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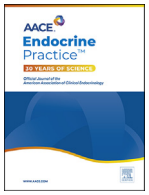

Editorial

In the Shadow of Enthusiasm: Hype, Hope, and Evidence Guiding the Vitamin D Debate

The role of vitamin D in skeletal health is well established, but over the past two decades, interest has grown in its potential effects on extra-skeletal diseases. This interest is driven mainly by observational studies linking low blood vitamin D levels to an increased risk of various acute and chronic conditions. Consequently, blood 25(OH)D testing and vitamin D supplementation have become widespread. In 2024, the Endocrine Society released a new Clinical Practice Guideline on the use of vitamin D (cholecalciferol [D_3] or ergocalciferol [D_2]) for disease prevention in individuals without specific indications for treatment or testing (Fig.).[1] These new guidelines have sparked considerable debate and strong reactions.[2]

The Review[3] by Holick examines various studies from the vast vitamin D literature and compares the 2011 Endocrine Society Guideline in Evaluation, Treatment, and Prevention of Vitamin D Deficiency[4] and the 2024 Guideline, while emphasizing findings that support the broader use of vitamin D. Although the Review may appear comprehensive, its main limitation lies in its selective presentation of evidence, focusing almost exclusively on observational studies to support the use of vitamin D and testing with serum 25(OH)D in the prevention and management of extra-skeletal diseases. For example, Table 1 cherry-picks observational studies with the largest favorable associations, resulting in a skewed and unbalanced depiction of the evidence. The review does not acknowledge studies that do not support a role for vitamin D, leading to a one-sided narrative. Ignoring evidence that challenges preconceived beliefs distorts the overall picture, risks drawing incorrect conclusions, and may compromise patient care. While the Review includes a few trials, it reserves its criticism for those that contradict preconceptions (e.g., the VITAL study). Underscoring the review's inconsistent standards in evaluating the quality of evidence is highlighting a randomized, controlled study among 40 patients with COVID-19 (16 given vitamin D for 21 days) that was open-label, did not have a placebo and did not describe the randomization method as evidence to support a role of vitamin D for COVID-19.[5]

In contrast, the 2024 Guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology, ensuring a rigorous and systematic approach.[6] The Guideline Development Panel (GDP) adhered strictly to the GRADE principles, which included collaboration with methodologists to ensure that all recommendations were grounded in the highest-quality evidence available rather than individual opinions. Through a structured voting process, the GDP prioritized clinically relevant questions that are most important for patients and providers, following the population-intervention-comparison-outcome approach. For each question, the independent evidence-synthesis team conducted detailed systematic reviews, and the GDP carefully evaluated the evidence across all aspects of the Evidence-to-Decision framework, including stakeholder values and preferences (incorporating input from clinical experts and a patient representative), resource requirements, cost-effectiveness, acceptability, feasibility, and the potential impact on health equity. In short, the 2024 Guideline reflects the standards for trustworthy guidelines by the National Academy of Medicine.[7]

The Review makes several statements that can be misleading as they imply causality. For example, the Review states, "Infant risk for dental caries was reduced by 70% if their mother had a prenatal serum concentration of 25(OH)D of at least 40 ng/mL." A more accurate phrasing would be, "Infant risk for dental caries was associated with a 70% lower risk." Although this may seem like a subtle change, it is crucial: in observational studies, the exposure (e.g., vitamin D) does not cause a change in risk—it is linked to a difference in risk. The Review frequently mentions the terms "deficiency" and "insufficiency," including when describing trials, with varied and inconsistent thresholds. In contrast, the GDP emphasized precise language when synthesizing the evidence to prevent misinterpretation. For example, the GDP deliberately moved away from commonly used but ambiguous terms like "normal," "deficiency," "insufficiency," and "sufficiency" to describe vitamin D status, as these terms lack agreed-upon definitions and are not based on clinical trial evidence.

The GDP prioritized evidence from clinical trials that reported on patient-important outcomes (vs. intermediate outcomes such as carotid-femoral arterial wall thickness, endothelial function, expression of cytokines), as they are better suited to evaluate the benefits and potential harms of an intervention. Observational studies with vitamin D, while valuable for generating hypotheses, are vulnerable to confounding, which limits drawing conclusions on the causal role of vitamin D in health and disease. Observational evidence can be sufficient for harmful behaviors (e.g., smoking or skydiving without a parachute) or when trials would be unethical to conduct, and can guide recommendations. Indeed, the GDP recommended vitamin D for preventing rickets based on well-established observational evidence rather than randomized placebo-controlled trials. However, because an association does not imply causality, the case for vitamin D as an intervention to prevent disease demands robust evidence from trials and thoroughly conducted meta-analyses, which provide a stronger foundation for decision-making.

The GDP sought to move beyond the simplified conclusions often drawn from observational studies, that "low 25(OH)D levels

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Ages 1-18	Ages 19-49	Ages 50-74	Ages ≥75	Pregnancy	Prediabetes
Empiric vitamin D supplementation*	**No empiric vitamin D supplementation***		**Empiric vitamin D supplementation***	**Empiric vitamin D supplementation***	**Empiric vitamin D supplementation***
To prevent nutritional rickets and because of the potential to lower the risk of respiratory tract infections.	Follow the Institute of Medicine Recommended Daily Allowance.		Because of the potential to lower the risk of mortality.	Because of the potential to lower the risk of preeclampsia, intrauterine mortality, preterm birth, small for gestational age birth and neonatal mortality.	Because of the potential to lower the risk of progression to diabetes.

The panel assumed that all should follow the Recommended Dietary Reference Intakes (DRI) established by the US Institute of Medicine (currently the National Academy of Medicine). The Recommended Daily Allowance (RDA) in the DRI is 600 IU (15 μg) for persons aged 1-70 years and 800 IU (20 μg) for persons older than 70 years. The RDA established by the the Institute of Medicine and the American College of Obstetricians and Gynecologists (ACOG) is 600 IU (15 μg) during pregnancy.

* **Empiric vitamin D supplementation** refers to vitamin D (cholecalciferol [D_3] or ergocalciferol [D_2]) intake (usually in pill or drop form) that (a) exceeds the DRIs and (b) is implemented without testing for 25-hydroxyvitamin D. Vitamin D doses in the included clinical trials varied considerably (see technical remarks under recommendations); hence, optimal doses remain unclear.

For people older than 50 years for whom vitamin D treatment is indicated, the panel suggests supplementation via daily administration of vitamin D, rather than intermittent high doses.

The panel suggests against routine 25-hydroxyvitamin D testing for generally healthy individuals who do not otherwise have established indications for 25-hydroxyvitamin D testing (e.g., hypocalcemia). The panel did not specifically address whether and how those who present with low levels of 25-hydroxyvitamin D should be evaluated and/or treated.

* Importantly, this guideline does not address individuals with underlying conditions that substantially alter vitamin D physiology, including various conditions associated with decreased absorption (e.g., short gut, gastric bypass, inflammatory bowel disease), increased catabolism/decreased activation (e.g., some medications), and increased renal losses (e.g., nephrotic syndrome). In addition, this guideline does not address persons known to be at high risk for fractures.

Fig. Recommendations for vitamin D for the prevention of disease according to the 2024 Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline.

indicate harm" and "high levels confer benefit." Although higher serum 25(OH)D levels are associated with lower disease prevalence or incidence, that does not imply causality or warrant intervention. A helpful analogy is with HDL cholesterol. High serum HDL concentrations have long been associated with better cardiovascular health. Yet, clinical trials aimed at raising HDL (e.g., using niacin or cholesteryl ester transfer protein inhibitors) have not shown benefit for cardiovascular outcomes. In some cases, such as torcetrapib, increasing HDL concentration led to worse outcomes, likely due to off-target effects.[8] This suggests that HDL concentration is more of a cardiovascular risk marker than a direct therapeutic target. Similarly, an elevated serum 25(OH)D concentration may serve as a marker of a healthier state rather than a causal factor that should be targeted for disease prevention.

The Review suggests a "minimum" threshold for serum 25(OH)D to achieve extra-skeletal benefits and proposes "preferred" ranges to optimize outcomes. However, these thresholds are not rigorously defined, lack trial-based evidence, and do not consider the nuances of different populations and specific health conditions. It is particularly problematic to assume that a single threshold can be applied universally to all individuals and all conditions. A helpful analogy is with LDL cholesterol, where trial evidence has established different targets based on individual risk profiles and clinical context. The GDP emphasized that optimal vitamin D levels likely vary across various populations, conditions, and desired outcomes; thus, a single 25(OH)D concentration cannot be universally recommended. Hence, the Endocrine Society no longer endorses the target 25(OH)D level of 30 ng/ mL (75 nmol/L) suggested in the 2011 guideline.[4]

The GDP emphasized that the benefit-risk ratio of vitamin D supplementation depends on the specific target population and health condition in question. Vitamin D at doses higher than the Dietary Reference Intakes is appropriate for specific populations or conditions but not for others. For example, the benefit-risk ratio of empiric vitamin D (i.e., without 25[OH]D testing) is favorable for reducing diabetes risk in adults with prediabetes, leading the GPD to issue a recommendation for diabetes prevention in this population. However, no evidence supports a similar effect in those with normal glucose tolerance. Consequently, the PICO-specific recommendations in the Guideline (Fig.) should not be extrapolated to other populations, conditions, or outcomes where the benefit-risk profile may differ.

The GDP did not find clear trial-based evidence to support establishing distinct 25(OH)D thresholds tied to outcome-specific benefits in the populations examined. Most vitamin D trials did not include a specific 25(OH)D level as an eligibility criterion, and no trials were designed or powered to address the effect of vitamin D in subgroups stratified by either baseline or achieved 25(OH)D levels. Although many systematic reviews include subgroup analyses according to the study average baseline 25(OH)D levels, such analyses are subject to ecological fallacy in which inferences about individuals are based on aggregate group data, not individual participant data. Such subgroup analyses can be misleading and lead to erroneous conclusions. In the absence of trial-based evidence and given that testing requires resources, the GDP refrained from proposing thresholds for 25(OH)D adequacy or providing target 25(OH)D levels for disease prevention, especially since 25(OH)D thresholds are likely to vary by population and outcome.

The 2024 Guideline should not be extrapolated to individuals with underlying medical conditions known to disrupt vitamin D metabolism, such as those with advanced kidney disease. However, low 25(OH)D levels in individuals with darker skin or obesity do not necessarily indicate abnormal vitamin D physiology. The Guideline did not provide specific recommendations for these groups because no clinical trial evidence supports tailored guidance.

The topic of vitamin D often elicits strong opinions on both sides of the debate. Recognizing these biases, the GDP focused on developing the 2024 Guideline based on rigorous, evidence-based

principles, striving to remain objective and adhere to the best available data. For instance, while screening for 25(OH)D may provide a sense of action for clinicians and patients, it does not guarantee better outcomes and may divert resources away from more effective interventions. The GDP emphasized the importance of ensuring adequate vitamin D intake based on the Dietary Reference Intakes for all individuals while determining that certain groups may require additional vitamin D to reduce the risk of developing specific conditions. With the release of the 2024 Guideline, the previous 2011 version has been formally retired,[9] and should no longer be used in clinical practice, ensuring that current care aligns with the latest evidence.

Disclosure

There is no conflict of interest. The author served as the co-chair of the 2024 Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline. The opinions in this commentary are the author's and do not reflect the views of the Guideline Development Panel or the Endocrine Society.

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