contains 1891 Hispanics (34.7%), 2353 Non-Hispanic Whites (43.2%), 1049 Non-Hispanic Blacks (19.3%), and 155 Others (2.9%). We limited our sample of participants for this analysis to adult participants ($\geq$17 years of age) who had dietary intake of magnesium available (n = 5021).

High sensitivity C-reactive protein (CRP) was measured as part of the NHANES 99–00 physical and laboratory examination. Standard phlebotomy techniques were used to obtain specimens. Serum specimens were frozen to $-20°C$ until used for laboratory analysis. CRP was analyzed using a high sensitivity assay technique that quantifies CRP by latex-enhanced nephelometry [19]. Further details about the specific method used in the laboratory procedures of the NHANES 99–00 are available on the NHANES web site (www.cdc.gov/nchs/nhanes.htm) and elsewhere [18]. The threshold of elevated CRP used in the current study was defined by recently published American Heart Association (AHA) guidelines that designate CRP levels $\geq$3.0 mg/L as associated with high cardiovascular risk [2].

Dietary intake in the NHANES 99–00 is based on recollection of foods eaten the previous day by the respondent coupled with known nutritional content of each of these foods (24 hour recall). The total daily dietary intakes for magnesium and other nutrients were derived from the 24 hour recall information for each respondent using the NHANES computer-assisted dietary interview (CADI) system, an automated data collection form that was developed using Power Builder™, and several databases (i.e., Quick List food list, brand name food list, and food amount unit list) linked to this system. We focused our analysis on people not taking magnesium supplements in order to concentrate on the physiologic effect of a magnesium deficient diet.

The US Office of Dietary Supplements of the National Institutes of Health (http://ods.od.nih.gov/index.aspx) and the Institute of Medicine (IOM) has established Recommended Daily Allowances (RDA) of magnesium intake based on gender and age (Table 1). For each person in the study population we calculated the percentage of the RDA that they had consumed. Four groups were established based on magnesium consumption: less than 50% of the RDA, 50–74% of the RDA, 75–99% of the RDA, and 100% or more of the RDA. Dietary fiber intake was included in the analysis using similar groups, as a percent of recommended daily intake of fiber of 22 g/day (recommended minimum of >21 g/day for adults, per the AHA (non-specific), IOM, and the American Dietetic Association, available on the web at: http://www4.nationalacademies.org/news.nsf/isbn/0309085373?OpenDocument).

Demographic variables (age group, race, sex) were included as control variables because of their known impacts on CRP [20]. In an effort to determine the independent relationship between specific eating behaviors and CRP, additional variables were included that might be linked to eating behavior or also influence CRP level. We controlled for body mass index (BMI - kg/m^2) because of its link to diet and its known association with CRP [4]. We also controlled for current smoking status, income level (above or below the poverty level), alcohol consumption, exercise, and the presence of certain medical conditions. These medical conditions include a history or diagnosis of congestive heart failure, coronary heart disease, angina, heart attack, diabetes, or hypertension due to the known effects of these conditions on CRP levels [2,18,20]. Because the quantity of magnesium and fiber consumed may be linked to the total amount of food consumed, total caloric intake was incorporated as another control variable [18,21].

Table 1. US RDA for Magnesium Based on Age and Gender (US Office of Dietary Supplements of The National Institutes of Health)

Age Group	Men	Women
14–18	410 mg	360 mg
19–30	400 mg	310 mg
31+	420 mg	320 mg

Table 2. Demographic Characteristics (Percentages) of Adults Not Taking Magnesium-Containing Supplements Who Fall into Each Magnesium Intake Group, with A χ^2 Analysis of the Distribution

Demographic Group	<50% RDA	50–74% RDA	75–99% RDA	≥RDA	χ^2 p=
Percent of Population	25.4	30.5	22.6	21.5	
Age					0.007
17–35	27.0	29.7	21.9	21.4	
36–55	21.0	32.0	21.8	25.2	
56–65	26.8	31.5	26.6	15.1	
66+	31.4	28.1	24.3	16.2	
Race					<0.001
White	21.7	28.9	24.8	24.6	
Non-White	32.6	33.5	18.3	15.5	
Gender					0.359
Male	23.6	30.2	23.6	22.6	
Female	27.2	30.8	21.6	20.4	
BMI					0.797
<25	23.8	31.3	23.0	21.9	
≥25	26.4	30.0	22.4	21.2	
Current Smoker					0.105
Yes	28.9	31.0	20.4	19.6	
No	23.8	30.2	23.6	22.4	
Income					0.029
PIR <1.0	30.7	33.5	19.8	16.0	
PIR >1.0	24.1	30.0	23.3	22.6	
Alcoholic Drinks					0.014
≤1/month	27.9	32.1	20.8	19.2	
>1/month	20.9	29.2	24.6	25.4	
Exercise					<0.001
None	31.1	29.1	21.4	18.4	
Some	21.1	31.6	23.5	23.8	
Medical Condition					0.159
Yes	27.7	30.2	24.0	18.2	
No	24.6	30.6	22.1	22.7	
Fiber Intake #					<0.001
<50% RDA	55.7	32.1	8.3	3.8	
50–74% RDA	12.3	47.5	28.7	11.5	
75–99% RDA	2.1	26.1	44.7	27.1	
≥100% RDA	0.2	6.6	24.0	69.2	
Caloric Intake					<0.001
Lowest Quartile	62.5	29.4	6.1	2.1	
Second Quartile	26.1	40.8	21.8	11.3	
Third Quartile	10.5	34.1	31.0	24.4	
Highest Quartile	2.8	18.2	31.5	47.5	

The "RDA" for fiber signifies the lower level of recommended range of intake of 22 g/day from IOM.

We used SUDAAN (Research Triangle Institute, Research Triangle, NC), a specialized statistical program that accounts for the complex weighting of the NHANES 99–00 sample [22]. Using SUDAAN allowed us to correct for unequal probabilities of selection and different response rates, ensuring that the results can be generalized to the non-institutionalized civilian population of the U.S. Thus the percentages and odds ratios in this study represent weighted values. SUDAAN also adjusts the standard errors to account for the weighting, stratification, and clustering of the complex sampling design to ensure that expressed p values are valid [23].

Descriptive statistics for the sample were performed to illustrate the demographic characteristics and dietary magnesium intake. For each of the demographic variables (age, race, gender, etc.), the association with the dietary magnesium quartile group was examined using χ^2 analyses. We also conducted a test for trend between Mg quartile and CRP.

Magnesium intake was examined in adjusted multivariate logistic regression analyses predicting elevated CRP (≥3.0 mg/L). The covariates age, race, gender, BMI, income, alcohol consumption, exercise, medical conditions, and total caloric intake were included in the models to control for their effects. Standardized betas, p-values, odds ratios, and 95% confidence intervals were obtained from the logistic regression output. Statistical significance was defined as ≤0.05 without correction for multiple-comparisons, since there was only one mineral examined, and the specific analyses were planned in advance. The models were run for the entire study population of adults

Table 3. Percent of Population with Elevated CRP ($\geq$3.0 mg/L) and Median CRP by Magnesium Intake Group

Group	All People	<50% RDA	50–74% RDA	75–99% RDA	$\geq$RDA	χ^2 p=
All People						
% Elevated CRP	35.5	37.2	35.7	34.7	35.0	0.807
Median CRP (mg/L)	2.02	2.12	1.91	1.97	2.03	
Not Taking Mg Supplements						
% Elevated CRP	33.8	36.9	34.9	33.9	28.4	0.045*
Median CRP (mg/L)	1.88	2.09	1.89	1.94	1.70	

* Test for trend significant p < 0.05.

and also for the subset of adults who did not consume dietary supplements containing magnesium. Another series of logistic regression models were created incorporating both magnesium and fiber to examine the combined effects of consuming various amounts of each. We also examined the relationship between dietary magnesium and CRP levels in the subgroup of people over the age of 40 with BMI $\geq$25, a group at higher risk of cardiovascular disease.

RESULTS

The 1999–2000 NHANES contained 5021 adults with daily magnesium intake values corresponding to a US population of 195,214,424. The average daily intake of magnesium (including magnesium from dietary supplements) was 328 mg, with a median of 293 mg. Among US adults, 68% consumed less than the RDA of magnesium, and 45% consumed less than 75% of the RDA. Supplements containing magnesium, including antacids, magnesium supplements, and vitamin and mineral supplements, were used by 30% of people.

Our focus was on people not taking magnesium or magnesium-containing supplements (n = 3799), 78.5% of whom consumed less than the RDA of magnesium (Table 2). People who were older, non-whites, living below the poverty level, consuming few alcoholic drinks, or non-exercisers tended to consume less than the RDA of dietary magnesium. Gender, BMI, smoking, and having a medical condition did not significantly relate to magnesium consumption.

The median CRP level for all adults was 2.02 mg/L, and 35.5% had a CRP level $\geq$3.0 mg/L. The percent of people having elevated CRP varied by magnesium intake (Table 3). Among people not taking supplements, those who consumed less dietary magnesium tended to be more likely to have elevated CRP (χ^2 p = 0.045). The median CRP value in people who consumed <50% of the RDA for magnesium was higher than the median CRP in people who consumed $\geq$RDA (Table 3).

In the logistic regression analysis, after controlling for age, race, gender, BMI, smoking, income, alcohol consumption, exercise, medical conditions, and total caloric intake, individuals in any quartile below the RDA of magnesium were significantly more likely to have elevated CRP than adults who consumed $\geq$RDA (Table 4). Among adults over the age of 40 with BMI $\geq$25 who do not use magnesium supplements, those who consumed <50% of the RDA of magnesium were 2.24

times more likely to have elevated CRP than those who consumed $\geq$RDA of magnesium (95% CI 1.13–4.46).

Adding fiber to the regression model eliminated associations between magnesium and elevation of CRP. Both fiber consumption and total caloric intake were significantly correlated with magnesium intake: Pearson Correlation Coefficients 0.60 (r < 0.0001) and 0.53 (r < 0.0001), respectively. In an attempt to further delineate the effects of magnesium and fiber intake, we examined the group of adults who consumed both magnesium and fiber at levels <50% of the RDA, and found that they were 2.09 times more likely to have elevated CRP (95% CI 1.30–3.37) than adults who consumed both at levels above the RDA.

DISCUSSION

This study investigated the relation between dietary magnesium intake and CRP levels, and found that dietary magnesium intake was inversely related to CRP (Table 3). Among the 70% of the population not taking supplements, magnesium intake below the RDA was significantly associated with a higher risk of having elevated CRP. The lower the magnesium intake, the higher was the likelihood of elevated CRP (Table 4). This association was maintained after controlling for important factors that might confound the association, including age, race, gender, BMI, smoking, income, alcohol, exercise, medical conditions, and total caloric intake. The impact of low magnesium intake on CRP was greater in people who were over age 40 and overweight.

Table 4. Likelihood (Odds Ratio (O.R.) and 95% Confidence Interval (95% C.I.)) of Having Elevated CRP ($\geq$3.0 mg/L) Calculated from the Logistic Regressions Incorporating Magnesium Intake. Adjusted for Age, Race, Gender, BMI, Smoking, Income, Alcohol Consumption, Exercise, Medical Conditions, and Caloric Intake

Mg Intake	All People		Not Taking Mg Supplements	
	O.R.	95% C.I.	O.R.	95% C.I.
<50% RDA	1.22	0.87–1.71	1.75	1.07–2.87
50–74% RDA	1.20	0.92–1.57	1.61	1.13–2.31
75–99% RDA	1.06	0.84–1.35	1.48	1.01–2.19
$\geq$RDA	1	1	1	1

The findings in the current study build upon the findings of previous studies. Fung [24] evaluated the association between dietary patterns and inflammatory biomarkers and found that a Western diet pattern (higher in red meat, high-fat dairy products, and refined grains, lower in magnesium-containing foods) was associated with higher CRP. Guerrero-Romero [14] found an association between low serum magnesium levels and elevated CRP. In another study, obese women following a weight loss diet high in magnesium-rich vegetables showed a significant decrease in CRP levels after two years [25]. Our findings extend the results of these studies by demonstrating an association between dietary magnesium intake and CRP in a nationally-representative cohort.

The mechanism by which adequate magnesium intake may reduce the likelihood of elevated levels of CRP is not known, but may be related to oxidative stress, endothelial dysfunction, or other mechanisms. In animal models, a magnesium-deficient diet causes a reduction in plasma anti-oxidants in rats, as well as hypertriglyceridemia and decreased HDL levels [9]. Magnesium supplementation given to diabetic rats reduces oxidative stress markers, and increases anti-oxidant enzyme activity [10]. In humans, low magnesium levels promote endothelial dysfunction, in part due to an up-regulation of inflammatory cytokines [26]. The findings of our study add to this evidence by documenting a link between magnesium and inflammation in an epidemiologic model.

Several implications emerge from our findings. The first is that the RDA appears to be an important risk threshold. People had a higher likelihood of elevated CRP at any level below the RDA, even when their intake was only slightly below the RDA (75–99% RDA) in our analyses. The second implication of our findings is that being older and overweight increased the odds of having elevated CRP in association with having a diet deficient in magnesium. Instead of the hoped-for improvement toward a magnesium-rich heart-healthy diet as age and cardiovascular risk increase, we observed magnesium deficiency worsening with age, which may increase cardiovascular risk [27,28]. Correction of low magnesium intake (below the RDA) through more emphasis on the AHA dietary guidelines [29] and/or through magnesium supplementation may provide an important means to reduce CRP levels and perhaps cardiovascular risk.

Magnesium intake was highly correlated with fiber consumption in the study population. The addition of fiber intake to the multivariate models eliminated the correlation between magnesium and CRP elevation. This finding reflects the high degree of similarity in the foods containing both fiber and magnesium, and emphasizes the challenge in separating the effects of these two diet components in a cross-sectional study. In a close examination of our data, there were too few people high in one nutrient and low in the other to make any firm conclusions. More clarification awaits the results of prospective studies that single out one or the other nutrient.

The strengths of this study include the use of a nationally representative sample which includes a diverse cross-section of non-institutionalized persons in the U.S., making our results more applicable to the general population. The availability of high sensitivity CRP levels in the NHANES provides high confidence in the accuracy of the laboratory measures. Further, the finding of an association between CRP and dietary magnesium intake was maintained after controlling for demographic and cardiovascular risk factors that could confound the association, making the findings less likely to be due to confounding or chance.

Limitations of the study include possible misclassification, random error, and bias due to the use of 24-hour recall for dietary information. Individuals may have overestimated their intake of fruits and vegetables, thus biasing the magnesium intake to make an overestimate in those calculations as well. If so, then our results are biased toward the null, and actual magnesium intakes are even lower. In addition, participants' 24-hour intake of magnesium and other nutrients may vary from day-to-day, thus providing a poor point estimate for intake in the study. There may also be uncontrolled or unknown factors that confound the relationship that have not been taken into account in our regression models, however, we have accounted for the most likely demographic and cardiovascular factors that could confound the results. Diet is a multidimensional exposure, and it is difficult to attribute changes in a biomarker to a single nutrient. The correlations between fiber, magnesium intake, and CRP seen in this study illustrate the difficulty in attempting to demonstrate an independent contribution from a single nutrient such as magnesium. The results of this study should be considered exploratory and lead to further, more definitive prospective clinical investigations rather than premature conclusions.

Further, we were unable to control for the effects of magnesium in the water supply, which could possibly skew our estimates for magnesium intake. However, the relative contribution of magnesium from drinking water to total intake is small, on the order of 4–8 mg per liter of water consumed per day [30], thus the impact on our analysis would likely be minimal. Further, we were not able to account for intake of L-arginine, another mineral associated with cardiovascular risk [31,32], due to the lack of information regarding intake of this particular amino acid in the NHANES database.

In conclusion, this study provides new information regarding an association between dietary magnesium intake and elevated CRP in the general adult population. Insufficient dietary intake of magnesium may be associated with increased inflammation that leads to cardiovascular events. These findings support the current AHA guidelines promoting adequate intake of fruits, vegetables, and legumes, which are high in magnesium. Prospective studies are needed to examine whether the elevation of CRP is truly a reflection of low magnesium intake, or is the result of influence from some other nutrient or combination of nutrients. Further research will be needed to determine whether increasing magnesium consumption can contribute to lower CRP and reducing subsequent cardiovascular risk.

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