EDITORIAL

Vitamin D Guidelines in Primary Care

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Around the turn of the 21st century, clinicians began hoping that vitamin D supplements would prevent a host of chronic conditions in pregnancy, childhood, and adulthood. These hopes rested on animal experiments showing that vitamin D supplementation reduces inflammation, improves bone mass, and inhibits cancer cell proliferation[1]; human intervention studies showing salutary effects on intestinal calcium and phosphate absorption and mobilization of skeletal calcium stores[2]; and observational population studies linking lower vitamin D intake with higher risks for fractures, malignancy, autoimmune diseases, infectious diseases, and hypertension.[3]

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While these sources of evidence were suggestive, only randomized clinical trials of vitamin D supplements with salient health outcomes could provide proof enough to change practice and policy. Fortunately, over the past decade, researchers have conducted many such trials. Alas, these trials show that vitamin D is not the blockbuster that some predicted.

The lack of clear-cut evidence for vitamin D supplementation as a staple of chemoprevention means that clinical guidelines must be nuanced. In the situation of small effect sizes, suboptimal interpretation of findings or small biases can lead to overstatement of benefit.

In this issue of *JAMA*, as part of its Clinical Guidelines Synopsis series, Liu and colleagues[4] summarize a 2024 clinical practice guideline for vitamin D supplementation from the Endocrine Society.[5] The society's guideline, whose development followed standard procedures and took advantage of evidence-based literature reviews, provides recommendations for general populations of pregnant women, children aged 1 to 18 years, and adults aged 19 to greater than 75 years.[5] Its expert panel found insufficient evidence for screening to detect, and thus treat, low 25-hydroxyvitamin D levels, so the guideline authors limited their recommendations to whole-of-population vitamin D supplementation.

If you are a primary care clinician considering incorporating this guideline into practice, you might weigh several factors in addition to the estimated quantitative benefit. First is the extent to which the participants in the cited studies match the patient in front of you. Second is the extent to which the clinical training and expertise of the guideline panel members match yours. Third is the feasibility of implementing the guidelines within your practice.

Consider the guideline recommendation for vitamin D intake—in the form of vitamin D–containing supplements as well as foods—for children aged 1 to 18 years to prevent respiratory illness and rickets. The guideline cited 12 randomized clinical trials, 6 conducted in South Asian countries, 5 in East Asia, and 1 in the Middle East. The participants in those studies likely had higher baseline risks for respiratory illness than typical patients in the United States or Europe, calling into question the applicability of the guideline to many of its consumers.

In assessing benefit, neither the guideline expert panel nor the *JAMA* synopsis authors interpreted the clinical importance of the average effect estimate. For example, across the 6 trials that addressed childhood lower respiratory tract infection, the most likely effect of vitamin D supplementation over 5 days to 3 years was avoiding 33 cases per 1000 users. The authors of the systematic evidence review supporting the guideline picked 30 per 1000 as the threshold for substantial benefit[6]; 33 is very close to the threshold, and the effect in real-life practice settings is likely lower than in clinical trials, in which adherence is usually stronger.[7] The lower and upper 95% confidence limits were consistent with substantial benefit, 81 fewer infections per 1000 adherent users, and modest harm—19 additional infections. In other words, this is a small effect, and its precision is questionable.

Moreover, none of the 12 trials among children and adolescents assessed the effect of vitamin D supplementation on prevention of nutritional rickets, the other rationale for intervention.[8] Instead, the expert panel generalized from infants and toddlers participating in seminal studies in the early 20th century to contemporary "children with open growth plates at risk for nutritional rickets."[9] Despite the guideline as a whole finding insufficient evidence to recommend a detect-and-treat strategy, this phrase suggests that a detection step may have already occurred, namely, vitamin D–related blood tests. No study has assessed this detect-and-treat strategy among a general population of youths. Nor does it seem sound to recommend a population-wide strategy by invoking children at nutritional risk.

The second consideration is the composition of the expert panel. Regardless of the rigor with which systematic reviewers do their work, panel members interpret study findings from their own perspectives. Even without financial conflicts of interest, and even with training in interpreting the medical literature, implicit biases may creep in as a result of experts' own clinical and research experiences. Because patients who see specialists are on average at higher risk of adverse outcomes than most of the patients generalists see every day, a generalist and a specialist might disagree with each other on interpretation of the same evidence.[10,11]

The expert panel for the Endocrine Society guideline apparently did not include a primary care pediatric practitioner, even though generalists are the main audience. Pediatric endocrinologists, whom the panel did include, are more likely to obtain radiographs and blood measurements of vitamin D,

calcium, phosphorus, and parathyroid hormone for their typical patients than are primary care pediatricians or family practitioners. Perhaps the unfounded assumption that laboratory results would materialize in the face of a do-not-screen guideline is how this panel of experts found it possible to endorse widespread vitamin D supplementation to prevent rickets in older children and adolescents in the absence of direct evidence.

A third issue is the context in which guidelines exist in clinical practice. When contemplating harms of vitamin D, many would invoke the possibility of hypercalcemia and kidney stones. In primary care practice, one might also lump unintended consequences of guideline adoption in with these other potential disadvantages. "Guideline fatigue" can plague practitioners and patients. As a result, evidence should be quite strong for any new health prevention recommendation. This admonition is especially true for chemoprevention (and screening) among asymptomatic patients. In that case, clinicians are not responding to a patient's symptoms, but rather saying, in essence, "I'm recommending a pill every day for years for something that is not currently bothering you." That type of recommendation requires a high burden of proof.

Primary care clinicians already face expectations to cover more topics than can reasonably fit within a routine health visit. One solution, from the American Academy of Pediatrics' Bright Futures program, is to encourage pediatric clinicians to select from a list of recommended anticipatory guidance topics based on parental priorities.[12] When clinicians discuss too many topics at health maintenance visits, patients or parents are unable to remember them all, and adherence can falter.[13] Adherence might be especially problematic for patients with multiple medical or social challenges. Taking daily vitamin D supplements may not be their highest priority. Even among all US infants less than 1 year old, in whom vitamin D demonstrably prevents rickets, less than 40% take the recommended amount.[14] Adherence in older children and adolescents may be lower.

Guidelines from the gold-standard US Preventive Services Task Force (USPSTF) are typically less likely to recommend a service than are those from professional societies of specialists, like the Endocrine Society. Because the USPSTF considers prevention in primary care practice, its members come from the fields of preventive medicine and primary care. In developing guidelines, the USPSTF invites comments from relevant specialists because the Task Force values their expertise, but the final recommendations are made by those closer to generalist practice. The USPSTF is as transparent as possible about how the experts develop ratings and recommendations from the evidence, which, to avoid bias, is compiled by evidence centers that do not include task force members as authors of their reports. The USPSTF also explicitly discusses the clinical context in which practitioners may adopt each recommendation. Given its strict standards, the USPSTF often concludes that evidence is insufficient to make a recommendation. These "I" statements can be frustrating for clinicians, but they are most often consistent with the conservative approach to clinical prevention we endorse.

Regarding vitamin D, a current USPSTF recommendation published in 2021 concluded that evidence is insufficient to recommend for or against routine screening to detect deficiency among US adults.[15] The 2024 guidelines of the Endocrine Society are consistent with this recommendation. Where the Endocrine Society extends too far, in our opinion, is recommending vitamin D supplements for general populations, including children and adolescents, for whom the evidence is not ironclad.

ARTICLE INFORMATION

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