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Magnesium for cardiovascular health: time for intervention^{1–3}

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Magnesium is a biologically active mineral found in foods rich in whole grains, green leafy vegetables, and nuts. In westernized populations such as in the United States, magnesium intake is known to be inadequate (1). In experimental studies of animals, magnesium deficiency was shown to accelerate atherosclerosis and magnesium supplementation suppressed its development (2, 3). Epidemiologic observations have also associated low intake of magnesium with various adverse health outcomes, including insulin resistance, the metabolic syndrome, type 2 diabetes, hypertension, and cardiovascular disease (CVD) (4). Several mechanisms have been proposed for the potential cardiometabolic benefits of magnesium intake, including improvement of glucose and insulin homeostasis; antihypertensive, antiarrhythmic, antiinflammatory, anticoagulant, or antiplatelet effects; improved lipid metabolism; reduced vascular contractility; and increased endothelium-dependent vasodilation (5).

In this issue of the Journal, Larsson et al (6) performed a meta-analysis using data from 8 prospective studies involving 6477 stroke cases and 241,378 participants and observed an inverse relation between dietary magnesium intake and stroke risk. In particular, magnesium intake was inversely associated with risk of ischemic stroke but not hemorrhagic stroke. This well-done study summarizes the body of literature concerning the important relation—albeit modest in strength—between magnesium intake and stroke incidence in human populations.

For nearly 8 decades, researchers have extensively studied the roles of magnesium in cardiovascular health. In 1935 Zwillinger (7) first reported that intravenous injection of magnesium sulfate suppressed digitalis-induced cardiac arrhythmia in humans. In the late 1950s the hypothesis that magnesium intake reduces cardiovascular risk gained further support from ecologic studies, including Kobayashi's (8) first report of inverse correlations between regions of different water hardness and mortality rates due to cerebrovascular diseases in Japan, which were subsequently confirmed in many additional ecologic studies of different geographical areas of diverse populations. Because ecologic correlations on the basis of grouped data at the population level may not reflect the corresponding association at the individual level due to confounding by other aspects of diet, lifestyle, or socioeconomic factors (known as ecologic fallacy) (9), making causal inferences of such ecologic data is problematic. Moreover, compared with magnesium intake from the diet, magnesium from drinking water is present in negligibly small amounts, dampening some enthusiasm for its importance as a preventive strategy.

In more recent decades, large, prospective studies have further evaluated the role of magnesium intake by using both well-tuned dietary assessment and magnesium blood concentrations in CVD development in apparently healthy individuals. Overall, there appears to be an inverse, albeit modest, pattern in the majority of these studies in diverse populations (10). Nevertheless, relatively few prospective studies have specifically investigated the relation between magnesium intake and stroke risk. Larsson et al (6) should be complimented for laboring such a meta-analysis that comprised 241,378 participants with a wide age range and generated summary statistics that provide the most relevant evidence today linking magnesium intake to lower risk of ischemic stroke. Because this meta-analysis involved ~5000 ischemic stroke cases, 600 intracerebral hemorrhage cases, and 400 subarachnoid hemorrhage cases (6), the null findings for hemorrhagic stroke may still be prone to statistical fluctuation due to inadequate sample sizes. Because of the inherent limitations in observational studies, as the authors also acknowledged, these observed associations, although statistically significant, may still be biased by residual confounding from other unmeasured lifestyle or socioeconomic variables. Because many variables were often associated with high magnesium intake (high education and household income and less smoking), even this well-done meta-analysis alone cannot be used to make causal inferences. Nevertheless, several lines of evidence do implicate a potential beneficial role of magnesium for stroke risk reduction. In the Atherosclerosis Risk in Communities Study in 14,221 men and women followed for 15 y, magnesium deficiency characterized by low serum concentrations was also associated with increased risk of ischemic stroke (11). Whereas serum magnesium concentration does not represent total magnesium status or the intracellular magnesium pool (12), it remains the most widely

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used method to define magnesium deficiency in humans to date. Studies using rodent stroke models (13–15) have also indicated potential neuroprotective effects due to magnesium supplementation. Apart from its pleiotropic cardiometabolic effects, magnesium may play a role in reducing cerebral ischemia through other pathways, including inhibition of ischemia-induced glutamate release, *N*-methyl-D-aspartate receptor blockade, calcium entry via antagonism of calcium influx via voltage-gated channels, enhancement of mitochondrial calcium buffering, prevention of ATP depletion, and vasodilatation of cerebral blood vessels (16).

The efficacy of magnesium treatment in the secondary prevention of stroke has also been suggested in some small pilot trials but was not confirmed in the IMAGES (Intravenous Magnesium Efficacy in Stroke) study, an international, multicenter, double-blind, placebo-controlled trial (17). Although magnesium treatment given within 12 h of stroke onset in 2589 patients failed to reduce mortality or disability at 90 d, subgroup analyses show possible benefits in ischemic lacunar strokes (17), indicating that this area still requires further investigation.

How should we move forward? First, from a mechanistic perspective, there is a compelling need for the development of an objective assessment of total body magnesium store and concentrations of intracellular magnesium or biologically active ionized or free magnesium. Second, we believe that it is time to perform a large, double-blinded and placebo-controlled randomized trial of magnesium intake for the primary prevention of CVD, especially among individuals who are at high risk of CVD and who have lower blood magnesium concentrations. Because much uncertainty exists regarding the validity of observational studies, more of the same type of observations would add little incremental value toward the confirmation of a cause-effect relation. Without a large trial that directly defines CVD as a primary outcome, it is safe to predict that another 8 decades will go by while generations of nutritional scientists continue to debate magnesium's efficacy for the primary prevention of CVD. Careful planning will be necessary to address the many logistic difficulties and the cost of a large efficacy trial in the primary prevention of CVD using magnesium. Meanwhile, it is also important to push for a better understanding of mechanisms to enable that eventual large efficacy trial. For example, integrating dietary and genetic markers of magnesium homeostasis with intermediate CVD phenotypes has provided additional insight concerning the homeostatic regulation of magnesium metabolism and its role in the etiology of CVD (18). The application of high-throughput systems biology technology in randomized controlled trial settings also has the potential to afford us important insight into the complex molecular pathways in response to magnesium intervention. In a small pilot trial of magnesium supplementation among overweight or obese young adults, we recently reported that oral magnesium supplementation (500 mg elemental Mg/d) for 4 wk led to significantly differential regulation of some genes and proteins related to metabolic and inflammatory pathways (19). While pursuing that definitive primary prevention trial, we'll

place our bets on consuming magnesium-rich foods for cardiovascular health.

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