Vitamin D Supplementation and Increased Risk of Falling
A Cautionary Tale of Vitamin Supplements Retold

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The randomized clinical trial (RCT) by Bischoff-Ferrari et al[1] in this issue of *JAMA Internal Medicine* shows that vitamin D supplementation is associated with the risk of falls. Two "high" doses (60 000 IU of vitamin D_3 per month or 24 000 IU vitamin D_3 plus 300 mg of calcifediol per month) achieved a serum 25-hydroxyvitamin D (25[OH]D) level of 30 ng/mL in 80% of participants, a level that has been recommended as best for reducing the risk of fractures and for other health benefits (to convert 25[OH]D to nanomoles per liter, multiply by 2.496).[2,3] However, compared with a dose of 24 000 IU of vitamin D_3 per month (equivalent to 800 IU per day), the higher doses had no effect on lower extremity physical performance and increased the risk of falls. A previous RCT[4] in women of the same age showed that 500 000 IU of vitamin D per year achieved serum 25(OH)D levels of at least 30 ng/mL in most participants but significantly increased risk of falls by 15% and fractures by 26%.

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A theoretical possibility has been raised that periodic administration of high doses of vitamin D accounts for the increased risk of falls and fractures.[5] That hypothesis should be tested by placebo-controlled trials showing that a daily dose of 2000 IU, for example, reaching serum 25(OH)D levels of at least 30 ng/mL reduces the risk of falls and fractures.

The trial in this issue[1] had no placebo group and, therefore, could not test the effects of supplementation with 800 IU of vitamin D per day. However, a recent placebo-controlled trial by Uusi-Rasi et al[6] found that an 800 IU per day supplement had no effect on physical function or risk of falls or injurious falls, whereas an exercise program reduced the risk of injurious falls by about half. Another trial found that 800 IU daily had no effect on lower extremity function or risk of falls in postmenopausal women 75 years or younger.[7]

It is uncertain whether any dose of vitamin D supplementation reduces the risk of falls or fractures in community-dwelling older adults. Previous meta-analyses of RCTs had differed about whether vitamin D supplements reduce the risk of falls[8-11] or fractures[8,12-14] in community-dwelling elderly individuals. In contrast meta-analyses[15-17] have shown that 800 IU of vitamin D and 1200 mg of calcium reduced the risk of hip fracture and mortality for patients dwelling in institutions. These patients should receive calcium and vitamin D supplements.

Clinicians should not recommend vitamin D supplements for other putative health benefits. There is no evidence from meta-analyses of RCTs that vitamin D supplementation reduces the risk of cardiovascular disease or cancer.[13,18] In addition, a recent trial[19] found that 1000 IU of vitamin D per day, with or without calcium, did not decrease the risk of colon cancer or recurrent adenomas in those with a history of colon adenomas.

The vitamin D story seems to be following the familiar pattern observed with antioxidant vitamins. Enthusiasm for the health benefits of vitamin supplements is coupled with the belief that "vitamins" are inherently safe and reinforced by observational studies showing, essentially, that healthy people have higher vitamin levels. Then RCTs and meta-analyses[20] proved that the supplements in fact increase mortality (β-carotene, vitamin E), or have no health benefits (vitamin A, vitamin C).

The strategy of supplementation with vitamin D to achieve serum levels of at least 30 ng/mL has not been established by RCTs to reduce the risk of falls and fractures. It may increase the risk of falling. Until that approach is supported by randomized trials with updated meta-analyses, it would be prudent to follow recommendations[21] from the Institute of Medicine (IOM) that people 70 years or older have a total daily intake of 800 IU of vitamin D without routine measurement of serum 25(OH)D levels. It is prudent to get recommended intakes of vitamin D and other vitamins from a balanced diet with foods that naturally contain what is manufactured into supplements.

ARTICLE INFORMATION

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Adverse Effects Associated With Proton Pump Inhibitors

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Proton pump inhibitors (PPIs) have been among the most widely prescribed medications in the United States for decades. This is largely due to 2 very common uses of PPIs: treatment of dyspepsia and prevention of gastrointestinal bleeding among patients prescribed antiplatelet therapy, coupled with the belief that PPIs have few adverse effects. However, mounting evidence demonstrates that PPIs are associated with a number of adverse effects and are overprescribed. This issue was highlighted in *JAMA Internal Medicine*'s launch of the Less Is More series in 2010.[1,2] Since then, additional evidence of adverse effects of PPIs has accumulated. In this issue of *JAMA Internal Medicine*, Lazarus et al[3] add chronic kidney disease to the list of possible harms of PPIs.

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To collate data on the adverse effects of PPIs, we surveyed recent studies focusing on systematic reviews. Most of the evidence supporting the adverse effects of PPIs is observational. Thus, it is possible that PPI users are sicker than nonusers, or that adverse effects are caused by other drugs or conditions associated with PPI use. However, some adverse effects have been documented by multiple high-quality observational studies and are likely causal (**Table**). Herein, we summarize recent data on the adverse effects of PPI use.

Kidney Disease

Among 10 439 patients followed for 13.9 years in the Atherosclerosis Risk in Communities study,[3] the risk of chronic kidney disease was 50% higher in PPI users compared with nonusers. The findings of this study are strengthened by a thorough assessment of potential confounding using both multivariable and propensity score adjusted analyses, by a dose response with higher risk among patients using twice daily compared with once daily PPI dosing, and by higher risk among PPI users compared with patients using histamine H_2 antagonists—a comparison group that should control for potential bias and confounding. Finally, the findings were replicated in a second large cohort using administrative data from patients in the Geisinger Health System.[3] Use of PPIs may lead to chronic kidney disease through recurrent acute kidney injury or hypomagnesemia. Although this is a large, high-quality observational study, additional confirmation would be helpful, especially since chronic kidney disease is a common condition.

Use of PPIs is also associated with increased risk of acute kidney injury, possibly mediated through acute interstitial nephritis. In a population-based study[4] of 290 592 people 66 or older, rates of acute kidney injury and acute interstitial nephritis were 2.5- and 3-fold higher in PPI users compared with nonusers. In a nested case-control study[10] of 184 480 patients 18 years or older, renal disease was 2-fold more common in patients who had used PPIs compared with those who had not after controlling for multiple potential confounding variables.