Urinary Magnesium Excretion and Risk of Hypertension
The Prevention of Renal and Vascular End-Stage Disease Study

Michel M. Joosten, Ron T. Gansevoort, Kenneth J. Mukamal, Jenny E. Kootstra-Ros, Edith J.M. Feskens, Johanna M. Geleijnse, Gerjan Navis, Stephan J.L. Bakker; the PREVEND Study Group

Abstract—Observational studies on dietary or circulating magnesium and risk of hypertension have reported weak-to-modest inverse associations, but have lacked measures of actual dietary uptake. Urinary magnesium excretion, an indicator of intestinal magnesium absorption, may provide a better insight in this association. We examined 5511 participants aged 28 to 75 years free of hypertension in the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective population-based cohort study. Circulating magnesium was measured in plasma and urinary magnesium in two 24-hour urine collections, both at baseline. Incident hypertension was defined as blood pressure ≥140 mmHg systolic or ≥90 mmHg diastolic, or initiation of antihypertensive medication. During a median follow-up of 7.6 years (interquartile range, 5.0–9.3 years), 1172 participants developed hypertension. The median urinary magnesium excretion was 3.8 mmol/24 hour (interquartile range, 2.9–4.8 mmol/24 hour). Urinary magnesium excretion was associated with risk of hypertension in an inverse log-linear fashion, and this association remained after adjustment for age, sex, body mass index, smoking status, alcohol intake, parental history of hypertension, and urinary excretion of sodium, potassium, and calcium. Each 1-unit increment in ln-transformed urinary magnesium excretion was associated with a 21% lower risk of hypertension after multivariable adjustment (adjusted hazard ratio, 0.79; 95% confidence interval, 0.71–0.88). No associations were observed between circulating magnesium and risk of hypertension. In conclusion, in this cohort of men and women, urinary magnesium excretion was inversely associated with risk of hypertension across the entire range of habitual dietary intake.

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Key Words: diet ■ epidemiology ■ hypertension ■ magnesium ■ risk factor

Although dietary macrominerals, particularly sodium and potassium, but also calcium, are thought to play an important role in the primary prevention and control of high blood pressure, less attention has been paid to the possible effects of magnesium. Prospective epidemiological studies have shown that higher dietary magnesium intake may have a modest effect on the risk of hypertension, although no such effect has been observed for circulating magnesium. However, both oral and circulating magnesium correlate moderately with actual systemic magnesium absorption and do not take into account that fractional intestinal absorption of magnesium is curvilinear, with relatively high values when dietary intake is low.

Because magnesium homeostasis is predominantly regulated via the balance between gastrointestinal uptake and renal excretion, urinary magnesium excretion provides an objective estimate of the amount of magnesium that is systemically absorbed. Magnesium absorption can accurately be determined from 24-hour urine specimens, and clinical trials have demonstrated that dietary manipulation of magnesium is reflected in urinary magnesium excretion. Thus far, urinary magnesium excretions from timed 24-hour urine collections have only been used in cross-sectional studies, which are limited by an inability to assess temporal relationships, in that blood pressure could potentially have altered urinary magnesium excretion. Therefore, we prospectively investigated the association of urine magnesium with risk of incident hypertension in a well-characterized cohort of men and women free of hypertension at baseline.

Methods

Study Design and Population
The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study is a prospective investigation of albuminuria,
Assessment of Covariates

Body mass index (BMI) was calculated as weight (kg) divided by height squared (m²). Smoking status was categorized as never, former, current <6 cigarettes/d, current 6 to 20 cigarettes/d, and current >20 cigarettes/d. Alcohol intake was categorized as none, 1 to 4 beverages/mon, 2 to 7 beverages/wk, 1 to 3 beverages/d, and ≥4 beverages/d. Urine calcium, sodium, potassium, and creatinine and circulating calcium, sodium, potassium, creatinine, albumin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein, and glucose were determined as previously described. Estimated glomerular filtration rate was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation.

Statistical Analysis

Baseline characteristics are presented in quartiles of urinary magnesium excretion and were made sex specific to reflect the Dietary Reference Intakes of the Institute of Medicine. Normally distributed variables are given as mean±SD, and skewed variables are given as median (interquartile range). The urinary magnesium concentration was multiplied by the 24-hour urine volume to obtain magnesium excretion (in mmol/24 hour). The Pearson product–moment correlation coefficient, as estimate of the intraclass correlation coefficient of reliability R, was used between the 2 urine specimens of each participants' magnesium excretion. Given the substantial variation of 1.3%, we applied the ln-transformation to the continuous magnesium variable to improve the model fit. We examined potential nonlinear relationships using restricted cubic spline transformations and tested nonlinearity by using the likelihood ratio test, comparing nested models with linear or linear and cubic spline terms. No significant deviations from linearity were detected. We used the Cox proportional hazards regression analysis to examine the association between urinary magnesium excretion and risk of hypertension. Person-time of follow-up was computed for each participant in the cohort from baseline until the date of the last screening round that participants attended, the incidence of hypertension, death, or relocation to an unknown destination, whichever came first. All models took into account the sampling design of the study (presence or absence of urinary albumin concentration >10 mg/L) by specifying stratum-specific baseline hazard functions. To determine the independent association of urinary magnesium excretion with risk of hypertension, the Cox proportional hazards regression model was adjusted for age and sex (age- and sex-adjusted model) and for age, sex, BMI, smoking (5 categories), alcohol intake (5 categories), and parental history of hypertension. In addition, we adjusted our multivariable models for important dietary macrominerals that have previously been associated with risk of hypertension, such as sodium intake, estimated from 24-hour urinary sodium excretions, and urinary potassium and calcium excretion. Additionally, we also investigated the effect of potential intermediate and biochemical variables by adding ln-transformed estimated glomerular filtration rate, ln-transformed C-reactive protein, total to high-density lipoprotein cholesterol ratio, ln-transformed triglycerides, and urinary levels of albumin (ln-transformed) and creatinine excretion. Multiplicative interaction was assessed by fitting models containing both main effects and their cross-product terms.

We performed several sensitivity analyses to study the robustness of significant associations between urine magnesium and risk of hypertension. First, we excluded 24-hour urine samples with possible over or under collections. Such samples were defined as the upper and lower 2.5% of the difference between the estimated and measured volume of a subject’s 24-hour urine sample. The estimated 24-hour urine volume was derived from the formula: Creatinine clearance=[urine creatinine×24-hour urine volume]/[Serum creatinine]), where creatinine clearance was estimated using the Cockcroft–Gault formula. If accurately collected, estimated creatinine clearance using 24-hour urine specimens and estimated creatinine clearance using a serum-based equation (which is entirely independent of the timed urine) should be similar. We also repeated
our analyses with urinary magnesium excretion corrected for body surface area by applying the formula of Du Bois.\textsuperscript{22} We addressed the oversampling of subjects with elevated urinary albumin excretion by using a design-based Cox proportional hazards regression model that took into account the probability of selection by statistical weighting. The statistical weighting enabled us to estimate the effect size on the general population level. To address potential reverse causation, we also repeated the analyses, excluding subjects with incident hypertension in the first 2 years of follow-up. To examine potential bias attributable to lost to follow-up, we also repeated the analysis restricted to subjects who were censored only on the basis of attended follow-up examinations (thus excluding subjects censored on the basis of relocation or death). Finally, instead of the Cox proportional hazards regression analysis, we reanalyzed the data using logistic regression, which is free of assumptions for the time-to-event definition for incident hypertension.

Similar analyses were performed for circulating magnesium. We used overall quartiles rather than sex-specific quartiles because no differences between sexes in plasma magnesium exist. We tested the association between magnesium in urine and plasma with age- and sex-adjusted Pearson partial correlation coefficients. Statistical analyses were performed by using the Statistical Package for Social Sciences (SPSS Inc, Chicago, IL) version 20.0 and SAS (SAS Institute, Cary, NC) version 9.2.

Results

Median baseline 24-hour urinary excretion of magnesium was 3.8 mmol (interquartile range, 2.9–4.8 mmol) and was higher in men 4.2 (3.2–5.2) than in women 3.6 (2.7–4.4). Under the assumption of an intestinal absorption of ≈30%,\textsuperscript{7,23} this median urinary excretion level would correspond to a daily dietary magnesium intake of ≈309 mg.

Table 1 shows baseline characteristics of participating subjects according to sex-specific quartiles of urinary magnesium excretion. In unadjusted analyses, higher urinary magnesium excretion levels were associated with slightly higher BMI, lower intakes of alcohol and, as expected, higher urinary levels of other cations. Urinary magnesium excretion levels were not associated with other risk factors for hypertension, including age, smoking status, family history, or with systolic and diastolic blood pressure at baseline. Urinary magnesium excretion was not correlated with plasma magnesium ($r=−0.02; P=0.12$).

During 7.6 years (interquartile range, 5.0–9.3 years) or 38740 person-years of follow-up, a total of 1172 new cases of hypertension occurred. After adjustment for age and sex, higher urinary magnesium excretion levels were significantly associated with a lower risk of hypertension (hazard ratio [HR] for each 1-unit increment [2.72 mmol/24 hour] in ln-transformed urinary magnesium excretion, 0.87; 95% confidence interval [CI], 0.78–0.96; Table 2). In the multivariable-adjusted model, risk of hypertension associated with magnesium excretion decreased by 21% (HR, 0.79; 95% CI, 0.71–0.88). The adjusted restricted spline curve confirmed the linear<0.001; $P_{\text{interaction}}$>0.10). Results were not appreciably altered with further adjustment for potential intermediate and biochemical variables. No associations were observed between plasma magnesium and risk of hypertension both in age- and sex-adjusted or multivariable-adjusted models (Table 3).

In a sensitivity analysis, the HR per 1-unit increment in ln-transformed urinary magnesium excretion was somewhat attenuated but remained highly significant after exclusion of 298 subjects with potentially inadequate urine collection (HR, 0.84; 95% CI, 0.78–0.92). Also, the design-based Cox proportional hazards model to address the oversampling of subjects with elevated urinary albumin excretion yielded similar results (HR, 0.83; 95% CI, 0.70–0.98). Furthermore, results were also not meaningfully changed when only incident events after the first 2 years of follow-up were considered (HR, 0.80; 95% CI, 0.71–0.90) or when controlled for body surface area instead of BMI (HR, 0.76; 95% CI, 0.68–0.85). Finally, results were more pronounced when we applied a logistic regression to the data instead of Cox proportional hazards regression (odds ratio, 0.76; 95% CI, 0.66–0.87) or when we reanalyzed the data restricted to subjects who were censored only on the basis of their last attended examination (HR, 0.73; 95% CI, 0.65–0.82; $n=4555$).

Discussion

The present investigation is to our knowledge the largest prospective study to date to examine the association of urinary magnesium excretion with incident hypertension in a general population cohort. Our results demonstrate an inverse dose–response association over the entire range of habitual intake between urinary magnesium excretion and risk of hypertension. This relationship remained in models that were controlled for multiple confounders, both dietary and nondietary, and was similar irrespective of sex, age, BMI, smoking status, alcohol intake, and urinary excretion of albumin or calcium. No associations were observed for plasma magnesium and risk of hypertension.

Our findings of higher urinary magnesium excretion, as estimate of dietary absorption, and lower risk of hypertension confirm previous observations of modest inverse associations noted in prospective studies on dietary magnesium intake.\textsuperscript{1–4} The dose–response association in our study corroborates with findings of a meta-analysis of 20 randomized trials (lasting 3 to 24 weeks) that observed a dose-dependent effect of magnesium supplementation on both systolic and diastolic blood pressure levels.\textsuperscript{26} However, this meta-analysis included trials with predominantly (pre)hypertensive subjects and with supradietary doses (up to 40 mmol/d equivalent to ≈972 mg/d) of magnesium supplementation. Magnesium from supplements may have other effects on blood pressure than that of modest dietary doses (usually <20 mmol/d equivalent to ≈486 mg/d), and purified nutrients do not necessarily have the same effects as nutrients obtained from a complex matrix as in foods.\textsuperscript{25} Regardless, these results suggest that oral magnesium intake may play a role in blood pressure regulation.

In line with previous prospective studies,\textsuperscript{5,6} we found no relation between plasma magnesium and risk of incident hypertension. Similar to weak correlations observed in studies assessing magnesium from dietary questionnaires and blood,\textsuperscript{26–28} we noted a very weak, nonsignificant and even
inverse correlation between urinary and circulating magnesium. Although circulating levels are routinely measured in a clinical setting, plasma magnesium only represents ≈1% of the total body store and is kept within a narrow homeostatic range, as shown by a low intraindividual and temporal variability. Decreased plasma levels may be compensated by release of magnesium deposited in bone, making circulating magnesium less reflective of dietary intake of magnesium. Taken together, it suggests that circulating magnesium and urinary magnesium excretion represent distinct exposures. A recent Dutch food consumption survey showed that >1 in 5 Dutch adults had a daily magnesium intake below the Estimated Average Requirement of 350 mg for men and 265 mg for women set by the Institute of Medicine. In this cohort, ≈54% of all men and 40% of all women would have been classified as having a magnesium intake below the Estimated Average Requirement.

| Table 1. Baseline Characteristics According to Sex-Specific Quartiles of Urinary Magnesium Excretion in 5511 Community-Dwelling Participants of the PREVEND Study |
|---|---|---|---|---|
| Characteristics | Quartiles of Urinary Magnesium Excretion, mmol/24 h | | | | | P Value |
| | Men: <3.2 | Men: 3.2–4.1 | Men: 4.2–5.2 | Men: >5.2 |
| Participants, n | 1375 | 1379 | 1380 | 1377 |
| Men, % | 45.2 | 45.3 | 45.4 | 45.3 |
| Age, y | 44±11 | 45±11 | 45±11 | 44±10 |
| Body mass index, kg/m² | 25.0±4.0 | 25.1±3.8 | 24.9±3.6 | 25.4±3.9 |
| Systolic blood pressure, mm Hg | 118 (110–128) | 118 (110–127) | 118 (110–127) | 119 (111–128) |
| Diastolic blood pressure, mm Hg | 70 (64–75) | 70 (65–75) | 70 (65–74) | 70 (65–75) |
| Parental history of hypertension, % | 27.6 | 29.5 | 28.8 | 30.1 |
| Smoking status, never, % | 31.4 | 30.3 | 30.7 | 30.5 |
| Alcohol consumption, none, % | 27.6 | 23.5 | 19.8 | 19.3 |
| Estimated GFR, mL/min per 1.73 m² | 88 (78–98) | 87 (77–97) | 87 (78–97) | 87 (79–97) |
| Serum total cholesterol, mmol/L | 5.48±1.15 | 5.50±1.11 | 5.48±1.05 | 5.47±1.10 |
| Serum HDL-cholesterol, mmol/L | 1.33±0.38 | 1.37±0.41 | 1.38±0.40 | 1.40±0.43 |
| Serum triglycerides, mmol/L | 1.05 (0.80–1.50) | 1.05 (0.78–1.48) | 1.03 (0.76–1.41) | 1.04 (0.74–1.43) |
| Serum glucose, mmol/L | 4.6 (4.2–4.9) | 4.6 (4.2–5.0) | 4.6 (4.2–4.9) | 4.5 (4.2–4.9) |
| Serum C-reactive protein, mg/L | 1.15 (0.49–2.79) | 1.04 (0.48–2.45) | 0.95 (0.45–2.14) | 0.81 (0.36–2.05) |
| Plasma magnesium, mmol/L* | 0.81 (0.78–0.85) | 0.81 (0.77–0.85) | 0.81 (0.78–0.85) | 0.81 (0.77–0.85) |
| Urine albumin, mg/24 h | 7.0 (5.2–10.6) | 7.9 (5.7–11.8) | 8.1 (6.1–12.2) | 9.0 (6.5–13.5) |
| Urine creatinine, mmol/24 h | 10.7 (8.6–13.0) | 11.3 (9.4–13.8) | 11.9 (9.9–14.6) | 12.7 (10.6–15.7) |
| Urine calcium, mmol/24 h | 2.6 (1.7–3.4) | 3.5 (2.5–4.5) | 4.1 (3.0–5.3) | 4.9 (3.8–6.4) |
| Urine sodium, mmol/24 h | 121 (93–153) | 128 (100–161) | 138 (109–170) | 152 (121–186) |
| Urine potassium, mmol/24 h | 62 (49–78) | 66 (54–79) | 72 (59–84) | 80 (68–94) |
| Urine magnesium, mmol/24 h | 2.2 (1.7–2.6) | 3.4 (3.1–3.6) | 4.3 (3.9–4.6) | 5.6 (5.1–6.4) |

Values are presented as median with interquartile range, means with SDs, or percentages. GFR indicates glomerular filtration rate; HDL, high-density lipoprotein; and PREVEND, Prevention of Renal and Vascular End-Stage Disease.

*Available in 4625 participants.

Hazard ratios (HRs) and 95% confidence intervals were derived from Cox proportional hazards regression models. The multivariable model was adjusted for age, sex, body mass index, smoking status, parental history of hypertension, alcohol consumption, sample design, and urinary excretion of sodium, potassium, and calcium.

Table 2. Association of Urinary Magnesium and Risk of Hypertension

| Measures | Continuous, per 1-Unit Increment (2.72 mmol/24 h) in Ln-Magnesium Excretion | Quartiles of Urinary Magnesium Excretion, mmol/24 h |
|---|---|---|---|---|---|
| | Men: <3.2 | Men: 3.2–4.1 | Men: 4.2–5.2 | Men: >5.2 |
| Person-years | 38 740 | 9594 | 9583 | 9728 | 9855 |
| No. of cases | 1172 | 305 | 299 | 297 | 272 |
| Age- and sex-adjusted HR | 0.87 (0.78–0.96) | 1.00 (reference) | 0.94 (0.80–1.10) | 0.90 (0.77–1.05) | 0.88 (0.75–1.04) |
| Multivariable HR | 0.79 (0.71–0.88) | 1.00 (reference) | 0.90 (0.76–1.05) | 0.85 (0.72–1.01) | 0.75 (0.63–0.91) |
| Multivariable HR+biomarkers* | 0.79 (0.71–0.89) | 1.00 (reference) | 0.91 (0.76–1.08) | 0.81 (0.68–0.97) | 0.77 (0.63–0.94) |

*The biomarkers (potential intermediate and biochemical variables) included estimated glomerular filtration rate, C-reactive protein, total to high-density lipoprotein cholesterol ratio, triglycerides, and urine levels of albumin and creatinine.
Average Requirement when assuming a fractional intestinal absorption of ~30% over the entire range of intake. According to 2 iterations of the National Health and Nutrition Examination Survey, even more than half of the US adults did not meet the Estimated Average Requirement of magnesium intake. The prevalence of inadequate magnesium intake by millions of adults combined with the lowered risk of hypertension associated with higher urinary magnesium excretion, as marker of dietary uptake, highlights an important, yet fairly underrecognized, potential for the primary prevention and control of high blood pressure.

The mechanisms by which magnesium may influence the pathogenesis of high blood pressure remain unclear, although several lines of experimental evidence may provide some explanation for the observed lower risk of hypertension associated with dietary magnesium. Magnesium may act as a calcium antagonist because it can act on most types of calcium channels in vascular smooth muscle. As such, magnesium is thought to decrease intracellular calcium, thereby lowering calmodulin-dependent myosin light chain kinase activity, which causes arterial relaxation and subsequent decreases in vascular resistance and arterial blood pressure. In addition, in vitro studies showed that magnesium enhances synthesis of nitric oxide, a potent vasodilator, and is involved in the regulation of endothelial function, which seems to correspond with the favorable effect of magnesium on some endothelial markers in cross-sectional studies.

Strengths of the present study include the prospective design, the large sample size, the extensive adjustment for covariables and cations associated with hypertension, the use of serial blood pressure measurements over time and participant...
pharmacy information on antihypertensive medication to define hypertension, and the use of 2 consecutive 24-hour urine specimens to objectively define magnesium uptake. Some limitations warrant consideration. First, although urinary magnesium excretion reflects a subject’s dietary magnesium uptake and overcomes limitations of recall bias and differences in intestinal absorption associated with dietary questionnaires, its precision depends on accurate collection. To evaluate this, we performed a sensitivity analysis, in which we excluded subjects with potentially inadequate 24-hour urine collection, which yielded similar results. Also, the correlation between the two 24-hour urinary magnesium excretions in this study was comparable with those reported in the INTERSALT (International Cooperative Study on Salt, Other Factors, and Blood Pressure) study. Second, magnesium was measured and risk of hypertension requires replication. If further studies replicate these findings, randomized controlled trials may be warranted to test whether increasing magnesium intake or magnesium uptake from the gut could lower blood pressure and prevent hypertension.

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Disclosures
None.

References


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**Novelty and Significance**

**What Is Relevant?**

- The inverse association between urinary magnesium excretion and risk of hypertension was independent of dietary (eg, sodium, potassium, and calcium) and nondietary risk factors for hypertension and was consistent in several subgroups.

**What Is New?**

- To prospectively investigate the association between urinary magnesium excretion, an objective estimate of magnesium uptake, and risk of hypertension in a well-characterized population-based cohort.

- Urinary magnesium excretion was associated with risk of hypertension in an inverse log-linear fashion.

- The current findings could have substantial public health implications given the highly prevalent inadequate magnesium intake in Western societies combined with the enormous burden associated with hypertension.

**Summary**

During a median follow-up of 7.6 years, 1172 participants developed hypertension. Higher urinary magnesium excretion, a reflection of dietary magnesium uptake, was associated with a lower risk of hypertension over the entire range of habitual intake levels after adjustment for both dietary and nondietary risk factors.
Urinary Magnesium Excretion and Risk of Hypertension: The Prevention of Renal and Vascular End-Stage Disease Study

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Urinary Magnesium Excretion and Risk of Hypertension: the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study

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Data were fit by a spline Cox proportional hazards regression model with three knots and adjusted for age, sex, body mass index, smoking status, parental history of hypertension, alcohol consumption, and urine calcium, sodium, and potassium. Dashed lines indicate the 95% confidence intervals. The spline curve is truncated at the 1st percentile and 99th percentile of the distribution curve.