Urinary magnesium excretion as a marker of heart disease risk1,2

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Magnesium is the fourth most abundant mineral in the body. Somewhat more than half of the body’s total magnesium is present in bone, with almost all of the rest inside muscle and other soft tissues (1). Only 1% of magnesium is present in the blood. Magnesium is involved in >300 biochemical reactions in the body and is crucial to nerve transmission, muscle contraction, vasomotor tone, and bone metabolism (2). In addition, magnesium plays an important role in the regulation of blood pressure and glucose and insulin metabolism (2). Epidemiologic studies have associated a low magnesium intake with adverse health outcomes such as insulin resistance, metabolic syndrome, type 2 diabetes, hypertension, inflammation, cardiac arrhythmias, and cardiovascular disease (CVD) (2–5). Foods rich in magnesium include whole grains, legumes, nuts, and green leafy vegetables.

In this issue of the Journal, Joosten et al (6) report results on the associations of urinary magnesium excretion, an indicator of dietary magnesium uptake, and plasma magnesium with ischemic heart disease (IHD) risk in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study, a prospective population-based cohort study in the Netherlands. Their study included 7664 adults of whom 462 experienced a fatal or nonfatal IHD event during a median follow-up of 10.5 y. Magnesium concentration in urine (two 24-h collections) and in plasma were measured at the beginning of the follow-up period. The authors found that a low urinary excretion of magnesium (lowest quintile compared with the highest 4 quintiles) was associated with a significant 60% increased risk of fatal and nonfatal IHD after adjustment for other risk factors for IHD and urinary concentrations of calcium, sodium, potassium, and creatinine. The association was similar for men and women and was not modified by diabetes or chronic kidney disease. Moreover, the relation was consistent across subgroups of CVD risk factors, and persisted in several sensitivity analyses. No association was observed between urinary magnesium excretion and all-cause mortality. This is the first prospective study that reports results on 24-h urinary magnesium excretion in relation to IHD risk.

Joosten et al (6) observed no association of plasma magnesium with IHD risk or all-cause mortality. Whether blood magnesium is a relevant biological marker for examining the role of magnesium in CVD is unclear because circulating magnesium is maintained within a narrow range and does not represent total body stores (7). The kidney plays a major role in magnesium homeostasis and in the maintenance of blood magnesium concentration. When there is a large reduction in the amounts of ingested and/or absorbed magnesium, there is a fairly rapid progressive reduction in the urinary excretion of magnesium by the healthy kidneys (1). In the early stages of magnesium depletion, blood magnesium concentration may still be within the normal range, whereas the concentration in urine may be significantly reduced (1). The tight homeostatic regulation of circulating magnesium along with the relatively restricted range of values for plasma magnesium (mean values in the lowest and highest quintiles were 0.73 and 0.89 mmol/L, respectively) in the PREVEND study may explain why Joosten et al (6) failed to observe an association between plasma magnesium and IHD. Misclassification of long-term plasma magnesium is another possible explanation for the lack of association. The correlation between urinary magnesium excretion and plasma magnesium concentration in the PREVEND study was very weak and even inverse (r = −0.03, P = 0.02) (6), which further indicates that plasma magnesium is a poor biomarker of magnesium status. The PREVEND study suggests that urinary magnesium excretion may be a more useful marker of magnesium balance than are plasma concentrations.

The study by Joosten et al (6) has important strengths, including the prospective design (which minimizes reverse causation bias), adequate length of follow-up, objective measures of actual magnesium uptake, adjustment for several potential confounders (including other minerals in the urine), and the robustness of the results. Furthermore, the absence of relation between urinary magnesium excretion and cancer-related and all-cause mortality reduces the possibility that the observed association was due to poor diet related to underlying disease. Despite adjustment for multiple potential confounders, the possibility of residual confounding by unmeasured dietary or nondietary factors cannot be ruled out.

Most previous prospective studies of magnesium intake or blood magnesium concentration in relation to IHD or total CVD morbidity or mortality have reported inverse associations (3). A recent meta-analysis of prospective studies showed a nonlinear inverse association between dietary magnesium intake and total CVD and a linear inverse association between serum magnesium concentrations and IHD risk (4). A recent meta-analysis of prospective studies showed a nonlinear inverse association between dietary magnesium intake and total CVD and a linear inverse association between serum magnesium concentration and IHD risk (4). The PREVEND study may explain why Joosten et al (6) failed to observe an association between plasma magnesium and IHD. Misclassification of long-term plasma magnesium is another possible explanation for the lack of association. The correlation between urinary magnesium excretion and plasma magnesium concentration in the PREVEND study was very weak and even inverse (r = −0.03, P = 0.02) (6), which further indicates that plasma magnesium is a poor biomarker of magnesium status. The PREVEND study suggests that urinary magnesium excretion may be a more useful marker of magnesium balance than are plasma concentrations.

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3 Abbreviations used: CVD, cardiovascular disease; IHD, ischemic heart disease; PREVEND, Prevention of Renal and Vascular End-stage Disease.

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nesium and total CVD (3). The relation between serum magnesium and CVD appeared to be stronger for fatal than for nonfatal events (3). Interestingly, in the studies of serum magnesium and CVD, the range of serum magnesium concentrations in the highest compared with lowest categories was narrow and within the “normal” range [ie, 0.75–0.96 mmol/L (7)]. This suggests that serum magnesium may have some use as a biological marker for CVD risk, despite the fact that serum magnesium poorly correlates with dietary magnesium intake and increases only marginally after magnesium supplementation (7, 8). Serum magnesium values in the normal range do not rule out the possibility of total body deficit. Nondietary factors such as diabetes, kidney and gastrointestinal diseases, alcohol consumption, and use of diuretics are associated with serum magnesium depletion (1, 7), suggesting that low serum magnesium concentration may be a marker of poor health or underlying disease. In fact, magnesium depletion is rather common in hospitalized patients (1).

In summary, the study by Joosten et al (6) suggests that urinary excretion of magnesium is associated with risk of IHD in a non-linear and threshold fashion. An increased risk of IHD was observed only among individuals in the lowest quintile of urinary magnesium excretion, reflecting an inadequate magnesium intake or absorption. This finding adds to and extends the evidence indicating that low magnesium intake and status may increase the risk of CVD. The potential use of urinary magnesium excretion as a marker of a CVD risk warrants further investigation in other prospective studies.

The author had no conflicts of interest.

REFERENCES