Dietary Magnesium and Kidney Function Decline: The HANDLS Study

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Abstract

Background—Prior studies suggest that certain aspects of the diet related to magnesium intake, such as dietary acid load, protein intake, and dietary patterns rich in fruits and vegetables, may impact kidney disease risk. We hypothesized that lower dietary magnesium intake would be prospectively associated with more rapid kidney function decline.

Methods—Among participants in the Healthy Aging in Neighborhoods of Diversity across the Life Span study with estimated glomerular filtration rate (eGFR) 60 mL/min/1.73 m^2 at baseline (2004-2009), dietary magnesium intake was calculated from two 24-hour dietary recalls. Rapid decline was defined as 3% eGFR decline per year.

Results—Median (25th, 75th percentile) dietary magnesium intake was 116 (96, 356) mg/1,000 kcal. Among 1,252 participants, those with lower dietary magnesium intake were younger, and were more likely to be African-American and male. A total of 177 participants (14.1%) experienced rapid eGFR decline over a median follow-up of 5 years. Lower dietary magnesium intake was significantly associated with a greater odds of rapid eGFR decline (odds ratio for tertile 1 vs. 3: 2.02, 95% confidence interval: 1.05, 3.86, p-value for trend across tertiles=0.02) in analyses adjusted for socio-demographics (age, sex, race, education level, health insurance status, poverty status), kidney disease risk factors (smoking status, diabetes, hemoglobin A1c, hypertension, body mass index), baseline eGFR, and dietary factors (total energy intake; diet quality; dietary intake of fiber, sodium, calcium, potassium, and phosphorus).

Conclusions—In this urban population, lower dietary magnesium intake was independently associated with greater odds of rapid kidney function decline.

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Introduction

Chronic kidney disease is a major public health issue. It affects approximately 13% of adults in the U.S. and is a strong risk factor for progression to end-stage renal disease, cardiovascular disease, and mortality [1-4]. Unfortunately, prevention and treatment options for chronic kidney disease and end-stage renal disease are limited [5]. Identifying novel risk factors for chronic kidney disease may increase our understanding of the pathogenesis of chronic kidney disease and reveal insights for prevention strategies.

Low levels of magnesium in the blood has recently been shown to be a novel risk factor for incident chronic kidney disease and incident end-stage renal disease [6, 7]. Among individuals with existing kidney disease, low blood magnesium levels may increase the risk of progression to end-stage renal disease, cardiovascular disease, and all-cause mortality [8-10]. Prior studies suggest that certain aspects of the diet related to magnesium, such as dietary acid load, dietary intake of protein from vegetable sources, and the Dietary Approaches to Stop Hypertension (DASH) dietary pattern, may impact kidney disease risk [11-14]. However, little is known about the relation of dietary intake of magnesium with kidney disease risk.

To inform future efforts to prevent chronic kidney disease and its associated adverse health consequences, the objective of this study was to determine whether low dietary magnesium intake was prospectively associated with change in kidney function in the Healthy Aging in Neighborhoods of Diversity across the Life Span (HANDLS) study, a cohort of African-American and Caucasian, adult men and women residing in Baltimore, Maryland.

Methods

Study Design

The HANDLS study is a population-based, prospective cohort study which was initiated to examine the influence and interaction of race and socio-economic status on cardiovascular and cerebrovascular health among racial minority and lower socio-economic population sub-groups. The study design has been previously described [15]. Briefly, city-dwelling, African-American and Caucasian men and women aged 30-64 years were recruited from 12 neighborhoods in Baltimore, Maryland that reflect socioeconomic and racial diversity. A total of 3,720 participants enrolled in the HANDLS study between August 2004 and March 2009 (wave 1; baseline for the present study). Follow-up study visits were planned at 3-4 year intervals. The first (partial) follow-up visit occurred in April 2006 to October 2011 (wave 2), and the second (complete) follow-up visit occurred in June 2009 to July 2013 (wave 3). Study participants provided written documentation of informed consent. Procedures were followed in accordance with ethical guidelines for human studies and the study protocol was approved by the institutional review board.

Study Population

In the present study, we included participants with serum creatinine measured at wave 1 using isotope-dilute mass spectrometry (IDMS), the recommended method for creatinine assay (n=2,517) [16]. Then, we excluded participants with baseline estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 (n=131), those with missing dietary intake data (n=587), those without measurements of serum creatinine at the wave 3 follow-up study visit (n=473), and those with missing information on covariates (n=74). After these exclusions, the analytic study population consisted of 1,252 HANLDS study participants. Study participants who were included were similar to those who were excluded on the basis of mean age (47 years vs. 48 years, respectively; p=0.14), African-American race (57% vs. 60%, respectively; p=0.07), and mean body mass index (30 kg/m^2 vs. 30 kg/m^2, respectively; p=0.66), but differed on the basis of male sex (41% vs. 48%, respectively; p<0.001), current smoking status (44% vs. 53%, respectively; p<0.001), and health insurance (69% vs. 65%, respectively; p=0.03).

Measurement of Dietary Intake

Dietary intake was assessed using two 24-hour dietary recalls which were administered by trained interviewers using the U.S. Department of Agriculture's Automatic Multiple Pass Method (AMPM versions 2.3-2.6) [17-19]. This dietary assessment instrument included illustrations of portion sizes to improve the accuracy of quantity of food consumed. The first dietary recall was administered during a household interview, and the second dietary recall was administered 7-10 days later in a mobile research vehicle. Food items were coded using Survey Net and linked to the Food and Nutrient Database for Dietary Studies version 3.0 to estimate nutrient intake. The average of the two estimated values of nutrient intake (magnesium, calcium, potassium, phosphate, sodium, fiber, total energy intake) based on the two 24-hour dietary recalls was used in the analysis. For this analysis, we categorized dietary intake of magnesium per 1,000 kcal by tertiles of the distribution, as most participants were below the recommended daily allowance (400-420 mg/day for men and 310-320 mg/day for women) [20]. Diet quality was assessed using the Healthy Eating Index-2010 (HEI-2010) score which is comprised of 12 components: total fruit; whole fruit; total vegetables; greens and beans; whole grains; dairy; total protein foods; seafood and plant proteins; fatty acids; refined grains; sodium; and empty calories [21]. Scores range from 0 to 100, with 100 representing optimal diet quality.

Ascertainment of Rapid eGFR Decline

Serum creatinine for included participants was measured by Quest Diagnostics, Inc. using isotope-dilution mass spectrometry (IDMS) and standardized to the reference laboratory at the Cleveland Clinic (Olympus America, Inc., Melville, New York). eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on serum creatinine at baseline (2004-2009) and the wave 3 follow-up study visit (2009-2013) [22]. The outcome of interest was rapid eGFR decline defined as 3% eGFR decline per year, which has been used in previously published studies [23, 24]. The time interval for the denominator of rate of eGFR decline was calculated as the difference between the date of the baseline study visit and the date of the wave 3 follow-up study visit.

Assessment of Other Variables

The baseline (wave 1) study visit consisted of two phases. Phase 1 took place during a household visit and involved a survey administered by trained interviewers to collect information on socio-demographics (age, sex, race, educational level), health behaviors (smoking status), household income, health insurance status, and other relevant participant characteristics. Phase 2 took place in the mobile research vehicle and consisted of: 1) a physical examination to measure blood pressure, body weight, and height; and 2) medical history to ascertain information on diagnosed disease (diabetes, hypertension) and medication use. Fasting blood specimens were collected for the measurement of glucose, hemoglobin A1c, creatinine, and other measures of health status.

Hypertension was defined as an average of seated and standing systolic blood pressure 140 mm Hg, an average of seated and standing diastolic blood pressure 90 mm Hg, a history of blood pressure medication use, or a self-report of diagnosed hypertension. Diabetes mellitus was defined as fasting plasma glucose concentration 126 mg/dL or self-report of diagnosed diabetes. Poverty status was defined as self-reported household annual income <125% of the 2004 U.S. Department of Health and Human Services poverty guidelines [25].

Statistical Analysis

Baseline characteristics of participants were reported using descriptive statistics and compared by tertiles of dietary magnesium intake using Wilcoxon rank sum tests for skewed continuous variables (education level and hemoglobin A1c), t-tests for non-skewed continuous variables, and χ^2 tests for categorical variables. The association between dietary magnesium intake and rapid eGFR decline was evaluated using logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) in a series of models. Model 1 evaluated the unadjusted association between tertiles of dietary magnesium intake (using tertile 3 as the reference group) and rapid decline in eGFR. Model 2 was adjusted for socio-demographic factors (age, sex, race, education level, health insurance status, poverty status), history of smoking, and total energy intake. Model 3 included the covariates in Model 2 and added baseline eGFR. Finally, model 4 additionally adjusted for hypertension, diabetes, body mass index, hemoglobin A1c, diet quality, and other dietary intake variables (fiber, sodium, calcium, potassium, phosphate). The p-value for trend was obtained by using the tertiles of dietary magnesium intake per 1,000 kcal as a continuous variable. We also examined potential effect modification of the association between dietary magnesium intake and rapid kidney function decline by race, sex, diabetes, hypertension status, and poverty status.

Results

At baseline, the study population had a mean age of 47 years, 57% were African-American, and 41% were male. The mean baseline eGFR in the overall study population was 97 mL/min/1.73 m². Median (25th, 75th percentile) dietary magnesium intake was 116 (96, 356) mg/1,000 kcal.

Those with lower dietary magnesium intake (tertile 1 vs. 3) were significantly younger (mean age of 46 vs. 49 years), more likely to be African-American (66% vs. 47%) and male (46% vs. 32%), more likely to be living in poverty (44% vs. 27%), less likely to have health insurance (61% vs. 76%) (p<0.001 for all comparisons; Table 1). Regarding kidney function and risk factors for kidney disease, those in the lowest vs. highest tertile of dietary magnesium intake had higher mean baseline eGFR (100 vs. 94 mL/min/1.73 m^2; p<0.001) and were less likely to have diabetes (11% vs. 18%) (p=0.004). Systolic blood pressure and hypertension status did not differ by tertile of dietary magnesium intake. Participants with lower dietary intake of magnesium also had lower dietary intake of fiber and overall diet quality (p<0.001 for both comparisons).

Over a median follow-up of 5 years, eGFR was stable in the overall study population on average [mean (standard deviation) eGFR change per year: 0.2% (3.6%)]. However, a total of 177 participants (14.1% of the total study population) experienced a rapid decline in eGFR (3% per year).

In our unadjusted analysis, participants in the lowest tertile of dietary magnesium intake had 79% greater odds of rapid eGFR decline (OR for tertile 1 vs. 3: 1.80, 95% CI: 1.22, 2.64, p-value for trend across tertiles=0.002; Table 2). The association between dietary intake of magnesium and kidney function decline was similar after adjusting for age, sex, race, education level, health insurance status, poverty status, smoking status, and total energy intake in Model 2, and after additionally adjusting for baseline eGFR in Model 3. In the fully adjusted model (Model 4), which was additionally adjusted for hypertension status, diabetes status, hemoglobin A1c, body mass index, diet quality, and dietary intake of fiber, sodium, calcium, potassium, and phosphate, participants in the lowest tertile of dietary magnesium intake had a two-fold greater odds of rapid decline (OR for tertile 1 vs. 3: 2.02, 95% CI: 1.05, 3.86, p-value for trend across tertiles=0.02). There was no statistically significant interaction by race, sex, diabetes, hypertension, or poverty status on the association between dietary magnesium intake and kidney function decline (all p-values >0.1).

Discussion

In the present study consisting of 1,252 city-dwelling African-American and Caucasian adult men and women, there were greater odds of rapid decline in kidney function in association with low dietary intake of magnesium. The association persisted even after accounting for socio-demographic characteristics, poverty status, established kidney disease risk factors, comorbidities, baseline kidney function, total energy intake, diet quality, and dietary intake of fiber and other micronutrients. The study findings were consistent across important subgroups of the population defined by race, sex, diabetes status, hypertension status, and poverty status.

In this study, dietary intake of magnesium was associated with rapid kidney function decline independent of multiple kidney disease risk factors. Similarly, in the Tehran Lipid and Glucose Study consisting of 1,692 Iranian adults without chronic kidney disease at baseline, those participants in the highest quintile of magnesium intake had a decreased risk of

chronic kidney disease, defined as eGFR <60 mL/min/1.73 m^2, over 3.6 years of follow-up (odds ratio: 0.41, 95% CI: 0.22, 0.76; p-value for trend across quintiles=0.002) after adjusting for age, sex, energy intake, serum triglycerides, serum cholesterol, body mass index, hypertension, diabetes, physical activity, and smoking [26]. In the Tehran Lipid and Glucose Study, dietary intake was assessed via a food frequency questionnaire. A stronger association was observed which may in part be due to a larger difference in quintiles of dietary intake of magnesium relative to the tertiles of dietary intake of magnesium in the present study.

Our findings are supported by previous research demonstrating that other dietary patterns inclusive of magnesium are predictive of kidney disease risk. For instance, magnesium is a component of the equation for potential renal acid load, a measure of dietary acid load [27]. Level of dietary acid load has been reported to be associated with markers of kidney disease in several studies of U.S. adults [11, 28-31]. Similarly, high intake of magnesium was one of the key nutrient targets of the Dietary Approaches to Stop Hypertension (DASH) diet and the DASH diet with reduced sodium, according to the design of the original trials [32-34]. The DASH diet is low in dietary acid load and several recent studies have shown that following a DASH-style diet is significantly associated with kidney health [12, 13, 31, 35, 36]. Also, nuts and legumes are two rich sources of magnesium, and their higher consumption, along with other vegetable sources of protein, may protect against the development of kidney disease possibly by favorably altering mineral metabolism [11, 14, 37, 38]. Finally, magnesium may simply be a proxy for other kidney-protective dietary components that have not been fully elucidated.

There are several potential pathophysiologic mechanisms through which low dietary intake of magnesium could accelerate the loss of kidney function [39, 40]. There is extensive research demonstrating that low blood levels of magnesium, which in part is influenced by dietary intake, can lead to an inflammatory, atherogenic, and thrombotic response in the vasculature [41-44]. Endothelial cells, layers of which form the endothelial lining of the vasculature, express a magnesium transporter (TRPM7) [45]. Low circulating levels of magnesium may lead to endothelial dysfunction through upregulation of this transporter [45, 46]. Further, hypomagnesemia may impair the healing process following vascular injury by regulating endothelial cell migration and proliferation [47]. Low magnesium levels in the blood has repeatedly been shown to promote vascular calcification [48, 49]. Further, higher intake of magnesium through oral supplementation may reduce blood pressure levels, which is an established risk factor for kidney disease [50].

It is worth mentioning the major strengths and limitations of our study. The prospective study design allows us to demonstrate a temporal relationship between dietary intake and kidney function decline. Reverse causality is unlikely since we were able to restrict the analysis to those participants with normal kidney function at baseline (eGFR 60 mL/min/1.73 m^2) and there was no statistical evidence of effect modification by diabetes or hypertension status. As is the case with any observational study, there is the possibility that residual confounding could, in part, explain the observed association due to imprecise measurement or lack of measurement of confounding factors. However, we were able to adjust for a number of known risk factors for kidney disease, socio-demographic

characteristics, baseline kidney function, and relevant dietary factors. In addition, we accounted for several co-morbid conditions (hypertension, diabetes, body mass index) which could be considered potential mediators of the association between dietary intake and kidney function decline. Use of self-reported data for dietary assessment could introduce measurement error and bias into the study [51, 52]. In the present study, we used the average of values from two 24-hour dietary using the AMPM administered by trained interviewers. This dietary assessment instrument has previously been shown to provide accurate estimates of intake of calories and nutrients and to represent frequently consumed foods [17-19]. Given the short time frame for which participants are asked to recount food consumption (24 hours), recall bias is unlikely. Another limitation is that we were only able to derive estimates of magnesium consumption based on food intake. We did not have access to data on use of magnesium supplements or multi-vitamins. Therefore, the absolute level of magnesium intake may be underestimated in our study. We are only able to assess kidney disease risk within the observed range of dietary intake of magnesium in our study population. It may be warranted to conduct a similar analysis in a population with a wider range of magnesium intake, and with higher levels of magnesium intake in particular. Lastly, the HANDLS study consists of a relatively large sample of an under-studied group: socio-economically diverse, but primarily low-income, urban population. HANDLS study participants were recruited from a single U.S. city. The analytic sample differed from those who were excluded (due to missing data) on the basis of sex, health insurance status, and smoking status; thus, the analytic sample may not be representative of the overall HANDLS study population. Replication in other cohorts would lend further credence to these findings and allow for broader generalizability.

In summary, the lowest tertile of dietary intake of magnesium was significantly associated with approximately two-fold greater odds of rapid kidney function decline independent of socio-demographics, kidney disease risk factors, baseline eGFR, and dietary factors in the HANDLS study. It may be warranted to assess risk of kidney disease incidence or progression in clinical trials of dietary supplementation with magnesium or other diet interventions related to magnesium intake for individuals with low dietary intake of magnesium. Given ours, and other recent reports, clinical guideline bodies might consider evaluating the overall evidence on renal protective diets for the preservation of kidney function.

Acknowledgments

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Table 1

Baseline Characteristics[a] of HANDLS Study Participants by Tertile of Dietary Intake of Magnesium

	Tertile of Dietary Intake of Magnesium (minimum-maximum, mg/1,000 kcal)			
	Tertile 1 (46.9-101.4)	Tertile 2 (101.4-131.8)	Tertile 3 (131.9-468.2)	P-value
N	418	417	417	
Age, years	45.8 (8.9)	47.4 (9.0)	49.1 (9.1)	<0.001
African-American	275 (65.8%)	243 (58.3%)	196 (46.0%)	<0.001
Male	190 (45.5%)	187 (44.8%)	134 (32.1%)	<0.001
Education level, years[b]	12 (11, 12)	12 (11, 14)	12 (12, 17)	<0.001
Health insurance status	254 (60.8%)	292 (70.0%)	317 (76.0%)	<0.001
Poverty status	183 (43.8%)	178 (42.7%)	112 (26.9%)	<0.001
Smoking status				
Never smoker	121 (28.9%)	143 (34.3%)	182 (43.6%)	
Former smoker	60 (14.4%)	82 (19.7%)	119 (28.5%)	<0.001
Current smoker	237 (56.7%)	192 (46.0%)	116 (27.8%)	
Prevalent CAD	7 (1.8%)	21 (5.1%)	10 (2.5%)	0.01
eGFR, mL/min/1.73 m^2	99.8 (17.2)	96.3 (17.1)	94.3 (16.7)	<0.001
Diabetes	46 (11.0%)	78 (18.7%)	75 (18.0%)	0.004
HbA1c, %[b]	5.7 (5.4, 6.0)	5.7 (5.4, 6.1)	5.6 (5.4, 6.0)	0.36
Hypertension	69 (16.5%)	63 (15.1%)	67 (16.1%)	0.85
Systolic blood pressure, mm Hg	119.1 (18.7)	119.3 (19.2)	119.4 (19.3)	0.98
Diuretic use	19 (4.5%)	32 (7.7%)	32 (7.7%)	0.11
Body mass index, kg/m^2	29.3 (7.4)	30.0 (7.4)	30.5 (8.1)	0.06
Dietary fiber, g/1,000 kcal[b]	4.1 (3.3, 5.2)	5.6 (4.4, 6.9)	8.3 (6.2, 10.9)	<0.001
Dietary sodium, mg/1,000 kcal	1,516 (383)	1,619 (424)	1,642 (524)	<0.001
Diet quality score[c]	35.2 (7.4)	41.2 (8.3)	52.8 (12.1)	<0.001

[a]Mean (standard deviation) for continuous variables and n (%) for categorical variable, unless otherwise stated

[b]Median (25th percentile, 75th percentile)

[c]Diet quality was assessed using the Healthy Eating Index-2010.

CAD, coronary artery disease; eGFR, estimated glomerular filtration rate, HANDLS, Healthy Aging in Neighborhoods of Diversity across the Life Span

Table 2

Odds[a] of Rapid Kidney Function Decline (3% eGFR decline/year) by Tertile of Dietary Intake of Magnesium

Model	Tertile of Dietary Intake of Magnesium			P-value for trend
	Tertile 1	Tertile 2	Tertile 3	
Model 1	1.80 (1.22, 2.64)	1.05 (0.69, 1.60)	1 [Reference]	0.002
Model 2	1.83 (1.20, 2.81)	1.04 (0.67, 1.61)	1 [Reference]	0.003
Model 3	1.80 (1.17, 2.77)	1.05 (0.68, 1.64)	1 [Reference]	0.005
Model 4	2.02 (1.05, 3.86)	1.07 (0.62, 1.84)	1 [Reference]	0.02

[a]Odds ratios (95% confidence intervals)

Model 1: unadjusted

Model 2: adjusted for age, sex, race, education level, health insurance status, poverty status, smoking status, and total energy intake

Model 3: Model 2 + baseline eGFR

Model 4: Model 3 + hypertension status, diabetes status, body mass index, hemoglobin A1c, diet quality score (Healthy Eating Index-2010), and dietary intake of fiber, sodium, calcium, potassium, and phosphate