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# Personalized magnesium intervention to improve vitamin D metabolism: applying a systems approach for precision nutrition in large randomized trials of diverse populations

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Greater intakes of micronutrients and minerals such as vitamin D, calcium, and magnesium have long been associated with decreased incidence of many late-onset disorders in observational studies (1–5), although large randomized intervention trials that directly evaluate their clinical efficacies have generated inconsistent results (6–8). Nevertheless, some observations have been well recognized, including high prevalence of vitamin D and magnesium insufficiency in westernized populations (9, 10) and the large interpersonal variations of vitamin D and magnesium metabolisms in the general population (11). Studies have shown that magnesium plays a critically important role in the synthesis and metabolism of vitamin D, raising the possibility that magnesium should be included in any vitamin D regimen for optimal biological functioning (12).

In this issue of the Journal, Dai et al. (13) report very interesting findings from a randomized trial showing that 12 wk of magnesium supplementation using a personalized dosing scheme adjusted to participants' dietary intakes significantly changed vitamin D metabolism dependent upon vitamin D status at baseline. Specifically, concentrations of 25-hydroxycholecalciferol [25(OH)$D_3$] were found to increase among those whose baseline concentrations of 25-hydroxyvitamin D [25(OH)D] were <30 ng/mL but decrease among those whose concentrations of 25(OH)D were in the range of 30–50 ng/mL. More interestingly, magnesium supplementation also appeared to selectively deactivate cytochrome P450 3A4 (CYP34A) to degrade vitamin $D_3$ over $D_2$ when plasma 25(OH)D was high. These data therefore provide for the first time some tantalizing evidence in support of the notion that adequate magnesium status could directly improve vitamin D deficiency and its related adverse events.

Dai et al. (13) also noted that all trial participants at baseline had a Ca:Mg intake ratio >2.6, which was reduced to 2.3 after being given magnesium supplementation. However, whether a 3-way interaction of calcium–magnesium–vitamin D existed and how it might have influenced the effects of the magnesium dosing strategy on vitamin D metabolites were not explored, probably owing to statistical inefficacy. Moreover, other limitations also need to be kept in mind when interpreting these findings. First, dietary intakes were assessed via 24-h recall, and measurement error was likely to affect the estimates of the Ca:Mg intake ratios reported. It would have been informative if the status of calcium and magnesium had also been assessed using biomarkers in different tissues (urine, plasma, and red blood cells). Second, the exact number of participants in each stratum of baseline 25(OH)D concentrations (<12, 20, 30, 40, 50, >50 ng/mL) was not reported but is likely to be small. As acknowledged by the authors, there were only 2 participants with baseline 25(OH)D <12 ng/mL, making it powerless to determine any magnesium–vitamin D interaction among those with such low concentrations at baseline. Similarly, findings of 25(OH)$D_2$ had wide 95% CIs among those whose baseline 25(OH)D was >50 ng/mL. Moreover, 2 other vitamin D metabolites—25(OH)$D_3$ and 24,25-dihydroxyvitamin $D_3$—appeared to decrease after magnesium supplementation among those with baseline 25(OH)D at 50 ng/mL, whereas when baseline 25(OH)D concentrations were <30 mg/mL, 25(OH)$D_3$ increased, but not for 24,25-dihydroxyvitamin $D_3$. These observations raise the possibility that both false positives and false negatives were possible alternative explanations for their findings. In fact, of the 265 participants who met the inclusion criteria and were randomly assigned, 239 completed the study and only 180 (68% of enrolled participants) were included in the current analysis. To improve statistical efficiency, the authors opted for not carrying out an intent-to-treat analysis, abolishing the randomization design. As such, the effect size measure for magnesium–vitamin D interaction may have been biased, particularly for those with baseline 25(OH)$D_3$ ≥30 ng/mL. Finally, trial participants had previously been diagnosed with colorectal adenomas or hyperplastic polyps (and 14 participants were polyp-free individuals with a high risk of colorectal cancer), thus they were clearly not representative of the general population

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with respect to calcium, magnesium, and vitamin D metabolism, which calls for further studies in additional populations.

Notwithstanding these limitations, Dai and colleagues (13) should be congratulated for conducting the first randomized and placebo-controlled intervention trial employing an individualized dosing scheme based on intakes of magnesium and calcium (assessed twice before and 4 times during the intervention). Their effort has set a new standard for the design and implementation of intervention trials to advance the emerging field of precision nutrition by incorporating relevant population ancestry (genotypes) and phenotypes (age, sex, ethnicity, and comorbidity).

How should we move forward? First, we need to identify specific biomarkers for magnesium status and establish a clinical guideline to define magnesium deficiency and insufficiency in a manner similar to vitamin D status (14). Magnesium intake, often estimated from food-frequency questionnaires, has been associated with improved cardiometabolic outcomes (15). Perhaps the magnesium tolerance test should be advocated as the gold standard for assessing magnesium status, particularly in conjunction with biomarkers sensitive to changes in magnesium concentrations after increasing magnesium intake. From both clinical and public health perspectives, there is a compelling need for the development of an objective assessment of total body magnesium stores and concentrations of intracellular magnesium or biologically active ionized or free magnesium.

Second, there is an urgent need to evaluate the quality of available magnesium supplements, their specific dosage and bioavailability, and, even more importantly, their impact on health outcomes in diverse populations. It is indeed timely to design and implement large randomized intervention trials with individualized dosing strategies that are targeted to diverse groups of individuals defined by age, sex, and intake levels of codependent minerals or vitamins, as well as genotypes such as TRPM6 and TRPM7 (16). The precision-based dosing strategy does present some challenging issues that need to be considered in the design of large and high-quality randomized trials of interactive nutrients or minerals in the future. Adding to the complexity of the codependency of magnesium and vitamin D is the homeostatic control of vitamin D metabolism that involves a feedback loop of other micronutrients and minerals such as calcium, and its regulators, including parathyroid hormone, calcitonin, and sex steroids (17). Clinically, hypomagnesemia is directly related to hypocalcemia (18), and calcium supplementation increases urinary excretion of magnesium, raising the concern that a high intake of calcium may lead to magnesium deficiency (19). Previously, Dai and colleagues (12) reported that dietary Ca:Mg intake ratios in the range of 1.7–2.6 appeared optimal in reducing the risk of colorectal cancer and cardiovascular disease mortality. A meta-analysis of prospective cohorts found that those whose calcium intakes were >700 mg/d experienced ~3% increased risk of ischemic stroke for every 300 mg/d increase in intake and that calcium appeared to have a beneficial effect only in Asian populations with low to moderate intake of calcium but not in American or European populations with high calcium intake (20).

Nevertheless, because of the large uncertainty regarding the validity of observational studies, conducting more of the same type of observational studies will not improve our understanding of these age-old questions of whether or how dietary or supplemental magnesium intake may play an independent causal role or interact with vitamin D or calcium status in affecting cardiometabolic health. To that end, conducting large and high-quality randomized dietary intervention trials in diverse populations offers a promising way forward (however challenging they may seem). Because of their relative accessibility and high prevalence of usage in the general population, large randomized intervention trials employing a personalized systems approach to evaluate the balance of benefits and risks for these dietary supplements are needed to improve clinical and public health practice (21). Integrating dietary, biochemical, and genetic markers of magnesium, calcium, and vitamin D metabolism in a systematic and personalized manner defined by relevant phenotypes should provide complementary insights into the homeostatic roles of these important micronutrients and minerals in health maintenance and disease development.

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