Clinical Nutrition xxx (2017) 1–9

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

Serum magnesium concentrations and all-cause, cardiovascular, and cancer mortality among U.S. adults: Results from the NHANES I Epidemiologic Follow-up Study☆

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ARTICLE INFO

Article history:
Received 5 April 2017
Accepted 22 August 2017

Keywords:
Serum Mg
Mg deficiency
All-cause mortality
CVD mortality
Cancer mortality
Stroke mortality

SUMMARY

Background: Few studies have examined the associations of serum magnesium (Mg) concentrations with total and cause-specific mortality in a nationally representative sample of US adults. We investigate the dose–response relationships of baseline serum Mg concentrations with risk of mortalities in a large, nationally representative sample of US adults.

Methods: We analyzed prospective data of 14,353 participants aged 25–74 years with measures of serum Mg concentrations at baseline (1971–1975) from the National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study (NHEFS). Mortality data was linked through December 31, 2011. We estimated the mortality hazard ratios (HRs), for participants within serum Mg categories of <0.7, 0.7–0.74, 0.75–0.79, 0.8–0.89 (referent), 0.9–0.94, 0.95–0.99, and ≥1.0 mmol/L using weighted multivariate-adjusted Cox proportional hazards models.

Results: During a median follow-up of 28.6 years, 9012 deaths occurred, including 3959 CVD deaths, 1923 cancer deaths, and 708 stroke deaths. The multivariate-adjusted HRs (95% CIs) of all-cause mortality across increasing categories of Mg were 1.34 (1.02, 1.77), 0.94 (0.75, 1.18), 1.08 (0.97, 1.19), 1.00 (referent), 1.05 (0.95, 1.16), 0.96 (0.79, 1.15), and 0.98 (0.76, 1.26). Similar trends were observed for cancer (HRs for serum Mg < 0.7: 1.39, 95% CI: 0.83, 2.32) and CVD mortality (HRs for serum Mg < 0.7: 1.28, 95% CI: 0.81, 2.02) but were not statistically significant. An elevated risk for stroke mortality was observed among participants with serum Mg < 0.70 mmol/L (HR: 2.55, 95% CI: 1.18, 5.48).

Conclusions: Very low serum Mg concentrations were significantly associated with an increased risk of all-cause mortality in US adults.

1. Introduction

As a cofactor in hundreds of enzymatic reactions in the human body [1], magnesium (Mg) plays a significant role in multiple biological systems. Low Mg level has been associated with increased risk of chronic diseases in prospective studies, including cardiovascular disease (CVD) [2,3], type 2 diabetes [4–8], metabolic related diseases [9,10], and colorectal cancer [11]. Mechanistic evidence supports a role for magnesium in cardiovascular diseases, including on blood pressure [12], oxidative stress [13], endothelial function [14] and thrombosis [15], and arrhythmia [16].

Abbreviations: Mg, magnesium; CVD, cardiovascular disease; NHANES I, National Health and Nutrition Examination Survey I; NHEFS, National Health and Nutrition Examination Survey I Epidemiologic Follow-up Study; CHD, congenital heart disease; ICD, International Classification of Diseases; CHD, congenital heart disease; HR, hazard ratio; CI, confidence interval.

☆ **Foundation**: The project described was supported by the Indiana University Health–Indiana University School of Medicine Strategic Research Initiative (Drs. X Zhang, Jin Xia, L Del Gobbo, and Y Song).

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http://dx.doi.org/10.1016/j.clnu.2017.08.021
0261-5614/

Additionally, Mg supplementation may improve glucose induced insulin response and insulin-mediated glucose disposal among nondiabetic participants [17,18].

Although multiple lines of evidence support a role of Mg in major chronic diseases, few longitudinal studies have examined the relationship between serum Mg and mortality. One study, based on data from NHANES I Follow-up Study 1971–75, examined the effects of serum Mg on risk of CVD and all-cause mortality and observed an inverse association between serum Mg and mortality from all cause and CVD in participants followed up through 1992 [19]. However, the low levels of serum Mg were defined according to statistical quantiles based on the respective distributions of serum Mg concentrations. While the threshold for defining insufficient Mg status is quite variable depending on health status and other population characteristics [20,21]. Serum Mg concentrations are usually relatively stable, within a narrow range of 0.70 and 1.00 mmol/L in healthy adults. It is possible that even very small changes in serum Mg concentrations are associated with an abrupt change in risk of an adverse health outcome.

Availability of a large nationally representative sample of the U.S. adults with baseline serum Mg and long follow-up data of mortality outcomes enable the robust estimation of thresholds for serum Mg with respect to mortality, which is necessary to establish an evidence-based reference interval for total serum Mg. Recently, the NHANES I mortality follow-up has been extended to include deaths events through a longer-term follow-up period, which provided more than double the number of mortality cases ($n = 9012$) to enable us to not only evaluate the associations of serum Mg with all-cause mortality, but also cause-specific mortality, including cancer and stroke.

2. Methods

2.1. Study design and population

We used data from the NHANES I 1971–1975, a multistage national probability survey designed to evaluate the health and nutritional status of US general population [22]. Among the representative sample of 32,000 US civilians selected, 14,407 participants at NHANES I (aged 25–74 years) with complete medical examinations were included in a longitudinal follow-up study, NHEFS, in 1982 [23]. The baseline information for NHEFS, including demographic and socioeconomic information and physical and laboratory examinations, was provided by NHANES I. After excluding 54 participants with missing measures of serum Mg, we finally included a total of 14,353 participants in the analysis. The design of the NHANES has been reviewed and approved by Institutional Review Board at the Centers for Disease Control and Prevention. All subjects provided written informed consent.

2.2. Outcome measures

The NHEFS cohort study included four waves of follow-up periods in 1982–1984, 1986, 1987, and 1992. The follow-up data contained information on health-related outcomes. Vital status was assessed and confirmed by proxy interviews, medical records, and death certificate through the National Death Index. New record linkages of NHEFS participants to death records through December 31, 2011 were conducted by National Center for Health Statistics [24,25]. Our primary outcomes included all-cause, CVD, cancer, and stroke mortality. Causes of mortality were divided into four categories using the Tenth Version of the International Classification of Diseases (ICD-10): cancer (C00-97), CVD (I00-78), ischemic heart disease (CHD) (I58-63), and stroke (I60-69) deaths.

2.3. Baseline Mg measurements

Non-fasting blood samples were collected and frozen and then sent to the Centers for Disease Control and Prevention for biochemical assays. Serum Mg concentrations were determined during the baseline survey by atomic absorption spectrophotometry using the method of Hansen and Freier [26]. Quality control samples were analyzed with every 20 specimens, and the repeat limits were below 1.40 and above 2.10 mEq/L [27,28]. We converted the unit of “mEq/L” for serum Mg concentrations into “mmol/L” for this study.

2.4. Confounders

Covariates were measured at baseline, including age, sex, race, body mass index (BMI) (kg/m^2), education ($\geq$high school degree, or <high school degree), alcohol intake (>2 times per week, or <2 times per week), levels of recreational and non-recreational physical activity (self-report of being very active, moderately active, or quite inactive), smoking (never, former current), sitting blood pressure (mmHg), history of diabetes (self-reported physician diagnosed diabetes, or use of hypoglycemic medication), history of hypertension (self-reported physician diagnosis, or taking antihypertensive drugs), history of CVD (self-reported physician diagnosed heart failure, heart attack, stroke, or possible heart or circulatory troubles), serum calcium and cholesterol levels, and intake of vitamin or mineral supplements (self-reported any vitamin or mineral supplementation within last 30 days before the interview).

2.5. Statistical analysis

We estimated the hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality for categories of serum Mg comparing to the reference group (0.80–0.89 mmol/L) using Cox proportional hazards models. Weights accounting for the complex sampling design of the survey were applied in Cox proportional hazards model. Age, sex, race, BMI, education, cigarette smoking status, alcohol consumption, physical activity, history of hypertension, history of diabetes, and use of vitamin and/or mineral supplements were included as covariates in the models.

In order to explore the possible dose–response relationship between serum Mg levels and all-cause and cause-specific mortality, we fitted restricted cubic spline regression models with four knots at 0.73, 0.82, 0.87, and 0.96 mmol/L.

Finally, pre-specified subgroup analyses and sensitivity analyses were also performed to explore potential effect modifications or assess the robustness of the results. The subgroup variables included age (<65 yr or $\geq$65 yr), sex (men or women), race (white, black, or other), BMI (<25 kg/m^2 or $\geq$25 kg/m^2), recreational physical activity (very active, moderately active, or quite inactive), non-recreational physical activity (very active, moderately active, or quite inactive), diabetes (yes or no), hypertension (yes or no), CVD (yes or no), cigarette smoking status (current smoker or non-smoker), alcohol consumption (current drinker or non-drinker), and use vitamin and/or mineral supplements (user or non-user). We also conducted survey logistic regression models adjusted for the above-mentioned covariates to identify the variable(s) that independently predicted low serum Mg (<0.70 mmol/L). Low serum Mg was defined as serum Mg < 0.75 mmol/L, according to the normal reference range for serum Mg (33); and a very low level of serum Mg was defined as serum Mg < 0.70, according to the clinical cut-off for hypomagnesemia. We performed the interaction analyses testing low serum Mg associations with all-cause mortality, CVD mortality, cancer mortality, and stroke mortality in

Please cite this article in press as: Zhang X, et al., Serum magnesium concentrations and all-cause, cardiovascular, and cancer mortality among U.S. adults: Results from the NHANES I Epidemiologic Follow-up Study, Clinical Nutrition (2017), http://dx.doi.org/10.1016/j.clnu.2017.08.021