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Clinical Practice Guideline

Vitamin D for the Prevention of Disease: An Endocrine Society Clinical Practice Guideline

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Abstract

Background: Numerous studies demonstrate associations between serum concentrations of 25-hydroxyvitamin D (25[OH]D) and a variety of common disorders, including musculoskeletal, metabolic, cardiovascular, malignant, autoimmune, and infectious diseases. Although a causal link between serum 25(OH)D concentrations and many disorders has not been clearly established, these associations have led to widespread supplementation with vitamin D and increased laboratory testing for 25(OH)D in the general population. The benefit-risk ratio of this increase in vitamin D use is not clear, and the optimal vitamin D intake and the role of testing for 25(OH)D for disease prevention remain uncertain.

Objective: To develop clinical guidelines for the use of vitamin D (cholecalciferol [vitamin D3] or ergocalciferol [vitamin D2]) to lower the risk of disease in individuals without established indications for vitamin D treatment or 25(OH)D testing.

Methods: A multidisciplinary panel of clinical experts, along with experts in guideline methodology and systematic literature review, identified and prioritized 14 clinically relevant questions related to the use of vitamin D and 25(OH)D testing to lower the risk of disease. The panel prioritized randomized placebo-controlled trials in general populations (without an established indication for vitamin D treatment or 25[OH]D testing), evaluating the effects of empiric vitamin D administration throughout the lifespan, as well as in select conditions (pregnancy and prediabetes). The panel defined "empiric supplementation" as vitamin D intake that (a) exceeds the Dietary Reference Intakes (DRI) and (b) is implemented without testing for 25(OH)D. Systematic reviews queried electronic databases for publications related to these 14 clinical questions. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was used to assess the certainty of evidence and guide recommendations. The approach incorporated perspectives from a patient representative and considered patient values, costs and resources required, acceptability and feasibility, and impact on health equity of the proposed recommendations. The process to develop this clinical guideline did not use a risk assessment framework and was not designed to replace current DRI for vitamin D.

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Results: The panel suggests empiric vitamin D supplementation for children and adolescents aged 1 to 18 years to prevent nutritional rickets and because of its potential to lower the risk of respiratory tract infections; for those aged 75 years and older because of its potential to lower the risk of mortality; for those who are pregnant because of its potential to lower the risk of preeclampsia, intra-uterine mortality, preterm birth, small-for-gestational-age birth, and neonatal mortality; and for those with high-risk prediabetes because of its potential to reduce progression to diabetes. Because the vitamin D doses in the included clinical trials varied considerably and many trial participants were allowed to continue their own vitamin D–containing supplements, the optimal doses for empiric vitamin D supplementation remain unclear for the populations considered. For nonpregnant people older than 50 years for whom vitamin D is indicated, the panel suggests supplementation via daily administration of vitamin D, rather than intermittent use of high doses. The panel suggests against empiric vitamin D supplementation above the current DRI to lower the risk of disease in healthy adults younger than 75 years. No clinical trial evidence was found to support routine screening for 25(OH)D in the general population, nor in those with obesity or dark complexion, and there was no clear evidence defining the optimal target level of 25(OH)D required for disease prevention in the populations considered; thus, the panel suggests against routine 25(OH)D testing in all populations considered. The panel judged that, in most situations, empiric vitamin D supplementation is inexpensive, feasible, acceptable to both healthy individuals and health care professionals, and has no negative effect on health equity.

Conclusion: The panel suggests empiric vitamin D for those aged 1 to 18 years and adults over 75 years of age, those who are pregnant, and those with high-risk prediabetes. Due to the scarcity of natural food sources rich in vitamin D, empiric supplementation can be achieved through a combination of fortified foods and supplements that contain vitamin D. Based on the absence of supportive clinical trial evidence, the panel suggests against routine 25(OH)D testing in the absence of established indications. These recommendations are not meant to replace the current DRIs for vitamin D, nor do they apply to people with established indications for vitamin D treatment or 25(OH)D testing. Further research is needed to determine optimal 25(OH)D levels for specific health benefits.

Key Words: vitamin D, 25-hydroxyvitamin D, vitamin D deficiency, mortality, pregnancy, infection, prediabetes, clinical practice guidelines, systematic reviews

Introduction

The role of vitamin D in the regulation of skeletal and mineral ion homeostasis is well established. Epidemiologic evidence has shown consistent associations of low vitamin D status with increased risk of a variety of common disorders, including musculoskeletal, metabolic, cardiovascular, malignant, autoimmune, and infectious diseases (1-3,). However, observational studies are prone to confounding and various forms of bias, and a causal link between low vitamin D status, as assessed by serum 25-hydroxyvitamin D (25[OH]D) levels, and many disorders has not been clearly established. Nonetheless, these associations have led to widespread supplementation and increased laboratory testing for 25(OH)D levels in the general population. In the United States, the prevalence of supplemental vitamin D use of 1000 IU (25 μg) or more per day increased from 0.3% in the 1999-2000 National Health and Nutrition Examination Survey (NHANES) to 18.2% in the 2013-2014 NHANES (4). The use of 25(OH)D testing in clinical practice has also been increasing; however, the cost-effectiveness of widespread testing has been questioned, especially given the uncertainty surrounding the optimal level of 25(OH)D required to prevent disease.

Vitamin D is not a true vitamin (defined as a nutrient that cannot be endogenously synthesized), as intake is not required in those who have adequate sun exposure. However, seasonal variation in UV-B availability and decreased sun exposure associated with clothing and limited time outdoors has resulted in the general population being increasingly reliant on oral intake of vitamin D in a few natural sources, foods fortified with vitamin D, and supplements containing vitamin D. Whether ingested or synthesized in the skin, vitamin D is converted to 25(OH)D in the liver (5). This process is not tightly regulated; therefore, the 25(OH)D concentration most accurately reflects vitamin D status. A second hydroxylation step (1-alpha) leads to the formation of the active metabolite, 1,25-dihydroxyvitamin D in many tissues. Circulating 1,25-dihydroxyvitamin D is thought to derive primarily from renal 1-alpha hydroxylation in the absence of pathologic conditions (6). Although loss of function mutations in vitamin D hydroxylases are rare, genetic variants and several pharmacologic agents may affect their activity (7-10). Vitamin D metabolites are secreted with bile acids and reabsorbed in the terminal ileum; therefore, terminal ileal disease, as well as general malabsorption and having a short gut (including from Roux-en-Y gastric bypass), can lead to low levels of serum 25(OH)D. There are other conditions that place individuals at risk for low 25(OH)D levels. For example, vitamin D metabolites bound to vitamin D–binding protein and albumin are lost in the urine of those with nephrotic syndrome. In addition, vitamin D metabolites are inactivated primarily by the 24-hydroxylase, which is induced by high levels of 1,25-dihydroxyvitamin D as well as by fibroblast growth factor-23, as seen in chronic kidney disease (11). Importantly, these guidelines do not apply to individuals with such underlying conditions that substantially alter vitamin D physiology.

The actions of vitamin D metabolites are mediated by the vitamin D receptor (VDR), which is expressed in most tissues. The VDR has been shown to regulate cellular differentiation and target gene expression in many cell types, including those of the immune system. The best-established physiologic role of the VDR is promoting intestinal calcium absorption, which is critical for maintaining skeletal and mineral ion homeostasis (12, 13). The skeletal effects of vitamin D are dependent on adequate calcium intake. The effects of vitamin D on the immune system are due to local activation of 25(OH)D to 1,25-dihydroxyvitamin D and induction of VDR expression (14). Thus, the optimal level of 25(OH)D to prevent disease likely depends on the clinical outcomes being evaluated. Similarly, the required duration of exposure to vitamin D for specific outcomes is expected to vary, depending on the underlying pathophysiology (eg, acute [infections] vs chronic [cancer]).

In contrast to previous guidelines that broadly addressed the evaluation, treatment, and prevention of vitamin D deficiency, with an emphasis on the care of patients who are at risk for deficiency (15), the goal of this Guideline Development Panel was to establish clinical guidelines for the use of vitamin D to lower the risk of disease in individuals without established indications for vitamin D treatment or 25(OH)D testing. The panel recognized that there are numerous important clinical questions regarding the use of vitamin D and 25(OH)D testing in the general population; however, due to limited resources, 14 of these clinical questions were prioritized and 4 to 6 outcomes were addressed for each question. Because patient-important clinical outcomes are

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expected to differ according to the target population, the panel proposed specific outcomes for the pediatric population (ages 1 to 18 years), and for ages 19 to 49 years, 50 to 74 years, and 75 years and older. Established guidelines recommend empiric vitamin D in the first year of life, specifically to prevent nutritional rickets (16-18); thus, this demographic was not addressed. Other populations examined were pregnant individuals and those with prediabetes, dark complexion, and obesity. The panel also addressed whether daily supplementation with vitamin D should be recommended rather than intermittent (nondaily), higher-dose vitamin D, and whether supplementation should be limited to those with circulating 25(OH)D levels below a threshold.

Evidence from randomized controlled trials (RCTs) was prioritized for the systematic reviews. Large (> 1000 participants) longitudinal observational cohort studies were considered if they included appropriate comparators (supplementation vs no supplementation) and outcomes, but only when an insufficient number of RCTs was available. Trials where the intervention was a vitamin D analog or metabolite other than vitamin D2 or vitamin D3 were excluded because these compounds are not globally available. Mendelian randomization studies were excluded because they do not evaluate response to supplementation. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology was used to assess the certainty of evidence and inform recommendations. The panel sought evidence relevant to all elements of the Evidence-to-Decision (EtD) framework, which included stakeholder values and preferences (including input from clinical experts and a patient representative), costs and other resources required, cost-effectiveness, acceptability, feasibility, and impact on health equity. The panel did not identify robust evidence pertinent to these EtD factors for most clinical questions.

Limitations

In formulating this Guideline, several challenges were encountered that influenced the formulation of the final recommendations.

1. Because those with lower baseline levels of 25(OH)D are expected to benefit more from vitamin D supplementation than those with higher levels (19), a major limitation in formulating recommendations was the paucity of RCTs addressing the efficacy and safety of vitamin D supplementation in populations with low baseline 25(OH)D levels. Average baseline levels of 25(OH)D in many large trials were in a range that most would consider adequate (eg, 31 ng/mL [78 nmol/L] in the VITAL trial) (20). In such trials, a lack of effect of vitamin D does not necessarily indicate that vitamin D does not influence the relevant outcome, but rather that the study populations had baseline levels of 25(OH)D that were adequate for the desired outcome.
2. Unlike typical trials for pharmacologic agents, in which control participants are not exposed to the intervention, all participants in vitamin D trials were routinely exposed to vitamin D through sun exposure and dietary sources. In addition, many trials allowed participants to remain on their current supplements that contained vitamin D which often reflected the DRI (eg, 600-800 IU [15-20 μg] daily for adults). Such circumstances may have biased trial results toward the null hypothesis.
3. 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. This prevented the panel 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. 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. Therefore, the commissioned systematic review informing this guideline does not include study subgroup analyses according to average baseline 25(OH)D levels.
4. Many trials were considered to be of insufficient duration to adequately assess the effect of the vitamin D intervention on some outcomes, due to the long latency for the development of chronic diseases such as cancer, diabetes, cardiovascular disease (CVD) and osteoporosis.
5. Because the included trials used various doses and administration schedules of vitamin D, specific dose recommendations for vitamin D could not be proposed for specific populations. Instead, in the technical remarks, vitamin D doses used in the included trials are summarized.
6. The trials that the panel considered were performed in overall healthy populations at average risk for the outcomes of interest; therefore, the recommendations are limited to generally healthy individuals without established indications for vitamin D treatment or 25(OH)D testing.
7. In most trials, study participants were largely of European ancestry or identified as non-Hispanic White, with very few trials including large numbers of participants from other races or ethnicities.
8. The panel developed clinical questions for different age groups of adults (<50 years, 50 to 74 years, and 75 years and older) to represent different stages of life. However, the panel recognizes the somewhat arbitrary nature of these categories and acknowledges that many trials included populations that spanned these age categories. As a result, it was challenging to directly apply study results to narrowly defined age groups.
9. Many trials in those aged older than 50 years combined vitamin D with calcium, making it difficult to isolate the effect of vitamin D from that of calcium. This is especially relevant to outcomes related to skeletal health, for which both vitamin D and calcium are considered essential.
10. Due to resource limitations, not all potential outcomes of interest were addressed in all populations of interest. The panel prioritized outcomes that they felt were most relevant to the specific populations under consideration.

Thus, these clinical guidelines relate to the use of vitamin D to lower the risk of disease in individuals without established indications for vitamin D treatment or 25(OH)D testing. The Guideline Development Panel assumed that the Institute of Medicine's (IOM, now known as the National Academy of Medicine) DRIs for vitamin D (21) represent a baseline standard for all individuals. Importantly, the panel's recommendations

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should not be extrapolated to those with underlying medical conditions that are known to negatively impact vitamin D physiology. For those living in countries where food fortification with vitamin D is not standard or where dietary supplements are not routinely used, interventions may be required to insure a baseline intake consistent with the IOM DRIs.

List of Recommendations

Question 1. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for children and adolescents (ages 1 to 18 years)?

Recommendation 1

In children and adolescents aged 1 to 18 years, we suggest empiric vitamin D supplementation to prevent nutritional rickets and potentially lower the risk of respiratory tract infections. (2 | ⊕⊕◯◯)

Technical remarks

- Empiric vitamin D may include daily intake of fortified foods, vitamin formulations that contain vitamin D, and/or daily intake of a vitamin D supplement (pill or drops).
- In the clinical trials included in the systematic review, with respect to respiratory tract infections in children, vitamin D dosages ranged from 300 to 2000 IU (7.5 to 50 μg) daily equivalent. The estimated weighted average was approximately 1200 IU (30 μg) per day.

Question 2. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for nonpregnant adults < 50 years of age?

Question 3. Should vitamin D supplementation vs no vitamin D supplementation be used for nonpregnant adults < 50 years of age only when 25(OH)D levels are below a threshold?

Recommendation 2

In the general adult population younger than age 50 years, we suggest against empiric vitamin D supplementation. (2 | ⊕◯◯◯)

Technical remark

- This recommendation relates to empiric vitamin D supplementation that exceeds the DRIs established by the IOM. Adults in this age group should follow the Recommended Daily Allowance established by the IOM (600 IU [15 μg] daily).

Recommendation 3

In the general adult population younger than age 50 years, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Question 4. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for adults aged 50 to 74 years?

Question 5. Should vitamin D supplementation vs no vitamin D supplementation be used for adults aged 50 to 74 years only when 25(OH)D levels are below a threshold?

Recommendation 4

In the general population aged 50 to 74 years, we suggest against routine vitamin D supplementation. (2 | ⊕⊕⊕◯)

Technical remark

- This recommendation relates to empiric vitamin D supplementation that exceeds the DRIs established by the IOM. Adults in this age group should follow the Recommended Daily Allowance established by the IOM (600 IU [15 μg] daily for those aged 50 to 70 years; 800 IU [20 μg] daily for those older than 70 years).

Recommendation 5

In the general population aged 50 to 74 years, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.

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- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Question 6. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used by adults aged ≥ 75 years?

Question 7. Should vitamin D supplementation vs no vitamin D supplementation be used by adults aged ≥ 75 years only when 25(OH)D levels are below a threshold?

Recommendation 6

In the general population aged 75 years and older, we suggest empiric vitamin D supplementation because of the potential to lower the risk of mortality. (2 | ⊕⊕⊕◯)

Technical remarks

- Empiric vitamin D may include daily intake of fortified foods, vitamin formulations that contain vitamin D and/or daily intake of a vitamin D supplement.
- For empiric supplementation, daily, lower-dose vitamin D is preferred over nondaily, higher doses.
- In the clinical trials included in the systematic review that reported on the mortality outcome, vitamin D dosage ranged from 400 to 3333 IU (10 to 83 μg) daily equivalent. The estimated weighted average was approximately 900 IU (23 μg) daily. Participants in many trials were allowed to remain on their routine supplements, including up to 800 IU (20 μg) of vitamin D daily.

Recommendation 7

In the general population aged 75 years and older, we suggest against routine testing for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D thresholds that provide outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Question 8. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used during pregnancy?

Question 9. Should vitamin D supplementation vs no vitamin D supplementation be used during pregnancy only when 25(OH)D levels are below a threshold?

Recommendation 8

We suggest empiric vitamin D supplementation during pregnancy, given its potential to lower risk of preeclampsia, intra-uterine mortality, preterm birth, small-for-gestational-age (SGA) birth, and neonatal mortality. (2 | ⊕⊕◯◯)

Technical remarks

- This recommendation is based on evidence from trials conducted in healthy individuals during pregnancy.
- Empiric vitamin D may include daily intake of fortified foods, prenatal vitamin formulations that contain vitamin D, and/or a vitamin D supplement (pills or drops).
- In the clinical trials included in the systematic review, the vitamin D dosages ranged from 600 IU to 5000 IU (15 to 125 μg) daily equivalent, usually provided daily or weekly. The estimated weighted average was approximately 2500 IU (63 μg) per day.

Recommendation 9

During pregnancy, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide pregnancy outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy pregnant individuals who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Question 10. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for adults with prediabetes (by glycemic criteria)?

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Recommendation 10

For adults with high-risk prediabetes, in addition to lifestyle modification, we suggest empiric vitamin D supplementation to reduce the risk of progression to diabetes. (2 | ⊕⊕⊕◯)

Technical remarks

- Lifestyle modification must be a routine management component for adults with prediabetes.
- The clinical trials informing this recommendation primarily related to adults with high-risk prediabetes, identified as meeting 2 or 3 American Diabetes Association glycemia criteria (fasting glucose, glycated hemoglobin [HbA1c], 2-hour glucose after a 75-gram oral glucose challenge) for prediabetes and those with impaired glucose tolerance.
- In the clinical trials included in the systematic review, the vitamin D dosages ranged from 842 to 7543 IU (21 to 189 μg) daily equivalent. The estimated weighted average was approximately 3500 IU (88 μg) per day. Participants in some trials were allowed to remain on their routine supplements, including up to 1000 IU (25 μg) of vitamin D daily.

Question 11. Should a daily, lower-dose vitamin D vs *nondaily (ie, intermittent), higher-dose vitamin D be used for nonpregnant people for whom vitamin D treatment is indicated?*

Recommendation 11

In adults aged 50 years and older who have indications for vitamin D supplementation or treatment, we suggest daily, lower-dose vitamin D instead of nondaily, higher-dose vitamin D. (2 | ⊕⊕◯◯)

Technical remark

- The panel did not identify evidence related to individuals younger than age 50 years.

Question 12. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for healthy adults?

Recommendation 12

In healthy adults, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In healthy adults, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.
- This recommendation relates to adults who do not otherwise have established indications for testing with 25(OH)D levels (eg, hypocalcemia).

Question 13. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for adults with dark complexion?

Recommendation 13

In adults with dark complexion, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- This recommendation relates to generally healthy adults with dark complexion who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).
- The panel did not identify any clinical trials that related clinical outcomes to skin complexion per se. A secondary analysis did not clearly suggest net benefit with vitamin D in those who self-identify as Black. The panel recognized that self-identified race is an inaccurate and otherwise problematic proxy for dark complexion.

Question 14. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for adults with obesity?

Recommendation 14

In adults with obesity, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In adults with obesity, 25(OH)D thresholds that provide outcome-specific benefits have not been established in clinical trials.
- This recommendation relates to generally healthy adults with obesity who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

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Notes:

- The Guideline Development Panel did not find clinical trial evidence that would support establishing distinct 25(OH)D thresholds tied to outcome-specific benefits in the populations examined. Hence, the Endocrine Society no longer endorses the target 25(OH)D level of 30 ng/mL (75 nmol/L) suggested in the previous guideline (15). Similarly, the Endocrine Society no longer endorses specific 25(OH)D levels to define vitamin D sufficiency, insufficiency, and deficiency.
- The current guideline suggests against routine 25(OH)D screening (in the absence of well-established indications), including in adults and children with obesity, in adults and children with dark complexion, and during pregnancy. This also represents a change from the 2011 guideline (15).

Methods of Development of Evidence-Based Clinical Practice Guidelines

This guideline was developed using the process detailed on the Endocrine Society website (https://www.endocrine.org/clinical-practice-guidelines/methodology) and summarized here. The Endocrine Society follows the GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology (22) (Tables 1 and 2). This methodology includes the use of evidence-to-decision (EtD) frameworks to ensure all important criteria are considered when making recommendations (23, 24). The process was facilitated by the GRADEpro Guideline Development Tool (GRADEpro GDT) (25). This Guideline Development Panel (GDP) consisted of content experts representing the following specialties: adult endocrinology, general internal medicine, obstetrics and gynecology, pediatric endocrinology, nutrition, and epidemiology. A patient representative was also included on the panel. Members were identified by the Endocrine Society Board of Directors and the Clinical Guidelines Committee (CGC) and were vetted according to the conflict-of-interest policy (26), which was adhered to throughout the guideline process to manage and mitigate conflicts of interest. Detailed disclosures of panel members and the management strategies implemented during the development process can be found in Appendix A. In addition, the group included a clinical practice guideline methodologist from the Mayo Evidence-Based Practice Center, who led the team that conducted the systematic reviews and meta-analyses, and a methodologist from the Endocrine Society, who advised on methodology and moderated the application of the EtD framework and development of the recommendations.

From the Guideline Development Panel, 2 to 3 members were assigned to lead each guideline question. The clinical questions addressed in this guideline were prioritized from an extensive list of potential questions through a survey of the panel members and discussion; 14 questions were identified as most important. The Mayo Evidence-Based Practice Center conducted a systematic review for each question and produced GRADE evidence profiles that summarized the body of evidence for each question and the certainty of the evidence (29). The systematic searches for evidence were conducted in February 2022 and updated in December 2023. In parallel to the development of the evidence summaries, the Guideline Development Panel members searched for and summarized research evidence for other EtD criteria, such as patients' values and preferences, feasibility, acceptability, costs/resource use, cost-effectiveness, and health equity. Research evidence summaries noted in the EtD frameworks were compiled using standardized terminology templates for clarity and consistency (30). During an in-person panel meeting and a series of video conferences, the Guideline Development Panel judged the balance of benefits and harms, in addition to the other EtD criteria, to determine the direction and strength of each recommendation (30, 31); see Tables 1 and 2.

The draft recommendations were posted publicly for external peer review and internally for Endocrine Society members, and the draft guideline manuscript was reviewed by the Society's Clinical Guidelines Committee, representatives of co-sponsoring organizations, a representative of the Society's Board of Directors, and an Expert Reviewer. Revisions to the guideline were made based on submitted comments and approved by the Clinical Guidelines Committee, the Expert Reviewer, and the Board of Directors. Finally, the guideline manuscript was reviewed before publication by the *Journal of Clinical Endocrinology and Metabolism's* publisher's reviewers.

This guideline will be reviewed annually to assess the state of the evidence and determine if there are any developments that would warrant an update to the guideline.

Evidence-to-Decision Considerations Common to Multiple Clinical Questions

Many of the EtD considerations were common to the clinical questions addressing empiric vitamin D supplementation. Most multivitamins contain 800 to 1000 IU (20-25 μg) of vitamin D. Vitamin D is inexpensive and available without a prescription, at costs varying from the equivalent of US $10 to $50 per year in North America, South America, New Zealand, Europe, and India. Because empiric vitamin D supplementation intervention would be limited to a daily supplement that is readily available, the panel judged that the intervention would be acceptable and feasible. Most vitamin D3 on the market is from animal sources (lanolin), but vegan vitamin D3 from lichen is also available. Vitamin D2, which is plant-based, is widely available, and the costs are similar. Evaluations of costs, acceptability, and feasibility refer to routine vitamin D use in the general population, and special considerations that pertain to children and specific demographics are discussed elsewhere.

When beneficial effects of empiric vitamin D were identified, the panel judged that empiric vitamin D will not likely have a negative impact on health equity and may have a favorable impact on improving health equity because low vitamin D status is more prevalent in disadvantaged populations, including those with lower socioeconomic status. In addition, disadvantaged persons tend to be at higher baseline risk for many of the outcomes assessed (eg, poor maternal-fetal outcomes, nutritional rickets, diabetes); thus, whenever benefit is expected for such outcomes, disadvantaged populations would be expected to derive greater absolute benefit.

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

Figure 1. Vitamin D for the prevention of disease.

Table 1. GRADE certainty of evidence classifications

Certainty of evidence	Interpretation
High ⊕⊕⊕⊕	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate ⊕⊕⊕O	We are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low ⊕⊕OO	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very Low ⊕OOO	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Source: Reprinted with permission from Schünemann HJ, Brożek J, Guyatt GH, Oxman AD. GRADE Handbook. Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach. Updated October 2013 (27).

When the intervention involved testing for 25(OH)D prior to treatment with vitamin D, the costs were felt to be moderate and the intervention less acceptable. The cost of a 25(OH)D assay varies from the equivalent of US $25 to $100 in North America, South America, New Zealand, and Europe. However, this does not include the cost of health care visits for ordering the test, interpreting the test result, and the potential need for additional testing and health care visits. Thus, while conditioning vitamin D supplementation on 25(OH)D test results would be acceptable to many, the panel judged that such an approach may be unacceptable to some. In addition, access to accurate 25(OH)D testing is variable across the globe, and an approach requiring such testing may not be feasible in some settings.

Even if there were beneficial effects to screening with 25(OH)D and treating based on the results, the panel was uncertain about the impact of such an approach on health equity. While the panel acknowledged the increased prevalence of low vitamin D status in disadvantaged populations, those with low socioeconomic status, and those with dark complexion, the costs and time commitment required to implement the intervention may limit its acceptability and feasibility in these populations and those across the globe with poor access to health care.

For each clinical question, additional details regarding all EtD considerations are included in the supplemental materials available online.

Vitamin D Use for Children Aged 1 to 18 Years

Background

The prevalence of low vitamin D status in childhood is high, with marked variability across the globe. In the United States, the population-based NHANES 2011-2014 survey found 25(OH)D levels lower than 20 ng/mL (50 nmol/L) in 7% of 1- to 5-year-olds, 12% of 6- to 11-year-olds, and 23% of 12- to 19-year-olds (32). Much higher prevalence of low vitamin D status is found in Northern Europe (33) and in

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Table 2. GRADE strength of recommendation classifications and interpretation

Strength of recommendation	Criteria	Interpretation by patients	Interpretation by health care providers	Interpretation by policy makers
1—Strong recommendation for or against	Desirable consequences CLEARLY OUTWEIGH the undesirable consequences in most settings (or vice versa)	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
2—Conditional recommendation for or against	Desirable consequences PROBABLY OUTWEIGH undesirable consequences in most settings (or vice versa)	The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients make decisions consistent with their individual risks, values and preferences.	Clinicians should recognize that different choices will be appropriate for each individual and that clinicians must help each individual arrive at a management decision consistent with the individual's values and preferences.	Policymaking will require substantial debate and involvement of various stakeholders. Performance measures should assess whether decision-making is appropriate.

Source: Reprinted from Schünemann HJ et al. Blood Adv, 2018;2(22):3198-3225. © The American Society of Hematology, published by Elsevier (28).

low- and middle-income countries, where the majority of children have 25(OH)D concentrations lower than 10 ng/mL (25 nmol/L) (34). Particularly high-risk pediatric groups include children with limited exposure to sunlight, children with dietary restrictions, and children with high skin melanin content.

Several well-established guidelines recommend empiric vitamin D in the first year of life, specifically to prevent nutritional rickets (16-18); thus, in this guideline and the associated systematic review, the panel did not address children aged 0-1 years. However, nutritional rickets is not limited to infancy. While rickets is often considered a historical disease, its incidence is rising in high-income countries. Recent surveys indicate an incidence of up to 24 per 100 000 patient-years in North America, Australia, and Europe (35). In Western countries, rickets mainly affects children from racial and ethnic minority groups and non-Western immigrants and refugees (36, 37). In low- and middle-income countries in the Middle East, South Asia, and Africa, the burden of nutritional rickets is substantially higher, with reported prevalence of 1% to 24% (35, 38). In Turkey, a survey of 946 children with rickets showed peak incidences at ages 0 to 2 years and 12 to 15 years (39), indicating risk throughout childhood and adolescence. Nutritional rickets leads to pain, deformity, delayed milestone acquisition, and poor growth, and can be complicated by seizure and dilated cardiomyopathy (40).

Vitamin D has been implicated in the prevention of respiratory infections, which are very common in children, with pneumonia being the most common infectious cause of death in the first 5 years of life (41-45). In addition, low vitamin D status is associated with tuberculosis infection (46), another major cause of childhood mortality, with an estimated 230 000 deaths annually (47). A potential role for vitamin D in additional health outcomes affecting childhood, including autoimmune disease, atopy, and diabetes, has also been proposed. For example, several Mendelian randomization studies have suggested an association between genetically determined 25(OH)D levels and multiple sclerosis (48-51). In addition, vitamin D is thought to play a role in immunity, and childhood offers a unique window of opportunity to train the immune system (52). Bone health is also important during childhood, since peak bone mass accrual occurs during this period, extending into early adulthood. Thus, inadequate vitamin D status in childhood may affect disease vulnerability throughout the lifespan. The guideline panel therefore addressed the question of whether empiric vitamin D supplementation should be continued throughout childhood and adolescence.

Question 1. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for children and adolescents (aged 1 to 18 years)?

Recommendation 1

In children and adolescents aged 1 to 18 years, we suggest empiric vitamin D supplementation to prevent nutritional rickets and potentially lower the risk of respiratory tract infections. (2 | ⊕⊕◯◯)

Technical remarks

- Empiric vitamin D may include daily intake of fortified foods, vitamin formulations that contain vitamin D, and/or daily intake of a vitamin D supplement (pill or drops).
- In the clinical trials included in the systematic review, with respect to respiratory tract infections in children, vitamin D dosages ranged from 300 to 2000 IU (7.5 to 50 μg) daily equivalent. The estimated weighted average was approximately 1200 IU (30 μg) per day.

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Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/gNMKfIPr5u4.

Benefits and Harms

The systematic review found no RCTs on the efficacy of vitamin D in children and adolescents to prevent symptomatic nutritional rickets. This was because vitamin D supplementation was studied and implemented widely for prevention of rickets long before clinical trial methodology was standardized (53), and a placebo-controlled trial for nutritional rickets would currently be considered unethical. Several lines of evidence, however, indicate that vitamin D supplementation prevents the development of nutritional rickets in children. In 1917, Hess and Unger treated 49 infants and toddlers aged 1 month to 17 months, who were at high risk of rickets, with cod liver oil, the active ingredient of which is vitamin D, and then compared them with 16 infants and children in the same community. Eight of 49 infants in the treatment group and 15 of 16 in the control group developed rickets (odds ratio 0.18, $P = .002$) (54). Chick and colleagues in Vienna compared institutionalized infants fed either a standard diet or one enriched with cod liver oil from 1920 to 1922 and observed that 58% of the control group developed rickets compared to none in the cod liver oil group (55). The institution of a free vitamin D distribution program (400 IU/d [10 μg/d]) in Turkey was associated with a reduction in the prevalence of nutritional rickets from 6% in 1998 to 0.1% in 2008 (56). These and other data were summarized in an earlier systematic review (18). While these interventions were primarily in infants, the panel judged that these observations can be reasonably generalized to all children with open growth plates at risk for nutritional rickets.

The systematic review informing this guideline identified 12 RCTs (57-68) (12 951 participants) reporting on the effect of vitamin D on the incidence of respiratory infection, with individuals experiencing any respiratory infection representing the unit of analysis. Five of these trials were conducted in South Asia (India and Bangladesh), 5 trials in East Asia (Taiwan, Vietnam, Mongolia, and Japan), and 1 each in Afghanistan and Israel. Vitamin D regimens varied greatly, ranging from daily dosing of 300 to 2000 IU (7.5 to 50 μg), weekly dosing of 10 000 and 14 000 IU (250 and 350 μg), and a single dose of 100 000 (2500 μg) to 120 000 IU (3000 μg). The relative risk (RR) for developing any respiratory tract infection was 0.94 (95% CI, 0.87-1.02), with an estimated absolute effect size of 43 fewer respiratory infections per 1000 (93 fewer to 14 more). Studies that had some concern for bias showed a lower risk (RR 0.75 [95% CI, 0.61-0.94]) while studies with low risk of bias showed no difference in risk (RR 0.99 [95% CI, 0.92-1.07]) (P for heterogeneity 0.022). Study subgroup analyses did not implicate vitamin D dosage or study participant age (younger vs older than 5 years) as significant predictors of outcomes. Among 6 trials (58, 60, 63, 64, 66, 68) that reported lower respiratory tract infection specifically (10 356 participants), the RR for infection was 0.93 (95% CI, 0.83-1.04), with an absolute effect size of 33 fewer lower respiratory infections per 1000 (81 fewer to 19 more). Study subgroup analysis suggested the possibility that higher vitamin D dosages led to greater reductions in lower respiratory tract infection risk (RR 0.82 [95% CI, 0.68-1.00]) compared to standard dosages (RR 0.98 [95% CI, 0.94-1.03]), although this was not a statistically significant interaction ($P = .087$). The RR of developing tuberculosis (2 trials, 10 533 participants) (68, 69) was 0.67 (95% CI, 0.14-3.11) in those supplemented with vitamin D (10 000 and 14 000 IU [250-350 μg] weekly) with an absolute effect size of 1 fewer per 1000 (from 2 fewer to 6 more). Three trials (58, 62, 70) reported data on the total number of respiratory infections as the unit of analysis. After combining data from these trials, the incidence rate ratio (IRR) favored vitamin D (0.64 [95% CI, 0.51-0.82]). Supporting this finding was the trial in which all patients had at least one acute respiratory infection in the 6 months following the intervention, but the proportion who had at least 3 infections was lower in the intervention group (7.7% vs 32.4%) (67). Study subgroup analyses did not strongly implicate study risk of bias or vitamin D dosage as significant predictors of these outcomes.

The panel found limited RCT data on the impact of vitamin D on the incidence of autoimmune disease, allergic disease, and asthma, with too few events to analyze. The panel found no RCT data on the effect of treating this population with vitamin D to lower the risk of prediabetes and type 2 diabetes, or fractures (in adulthood).

The systematic review did not find clear evidence that vitamin D increases adverse events in children. Available trials documented one case of symptomatic hypercalcemia in an individual assigned to vitamin D and one case of kidney failure in an individual assigned to the control group; there were no reported kidney stones.

Based on the panel's best estimates of treatment effects, the panel judged that the anticipated desirable effects of empiric vitamin D supplementation are likely to be beneficial for many, and that the anticipated undesirable effects are likely to be trivial for all.

Other Evidence-to-Decision Criteria and Considerations

The cost of vitamin D supplementation is low, although variable in different countries. Cost-effectiveness of universal vitamin D supplementation for the prevention of rickets has been addressed in economic modeling studies in the United Kingdom. Two studies suggested that targeted vitamin D administration to those with moderate-to-dark complexion (defined in the study as having Afro-Caribbean ancestry) and those with Asian ancestry would be either cost-saving or cost-effective (71, 72). An additional study suggested that universal vitamin D supplementation via flour fortification would be cost-saving, while targeted supplementation of children would be cost-effective (73). Given that the risk of nutritional rickets is likely substantially increased among children with darker complexion and among immigrants to high-income countries (35, 40, 74-77)—populations that may experience lower health equity as a group—the panel concluded that vitamin D supplementation in children could potentially improve health equity.

There is limited evidence regarding the acceptability of vitamin D supplementation in children and among their caregivers. In one trial in which children aged 9 to 12 years were

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offered various forms of vitamin D and calcium, 44% agreed to continue fortified milk, 66% agreed to fortified orange juice, and 95% agreed to supplements, suggesting that supplement use may be the most accepted formulation (78). In one small survey study in the United Kingdom, approximately 25% of caregivers aware of governmental recommendations about vitamin D supplementation were not adherent to the recommendations. Reasons for nonadherence included the child's dislike of drops, low priority, and belief that other strategies such as breastfeeding, outdoor play, and a varied diet were sufficient (79).

Justification for the Recommendation

Given the high stakes of very low vitamin D status during skeletal growth—the risk of nutritional rickets in particular—the panel judged that empiric vitamin D supplementation may be prudent in growing children/adolescents, especially for those who are not otherwise expected to have adequate vitamin D stores via sun exposure (for example, from adequate levels of sun-safe outdoor physical activity) and ingestion of vitamin D–containing or vitamin D–fortified foods, and those for whom confidence is low that IOM DRIs are being achieved reliably. The panel agreed that low- to moderate-certainty evidence suggests that vitamin D supplementation in children may be beneficial for respiratory infections, which are a leading cause of mortality. The panel also concluded that supplementation costs are generally low, that supplementation is likely to be feasible and acceptable, and that empiric supplementation may improve health equity. Given the low overall certainty of evidence, and since net benefits may vary according to individual circumstances, a conditional recommendation was issued.

Additional Considerations

The optimal dosage for prevention of respiratory tract infections in children remains uncertain. In the trials included in this systematic review, the vitamin D dosages ranged from 300 to 2000 IU (7.5 to 50 μg) daily equivalent. The estimated median vitamin D dosage used in these studies was 811 IU (20 μg) daily, and estimated weighted average dosages were 1203 IU (30 μg) per day for the any respiratory infection outcome and 1473 IU (37 μg) per day for the lower respiratory tract infection outcome. (Here and elsewhere in this document, the estimated weighted average dosage for an outcome represents each relevant study's vitamin D dosage weighted according to the study's weight in the meta-analysis for that outcome.)

Research Considerations

Proposed areas for research include:

1. Adequately powered trials among children with appropriate controls to detect rare outcomes and long-term follow-up should be conducted in specific populations (eg, children with a history of asthma, risk of type 1 diabetes, new-onset type 1 diabetes) with outcomes specific to these populations (eg, asthma exacerbations, incident type 1 diabetes, progression of type 1 diabetes).
2. Since the majority of trials in children were conducted in Asia, it is important to undertake studies examining the effects of vitamin D on outcomes in other populations that may differ in terms of diet, sun exposure, and complexion.

Vitamin D Use in Nonpregnant Adults Aged < 50 Years

Background

While adults younger than age 50 years have lower health care usage compared to older individuals (80), this is a critical time during which many chronic diseases linked to environmental and nutritional factors develop. A significant percentage of adults in this age group have low vitamin D status. Levels of 25(OH)D lower than 12 ng/mL (30 nmol/L) were seen in 14% of Europeans and lower than 20 ng/mL (50 nmol/L) in 40% (81). In the United States, 24% and 6% of adults have 25(OH)D levels lower than 20 ng/mL (50 nmol/L) and 10 ng/mL (25 nmol/L), respectively (82). Numerous studies have found associations between low 25(OH)D levels, low BMD, and fractures. Low 25(OH)D levels have also been associated with fatigue and higher risks for respiratory infections, including COVID-19 (83).

The age span of 18 to 50 years is when peak bone mass occurs, and the National Osteoporosis Foundation's systematic review and implementation recommendations suggest that vitamin D plays an important role in peak bone mass accrual (84), which has implications for risk of osteoporotic fractures later in life. Most pregnancies occur between ages 19 and 50 years, and, while pregnancy-specific recommendations are addressed elsewhere, those who are pregnant most often do not present for care before the end of the first trimester, and having adequate vitamin D status preconception may be important. Fatigue is also common in this age group and, like respiratory infections, contributes to loss of productivity and increased medical care.

Question 2. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for nonpregnant adults < 50 years of age?

Question 3. Should vitamin D supplementation vs no vitamin D supplementation be used for nonpregnant adults < 50 years of age only when 25(OH)D levels are below a threshold?

Recommendation 2

In the general adult population younger than age 50 years, we suggest against empiric vitamin D supplementation.
(2 | ⊕◯◯◯)

Technical remark

- This recommendation relates to empiric vitamin D supplementation that exceeds the DRIs established by the IOM. Adults in this age group should follow the Recommended Daily Allowance established by the IOM (600 IU [15 μg] daily).

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Recommendation 3

In the general adult population younger than age 50 years, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/5NvU2k7Tig0 and https://guidelines.gradepro.org/profile/PdgmJZLRZTs.

Benefits and Harms

The systematic review identified 2 RCTs (85, 86) (17 074 participants in New Zealand and Norway) reporting on the development of a respiratory infection, with participants as the unit of analysis. There was no significant difference between the vitamin D and placebo groups (RR 1.02 [95% CI, 0.96-1.08]), with an estimated absolute effect size of 5 more per 1000 (11 fewer to 22 more). In the New Zealand study (85), the baseline mean 25(OH)D level was 29 ng/mL (73 nmol/L), and vitamin D was given as 200 000 IU (5000 µg) monthly for 2 months, followed by 100 000 IU (2500 µg) monthly for 18 months. In the Norwegian study (86), the baseline mean 25(OH)D level was not reported and vitamin D was given as 400 IU (10 µg) of cod liver oil daily.

The systematic review identified 4 studies (85, 87-89) (1120 participants, New Zealand, Finland, Canada, Australia) addressing the total number of respiratory infections as the unit of analysis; the IRR was 0.95 (95% CI, 0.83-1.07). The baseline mean 25(OH)D levels in these trials were 24 to 30 ng/mL (60 to 75 nmol/L) (one trial did not report baseline 25[OH]D). The intervention in 2 trials was daily vitamin D (400 IU [10 µg] and 5000 IU [125 µg]), whereas nondaily doses were administered in 2 other trials (10 000 IU [250 µg] per week and 20 000 IU [500 µg] per week).

The systematic review did not identify any trials examining the effects of vitamin D on new-onset fatigue. One small RCT (120 participants, Switzerland) (90) examined improvement in fatigue among participants with fatigue and baseline 25(OH)D levels lower than 20 ng/mL (50 nmol/L) with a mean level of 13 ng/mL (33 nmol/L). Participants were randomized to receive a single dose of 100 000 IU (2500 µg) of vitamin D or placebo. Four weeks later, those who received vitamin D were more likely to report amelioration of fatigue (72% vs 50%; RR 1.49 [95% CI, 1.08-1.94]), suggesting an improvement in 245 per 1000 (40 fewer to 470 more). The improvement in fatigue was modest (change in the Fatigue Assessment Scale [maximum score = 50] from 24.9 ± 5.4 to 21.6 ± 5.8 in the intervention group vs 23.3 ± 5.4 to 22.5 ± 5.9 in the placebo group).

Studies examining the effects of vitamin D on BMD tested different dosage regimens. Four studies (91-94) examined lumbar spine BMD, 2 examined total hip BMD (93, 94), 2 examined femoral neck BMD (92, 94) and 2 (95, 96) reported on volumetric tibial bone density by high-resolution peripheral quantitative computed tomography (HR-pQCT) (Denmark, Norway, Bangladesh, Austria, USA). Vitamin D was administered either daily (400 IU [10 µg], 800 IU [20 µg], 1000 IU [25 µg], 4000 IU [100 µg], or 7000 IU [175 µg]) or nondaily (40 000 IU [1000 µg] per week, or 50 000 IU [1250 µg] twice monthly). Estimated mean differences in BMD were 0.003 g/cm^2 lower at the lumbar spine (0.042 lower to 0.036 higher), 0.049 g/cm^2 lower at the total hip (0.060 lower to 0.038 higher), and 0.033 g/cm^2 higher at the femoral neck (0.023 lower to 0.090 higher); volumetric bone density by HR-pQCT was 6.862 mg/cm^3 higher at the tibia (8.082 lower to 21.805 higher). Some trials were felt to be of insufficient duration (< 1 year) to robustly evaluate the effects of vitamin D on bone density.

The systematic review found no evidence of increased adverse events (symptomatic hypercalcemia, nephrolithiasis, and kidney disease/kidney failure) in trial participants assigned to vitamin D.

Based on the panel's best estimates of treatment effects (the point estimates derived from meta-analyses), the panel judged that the anticipated desirable effects of vitamin D are likely to be small at best, and that the anticipated undesirable effects are likely to be trivial.

Other Evidence-to-Decision Criteria and Considerations

Considerations related to required resources, costs, acceptability, and feasibility have been previously addressed. A comprehensive review of studies addressing female patients' views of osteoporosis therapy revealed that calcium and vitamin D were viewed as safe and natural (97). Panel members judged that empiric vitamin D would likely be acceptable to individuals in this age group, especially females with risk factors for developing osteoporosis.

Justification for the Recommendation

While vitamin D supplementation appears to be safe, inexpensive, and readily available, the trials identified in the systematic review did not clearly show a substantive benefit of vitamin D supplementation. For this reason, the panel issued a conditional recommendation against routine vitamin D supplementation above what would be required to meet dietary reference guidelines.

The panel was unable to recommend a 25(OH)D threshold below which vitamin D administration provides outcome-specific benefits, primarily due to the absence of large RCTs designed to assess the effects of the intervention in those with low baseline 25(OH)D levels. In addition, the financial costs associated with both 25(OH)D testing and medical

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visits, as well acceptability of testing in this age group, where routine phlebotomy is not typically indicated for healthy individuals, factored into the panel's judgment. The panel also acknowledged that feasibility of 25(OH)D testing is variable across the globe; and in the absence of evidence for benefit, a recommendation for 25(OH)D testing could decrease health equity. For all these reasons, the panel suggested against routine 25(OH)D testing in generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Additional Considerations

The panel judged that healthy adults in this age group could rationally choose to take vitamin D supplements if they are not expected to have adequate vitamin D status via sun exposure and do not reliably meet DRI of vitamin D from vitamin D–containing or fortified foods.

Testing to identify those with low 25(OH)D level, or to monitor response to therapy, may be required in special populations who are expected to require more than the DRI of vitamin D to prevent/reverse low vitamin D status, including those with malabsorption (eg, from short gut syndrome, gastric bypass, inflammatory bowel disease), those with increased vitamin D catabolism (eg, due to certain medications), and those with increased renal losses of vitamin D (eg, nephrotic syndrome).

Research Considerations

1. Large clinical trials in populations with low baseline 25(OH)D levels will be required to determine if vitamin D prevents disease and what dosages are required for the desired outcomes. Although placebo-controlled trials in those known to have low 25(OH)D levels may be viewed as unethical, inclusion of various daily dosages and targeting several levels of 25(OH)D would inform the dosages and target levels required for disease prevention.
2. Clinical trials must be designed to be of sufficient duration to address the outcomes being examined, considering the natural history and pathophysiology of the diseases of interest (eg, acute infectious diseases vs fractures or cancer).

Vitamin D Use in Adults Aged 50 to 74 Years

Background

Vitamin D status may decrease with age due to impaired biosynthesis (reduced biosynthesis capacity, lower sun exposure), low dairy and fish consumption, and increased weight, although the decrease is most marked above age 75 years. Population-based data from the United States (NHANES) in 3377 adults aged 40 to 59 years and 3602 adults aged 60 years and older indicate that 24% and 22%, respectively, had 25(OH)D concentrations lower than 20 ng/mL (50 nmol/L), and 5.9% and 5.7%, respectively, had 25(OH)D concentrations lower than 10 ng/mL (25 nmol/L), with similar values for women and men (82). Population-based data from Europe (ODIN) in children and adults (all ages) show a higher prevalence of low vitamin D status, with 40% having values lower than 20 ng/mL (50 nmol/L) and 13% having values lower than 12 ng/mL (30 nmol/L), with similar values for women and men (81). The prevalence of low 25(OH)D levels is most marked in housebound and institutionalized individuals (98).

The period between 50 and 74 years of age corresponds to a time of bone loss related to menopause and normal aging, decreasing muscle function, and increasing fall risk, all predisposing to increased risk of fractures. Importantly, some studies suggest that these risks can be attenuated by vitamin D and calcium (99). Vitamin D has also been hypothesized to have a role in modifying the risk of CVD, diabetes, cancer, acute respiratory infections, and mortality, all of which are important outcomes relevant to this age group (100-102).

Many of the RCTs designed to address these questions involved groups with mean baseline 25(OH)D levels that would be considered adequate (approximately 25 ng/mL [63 nmol/L]). This has contributed to uncertainty regarding whether empiric vitamin D supplementation in those aged 50 to 74 years can reduce risk of chronic conditions common to this population. Additionally, it is unclear whether this age group should undergo screening to identify those with low levels of 25(OH)D who might be more likely to benefit from vitamin D supplementation. For example, a meta-analysis of RCTs suggests that vitamin D combined with calcium appears to decrease the incidence of fractures in the older and institutionalized population (103). However, several recent clinical trials (104, 105) did not reveal similar findings, perhaps because many participants in these trials did not have low baseline 25(OH)D levels. This suggests—but does not prove—that the individuals most likely to benefit from vitamin D supplementation are those at risk for low baseline 25(OH)D levels, a group that is overrepresented in housebound and institutionalized populations (106, 107). However, 25(OH)D thresholds required to prevent disease may differ according to the outcome, as suggested by epidemiological studies (108). Trials specifically targeting people with low vitamin D status and/or "treat-to-target" trials documenting the benefit of achieving and maintaining specific 25(OH)D levels with vitamin D have not been done.

Question 4. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for adults aged 50 to 74 years?

Question 5. Should vitamin D supplementation vs no vitamin D supplementation be used for adults aged 50 to 74 years only when 25(OH)D levels are below a threshold?

Recommendation 4

In the general population aged 50 to 74 years, we suggest against routine vitamin D supplementation. (2 | ⊕⊕⊕◯)

Technical remark

- This recommendation relates to empiric vitamin D supplementation that exceeds the DRIs established by the IOM. Adults in this age group should follow the Recommended Daily Allowance established by the IOM (600 IU [15 μg] daily for those aged 50 to 70 years; 800 IU [20 μg] daily for those older than 70 years).

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Recommendation 5

In the general population aged 50 to 74 years, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/9FN6GJZdDJ4 and https://guidelines.gradepro.org/profile/-NxdICB9sYc.

Benefits and Harms

The systematic review identified 13 RCTs (104, 105, 109-119) (86 311 community-dwelling participants) comparing vitamin D vs placebo with any fracture as the outcome. The vitamin D dosages varied between 300 and 3500 IU/daily equivalent (7.5 and 88 μg) with a median dosage of 1500 IU (37.5 μg) daily. In many trials, the participants were allowed to take a daily supplement that contained no more than 400 to 800 IU of vitamin D. The median of the average baseline 25(OH)D concentrations in these studies was 24 ng/mL (ranging from 13 to 32 ng/mL) (60 nmol/L [32 to 80 nmol/L]). The RR for any fracture with vitamin D was 0.97 (95% CI, 0.91-1.03), with an estimated absolute risk reduction of 2 fewer per 1000 (7 fewer to 2 more). Study subgroup analyses suggested that the effect of vitamin D on fracture risk was not modified by risk of bias, sex, dosage of vitamin D, or calcium co-administration.

All-cause mortality was reported as an outcome in 13 RCTs (20, 109, 111, 116, 119-127) (81 695 participants). The estimated daily vitamin D dosage varied between 400 IU (10 μg) and 4800 IU (120 μg), with a median of 2000 IU (50 μg). Most trials allowed participants to take a supplement with vitamin D between 400 to 800 IU/d. The median of the average baseline 25(OH)D concentrations in these studies was 24 ng/mL (ranging from 18 to 31 ng/mL) (60 nmol/L [45-78 nmol/L]). The RR for mortality was 1.07 (95% CI, 0.95-1.20), translating to 2 more per 1000 (2 fewer to 6 more). The risk of mortality in studies involving calcium co-administration (RR 0.90 [95% CI, 0.79-1.01]) appeared to be lower than those involving vitamin D alone (RR 1.12 [95% CI, 1.01-1.24]) (*P* for heterogeneity = .021). In addition, the risk of mortality appeared to be higher with vitamin D in the studies involving high dosages of vitamin D (RR 1.22 [95% CI, 1.06-1.39]) relative to those involving standard dosages (RR 0.95 [95% CI, 0.86-1.04]) (*P* for heterogeneity = .003). Study subgroup analyses suggested that the effect of vitamin D on mortality risk was not modified by risk of bias or sex.

Cancer was reported as an outcome in 15 RCTs (20, 109, 111, 119, 123, 125, 126, 128-135) (91 223 participants), using dosages of 300 to 4800 IU/daily equivalent, with a median dosage of 2000 IU/d (50 μg/d). In many trials, the participants were allowed to take a daily supplement that contained no more than 400 to 800 IU of vitamin D. Mean baseline 25(OH)D ranged from 13 to 33 ng/mL (median 26 ng/mL) (33 to 83 nmol/L [median 65 nmol/L]). The relative risk for cancer with vitamin D was 1.00 (95% CI, 0.97-1.03) translating to 0 fewer patients with cancer per 1000 (4 fewer to 4 more). Study subgroup analyses suggested that the effect of vitamin D on cancer outcomes was not modified by risk of bias, sex, dosage of vitamin D or calcium co-administration.

Fourteen RCTs (20, 109, 111, 116, 118, 119, 122, 125-127, 131, 134, 136, 137) involving 80 547 participants reported on CVD events using dosages of 300 to 4800 IU/daily equivalent, with a median dosage of 2000 IU/d (50 μg/d). In addition, most trials allowed a vitamin D–containing supplement from 400 to 800 IU/d. Mean baseline 25(OH)D ranged from 13 to 31 ng/mL (mean 24 ng/mL) (33 to 78 nmol/L; mean 60 nmol/L]). The relative risk for CVD with vitamin D was 1.00 (95% CI, 0.93-1.08), translating to 0 fewer patients with CVD per 1000 (2 fewer to 3 more). Seven RCTs (20, 109, 111, 119, 122, 125, 136) reported stroke with a summary RR of 0.95 (95% CI, 0.83-1.09), translating to 1 fewer patient with stroke per 1000 (2 fewer to 1 more). Myocardial infarction (MI) was an outcome in 7 RCTs (20, 109, 111, 119, 122, 125, 131), with a summary RR of 1.00 (95% CI, 0.83-1.20), translating to 0 fewer patients with MI per 1000 (2 fewer to 2 more). Study subgroup analyses suggested that the effects of vitamin D on cardiovascular events, stroke, and MI were not modified by risk of bias, sex, dosage of vitamin D or calcium co-administration.

Kidney stones were reported in 10 RCTs (20, 109-111, 118, 125, 129, 135, 138, 139) with a summary RR of 1.10 (95% CI, 1.00-1.19), translating to 2 more patients with kidney stones per 1000 (0 fewer to 4 more). Kidney disease was reported in 4 RCTs (20, 119, 127, 134) with a summary RR of 1.04 (95% CI, 0.76-1.42), translating to 0 fewer patients with kidney disease per 1000 (1 fewer to 2 more). Study subgroup analyses suggested that the effects of vitamin D on kidney stones and kidney disease were not modified by risk of bias, sex, dosage of vitamin D, or calcium co-administration.

The systematic review identified 3 RCTs that reported outcomes specifically in participants with baseline serum 25(OH)D below 20 ng/mL (50 nmol/L) (or the lowest quartile, ie, < 24 ng/mL [60 nmol/L]) receiving vitamin D vs placebo (29). Meta-analysis of such data from 2 of these RCTs (20, 124) suggested an RR of 1.11 (95% CI, 0.85-1.46) for the mortality outcome. Cancer was reported in 2 RCTs (20, 130), and vitamin D was associated with a RR of 0.91 (95% CI, 0.70-1.19) compared to placebo. Cardiovascular disease events were reported in 3 RCTs (20, 122, 137) with a RR of 1.02 (95% CI, 0.87-1.19) compared to placebo. Subgroup analyses in single trials suggested no clear impact on fractures (RR 1.01 [95% CI, 0.81-1.24]), stroke (RR 1.04 [95% CI, 0.39-2.75]), MI (RR 0.93 [95% CI, 0.38-2.29]), and adverse events (RR 1.26 [95% CI, 0.77-2.12]).

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Based on the panel's best estimates of treatment effects, the panel judged that the anticipated desirable effects of vitamin D, in addition to the anticipated undesirable effects, are likely to be trivial.

Other Evidence-to-Decision Criteria and Considerations

Considerations related to required resources (costs), acceptability, and feasibility of vitamin D have already been addressed. Prevention of hip fractures in older people at risk is highly valued, as demonstrated by time-trade-off studies (140). The effect of coronary artery disease on quality of life may be small except for recurrent angina (141).

A cost-benefit analysis concluded that the costs of vitamin D and calcium would be much lower than the costs of fractures resulting from no supplementation. This result was mainly driven by the age group older than 65 years (142). Although a French study concluded that treatment based on 25(OH)D concentrations was more cost-effective than treating everybody (143), a systematic review of economic evaluations concluded that there was insufficient economic evidence to draw conclusions about the cost-effectiveness of population strategies (144). The panel found these cost-effectiveness studies difficult to contextualize given that the commissioned systematic review of clinical trials did not disclose a substantive benefit of vitamin D on fractures in those aged 50 to 74 years.

A comprehensive review of studies addressing women's views of osteoporosis therapy revealed that vitamin D and calcium were viewed as safe and natural and preferred to hormones and other treatments (97). As such, vitamin D is likely to be considered acceptable. The panel judged that empiric vitamin D supplementation is feasible to implement, although conditioning vitamin D supplementation on 25(OH)D levels could represent an important barrier for some.

Justification for the Recommendations

Vitamin D supplementation appears to be safe when taken as outlined in the IOM DRIs. Vitamin D is also inexpensive, readily available, acceptable to patients, and relatively easy to implement. Adherence may be a challenge, because supplementation typically involves lifelong use of vitamin D. Based on the meta-analyses of the available trials, which yielded high certainty of evidence for fractures, CVD events, cancer and mortality, the panel judged that vitamin D supplementation appears to have little or no beneficial impact on the outcomes analyzed in healthy populations aged 50 to 74 years. There was therefore no compelling rationale to recommend empiric vitamin D in this age group, especially since supplementation would involve costs (admittedly minor) and inconvenience.

Importantly, most of the recent trials were completed in populations that were meeting their DRI and did not have low vitamin D status at baseline. Given the well-established harmful consequences of very low vitamin D status on skeletal health and calcium homeostasis, the panel judges that some subgroups in this age group could rationally choose to take vitamin D supplementation, especially if they are not expected to have adequate vitamin D status via sun exposure (dark complexion, housebound, clothing style) or reliable IOM-recommended intake via diet, supplements or ingestion of vitamin D–fortified foods.

Subgroup analyses did not provide evidence for benefit with vitamin D in subgroups with 25(OH)D below 20 to 24 ng/mL (50-60 nmol/L). In addition, there are monetary costs associated with both 25(OH)D testing and medical visits, the panel judged that a recommendation for 25(OH)D testing could decrease feasibility and health equity (especially when compared to empiric vitamin D supplementation). For all these reasons, the panel suggested against routine 25(OH)D testing (eg, screening) in generally healthy adults aged 50 to 74 years.

Additional Considerations

These recommendations should not be extrapolated to individuals with conditions known to substantially impact vitamin D physiology, including malabsorption (eg, from gastric bypass), increased vitamin D catabolism, renal loss of vitamin D metabolites, and decreased vitamin D activation.

With regard to 25(OH)D screening, the panel noted that 2 risk scoring systems can predict serum 25(OH)D concentrations lower than 20 ng/mL and 12 ng/mL (< 50 and < 30 nmol/L), respectively, with reasonable accuracy, and thus may be useful in clinical practice to identify persons aged 55 to 85 years at high risk for low vitamin D without the need for 25(OH)D testing (145). Risk factors in these scoring systems include female sex, alcohol use, smoking, season, medication use, no vitamin use, and limited outdoor activities such as gardening and bicycling.

Research Considerations

1. The age group 65 to 74 years requires more attention, since the risks of chronic diseases and the outcomes being examined are higher than in those aged 50 to 64 years. The age group of 50 to 74 years is a heterogenous population in which some may be in excellent health, whereas others may have chronic conditions and may be housebound. Thus, trials addressing the effect of vitamin D on individuals with different health status are required.
2. RCTs specifically in those with low baseline 25(OH)D levels are required to clarify the risks and benefits of vitamin D and/or calcium supplementation.
3. Studies with longer follow-up may be needed, as some outcomes may become apparent only after 5 years (117).
4. In secondary, exploratory analyses, vitamin D in this age group has been implicated in the prevention of autoimmune disease such as rheumatoid arthritis, polymyalgia rheumatica, and autoimmune thyroid disease (146). These data need confirmation by additional RCTs.
5. Studies of the effect of vitamin D fortification on vitamin D status in different populations at risk of low vitamin D status are needed.

Vitamin D Use in Adults Aged ≥ 75 Years

Background

Low 25(OH)D levels are common among older people in the United States. Recent results from NHANES surveys during 2001-2018 showed that the prevalence of low vitamin D status (25[OH]D ≤ 20 ng/dL [50 nmol/L]) in the US population older than 80 years was 19.6% in females and 18.9%

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in males (147). Many observational studies have reported inverse associations between 25(OH)D levels and adverse health outcomes such as falls, fractures, and respiratory disease (148-152). These conditions contribute significantly to morbidity and mortality in older people. For example, falls occur commonly in older people, with more than 14 million US adults 65 years and older falling one or more times each year (153), resulting in an estimated 9 million fall injuries annually (154). Falls are the leading cause of injury-related death in this age group, which is an increasing subset of the population (155). The annual health care costs from fall injuries are about $50 billion (156). More than 95% of hip fractures are caused by falling (157), with more than 300 000 people 65 years and older hospitalized for a hip fracture each year in the United States (158-160). Hip fractures are also associated with increased mortality (161). Despite the importance of these conditions associated with low vitamin D status in observational studies, it remains unclear whether vitamin D supplementation lowers the risks of such conditions: the data from randomized, placebo-controlled trials of vitamin D supplementation are inconsistent, and systematic reviews and meta-analyses of RCTs have reported heterogeneous results for these outcomes (162-165).

Question 6. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used by adults aged ≥ 75 years?

Question 7. Should vitamin D supplementation vs no vitamin D supplementation be used by adults aged ≥ 75 years only when 25(OH)D levels are below a threshold?

Recommendation 6

In the general population aged 75 years and older, we suggest empiric vitamin D supplementation because of the potential to lower the risk of mortality. (2 | ⊕⊕⊕◯)

Technical remarks

- Empiric vitamin D may include daily intake of fortified foods, vitamin formulations that contain vitamin D and/or daily intake of a vitamin D supplement.
- For empiric supplementation, daily, lower-dose vitamin D is preferred over nondaily, higher doses.
- In the clinical trials included in the systematic review that reported on the mortality outcome, vitamin D dosage ranged from 400 to 3333 IU [10 to 83 μg] daily equivalent. The estimated weighted average was approximately 900 IU (23 g) daily. Participants in many trials were allowed to remain on their routine supplements, including up to 800 IU (20 μg) of vitamin D daily.

Recommendation 7

In the general population aged 75 years and older, we suggest against routine testing for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D thresholds that provide outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy adults who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/3knvwnbvIkQ and https://guidelines.gradepro.org/profile/ySx1d8ko_C4.

Benefits and Harms

The systematic review included 25 trials (20, 104, 121, 124, 166-186) (49 879 participants) that reported on the effect of vitamin D on all-cause mortality. These trials involved participants from community settings (n = 17), nursing homes (n = 6), and hospital clinics (n = 2). Most trials assessed the impact of vitamin D3 (cholecalciferol), commonly given as a daily dose (13 trials), either alone or combined with calcium. Follow-up durations ranged from 12 weeks to 7 years, with a median of 2 years. Meta-analysis suggested that vitamin D lowers mortality compared to placebo (RR 0.96 [95% CI, 0.93-1.00]), with an estimated absolute effect size of 6 fewer deaths per 1000 people (from 11 fewer to 0 more). Study subgroup analyses revealed no differences according to risk of bias, gender, calcium co-administration, vitamin D dosage (high vs standard), or setting (community, hospitalized, institutionalized). When restricting analysis to community-based studies, vitamin D appeared to be associated with a similar reduction in mortality risk (RR 0.95 [95% CI, 0.90-0.99]). Among study participants with low vitamin D status (< 20 ng/mL [50 nmol/L]), the results were consistent with those observed in the broader population (RR of mortality 0.88 [95% CI, 0.46-1.67]).

The systematic review identified 14 trials (104, 117, 170, 171, 173, 177, 178, 180, 181, 183, 184, 187-190) that reported the number of participants with a fracture as the unit of measure (43 585 participants), and the RR for vitamin D was 1.01 (95% CI, 0.94-1.08), with an estimated absolute effect size of 1 fewer per 1000 people (from 5 fewer to 6 more). Fourteen trials (168, 172, 175, 191) [male and female,

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separately] (174, 180, 184, 185, 188, 189, 192-195) reported the total number of fractures as the unit of measure, and the IRR was 0.95 (95% CI, 0.82-1.10). Study subgroup analysis suggested that estimated IRR may vary according to study risk of bias, with IRR estimates appearing to be lower in studies with some concerns compared to those with either low or high risk of bias. The IRR for number of fractures was lower in studies involving calcium co-administration (0.78 [95% CI, 0.68-0.90]) vs no calcium co-administration (1.05 [95% CI, 0.88-1.28]) (*P* for heterogeneity .005), but a similar interaction was not observed when participants with fractures served as the unit of analysis. Study subgroup analyses did not implicate sex, vitamin D dosage, or setting (community vs institutional) as significant predictors of fracture outcomes. Data addressing fracture outcomes specifically in those with 25(OH)D levels < 20 ng/mL (50 nmol/L) were unavailable.

The systematic review identified 16 trials (104, 166, 170, 171, 173, 174, 176, 184, 188, 189, 193, 194, 196-199) that reported the number of participants with any fall as the unit of measure (12 342 participants) and the RR for vitamin D was 0.97 (95% CI, 0.91-1.03), with an absolute effects size of 16 fewer people with falls per 1000 (from 48 fewer to 16 more). Fifteen trials (166, 173, 175, 184, 185, 187-190, 194, 195, 197-200) reported the number of falls as the unit of measure, and the IRR was 0.91 (95% CI, 0.81-0.99). The reduction in IRR for falls was confined mainly to studies with high risk of bias, and no effect was seen in studies with low risk of bias (IRR 1.03 [95% CI, 0.92, 1.11]). Study subgroup analyses suggested that vitamin D reduced fall risk more so in studies involving standard vitamin D dosages (RR 0.93 [95% CI, 0.85-1.01]; IRR 0.88 [95% CI, 0.76-1.00]) compared to studies involving high vitamin D dosages (RR 1.06 [95% CI, 1.01-1.11]; IRR 1.02 [95% CI, 0.86-1.10]) (*P* for interaction = .007 for RR and 0.033 for IRR). The risk for falls appeared to be reduced by vitamin D to a greater degree in studies involving calcium co-administration (RR 0.85 [95% CI, 0.74-0.97]; IRR 0.73 [95% CI, 0.53-0.92]) vs studies without calcium co-administration (RR 1.04 [95% CI, 1.01-1.08]; IRR 0.99 [95% CI, 0.91-1.07]) (*P* for interaction = .004 for RR and 0.007 for IRR). In addition, study subgroup analysis suggested that vitamin D reduced total number of falls more so in institutional-based studies (IRR 0.82 [95% CI, 0.69-0.94]) compared to community-based studies (IRR 0.96 [95% CI, 0.83-1.05]) (*P* for interaction = .024), but a similar interaction was not observed when persons with falls served as the unit of analysis. Analysis of 2 studies reporting falls among participants with low vitamin D status (< 20 ng/mL [50 nmol/L]) (194, 199), the RR for fall with vitamin D was 0.65 (95% CI, 0.40-1.05).

The systematic review identified only 2 trials (168, 201) that reported on the effect of vitamin D on respiratory infections in adults older than age 75 years. Both trials reported subgroup analyses for both upper and lower respiratory tract infections combined. The ViDA study compared monthly vitamin D3 with placebo, with number of participants experiencing respiratory tract infection as the unit of measure, and the adjusted hazard ratio (HR) was 1.11 (95% CI, 0.94-1.30) (201). In the DO-HEALTH trial, which evaluated the total number of infections as the unit of measure, the adjusted IRR was 1.15 (95% CI, 0.94-1.41) for daily 2000 IU (50 µg) vitamin D3 (168). No trials reported subgroup analyses related to the impact of vitamin D on respiratory infections specifically for those with low 25(OH)D levels in this age group.

Four trials reported possible undesirable outcomes in adults aged 75 years and older (29). With the number of participants as the unit of measure, the RR for nephrolithiasis among 6306 participants in 3 trials (20, 138, 168) was 0.94 (95% CI, 0.54-1.65) for vitamin D vs placebo, with an estimated absolute effect size of 1 fewer per 1000 [7 fewer to 10 more]), and the RR for kidney disease among 5634 participants in 3 trials (20, 166, 168) was 0.76 (95% CI, 0.44-1.32) with an estimated absolute effect size of 3 fewer per 1000 [6 fewer to 3 more]).

Based on the panel's best estimates of treatment effects (ie, stipulating the veracity of point estimates), the panel judged that the anticipated desirable effects of vitamin D are likely small, and that the anticipated undesirable effects are likely trivial. Among study participants with low vitamin D status, the results were consistent with those observed in the broader population.

Other Evidence-to-Decision Criteria and Considerations

The panel concluded that the costs of empiric vitamin D supplementation were negligible because vitamin D is inexpensive. Although the panel identified some cost-effectiveness analyses related to falls and fractures, these were difficult to apply because the systematic review suggested little to no benefit for the fall and fracture outcomes. Regardless, given minimal costs of vitamin D supplementation, the panel reasoned that vitamin D is likely to be cost-effective with regard to its (likely) mortality benefit. Given that low vitamin D status tends to be more prevalent among those with lower health equity, assuming that vitamin D supplementation is most likely to benefit those with low vitamin D status, and recognizing that vitamin D supplementation is inexpensive, the panel reasoned that vitamin D probably improves equity, based on its (likely) mortality benefit. The panel judged that empiric vitamin D supplementation would be feasible and acceptable to stakeholders.

The systematic review did not find evidence suggesting that benefit with vitamin D is restricted to those with baseline 25(OH)D levels below a threshold. In addition, the panel concluded that conditioning vitamin D supplementation/treatment on 25(OH)D screening may create barriers for some (eg, in places where access to laboratory testing is difficult). Moreover, the addition of a 25(OH)D testing requirement would increase costs, possibly decreasing acceptability for some.

Justification for the Recommendations

Based on the systematic review, vitamin D probably results in a slight decrease in all-cause mortality in this age group (high certainty of evidence), and probably results in little to no difference in fractures (high certainty of evidence), or adverse events (moderate certainty of evidence), including falls. The panel had concerns that clinical trials using high dosages of vitamin D may have masked improvement in fall risk, and study subgroup analysis suggested that fall risk was likely reduced in trials employing standard vitamin D dosages.

While specific data related to respiratory infections were inadequate (low certainty of evidence), indirect data from general populations suggest that vitamin D is unlikely to be

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harmful in this regard, and the panel prioritized the mortality outcome. Given that the best available evidence suggests a small but important benefit in terms of mortality risk and minimal to no harms, the panel judged that the balance between desirable and undesirable effects probably favors empiric vitamin D supplementation. In addition, the panel judged that empiric vitamin D supplementation is typically inexpensive, may be cost-effective, may increase health equity, and is probably both acceptable to key stakeholders and feasible to implement. For these reasons, the panel suggests empiric vitamin D supplementation. In the absence of high overall certainty of evidence, the panel issued a conditional recommendation in this regard.

The systematic review did not find evidence suggesting that net benefit is restricted to those with 25(OH)D below a threshold, and the few available clinical trials that reported subgroup results by 25(OH)D level did not clearly implicate baseline 25(OH)D level as a significant predictor of treatment effect; however, data were judged to be sparse in this regard. In addition, 25(OH)D testing and medical visits involve monetary costs, and the panel judged that a recommendation for 25(OH)D testing could decrease feasibility and health equity (especially when compared to empiric vitamin D supplementation). For these reasons, the panel suggests against routine 25(OH)D testing (eg, screening) in adults aged 75 years and older.

Additional Considerations

When considering all 25 clinical trials reporting mortality data, the median (interquartile range) vitamin D dosage approximated 833 (800-1370) IU/day (21 µg/day [20-34 µg/day]), and the estimated weighted average vitamin D dosage (ie, each study's vitamin D dosage weighted according to the study's weight in the meta-analysis for the mortality outcome) was approximately 909 IU/day (23 µg/day). In many trials, participants were permitted to remain on vitamin D supplements up to 800 IU (20 µg)/day.

Vitamin D with calcium may be superior to vitamin D alone at decreasing the risk of falls and fractures. Subgroup analysis revealed that vitamin D significantly lowers fracture risk with calcium co-administration when number of fractures was the outcome; however, when the number of participants with fracture was the unit of measure, the interaction was not statistically significant. The median dosage of calcium used in the included trials was 1000 mg per day (500-1500 mg/day). Calcium supplementation does not appear to increase the risk of CVD overall (202) nor mortality risk in the current meta-analysis (29).

Research Considerations

1. Based on the known effects of vitamin D on the musculoskeletal system, it may be unethical to keep a group of people with low 25(OH)D levels on placebo for long periods to evaluate the effectiveness of vitamin D supplementation on falls or fractures, both long-term outcomes. However, studies using several different daily dosages of vitamin D and targeting several achieved 25(OH)D levels are feasible and would define the achieved levels that prevent adverse outcomes.
2. The great variability of protocols used in clinical trials may have interfered in the evaluation of supplementation on musculoskeletal health in this group of older individuals. Future studies will require specific protocols, avoiding bolus doses, and selecting individuals at risk for fractures and falls to evaluate the effect of the intervention.

Vitamin D Supplementation During Pregnancy

Background

Nutritional status during pregnancy plays a critical role in perinatal health, fetal growth, and infant development. The fetus is dependent on maternal circulating 25(OH)D for placental metabolism and transfer of vitamin D metabolites (203, 204). In pregnancy, very low vitamin D status (25[OH]D < 10-12 ng/mL [< 25-30 nmol/L]) is associated with increased risk of neonatal hypocalcemic seizures, cardiomyopathy, and neonatal rickets, with life-limiting and potentially fatal outcomes (18, 205). Very low vitamin D status during pregnancy is prevalent in both low- and high-income settings (206, 207).

Many studies, for example (208), have described associations between 25[OH]D levels < 20 ng/mL (<50 nmol/L) and increased risk of hypertensive disorders of pregnancy (gestational hypertension, preeclampsia, eclampsia, and HELLP syndrome [Hemolysis, Elevated Liver enzymes and Low Platelets]). Hypertensive disorders of pregnancy increase risks for fetal growth restriction, small-for-gestational-age (SGA) infants, and induced preterm delivery, with potentially serious and lifelong consequences for infant bone and brain development, as well as maternal and offspring long-term cardiometabolic health (209). Economic costs of preeclampsia have been estimated at twice those of healthy pregnancies for maternal postnatal care (210). Hao et al (211) estimated a 3-fold higher cost for pregnancies complicated by hypertensive disorders relative to uncomplicated care when both maternal and infant costs were included.

Whether nutritional requirements for vitamin D change during pregnancy is not known, and evidence for the role of vitamin D in improving perinatal outcomes is conflicting (212). Accordingly, preconception or pregnancy-specific recommendations for vitamin D are not universal, nor is there a consensus on the dosage of vitamin D or 25(OH)D level required to support a healthy pregnancy. While harmonized global estimates do not yet exist, reported prevalence rates for low and very low vitamin D status (25[OH]D < 20 and < 12 ng/mL [< 50 and < 30 nmol/L], respectively) are high among women of reproductive age and during pregnancy, particularly among individuals with decreased skin synthesis due to low exposure to UV-B light, low vitamin D intakes, low nutrient-dense diets, and dark complexion (34, 213-216). This, along with the fetal dependence on maternal vitamin D and the inverse associations of low vitamin D status with undesirable outcomes in the perinatal period, make it important to evaluate the role of vitamin D supplementation during pregnancy. Additional high-priority clinical questions relate to the potential utility of 25(OH)D testing during pregnancy and optimal maternal 25(OH)D concentrations during pregnancy.

Question 8. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used during pregnancy?

Question 9. Should vitamin D supplementation vs no vitamin D supplementation be used during pregnancy only when 25(OH)D levels are below a threshold?

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Recommendation 8

We suggest empiric vitamin D supplementation during pregnancy, given its potential to lower risk of preeclampsia, intra-uterine mortality, preterm birth, SGA birth, and neonatal mortality. (2 | ⊕⊕◯◯)

Technical remarks

- This recommendation is based on evidence from trials conducted in healthy individuals during pregnancy.
- Empiric vitamin D may include daily intake of fortified foods, prenatal vitamin formulations that contain vitamin D, and/or a vitamin D supplement (pills or drops).
- In the clinical trials included in the systematic review, the vitamin D dosages ranged from 600 to 5000 IU (15 to 125 μg) daily equivalent, usually provided daily or weekly. The estimated weighted average was approximately 2500 IU (63 μg) per day.

Recommendation 9

During pregnancy, we suggest against routine 25(OH)D testing. (2 | ⊕◯◯◯)

Technical remarks

- In this population, 25(OH)D levels that provide pregnancy outcome-specific benefits have not been established in clinical trials.
- The panel suggests against (a) routine screening for a 25(OH)D level to guide decision-making (ie, vitamin D vs no vitamin D) and (b) routine follow-up testing for 25(OH)D level to guide vitamin D dosing.
- This recommendation relates to generally healthy pregnant individuals who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/kZ8sir4uV7M and https://guidelines.gradepro.org/profile/QSOmqUUCVGE.

Benefits and Harms

The systematic review identified 10 RCTs that met the inclusion criteria (29). Due to the panel's a priori decision to include only trials involving placebo-treated controls (rather than allowing the control group to remain on routine supplements or receive low-dose vitamin D), many RCTs were excluded, including many from the United States, where 400 IU (10 μg) was often given to the control group. Three included studies were conducted in Europe; 2 in Bangladesh; 2 in India; 2 in Iran and 1 in Pakistan. Of the 2979 participants, almost half (n = 1298) came from the trial by Roth et al (217) in Bangladesh. The included trials varied greatly in terms of dose frequency (one-time vs daily vs intermittent dosing) and dose ranges (600 to 200 000 IU [15 to 5000 μg]). The median gestational age at which the intervention (vitamin D vs placebo) was initiated was about 20 weeks. Of the 7 trials that reported baseline 25(OH)D concentrations, mean values were below 12 ng/mL (30 nmol/L) in 4 (217-220).

When combined, data from 8 studies (217, 219, 221-226) (2674 participants) suggest that vitamin D may reduce the risk of preeclampsia (RR 0.73; 95% CI, 0.46-1.15]) with an estimated absolute effect size of 23 fewer per 1000 (46 fewer to 13 more).

Data from 4 trials (217-219, 223) (1738 participants) suggest that vitamin D may reduce the risk of intra-uterine mortality slightly (RR 0.70 [95% CI, 0.34-1.46]) with an estimated absolute effect size of 6 fewer per 1000 (13 fewer to 9 more). Similarly, data from 3 trials (217, 218, 223) (1576 participants) indicate that vitamin D may reduce the risk of neonatal mortality slightly (RR 0.57 [95% CI, 0.22-1.49]), with an estimated absolute effect size of 8 fewer per 1000 (14 fewer to 9 more).

Data from 6 trials (217, 219, 222-225) (2085 participants) suggest that vitamin D may reduce the risk of preterm birth (RR 0.73 [95% CI, 0.39-1.36]) with an estimated absolute effect size of 28 fewer per 1000 (62 fewer to 37 more). Data from 5 trials (217, 219, 220, 224, 225) (2355 participants) suggest that vitamin D may reduce the risk of SGA birth (RR 0.78 [95% CI, 0.50-1.20]) with an estimated absolute effect size of 41 fewer per 1000 (94 fewer to 38 more). SGA status was variably defined in the different trials.

Adverse events of interest (nephrolithiasis, symptomatic hypercalcemia, kidney disease) were rare (one case of proteinuria related to nephrotic syndrome in the vitamin D arm), but most trials did not prespecify adverse events except for the trials by Roth et al (217, 223), which reported no cases of symptomatic hypercalcemia.

Study subgroup analyses did not implicate either risk of bias or vitamin D dosage as a significant predictor of study outcomes. Data were insufficient to address whether baseline 25(OH)D level was a significant predictor of treatment effects.

Based on the panel's best estimates of treatment effects (ie, stipulating the veracity of point estimates), the panel judged that the anticipated desirable effects of vitamin D during pregnancy for the outcomes specified are likely to be moderate. Although the panel recognized that the 95% CIs included the possibility for harm for each outcome, the panel noted that all point estimates favored benefit and judged that the anticipated undesirable effects are likely to be trivial.

The panel also considered a 2019 systematic review performed by Palacios et al (227). According to this meta-analysis, vitamin D supplementation during pregnancy reduced risks of preeclampsia (RR 0.48 [95% CI, 0.30-0.79]), low birthweight (RR 0.55 [95% CI, 0.35-0.87]), and gestational diabetes (RR 0.51 [95% CI, 0.27-0.97]), with a nonsignificant reduction in preterm birth (RR 0.66 [95% CI, 0.34-1.30]).

Other Evidence-to-Decision Criteria and Considerations

Although the panel identified no direct evidence, the panel judged that vitamin D supplementation would be acceptable

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and feasible to implement during pregnancy, when health care supervision is frequently available. The panel judged that preventing low vitamin D status during pregnancy, particularly among individuals most at risk for low vitamin D status (206, 213), may improve health equity. Floreskul (71) reported that free-of-charge provision of vitamin D supplements to pregnant individuals and children younger than age 4 years for rickets prevention in the United Kingdom would be clinically effective and cost-saving in participants with "dark and medium skin tone," especially in regions with high incidence of rickets.

Justification for the Recommendations

The systematic review suggested anticipated benefit with empiric vitamin D for all selected outcomes: preeclampsia (2.3% anticipated absolute reduction with low certainty of evidence), intra-uterine mortality (0.6% anticipated absolute reduction with moderate certainty of evidence), preterm birth (2.8% anticipated absolute reduction with low certainty of evidence), SGA birth (4.1% anticipated absolute reduction with low certainty of evidence) and neonatal mortality (0.8% anticipated absolute reduction with moderate certainty of evidence). The meta-analysis by Palacios et al (227) showed benefits in the same direction (lower risk of preeclampsia, low birthweight, gestational diabetes, and preterm birth). When taken together, and if stipulating the veracity of these point estimates, the panel judged that these desirable anticipated effects were moderately substantial. However, for all the described outcomes, the 95% CIs included the potential for harm, and available evidence for maternal mortality and maternal adverse events was not very robust. Nonetheless, given that the best available evidence (point estimates) suggested moderate benefit and minimal harm, the panel judged that the balance between desirable and undesirable effects probably favors empiric vitamin D supplementation. In addition, the panel judged that empiric vitamin D is typically inexpensive, may be cost-effective, may increase health equity, and is probably acceptable to key stakeholders and feasible to implement. Thus, the panel suggests empiric vitamin D supplementation during pregnancy. Given the low overall certainty of evidence, the panel issued a conditional recommendation.

Available evidence did not permit a well-supported judgment about the net benefit of 25(OH)D testing during pregnancy followed by vitamin D supplementation only in those with low 25(OH)D levels. In addition, compared to empiric vitamin D supplementation, adding the need for 25(OH)D testing would add costs, and the panel judged that testing could also decrease feasibility and health equity. For all these reasons, the panel suggests that vitamin D supplementation should generally proceed without testing for baseline 25(OH)D levels and without the need for subsequent monitoring of 25(OH)D levels to assess response to supplementation, provided that vitamin D dosages are within the tolerable upper intake level as established by the IOM.

Additional Comments

This guideline is different from the World Health Organization (WHO) guideline on vitamin D supplementation in pregnancy, which was published in 2016 (228) and updated in 2020 (229). Largely based on the systematic reviews by De-Regil (230), which found a possible beneficial effect of vitamin D on reducing preeclampsia, low birthweight, and preterm birth but a potential adverse effect of calcium plus vitamin D supplementation on preterm birth, the guideline group did not recommend vitamin D for pregnancy to improve maternal and infant health outcomes (228). The updated WHO 2020 guideline (229), which also did not recommend vitamin D, was largely based on the systematic review by Palacios et al (227), which reported outcomes similar to those of the present guideline for pre-eclampsia, preterm birth, low birth weight, and adverse effects. There were some differences in the studies selected for data synthesis, as Palacios et al (227), included a larger number of studies, including trials that administered, or allowed control participants to take, a low dosage of vitamin D and trials that co-administered vitamin D and calcium. The current guideline had access to more recent RCTs, including Roth et al (217). Overall, the current panel found very little evidence for harm with vitamin D supplementation, along with some evidence for benefit.

The optimal dosage of vitamin D for the prevention of maternal and fetal complications remains unclear. In the studies included in the commissioned systematic review, the estimated median vitamin D dosage for preeclampsia evaluation was 3161 IU (79 μg) daily, and the estimated weighted average dosage was 2639 IU (66 μg) per day. The estimated median vitamin D dosages in the studies assessing intra-uterine and neonatal mortality were 3375 IU (84 μg) and 2750 IU (69 μg) daily, respectively, and corresponding estimated weighted average dosages were 2908 IU (73 μg) and 3052 IU (76 μg) per day. For preterm birth and SGA birth studies, the estimated median dosages were 3375 IU (84 μg) and 2750 IU (69 μg) daily, respectively, while estimated weighted average dosages were 2735 IU (68 μg) and 2642 IU (66 μg) per day.

Research Considerations

Proposed areas for research include:

1. Adequately powered clinical trials with prespecified outcomes to address whether and to what degree vitamin D impacts patient-important perinatal outcomes, in both healthy individuals and those with high-risk pregnancies. Particular attention should be paid to individuals at high risks for adverse pregnancy and perinatal outcomes, with medium and dark complexion, those with low UV-B exposure, and those living with obesity. In future trials, it will be critically important to assess baseline vitamin D status and to gain a complete understanding of the roles of vitamin D dosing strategies and calcium co-supplementation.
2. Future trials should include umbilical cord blood 25(OH)D analysis and a plan to follow the offspring throughout early childhood.

Vitamin D for Adults With Prediabetes

Background

Diabetes mellitus poses a significant challenge to global health care. Prediabetes increases the risk of developing diabetes and CVD. In the United States, more than one in three adults 18 years and older have prediabetes, and only about 20% of these individuals have been informed of their prediabetes status by a health care professional.

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Worldwide, diabetes affects more than 537 million people, and this number is predicted to rise to 643 million by 2030 and 783 million by 2045 (231). In clinical trials, intensive lifestyle changes focused on weight loss and increased physical activity reduced the risk of developing diabetes among adults with prediabetes who have impaired glucose tolerance. However, these lifestyle modifications are challenging to maintain over the long term. Even with successful implementation, a residual risk remains, and most individuals with prediabetes eventually progress to diabetes. While certain medications approved for treating type 2 diabetes have been shown to reduce diabetes risk among people with prediabetes (232), the use of pharmacotherapy for diabetes prevention is not widely practiced or generally recommended due to the associated burden and cost. The search for weight-independent, easy-to-implement, and low-cost interventions continues to be a priority to lower diabetes risk. Over the last decade, several studies have reported on the role of vitamin D in attenuating the progression to type 2 diabetes in adults with prediabetes.

Question 10. Should empiric vitamin D supplementation vs no empiric vitamin D supplementation be used for adults with prediabetes (by glycemic criteria)?

Recommendation 10

For adults with high-risk prediabetes, in addition to lifestyle modification, we suggest empiric vitamin D supplementation to reduce the risk of progression to diabetes. (2 | ⊕⊕⊕◯)

Technical remarks

- Lifestyle modification must be a routine management component for adults with prediabetes.
- The clinical trials informing this recommendation primarily related to adults with high-risk prediabetes, identified as meeting 2 or 3 American Diabetes Association glycemia criteria (fasting glucose, HbA1c, 2-hour glucose after a 75-gram oral glucose challenge) for prediabetes and those with impaired glucose tolerance.
- In the clinical trials included in the systematic review, the vitamin D dosages ranged from 842 to 7543 IU (21 to 189 μg) daily equivalent. The estimated weighted average was approximately 3500 IU (88 μg) per day. Participants in some trials were allowed to remain on their routine supplements, including up to 1000 IU (25 μg) of vitamin D daily.

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/zE0nxO7MCXw.

Benefits and Harms

The commissioned systematic review included 11 RCTs (233-243) that reported on the effect of vitamin D on new-onset diabetes in adults with prediabetes (total of 5316 participants). The trials were conducted in India (n = 4), Iran (n = 1), Greece (n = 1), Norway (n = 1), Japan (n = 1), and the United States (n = 3). The panel also considered a recently published individual participant data meta-analysis (IPD-MA) (101) of the 3 vitamin D trials (233, 234, 243) that were specifically designed for diabetes prevention. In contrast to aggregate data meta-analysis, an IPD-MA increases the statistical power to detect benefits and risks; avoids ecological fallacy in examining sources of between-study heterogeneity; and, through data harmonization, improves the precision of results and allows for additional analyses.

Nine trials (233-239, 241, 242) used cholecalciferol (vitamin D3), one trial (240) used both cholecalciferol and ergocalciferol (D2), and one trial (243) used eldecalcitol, an active vitamin D analog. While the panel did not specifically address vitamin D analogs in its other questions, the panel recognized the importance of including the second largest trial for diabetes prevention (DPVD) (243), which tested eldecalcitol, when addressing the question about vitamin D and diabetes prevention; consequently, the findings from the DPVD trial were incorporated in the evidence synthesis. This approach aligns the commissioned systematic review with 3 other recent meta-analyses in this topic (101, 244, 245), ensuring consistency of the evidence synthesis. The results of the commissioned systematic review were similar with or without the DPVD trial; however, to be consistent with the rest of the guideline, we first present the meta-analysis results without the DPVD trial, thereafter, presenting results with the DPVD trial.

Participants in the included trials were at high risk for diabetes, based on having impaired glucose tolerance or meeting 2 or 3 glycemic criteria (fasting glucose, HbA1c, 2-hour glucose after a 75-gram oral glucose challenge) for prediabetes. The baseline mean 25(OH)D level in the 11 trials was 12 to 28 ng/mL (30-70 nmol/L). Among the 8 trials that did not include low baseline 25[OH]D as an eligibility criterion, the baseline mean level of 25[OH]D was 18 to 28 ng/mL (45-70 nmol/L). When combining data from the 10 trials (233-242) that used either cholecalciferol or ergocalciferol, vitamin D reduced the risk of developing diabetes (RR 0.90 [95% CI, 0.81-1.00]). The estimated absolute effect size was 24 fewer per 1000 progressing to type 2 diabetes (46 fewer to 0 fewer). When the DPVD trial (243) was included, the results were similar (RR 0.90 [95% CI, 0.81-0.99]). The IPD-MA of the 3 trials (233, 234, 243) that were specifically designed for diabetes prevention (total of 4190 participants) showed a 15% reduction in new-onset diabetes in adults with prediabetes randomized to vitamin D compared to placebo (HR 0.85 [95% CI, 0.75-0.96]) (101). In these trials, the impact of vitamin D on new-onset diabetes was in addition to participants receiving lifestyle interventions for diabetes prevention.

In the commissioned systematic review, the beneficial effect of vitamin D on diabetes risk was consistent across subgroups by risk of bias or vitamin D dosage. In the IPD-MA, the effect of vitamin D appeared to be more pronounced in the following subgroups: age older than 62 years (HR 0.81 [95% CI,

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0.68-0.98]), baseline 25(OH)D level lower than 12 ng/mL (30 nmol/L) (HR 0.58 [95% CI, 0.35-0.97]), and body mass index (BMI) less than 30 kg/m^2 (HR 0.79 [95% CI, 0.66-0.95]) (101). However, the *P* values for these interactions were not statistically significant.

The commissioned systematic review included 15 RCTs (234-240, 242, 246-252) that reported the effect of cholecalciferol or ergocalciferol on HbA1c in adults with prediabetes, 12 RCTs (234-238, 241, 242, 246-248, 251, 253) that reported on fasting blood glucose, and 13 RCTs (234-238, 241, 242, 246, 248-251, 254) that reported on blood glucose 2 hours after a 75-gram oral glucose load. Compared to placebo, vitamin D lowered fasting blood glucose (mean difference −5.3 mg/dL [95% CI, −7.9 to −2.7]) and 2-hour blood glucose after a 75-gram oral glucose tolerance test (mean difference −7.6 mg/dL [95% CI, −12.6 to −2.7]). There was a trend for vitamin D to lower HbA1c (mean difference −0.05% [95% CI, −0.10 to 0.01]). When the DPVD trial (243) was included, the results were similar (mean difference in fasting blood glucose −4.9 mg/dL [95% CI, −7.3 to −2.4; 2-hour blood glucose −6.6 mg/dL [95% CI, −11.2 to −2.1]; HbA1c −0.04% [95% CI, −0.90 to 0.00).

The commissioned systematic review also examined other outcomes aside from the risk of diabetes in this population. The Tromsø study (234) found no differences in upper respiratory infections between those who took 20 000 IU (500 μg) of vitamin D per week and those who took a placebo. In the same study, men who received vitamin D had less reduction in BMD at the femoral neck compared to those who took a placebo (0.000 vs −0.010 g/cm^2; $P = .008$). There were no differences in BMD at the femoral neck in women and no differences in BMD at the hip in either gender. The study found no difference in fractures between the vitamin D and placebo groups; however, the data on fractures was sparse.

Meta-analyses of the 2 trials (234, 255) that used cholecalciferol suggested no clear differences in all-cause mortality with vitamin D (RR 0.75 [95% CI, 0.26-2.18]; estimated absolute effect size of 1 fewer per 1000 [4 fewer to 6 more]) or CVD events (234, 256) with vitamin D (RR 1.08 [95% CI, 0.33-3.57]; estimated absolute effect size of 1 more per 1000 [8 fewer to 31 more]). After including the DPVD trial, results did not change.

The commissioned systematic review found no clear difference in nephrolithiasis (234, 255) with vitamin D (RR 1.20 [95% CI, 0.71-2.03]; estimated absolute effect size of 3 more per 1000 [5 fewer to 17 more]). There were no cases of symptomatic hypercalcemia reported in any trial. In the D2d study, there was 1 case of new-onset kidney disease in the vitamin D group and 2 cases in the placebo group (RR 0.50 [95% CI, 0.05-5.51]) (255). In the IPD-MA, the frequency of the prespecified adverse events of interest (nephrolithiasis, hypercalcemia, and hypercalciuria) was low, and there were no differences between vitamin D and placebo (101). In the D2d study, adverse events were overall less frequent in the vitamin D group (4000 IU/day [100 μg/day] of cholecalciferol) compared to placebo (IRR 0.94 [95% CI, 0.90-0.98]) (255).

Based on the point estimates derived from meta-analyses of available clinical trials, the panel judged that the anticipated desirable effects of vitamin D for diabetes prevention are likely moderate, while the anticipated undesirable effects are likely trivial.

Other Evidence-to-Decision Criteria and Considerations

Vitamin D is generally available over the counter, and it is inexpensive. There are no cost-effectiveness studies of vitamin D for preventing diabetes, fractures, all-cause mortality, cardiovascular events, or respiratory infections in adults with prediabetes. However, there is ample evidence of substantial economic value in preventing the development of type 2 diabetes with non–vitamin D interventions (eg, lifestyle, metformin) that are more expensive and burdensome to implement than vitamin D (257). Therefore, the panel reasoned that there are likely cost savings with using vitamin D for diabetes prevention.

The panel judged vitamin D use would be acceptable to adults with prediabetes and to other stakeholders, such as clinicians. Given ease of administration and low cost, the panel judged empiric vitamin D to lower diabetes risk as a feasible intervention for adults with prediabetes.

The risk of developing diabetes, the prevalence of diabetes, and the burdens related to having diabetes are higher among racial and ethnic minority groups (primarily Hispanic and non-Hispanic Asian populations) in the United States. In clinical trials, intensive lifestyle changes have been found to lower the risk of diabetes, regardless of race or ethnicity. However, accessing the necessary resources, such as nutritionists and exercise facilities, can be difficult, and there are disparities in access to these resources. Racial and ethnic minority groups (in the United States) are also at higher risk for having low vitamin D status, and consumption of vitamin D supplements in these groups is about half of that compared to non-Hispanic White groups, suggesting differences in vitamin D use. Although vitamin D should not be viewed as a replacement for lifestyle approaches to diabetes prevention, the panel judged that using vitamin D in adults with prediabetes would likely have a favorable impact on health equity, especially in low-resource environments.

Justification for the Recommendation

The panel justified a recommendation favoring empiric vitamin D in adults with prediabetes based on moderate certainty of evidence that vitamin D likely decreases progression to type 2 diabetes, likely without harm. In the commissioned systematic review, there was low certainty of evidence for the cardiovascular and mortality outcomes with wide 95% CIs; however, none of the included trials were designed or powered for cardiovascular events or mortality, and only 3 trials (including the DPVD trial) reported on these outcomes. Specific data related to fractures and respiratory infections were inadequate.

The benefits of vitamin D supplementation may preferentially accrue to those at highest risk for vitamin D deficiency. Although not addressed in the commissioned systematic review, the IPD-MA suggested that the benefit may be greatest for those with baseline 25(OH)D level lower than 12 ng/mL (20 nmol/L) (HR 0.58 [95% CI, 0.35-0.97]) (101). However, overall evidence did not support the net benefit of 25(OH)D testing in adults with prediabetes followed by vitamin D supplementation in those with low 25(OH)D levels. Vitamin D supplementation that leads to higher 25(OH)D levels may further lower the risk of diabetes (101, 258), but it could potentially increase the risk of adverse effects (hypercalcemia, hypercalciuria, kidney stones), although there was no evidence of this in in the IPD-MA (101). In addition, compared to empiric vitamin D supplementation alone, adding 25(OH)D testing would

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increase costs, thus decreasing feasibility and health equity. Given these uncertainties, the panel did not recommend screening or routine monitoring with 25(OH)D in individuals with prediabetes to guide vitamin D supplementation.

Additional Considerations

Ten trials (including the DPVD trial) reported on the effect of vitamin D and regression to normal glucose regulation, defined as having glycemic measures in the normal range, in people with prediabetes. The commissioned systematic review did not combine data on the effect of vitamin D on regression to normal glucose regulation; however, other meta-analyses have synthesized data on this outcome. Zhang et al combined aggregate data from 5 trials totaling 1080 participants with prediabetes and found a significant vitamin D benefit for regression to normal glucose regulation by 48% compared to placebo (RR 1.48 [95% CI, 1.14-1.92]) (244). In the IPD-MA, vitamin D increased the likelihood of regression to normal glucose regulation by 30% (RR 1.30 [95% CI, 1.16-1.46]) (101).

The clinical trials informing this recommendation primarily related to adults with high risk for diabetes, identified by meeting 2 or 3 American Diabetes Association glycemia criteria (fasting glucose, HbA1c, 2-hour glucose after a 75-gram oral glucose challenge) for prediabetes or by having impaired glucose tolerance. The panel's use of the term "high-risk prediabetes" aligns with the clinical trial evidence and aims to focus the recommendation on adults at the highest risk for diabetes, not to mandate specific testing methods.

The included trials used varying dosages of cholecalciferol or ergocalciferol. The median (interquartile range) dosage employed was approximately 2663 (1410-3893) IU/day (67 [35-97] µg/day), and the estimated weighted average was 3520 IU (88 µg) per day. Due to this variability, the panel could not recommend a specific dosage of vitamin D. In general, trial participants in both active and placebo groups were allowed to take vitamin D supplements on their own, up to a certain dosage specific for their age.

While the absolute reduction in the risk of developing new-onset diabetes may be relatively small, the panel considered that such interventions with modest benefits could significantly impact prevalent conditions like prediabetes. For example, the absolute 3-year risk reduction in diabetes risk with vitamin D (24 fewer per 1000 participants based on the systematic review or 33 fewer per 1000 based on the IPD-MA) compares favorably with metformin in the Diabetes Prevention Program in the United States (70 fewer per 1000), especially when considering that in the clinical trials, the vitamin D intervention was applied in addition to recommended lifestyle changes.

Research Considerations

Proposed areas for research include:

1. Randomized controlled trials to evaluate a treat-to-target strategy to define the 25(OH)D level that optimally reduces the risk of new-onset diabetes and increases time spent in normoglycemia.
2. Randomized controlled trials designed to identify subpopulations with prediabetes who are more likely to benefit from vitamin D, focusing not only on biological variables, including body composition, but on environmental, lifestyle, and dietary factors.
3. Cost-effectiveness analyses.
4. Implementation studies to assess the practicality and effectiveness of vitamin D in real-world settings.
5. Studies on the effect of vitamin D in people at risk for or with new-onset type 1 (autoimmune) diabetes.

Vitamin D Dosing

Background

There is uncertainty regarding the best approach to vitamin D supplementation. Options range from daily intake to less frequent regimens, such as weekly or monthly. While infrequent dosing may improve adherence, large doses of vitamin D have been associated with higher levels of inactive 24,25(OH)2 vitamin D (259), raising concerns about the benefit-risk ratio of intermittent, high doses of vitamin D. Important questions include the effect of nondaily dosing on clinical outcomes and potential impact on the risk of adverse events.

Question 11. Should a daily, lower-dose vitamin D vs nondaily (ie, intermittent), higher-dose vitamin D be used for nonpregnant people for whom vitamin D treatment is indicated?

Recommendation 11

In adults aged 50 years and older who have indications for vitamin D supplementation or treatment, we suggest daily, lower-dose vitamin D instead of nondaily, higher-dose vitamin D. (2 | ⊕⊕◯◯)

Technical remark

- The panel did not identify evidence related to individuals younger than age 50 years.

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/rzh7ywOCsRY.

Benefits and Harms

Two trials (260, 261) with a total of 537 patients met the original inclusion criteria, which specified a direct comparison between intermittent high-dose vs daily lower-dose vitamin D supplementation. After expanding eligibility criteria to include trials that compared high-dose intermittent doses vs placebo, the systematic review included 19 manuscripts derived from 15 studies (29) involving 53 527 participants. In the included trials, daily vitamin D doses ranged from 400 to 800 IU (10-20 µg). Doses given at nondaily intervals included 50 000 IU (1250 µg) every 2 weeks, 60 000-100 000 IU (1500-2500 µg) monthly, 96 000-150 000 IU (2400-3750 µg) every 2 to 4 months, and 300 000 IU-500,000 IU (7500-12 500 µg) annually.

The systematic review identified 5 studies (104, 119, 180, 184, 190) that evaluated fractures with participants as the unit of analysis. There was a trend for intermittent high-dose vitamin D to increase fracture risk (RR 1.08 [95% CI, 0.98-1.19]), with an estimated absolute effect size of 5 more participants with a fracture per 1000 (1 fewer to 11 more). In subgroup analyses, studies involving doses higher than

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100 000 IU (2500 μg) may have had higher risk of fracture (RR 1.14 [95% CI, 1.02-1.27]) than those involving lower doses (RR 0.94 [95% CI, 0.79-1.12]) ($P = .07$ for interaction). When examining the 7 studies (118, 174, 180, 184, 185, 260, 261) reporting the total number of fractures as the unit of analysis, the IRR for fractures was 0.96 (95% CI, 0.75-1.21) for intermittent high-dose vitamin D. Studies involving doses higher than 100 000 IU (2500 μg) had an IRR of 1.23 (95% CI, 0.81-1.61) compared to an IRR of 0.86 (95% CI, 0.71-1.02) for studies involving doses 50 000-100 000 IU (1250-2500 μg) ($P = .026$ for interaction). In study subgroup analyses, dosing interval (every 1-12 weeks vs > 12 weeks for intermittent high-dose vitamin D) was not a significant predictor of fracture risk.

In the meta-analysis of 6 studies (104, 118, 119, 174, 176, 184) reporting on falls with participants as the unit of analysis, the RR for intermittent high-dose vitamin D was 1.01 (95% CI, 0.93-1.10). Study subgroup analyses suggested the possibility that doses greater than 100 000 IU (2500 μg) may have higher fall risk (RR 1.04 [95% CI, 0.96-1.12]) compared to lower doses (RR 0.79 [95% CI, 0.61-1.03]) ($P = .056$ for interaction). Studies employing a dosing interval greater than every 12 weeks showed higher fracture risk with vitamin D (RR 1.08 [95% CI, 1.03-1.14]) compared to dosing intervals of 1 to 12 weeks (RR 0.98 [0.92-1.04]) ($P = .01$ for interaction). Analysis of 6 studies (118, 184, 185, 190, 200, 260) that reported on the number of falls as the unit of analysis revealed an IRR of 1.05 (95% CI, 0.96-1.13) for intermittent, high-dose vitamin D; subgroup analyses for falls as a unit of analysis did not disclose significant study subgroup effects according to dose or dosing interval.

For the 5 studies (85, 119, 123, 201, 260) reporting participants with respiratory infections as the unit of analysis, there were no differences between high-dose nondaily vitamin D vs placebo (OR 1.00 [95% CI, 0.98-1.03]). Similarly, analysis of 4 studies (85, 123, 139, 260) that reported on the number of respiratory infections as the unit of analysis revealed an IRR of 0.98 (95% CI, 0.88-1.03) for intermittent, high-dose vitamin D. Study subgroup analyses did not implicate vitamin D dose as a predictor of these study outcomes.

The 3 studies (118, 124, 138) that reported on nephrolithiasis administered 50 000 to 100 000 IU (1250-2500 μg) vitamin D every 2 to 4 weeks. The RR for nephrolithiasis was 1.00 (95% CI, 0.84-1.19) for intermittent, high-dose vitamin D. Two studies (119, 166) did not disclose a clear difference in kidney disease (RR 0.64 [95% CI, 0.28-1.47]), with an estimated absolute effect size of 2 fewer per 1000 (3 fewer to 2 more). No trials reported cases of symptomatic hypercalcemia.

Based on the panel's best estimates of treatment effects in adults aged 50 years and older, the panel judged that any desirable effects of intermittent, high-dose vitamin D (compared to lower-dose, daily vitamin D) are likely trivial, while the anticipated undesirable effects are likely to be small.

Other Evidence-to-Decision Criteria and Considerations

Vitamin D is relatively inexpensive and available over the counter; however, higher dosages may require prescriptions, which increase cost and burden. The panel did not identify any cost-effectiveness studies addressing daily lower-dose vitamin D vs intermittent, higher-dose vitamin D. The panel did not identify any studies that addressed the potential impact of intermittent high-dose vitamin D vs daily lower-dose vitamin D on health equity, although any additional costs and requirements for health care visits could decrease health equity. The panel identified no studies that addressed the possibility of differential acceptability or feasibility of intermittent high-dose vitamin D vs daily lower-dose vitamin D. Nonetheless, the panel assumed that less frequent dosing (weekly, monthly, or yearly) may be more acceptable to some individuals and may possibly be associated with better adherence, based on experience with medications like bisphosphonates, for which nondaily administration improves adherence (262).

Justification for the Recommendation

The available evidence (which is specifically pertinent to persons age > 50 years) suggests that, compared to daily lower-dose vitamin D or placebo, intermittent high-dose vitamin D offers no desirable effects, and may be associated with undesirable anticipated effects (namely, moderate certainty of evidence suggests an estimated 0.5% absolute increase in fracture risk). The panel judged that the potential convenience advantage of intermittent high-dose vitamin D may be outweighed by the potential for undesirable anticipated effects. The panel identified no evidence to suggest material differences in cost, equity, or feasibility, although cost likely favors daily, lower-dose vitamin D, since the higher dosages commonly require a prescription and thus involve the costs of health care visits. Since overall certainty of evidence was very low, and since individuals may value anticipated advantages and disadvantages differently, the panel issued a conditional recommendation.

Screening for Low Vitamin D Status With 25(OH)D Testing

Vitamin D deficiency is traditionally defined clinically as having symptoms and signs of rickets or osteomalacia. Although these conditions are not uncommon, vitamin D "deficiency" is more frequently defined based on circulating 25(OH)D levels. However, the 25(OH)D level for defining deficiency has been controversial, thus the prevalence of vitamin D deficiency varies depending on the 25(OH)D threshold used. For example, if vitamin D deficiency is defined as a 25(OH)D concentration less than 20 ng/mL (50 nmol/L), 24% of US adults meet that criterion, whereas if defined as a 25(OH)D concentration less than 10 ng/mL (25 nmol/L), 6% of US adults would be considered vitamin D–deficient (82).

Low vitamin D status has been associated with increased risks for several common chronic conditions, such as osteoporosis (risk of fractures), CVD, and diabetes. However, whether vitamin D supplementation lowers risk for developing such outcomes in generally healthy populations has remained unclear. Nonetheless, rates of screening for low 25(OH)D levels have increased in recent years. For example, in one study, testing with 25(OH)D rose from 0.29 per 1000 person-years at risk (95% CI, 0.27-0.31) in 2005 to 16.1 per 1000 person-years at risk (95% CI, 15.9-16.2) in 2015 (263).

The panel prioritized 3 clinical questions related to screening for 25(OH)D levels and whether vitamin D should be given only to individuals who have 25(OH)D levels below a threshold, recognizing that appropriate thresholds likely vary based on the outcome of interest. In particular, the panel

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chose to address 25(OH)D screening in adults with dark complexion, in adults with obesity, and in the general adult population who do not have otherwise an established indication for screening (eg, hypocalcemia). These screening questions relate to whether vitamin D administration may be primarily—or perhaps even exclusively—beneficial for adults with 25(OH)D levels below a population- and condition-specific (and thus far undetermined) threshold. If the net benefit of vitamin D supplementation *specifically* accrues to those with low 25(OH)D levels, then it could be important to perform 25(OH)D testing to identify those individuals. In contrast, if the net benefit of vitamin D supplementation does not specifically accrue to those with 25(OH)D levels below a threshold (ie, if net benefit is also realized in those with 25[OH]D levels above that threshold), or if no net benefit of vitamin D administration is apparent, then 25(OH)D screening in these populations would presumably be unnecessary.

Importantly, for all 3 screening questions, no studies were identified that compared a screening approach (testing for 25[OH]D levels followed by vitamin D treatment as indicated) to a nonscreening approach. Therefore, the panel's approach to the 3 screening questions followed a framework proposed by Murad and colleagues (264). These criteria can be broadly grouped into considerations related to the medical condition in question, the test's characteristics, and the overall impact on patient care. According to this framework, screening would be justified when the following conditions are met:

- Importance: The condition is an important health problem in terms of prevalence and/or consequences.

The panel noted that low vitamin D status has been linked to a number of important health problems.

- Natural history: The condition for which screening is being performed has a well-understood natural history that includes a latent (preclinical) phase.

The panel agreed that the adverse effects of low vitamin D status may manifest only after a long latency period, and early detection could plausibly lead to better long-term outcomes.

- Difference in management and treatment availability: Persons with positive screening test results would be managed differently from those with negative screening test results.

The panel agreed that vitamin D supplementation is widely available, inexpensive, and highly effective at raising 25(OH)D levels.

- Test accuracy and safety: High- or moderate-certainty evidence supports acceptable accuracy of the screening test (eg, acceptable false-positive and false-negative rates).

There have been considerable efforts over the last decade to standardize the 25(OH)D assays, and the assays are significantly more reproducible than in the past, as most large laboratories follow a standardization protocol based on the work of the Vitamin D Standardization Protocol (https://www.cdc.gov/labstandards/csp/pdf/hs/vitamin_d_protocol-508.pdf). However, there is still considerable variability of 25(OH)D assays. The systematic review did not identify any studies showing that 25(OH)D testing is harmful.

- Available treatment: Effective management is available that improves patient-important outcomes when implemented in the latent (preclinical) phase.

Vitamin D supplementation is highly effective at raising 25(OH)D levels. Questions regarding whether vitamin D supplementation lowers the risks of patient-important outcomes—including in those with low 25(OH)D concentrations specifically—were the primary objective of the commissioned systematic reviews described throughout this document.

- Difference in outcomes: The benefits of management according to screening results outweigh the harms of screening (eg, overdiagnosis, unnecessary treatment for false positives, anxiety, stigma, etc.).

The panel did not identify any harms related to screening other than the financial costs associated with tests, health care visits, and (potentially) unnecessary treatment.

- Other considerations: The screening strategy should be cost-effective, acceptable to relevant stakeholders, and feasible to implement.

Vitamin D supplementation and 25(OH)D testing are judged to be acceptable and feasible. Data on implementation costs and cost-effectiveness considerations are scant.

This section addresses whether to screen with a 25(OH)D test in generally healthy populations. The panel did not specifically address whether and how those who present with documented low levels of 25(OH)D should be evaluated and/or treated.

Vitamin D Screening With a 25(OH)D Test for Healthy Adults

Background

Recent trends have shown a rise in screening rates for vitamin D status using serum 25(OH)D in the general population. Specifically, 25(OH)D testing frequency rose from 0.29 per 1000 person-years at risk in 2005 to 16.1 per 1000 person-years at risk by 2015, highlighting a growing interest by patients and physicians in assessing vitamin D status (263, 265). Advocating for the routine screening of 25(OH)D levels in healthy adults is contingent upon demonstrating that such screenings can effectively identify individuals with low 25(OH)D who might not be detected through traditional risk factor assessments, and that vitamin D supplementation, following the identification of a low 25(OH)D level, leads to improvements in clinical outcomes (eg, prevention of osteoporosis, CVD, diabetes, respiratory infections, overall mortality).

Screening for low 25(OH)D in generally healthy adults (ie, those who are not at increased risk for vitamin D deficiency) would involve testing large numbers of people, with important implications for health care systems.

The US Preventive Services Task Force (USPSTF) recently concluded that there was insufficient evidence to inform a

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decision regarding the balance of benefits and harms of screening for vitamin D status with 25(OH)D in asymptomatic adults (266). A recommendation against population screening for vitamin D deficiency with 25(OH)D is included in the "Choosing Wisely" campaign, an initiative by the American Board of Internal Medicine to spark conversations between clinicians and patients about the value of common tests (choosingwisely.org).

Question 12. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for healthy adults?

Recommendation 12

In healthy adults, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In healthy adults, 25(OH)D levels that provide outcome-specific benefits have not been established in clinical trials.
- This recommendation relates to adults who do not otherwise have established indications for testing with 25(OH)D levels (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/7Pf6NRYV8TE.

Benefits and Harms

The benefits and harms of vitamin D supplementation in nonpregnant adults with a 25(OH)D concentration below a threshold are addressed in clinical questions 3, 5, and 7. The available clinical trial data were insufficient to satisfactorily assess whether net benefit varied according to baseline 25(OH)D level. When available, trial subgroup analyses did not clearly indicate that net benefit of vitamin D specifically accrues to those with low baseline 25(OH)D level. However, conclusions drawn from subgroup analyses in each individual trial are limited as subgroups lacked adequate statistical power. Meta-analyses that combine aggregate study data and perform subgroup analyses according to average 25(OH)D in each study are subject to ecological fallacy, and thus were not included in the systematic reviews commissioned for this guideline.

Other Evidence-to-Decision Criteria and Considerations

The panel judged that screening for 25(OH)D would be acceptable to relevant stakeholders, assuming net benefit is expected. While the panel judged that screening would be feasible for many individuals, there are costs that accompany screening, including the direct and indirect costs of a visit for the test, the cost of the 25(OH)D test itself, the time and cost for a health care provider visit to review results, and potentially follow-up visits for consultation and more testing. Variable access to 25(OH)D testing could be an important barrier for some. In addition, screening entire adult populations would involve substantial costs and effort, thus feasibility from a societal perspective is unclear. The panel did not identify studies that adequately addressed the cost-effectiveness of 25(OH)D screening in all adults. One study estimated that among White adults aged 65 to 80 years, screening would be slightly more effective than universal supplementation for reducing falls and mortality (267). However, this modeling study relied on trials published more than 15 years ago, so its current relevance is unclear.

The effect of screening on health equity is unclear. Screening with 25(OH)D may worsen health equity because screening requires resources that may not be universally available or accessible, but it could improve health equity if screening led to the identification and effective treatment of prevalent and important health conditions in disadvantaged populations.

Justification for the Recommendation

The panel's conditional recommendation against routine screening for 25(OH)D levels in generally healthy adults primarily related to the lack of clinical trial–based evidence regarding what 25(OH)D levels would inform a treatment decision and the resultant effect of treatment with vitamin D, compared with no screening. The panel also considered the lack of clinical trial evidence that clearly supports the hypothesis that net benefit specifically accrues to those with a 25(OH)D level below a threshold. The panel was uncertain that any putative benefits of screening would outweigh the increased burden and cost, and whether implementation of universal 25(OH)D screening would be feasible from a societal perspective. Importantly, the panel recognized that it is possible that there is no single threshold 25(OH)D level appropriate for the entire general population.

Vitamin D Screening With a 25(OH)D Test for Adults With Dark Complexion

Background

"Dark complexion" is defined by a phenotype that involves the color of eyes, hair, and skin. In relation to vitamin D, the panel was especially interested in skin pigmentation, determined by the amount of melanin that can interfere with the production of vitamin D in response to exposure to UV-B rays. People at higher risk of low vitamin D status include individuals with dark skin, generally those whose ancestors originated from sunnier regions of the planet, including those with African heritage and descendants of indigenous peoples of the Americas, Oceania, and Asia. In addition, some (268, 269) but not all (270) studies suggest that the increase in 25(OH)D levels in response to vitamin D supplementation is not as robust in those with dark complexion compared to those with lighter complexion. Importantly, many such studies assessed groups according to race/ethnicity rather than skin complexion, introducing uncertainty regarding the degree to which dark complexion per se impacts circulating 25(OH)D concentrations. Nonetheless, since lower

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25(OH)D levels have been consistently observed in populations who tend to have darker complexion (147), the panel judged that it would be important to determine whether screening for 25(OH)D levels is beneficial in persons with dark complexion.

Question 13. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for adults with dark complexion?

Recommendation 13

In adults with dark complexion, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- This recommendation relates to generally healthy adults with dark complexion who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).
- The panel did not identify any clinical trials that related clinical outcomes to skin complexion per se. A secondary analysis did not clearly suggest net benefit with vitamin D in those who self-identify as Black. The panel recognized that self-identified race is an inaccurate and otherwise problematic proxy for dark complexion.

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/pHw68lfsrzU.

Benefits and Harms in Persons With Dark Complexion

The systematic review did not identify any trials that examined whether screening with 25(OH)D (and vitamin D treatment when 25[OH]D is found to be low) improves the outcomes of interest in people with dark complexion per se. The systematic review also did not identify any vitamin D trials that assessed whether outcomes of interest vary according to skin complexion per se. This absence of high-quality supportive data was the primary reason why the panel suggested against routine 25(OH)D screening in adults with dark skin complexion.

Benefits and Harms in Persons Who Self-Identify as Black

The panel specifically aimed to address screening for 25(OH)D in persons with dark complexion given that melanin can interfere with endogenous vitamin D production in response to sun (UV-B) exposure. The panel also recognized that clinical questions about the utility of 25(OH)D screening are frequently posed for racial groups in which dark complexion is common (although variable). The panel judged that such clinical questions are not without merit, especially given differences in 25(OH)D levels in people of different races and ethnicities. In a recent analysis of the NHANES in the United States, 25(OH)D levels lower than 10 ng/mL (< 25 nmol/L) were present in 1% of those who self-identified as White and in 11% of those who self-identified as Black, with levels of 12 to 20 ng/mL (25-50 nmol/L) in 14% and 49% of those self-identifying as White and Black, respectively (147). However, the panel recognized that racial categories represent social rather than biological constructs, and self-identified race is an inaccurate proxy for skin complexion (271). Although as a group, persons who self-identify as Black have darker skin complexion, they have highly variable skin pigmentation. Accordingly, using race as a proxy for skin complexion is subject to ecological fallacy and will misclassify many individuals. In addition, other factors (eg, social determinants of health) may be associated with both self-identified race and risk of low 25(OH)D levels, and outcomes of interest (eg, risk of diabetes), yielding uncertainty regarding the degree to which skin pigmentation per se predicts vitamin D-related outcomes in clinical studies (271). Nonetheless, given that clinicians frequently pose similar clinical questions for subgroups defined by race, the systematic review included a secondary analysis that addressed the potential benefits and harms of 25(OH)D screening in persons who self-identified as Black or African American.

The systematic review did not identify any trials that examined whether outcomes are improved by screening with 25(OH)D (with vitamin D treatment when 25[OH]D is found to be low) in people who self-identify as Black. Hence, the panel gathered evidence from clinical trials that reported results for the prespecified outcomes of interest in subgroup analyses by self-identified race.

The systematic review identified 2 RCTs that reported subgroup analyses on fracture risk in individuals who self-identified as Black. The VITAL trial (105) reported no difference in the incidence of total, nonvertebral, and hip fractures among 5106 Black participants who received 2000 IU (50 µg /day) of vitamin D daily vs placebo (HR 0.89 [95% CI, 0.62-1.30]). The baseline 25(OH)D level among Black participants was 25 ng/mL (62.5 nmol/L), and the cohort was at low baseline risk for fractures. The Women's Health Initiative (WHI) study (110) showed no statistically significant benefit of low-dose vitamin D (400 IU/day; 10 µg/day) (co-administered with calcium) over placebo (HR 0.73 [95% CI, 0.16-3.32]) on hip fractures in the subgroup of 3317 postmenopausal women who self-identified as Black.

One study (272) reported subset analyses on all-cause mortality in women who self-identified as Black, showing no difference between vitamin D (co-administered with calcium) and placebo (HR 0.97 [0.84-1.11]).

Three RCTs (20, 126, 272, 273) reported on the impact of vitamin D on cardiovascular adverse events in Black persons. In the VITAL trial (20), the risk of major adverse cardiovascular adverse events in those randomized to vitamin D vs placebo was similar in those who self-identified as Black (HR 0.91 [95% CI, 0.65-1.26], 5106 participants) and those who self-identified as White (HR 0.93 [95% CI, 0.79-1.10]). No differences in CVD between vitamin D vs placebo groups were observed in the PODA trial (Physical Performance, Osteoporosis and Vitamin D in African American Women trial) (HR 2.23 [95% CI, 0.85-6.23]; 260 African American female participants) (126) and the WHI study (vitamin D co-administered with calcium, HR 0.99 [95% CI, 0.87-1.13]; 3325 Black female participants) (272). Among Black women

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in the WHI (272, 273), there was no significant difference between vitamin D (co-administered with calcium) vs placebo on the risk of MI (HR 0.89 [95% CI, 0.66-1.20]), heart failure (HR 0.95 [95% CI, 0.73-1.23]), stroke (HR 0.87 [95% CI, 0.68-1.12]), transient ischemic attack (HR 0.99 [95% CI, 0.71-1.38]), or undergoing coronary artery bypass grafting or percutaneous transluminal coronary angioplasty (HR 1.05 [95% CI, 0.80-1.38]).

The systematic review identified 2 RCTs (20, 272) and 1 observational study (274) that reported on the risk of developing cancer in Black participants. The VITAL trial (20) reported a HR of 0.77 (95% CI, 0.59-1.01; 5106 participants), and the WHI (272) reported a HR of 0.99 (95% CI, 0.84-1.16) Among Black participants in the WHI trial, vitamin D co-administered with calcium was not statistically different than placebo for gastrointestinal cancer (HR 0.83 [95% CI, 0.60-1.15]), hematologic cancer (HR 0.72 [95% CI, 0.52-1.23]), lung cancer (HR 0.98 [95% CI, 0.63-1.51]), or breast cancer (HR 0.95 [95% CI, 0.74-1.23]) (272). In a 10-year observational cohort study (274) of women with sisters who had breast cancer, no association was found between use of use of vitamin D supplements and breast cancer among Black women (HR 0.89 [95% CI, 0.68-1.2]).

The systematic review did not identify trials addressing the role of vitamin D in preventing respiratory infections in adults who self-identify as Black.

No significant differences in kidney stones, symptomatic hypercalcemia, kidney disease, or renal failure were observed in the RCTs that performed subgroup analyses of adults who self-identified as Black.

In summary, based on an assessment of the small number of clinical trials that reported results according to self-identified race, vitamin D did not clearly have a beneficial effect on fractures, mortality, cardiovascular events, or cancer among participants who self-identified as Black or African American. Available studies only addressed US individuals who self-identified as Black or African American, limiting generalizability. Data were insufficient for other populations in which dark complexion is common (eg, descendants of certain indigenous populations of Asia, the Americas, or Oceania).

Other Evidence-to-Decision Criteria and Considerations

The panel judged that testing for 25(OH)D levels (with vitamin D supplementation/treatment as indicated) would be acceptable to many, although access to testing is variable across the globe, which may limit feasibility for some. Conditioning vitamin D supplementation on 25(OH)D test results would be expected to increase costs and burden, and the panel did not identify any studies that adequately addressed the cost-effectiveness of such an approach.

The panel did not identify any studies that adequately addressed the potential equity impact of 25(OH)D screening for people with dark complexion, although the panel had concerns that such a testing approach could negatively impact health equity, especially given the absence of evidence for a net benefit with vitamin D supplementation in those with both dark complexion and low 25(OH)D. The panel also considered the potential equity impact of a 25(OH)D screening strategy vs empiric vitamin D supplementation in those with dark complexion. Similar to the general population, from an equity standpoint, the panel judged that empiric vitamin D supplementation could possibly be preferred to a screening strategy—assuming that net benefit is expected from vitamin D supplementation—since it does not require healthcare access, overall anticipated costs would be lower, and since vitamin D supplementation is judged to be safe when kept within tolerable upper intake levels as recommended by the IOM.

Justification for the Recommendation

The panel's conditional recommendation against routine 25(OH)D screening for those with dark complexion primarily related to the lack of clinical trial evidence that would support the benefit of 25(OH)D screening in addition to the lack of clinical trial evidence that would support net benefit related to vitamin D supplementation in those with dark complexion. The panel was also uncertain that any putative benefits of screening would outweigh potential downsides, including the costs of 25(OH)D tests, and whether implementation of 25(OH)D screening for those with dark complexion would be feasible from a societal perspective.

Research Considerations

1. Clinical trials should address whether the benefits and harms of vitamin D screening (and treatment) vary according to skin complexion per se (a biological characteristic relevant to vitamin D), rather than using self-identified race (a social construct) as a proxy for skin complexion. At the same time, research is needed to assess whether the benefits and harms of vitamin D screening and/or treatment vary according to race/ethnicity, as well as to define how social determinants of health vs biological factors (eg, skin pigmentation) impact clinical outcomes. Research should also address whether advisable vitamin D intake (ie, DRIs) varies according to skin complexion, race/ethnicity, or both.
2. It will be important to undertake studies to determine the concentrations of 25(OH)D that are considered optimal for disease prevention in individuals with dark complexion, and what dosages of vitamin D are required to achieve these levels.
3. People with dark complexion are overrepresented in immigrants to northern latitudes and in resource-poor settings. The consequences of low vitamin D levels in this population are not well studied.

Vitamin D Screening With a 25(OH)D Test for Adults With Obesity

Background

Low serum 25(OH)D levels are common among people with obesity. This is likely multifactorial, including insufficient dietary intake of vitamin D; reduced sun exposure; diminished 25-hydroxylase activity (275); and changes in the gut microbiome, which have been shown to affect vitamin D absorption (276, 277). Notably, the absolute increase in 25(OH)D levels observed after 2 years of vitamin D supplementation (2000 IU [50 µg] per day) was attenuated in participants with obesity, relative to those with a BMI < 25 kg/m^2 (10.5 vs 13.5 ng/mL [26 vs 34 nmol/L]) (278). After adjustment for other potential predictors, adults with obesity in the United States were found to have a 3-fold higher prevalence of 25(OH)D less than 20 ng/mL (50 nmol/L) and 2-times higher prevalence of

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25(OH)D between 20 and 30 ng/mL (50-75 nmol/L) than adults without obesity (279).

While obesity is associated with higher bone density, this does not necessarily translate into a reduced risk of fractures. In fact, postmenopausal females with obesity were shown to have a 50% higher risk of ankle and 70% higher risk of upper leg fractures (280). Obesity has also been associated with an increased risk of diabetes, all-cause mortality, CVD, cancer, and lower tract respiratory infections. Notably, levels of 25(OH)D lower than 20 ng/mL (50 nmol/L) are associated with an increased risk of cardiometabolic mortality. Data from NHANES suggest an additive effect of obesity and low vitamin D status (25[OH]D less than 12 or 20 ng/mL [30 or 50 nmol/L]) on CVD, cancer mortality, and all-cause mortality (281).

Thus, if optimizing 25(OH)D levels lowers risk of these conditions, high value could be realized at both individual and health care system levels.

Question 14. Should screening with a 25(OH)D test (with vitamin D supplementation/treatment only if below a threshold) vs no screening with a 25(OH)D test be used for adults with obesity?

Recommendation 14

In adults with obesity, we suggest against routine screening for 25(OH)D levels. (2 | ⊕◯◯◯)

Technical remarks

- In adults with obesity, 25(OH)D thresholds that provide outcome-specific benefits have not been established in clinical trials.
- This recommendation relates to generally healthy adults with obesity who do not otherwise have established indications for 25(OH)D testing (eg, hypocalcemia).

Summary of Evidence

The evidence summaries, meta-analysis results, and a detailed summary of the evidence and EtD tables can be found online at https://guidelines.gradepro.org/profile/iNI2fGcamG8.

Benefits and Harms

The systematic review did not identify any trials that examined whether screening for 25(OH)D levels (with vitamin D treatment when 25[OH]D is found to be low) in people with obesity improves the prespecified outcomes of interest. Thus, clinical trials in which subgroup analyses were performed by baseline BMI were examined.

Vitamin D supplementation in adults with a BMI higher than 30 kg/m^2 was not shown to have a significant effect on fractures in 2 RCTs reporting on fractures in participants with obesity. The VITAL RCT performed in the United States (105) showed no reduction in fracture risk in adults with a BMI higher than 30 kg/m^2 randomized to 2000 IU (50 µg) vitamin D daily vs placebo (HR 1.17 [95% CI, 0.95-1.44]). However, the average baseline 25(OH)D level in those with a BMI higher than 30 kg/m^2 was 28 ng/mL (72 nmol/L), the cohort was at low risk for fractures, and outcomes based on baseline 25(OH)D in individuals with obesity were not presented. The WHI, which was also performed in the United States (110) showed a HR of 0.73 (95% CI, 0.49-1.09) for femoral fractures in female individuals with a BMI higher than 30 kg/m^2 who were randomized to 1000 mg calcium and 400 IU (10 µg) vitamin D supplementation daily vs placebos. Baseline 25(OH)D levels were not available in this subgroup. In the entire study cohort, the risk of fracture decreased among those who were adherent to calcium and vitamin D treatment, but there are no available data among those with a BMI higher than 30 kg/m^2 who were adherent to study medications.

The WHI also examined the effects of vitamin D (400 IU [µg] with 1000 mg calcium daily) on all-cause mortality in individuals with obesity and did not show a statistically significant effect (HR 0.93 [95% CI, 0.80-1.09]), including among participants adherent to study medications (HR 0.87 [95% CI, 0.73-1.04] (121).

Two RCTs (20, 125) examining the incidence of major cardiovascular events in individuals with obesity found no overall benefit in those who were randomized to vitamin D. In the VITAL study, participants with obesity who received 2000 IU (50 µg) of vitamin D daily and those who received placebo had a comparable risk of cardiac events (HR 0.98 [95% CI, 0.76-1.26] (20). Of interest, the FIND trial, performed in Finland (125), suggested a reduction in the risk of developing a major cardiovascular event in those with a BMI higher than 30 kg/m^2 receiving higher dosages of vitamin D (3200 IU/day [80 µg /day]), which increased 25(OH)D levels from 30 ng/mL (75 nmol/L) at baseline to 48 ng/mL (120 nmol/L) (HR 0.19 [95% CI, 0.04-0.82]).

Three RCTs and one observational study examined the effect of vitamin D on the development of cancer in adults with obesity (29). None of these trials demonstrated a significant effect of vitamin D on developing cancer. An HR of 1.13 (95% CI, 0.9-1.37); 2000 IU [50 µg] vitamin D/day) was reported in the VITAL trial (20). In the FIND trial (125) neither the high (3200 IU/d, 80 µg/d) nor the lower dosage (1600 IU/d; 40 µg/d) decreased cancer risk (HR 0.91 [95% CI; 0.36-2.32] and HR 1.61 [95% CI; 0.72-3.59 respectively). In the WHI, vitamin D plus calcium supplementation did not alter the risk of colorectal cancer (282) (HR 1.07 [95% CI, 0.76-1.52]); invasive breast cancer (283) (HR 0.93 [95% CI, 0.77-1.12]), or in situ ductal breast cancer (284) (HR 0.81 [95% CI, 0.62-1.06]). In the Sister observational study (274) use of vitamin D supplements did not decrease the risk of breast cancer in obese women whose sisters had breast cancer (HR 0.94 [95% CI, 0.82-1.10). Baseline 25(OH)D levels for individuals with obesity were not available for all these trials, but in the VITAL trial, the average baseline level in those with a BMI higher than 30 kg/m^2 was 28 ng/mL (72 nmol/L).

The ViDA trial, performed in New Zealand, reported no beneficial effect of vitamin D on the risk of developing respiratory infections in adults with obesity. The baseline 25(OH)D levels of participants with obesity were not presented.

The systematic review did not identify studies that reported the risk of developing hypercalcemia in patients with obesity receiving vitamin D. The risk of nephrolithiasis and a decline in kidney function were examined in 1 RCT each, and no statistically significant effect of vitamin D supplementation was observed (120, 126).

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Other Evidence-to-Decision Criteria and Considerations

Considerations related to required resources (costs), acceptability, and feasibility have been discussed. The panel did not identify any studies that adequately addressed the cost-effectiveness, or the potential equity impact of 25(OH)D screening, for people with obesity. However, since obesity has been associated with reduced health equity, if optimizing 25(OH)D levels were to preferentially improve outcomes in persons with obesity and low 25(OH)D, then 25(OH)D screening in those with obesity could possibly improve health equity. The panel judged that screening would be acceptable to most, assuming that a net benefit is expected. Although there is variability in the cost and availability of testing for 25(OH)D levels across the globe, the panel judged that this is feasible in many settings, as is the resultant intervention of taking a daily nonprescription supplement. Given the very high prevalence of obesity in many countries (eg, the prevalence of obesity in the United States is estimated to be 41.9% (285), a 25(OH)D screening strategy for all individuals with obesity would require significant effort and resources, which may not be feasible from a societal perspective.

Justification for the Recommendation

The panel's conditional recommendation against routine 25(OH)D screening for those with obesity is related primarily to the lack of clinical trials examining the benefit of 25(OH)D screening in those with obesity and treating only those with a 25(OH)D level below a threshold. Moreover, subgroup analyses from available clinical trials did not clearly demonstrate a net benefit of vitamin D in individuals with obesity as a group. The panel was also uncertain that any putative benefits of screening would justify the additional burden and costs of 25(OH)D testing, including health care visits (cost-effectiveness); and whether implementation of universal 25(OH)D screening for those with obesity would be feasible from a societal perspective. In addition, the panel was uncertain about what 25(OH)D level would necessitate subsequent vitamin D administration.

Research Considerations

1. Large RCTs in participants with obesity will be required to determine if vitamin D lowers the risk of disease, whether benefit is limited to those with low baseline levels (and defining what these levels are), what target levels are required for optimal disease prevention, and what dosages are required to achieve these target levels/desired outcomes. Although placebo-controlled vitamin D trials may be viewed as unethical for participants known to have low 25(OH)D levels, inclusion of several daily dosages and targeting several levels of 25(OH)D would inform the dosages and target levels required for disease prevention.
2. Clinical trials must be designed to be of sufficient duration to address the outcomes being examined, considering the natural history and pathophysiology of the diseases of interest (eg, acute infectious diseases vs cancer).

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Disclaimer

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Disclosures

Summary

- Total number of Guideline Development Panel members = 14
- Percentage of total Guideline Development Panel members with relevant (or potentially relevant) conflicts of interest = 7%

Data availability

The data underlying this article are available in the article, in its online supplementary material, and in the accompanying systematic review publication.

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Individual Disclosures, Conflicts, and Management Strategies

Chair: Marie Demay, MD
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Expertise: Adult endocrinology

Disclosures (2020-2024):

- National Institutes of Health: Investigator on vitamin D action, growth plate
- Endocrine Society: Annual Meeting Steering Committee Member

Open Payments Database: N/A

Assessment and Management:

- No conflict of interest (COI) relevant to this CPG.
- No management required.

Co-Chair: Anastassios G. Pittas, MD, MS
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Disclosures (2020-2024):

- National Institutes of Health: Investigator on vitamin D
- National Institutes of Health: Data Safety Monitoring Board for melatonin, lifestyle intervention
- National Institutes of Health: Data Safety Monitoring Board for the DISCOVERY study, diabetes risk in children
- Expert testimony for various hospitals on cases that involved diabetes

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Daniel Bikle, MD, PhD
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Disclosures (2020-2024):

- Radius: Investigator on abaloparatide
- Elsevier: Journal Associate Editor
- Amgen: own stocks/shares
- International Vitamin D Workshop
- Endocrine Society
- American Society for Bone and Mineral Research
- Author on "Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows" (Giustina A, Bilezikian JP, Adler RA, et al. Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows. Endocr Rev. Published online April 27, 2024. doi:10.1210/endrev/bnae009)

Open Payments Database: https://openpaymentsdata.cms.gov/physician/74931

Assessment and Management:

- Dr. Bikle's authorship on this consensus statement was made known after the completion of this guideline. Although participation in multiple consensus statements or guidelines could generate intellectual dualities of interest, an evaluation indicated no potential conflict with the present guideline.

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Disclosures (2021-2024):

- American Association of Clinical Endocrinology: Vice Chair for the Bone Network

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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Disclosures (2020-2024):

- Research funding: Irish Government Department of Agriculture Food and the Marine
- Research funding: Science Foundation Ireland
- Research funding: European Commission
- Research funding: Enterprise Ireland Meat Technology Institute
- Research funding: Wellcome Leap 1KD
- Member: UK Scientific Advisory Committee for Nutrition (SACN)
- Member: Vitamin D Workshop Executive Committee; Co-chair 2024 Workshop

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Marise Lazaretti-Castro, MD, PhD
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Expertise: Adult endocrinology

Disclosures (2020-2024):

- Mantecorp-Farmasa: Primary Investigator on pharmaceutical product
- Mantecorp-Farmasa: Consultant on pharmaceutical product
- Alexion: Speaking engagement for pharmaceutical product
- Amgen: Advisory Board for pharmaceutical product
- Associacao Brasileira de Avaliaçcao Ossea e Osteometabolismo

Open Payments Database: N/A

Assessment and Management:

- It was determined that Dr. Lazaretti-Castro would refrain from future consultation for products related to vitamin D.

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Disclosures (2020-2024):

- Abiogen: Speaking Engagement on controversies in vitamin D
- Vitamin D Workshop: Scientific Programme Advisory Board

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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Expertise: Pediatric endocrinology

Disclosures (2020-2024):

- Amolyt: Consultant for hypoparathyroidism
- American Society for Bone and Mineral Research: Education Committee Member, Chair of the Pediatric Working Group

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Shelley Powers
Patient Representative

Disclosures (2020-2024):

- American Bone Health: Board of Directors, Committee Chair
- International Society for Clinical Densitometry: Patient Advocate

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Sudhaker Rao, MD
Henry Ford Hospital and Michigan State University
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Disclosures (2020-2024):

- Department of Defense: Investigator on bone quality using digital tomosynthesis

Open Payments Database: https://openpaymentsdata.cms.gov/physician/390118

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Robert Scragg, MBBS, PhD
University of Auckland
Expertise: Epidemiology

Disclosures (2020-2024):

- Health Research Council of New Zealand: Investigator on arterial function and cardiovascular disease

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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Disclosures (2021-2024):

- Ajinomoto USA: Investigator for amino acid supplements in end-stage renal disease (ESRD)

Open Payments Database: https://openpaymentsdata.cms.gov/physician/165331

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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Oregon Health and Sciences University
Expertise: Obstetrics and gynecology

Disclosures (2022-2024):

- Dexcom: Investigator for device
- Dexcom: Consultant

Open Payments Database: https://openpaymentsdata.cms.gov/physician/1355801

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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- National Institutes of Health: Investigator on cancer screening, primary care, smoking cessation
- Up to Date: Consultant on colon cancer screening
- Kaiser Permanente Medical Center: Speaking engagement on cancer screening, women's health

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
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- Endocrine Society: Editor or member of an editorial board, Vice Chair Ethics and Professionalism Committee, Chair of COI Advisory Group, Clinical Science Chair Annual Meeting Steering Committee

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

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Disclosures (2020-2024):

- Society for Vascular Surgery: Methodology Consultant
- American Society of Hematology: Methodology Consultant
- CHEST: Methodology Consultant
- World Health Organization: Methodology Consultant
- Evidence Foundation: Board Member

Open Payments Database: N/A

Assessment and Management:

- No COI relevant to this CPG.
- No management required.

Appendix A. Guideline Development Panel (GDP) makeup, roles, and management plans

Role	Name	Relevant COI?	Representative
Chair	Marie Demay	No	
Co-Chair	Anastassios Pittas	No	
Members	Daniel Bikle	No	ASBMR Vitamin D Workshop
	Dima Diab	No	AACE
	Mairead Kiely	No	ASN
	Marise Lazaretti-Castro	Yes	SBEM
	Paul Lips	No	ESE
	Deborah Mitchell	No	PES
	Shelley Powers	No	
	Sudhaker Rao	No	ESI
	Robert Scragg	No	
	John Tayek	No	
	Amy Valent	No	ACOG
	Judith Walsh	No	SGIM
Methodologists	M. Hassan Murad	No	
	Christopher McCartney	No	

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