Expert consensus on vitamin D in osteoporosis

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Background: Adequate vitamin D is essential for maintaining optimal bone health, preventing and treating of osteoporosis. However, in recent years, large clinical trials and meta-analyses on the efficacy of vitamin D supplementation to prevent fractures in populations at different risks have been equivocal. The optimal level of 25-hydroxyvitamin D (25[OH]D) remains controversial. Recommendations vary between societies. The lack of standardized assays also poses a challenge in interpreting available research data.

Methods: We systematically searched for articles in MEDLINE database through PubMed, which included meta-analysis, systematic reviews of randomized controlled trials (RCTs) and observational studies that assessed measurement, diagnosis and treatment about vitamin D deficiency. The experts evaluated the available literature, graded references according to the type of study and described the strength recommendations.

Results: This expert consensus is based on the review of relevant clinical evidence and provides nine key recommendations on vitamin D deficiency in populations at different risks, especially in patients with osteoporosis. Supporting information is provided in the subsequent appendix box.

Conclusions: This expert consensus is a practical tool for endocrinologists, general physicians for the diagnosis, assessment, and treatment of populations at different risks of vitamin D deficiency, especially in patients with osteoporosis. Clinicians should be aware of the evidence but make individualized decisions based on specific patients or situation.

Keywords: Vitamin D deficiency; measurement of vitamin D; vitamin D deficiency threshold; osteoporosis

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Introduction

Osteoporosis which was defined by the World Health Organization (WHO) in 1994 as a "progressive systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture" remains a major public health concern (1). Osteoporotic-related fractures occur as a result of bone fragility, which greatly reduce quality and length of life and lead to significant social and economic burden, particularly in aging individuals. Approximately 40.9% of the Chinese women aged 50 years will have osteoporotic fracture during their remaining lifetime (2). Osteoporotic fractures are associated with high morbidity, increased mortality, and reduced quality of life (3). The aim of osteoporosis therapy is to reduce the risk of fragility fractures in patients at increased risk.

Vitamin D has been considered crucial for maintaining optimal bone health, preventing and treating of osteoporosis (4). However, in recent years, numerous observational studies and meta-analysis on the efficacy of vitamin D supplementation to prevent fractures in postmenopausal women have been equivocal (5-7). Therefore, it is important to determine the roles of vitamin D in osteoporosis. This expert consensus is based on the review of relevant clinical evidence and provides recommendations on vitamin D measurement and therapy in osteoporosis.

Methods

Primary writers submitted the outlines to all the panel members, which were subsequently reviewed by an international expert panel in the field of vitamin D on controversial topics related to vitamin D. All the recommendations were subsequently revised, discussed, and integrated into the final document. All authors contributed to this process, reaching consensus through electronic communications. This consensus was approved by all primary writers and invited expert reviewers. Evidence was obtained through literature searches using the MEDLINE database through PubMed, which included meta-analysis, systematic reviews of randomized controlled trials (RCTs) and observational studies that assessed measurement, diagnosis and treatment about vitamin D deficiency in different risk populations, especially in patients with osteoporosis. We used the assessment of multiple systematic reviews to assess the methodologic quality of systematic reviews. The experts evaluated the available literature and graded references according to the type of study. Levels of evidence were defined using the following criteria: level 1: based on high level evidence, including systematic overview, meta-analysis of RCTs and RCT; level 2: based on intermediate level evidence, including RCT that does not meet level 1 criteria; level 3: based on low level evidence, including nonrandomized clinical trial or cohort study; level 4: based on lower level evidence, including before-after study, case-control study and case series. This consensus used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (8) to describe the strength recommendations. A "strong" recommendation usually refers to recommendations based on high-level evidence that clinical behavior and outcome expectations are consistent; in contrast, a "weak" recommendation is often based on low-level evidence with uncertain clinical behavior and outcome expectations.

Key recommendations

- Best measurement method: serum 25[OH]D is identified as the optimal method for assessing vitamin D status (level 1 evidence, strong recommendation).

In humans, the skin is the natural source of vitamin D. It is produced locally from 7-dehydrocholesterol in photoreaction induced by ultraviolet B (UVB) radiation from the sun (9). After synthesis in the skin, Vitamin D enters the bloodstream reaching various tissues, including the liver, adipose tissue, and muscle. In the liver, vitamin D is metabolized to 25[OH]D (calcifediol), which is the major metabolite of vitamin D (10).

Serum 25[OH]D circulates in serum bound to a specific, high affinity, transport protein, vitamin D-binding protein (VDBP), with relatively low free levels. Measurement of circulating 25[OH]D is considered to be the best approach to assess an individual's vitamin D status (11). In the kidney, 25[OH]D is further metabolized to produce the biologically active 1,25-dihydroxyvitamin D3 (10), which plays an important role in regulating intestinal calcium and phosphate absorption. However, it is not an appropriate indicator of clinical vitamin D status (11).

Key recommendations

- Standardization issues: in the absence of standardized 25[OH]D assays, serum 25[OH]D levels from different clinical laboratories may not be comparable (level 2 evidence, strong recommendation).

A multitude of techniques are widely used for measuring 25[OH]D, but assay methodology can be grouped into two general categories: immune based and chromatography based (12). The chromatography-based assays are becoming the gold standard assay method in the assessment of the vitamin D status, which offer high specificity and sensitivity (13). However, the data used to define range levels for normal vitamin D status have been obtained by immune-based assays (14). Serum 25[OH]D levels vary widely between assay methodologies. It is necessary that clinical and research laboratories use standardized 25[OH]D assays including application of standard reference material such as the National Institute of Standards and Technology (NIST) and participation in the Vitamin D External Quality Assessment Scheme (DEQAS) quality control program. Therefore, in the absence of standardized 25[OH]D assays, serum 25[OH]D values from different clinical laboratories cannot be assumed to be comparable (15). Therefore, the latest consensus on vitamin D states that it is important to consider the accuracy and standardization of assay methodology when assessing vitamin D status (16).

Key recommendations

- At-risk patients: measurement of serum 25[OH]D is recommended for patients at risk of vitamin D deficiency (level 2 evidence, strong recommendation).

Vitamin D deficiency is a worldwide condition, and may cause secondary hyperparathyroidism, high bone turnover, bone loss and mineralization defects that may lead to fractures (17). The Institute of Medicine (IOM) defined the sufficient 25[OH]D level based on observational bone mineral density (BMD) data, as ≥50 nmol/L (18). The review of epidemiological studies contained data on a total of 168,389 participants from 44 countries on vitamin D status conducted in Europe, South America, North America, Asia and Oceania concluded that mean population-level 25[OH]D values varied considerably across the studies (range, 4.9–136.2 nmol/L), with 37.3% of the studies reporting mean values below 50 nmol/L (19). The screening of vitamin D deficiency by measuring serum 25[OH]D is thus recommended in individuals at high risk of deficiency. This includes patients with diseases affecting vitamin D metabolism and absorption; patients with osteoporosis or rickets/osteomalacia; older adults with a history of falls or nontraumatic fracture; bariatric surgery; people with a debilitating/chronic disease; people working long hours indoors; obesity or primary hyperparathyroidism; and patients with granulomatous disorders (16,20-22).

Key recommendations

- Osteoporosis and serum levels: serum 25[OH]D levels should be maintained at ≥75 nmol/L in patients with osteoporosis (level 1 evidence, strong recommendation).

There is controversy concerning which levels of circulating 25[OH]D supplementation should be considered as an optimal or adequate serum level. Most endocrine societies consider that serum concentration of 25[OH]D above 75 nmol/L is necessary to achieve health benefits. The American Association of Clinical Endocrinologists (AACE) practice guideline recommends that maintenance

serum 25[OH]D ≥75 nmol/L in osteoporosis (23). The guideline statement from Osteoporosis Canada and the Endocrine Society on Vitamin D Deficiency, an optimal level of 25[OH]D ≥75 nmol/L is also recommended in patients with osteoporosis (24,25). In line with the AACE guideline, Chinese vitamin D consensus supports the serum 25[OH]D threshold above 75 nmol/L for sufficient, which consider that this cutoff is necessary to achieve health benefits and these are the recommendations on which we should base ourselves. In contrast, other groups including the IOM and the National Osteoporosis Society of UK recommend that 25[OH]D values ≥50 nmol/L be considered adequate (18,26). This value of 50 nmol/L is now accepted by major European countries (27).

Vitamin D deficiency results in abnormalities in calcium, phosphorus, and bone metabolism. Specifically, vitamin D deficiency causes a decrease in the efficiency of intestinal calcium and phosphorus absorption from diet, resulting in an increase of parathyroid hormone (PTH) levels. A review evaluated thresholds for serum 25[OH]D concentrations for multiple health outcomes including extremity function, dental health, risk of falls, fractures, and colorectal cancer. For all endpoints, the optimal serum concentrations of 25[OH]D begin at 75 nmol/L, and the best are between 90 and 100 nmol/L (28). Serum PTH levels had a significant negative correlation with 25[OH]D and began to plateau in adults who had the levels of 25[OH]D between 75 and 100 nmol/L (29). Consistent with this threshold, one meta-analysis of double-blind RCT with oral vitamin D showed that serum 25[OH]D levels of about 75 to 110 nmol/L provided optimal benefits for hip and nonvertebral fracture prevention (30). Evidence was reviewed that showed setting an optimal threshold of 75 nmol/L was associated with increased absorption of calcium from the gut (31). In the absence of vitamin D, the intestine is capable of absorbing only 10% to 15% of calcium and about 60% of phosphorus from the diet. Adequate vitamin D increases the absorption of calcium and phosphorus by 30–40% and 80%, respectively (32,33). Thus, based on these and other studies, we recommend that supplementation of vitamin D should be maintained at a serum 25[OH]D level ≥75 nmol/L, particularly for individuals with osteoporosis.

Key recommendations

- Low-risk adults: in adults under 50 with a low risk of vitamin D insufficiency, daily supplementation exceeding 400 IU of vitamin D and 1,000 mg of calcium is not recommended (level 1 evidence, weak recommendation).

The supplementation of vitamin D and calcium has long been a subject of controversy within the medical and scientific communities. While some studies suggest potential benefits, such as improved bone health and reduced risk of certain diseases, others raise concerns about potential risks, including adverse cardiovascular outcomes and kidney stones. As researchers continue to explore the complex interactions between these nutrients and their impact on overall health, the debate surrounding their supplementation remains a topic of ongoing discussion and investigation.

Numerous studies have provided evidence supporting the potential benefits of vitamin D supplementation, especially in specific populations. Research indicates that individuals with inadequate sun exposure, such as those living in northern latitudes or confined indoors, are at a higher risk of vitamin D deficiency. Moreover, older adults, who might have reduced skin synthesis of vitamin D, have shown improvements in bone density and fracture prevention with supplementation. Additionally, individuals with certain medical conditions like osteoporosis or malabsorption disorders can also benefit from vitamin D supplementation as it aids in calcium absorption and supports bone health. These findings have led to recommendations for targeted supplementation in these high-risk populations to address deficiencies and enhance overall health. However, the optimal dosages and potential interactions with other factors remain subjects of ongoing research and clinical discussion.

Various health organizations and guidelines have taken nuanced stances on the supplementation of vitamin D and calcium. For instance, the U.S. Preventive Services Task Force (USPSTF) suggests that there is currently insufficient evidence to recommend routine supplementation of these nutrients for the prevention of fractures in postmenopausal women and older men. The USPSTF has concluded that the current evidence to assess the relative benefits and harms of combined vitamin D and calcium supplementation for the primary prevention of fractures in premenopausal women or men without osteoporosis or vitamin D deficiency is insufficient (34). The IOM has recommended dietary allowances for 600 IU of vitamin D and 1,000 mg of calcium in people younger than 50 years. However, the benefits and harms of daily supplementation with greater than 400 IU of vitamin D and greater than 1,000 mg of calcium to prevent fractures are not clear. Two meta-

analyses suggest that vitamin D supplementation with or without calcium was inappropriate in community-dwelling adults (35,36). Another systematic review and meta-analysis of 11 RCTs of vitamin D supplementation alone (daily or intermittent dose of 400–30,000 IU) did not reduce risk of any fracture or hip fracture (37). Moreover, alone or combined use of calcium and vitamin D supplementation did not improve BMD in the total hip or lumbar spine in healthy premenopausal women (38). Recently, a double-blind, randomized clinical trial including 311 community-dwelling healthy adults without osteoporosis demonstrated that treatment with vitamin D for 3 years at a dose of 4,000 IU per day or 10,000 IU per day, compared with 400 IU per day, resulted in statistically significant lower radial BMD (39), and thus did not indicate a high-dose vitamin D supplementation as beneficial for bone health. The Endocrine Society's guidelines highlight that vitamin D supplementation may be warranted for individuals with documented deficiencies or those at high risk of deficiency due to limited sun exposure. However, they also emphasize the need for further research to clarify the optimal dosages and potential benefits of supplementation in different populations. These studies reflect the ongoing uncertainty and complexity surrounding the use of these supplements, reinforcing the need for a personalized and evidence-based approach when considering vitamin D and calcium supplementation, especially in adults with low risk of fractures.

Meanwhile, several studies have produced results that challenge the notion of universal benefits from vitamin D and calcium supplementation. Large-scale RCTs have failed to consistently demonstrate significant reductions in fracture risk or improvements in overall mortality rates among individuals taking these supplements (35,37,40,41). In fact, some trials have even reported potential harm, such as an increased risk of kidney stones or cardiovascular events in certain populations (42). For instance, a meta-analysis published in a prominent medical journal found no significant reduction in hip fracture risk with vitamin D and calcium supplementation in community-dwelling older adults (35). These conflicting outcomes have led to skepticism about the widespread use of these supplements and emphasize the importance of individualized approaches to supplementation based on factors such as baseline nutrient levels and medical history.

Though the literature concerning this issue is contradictory, because of the small risk and cost, we believe that it is essential not to discourage older adults with calcium and vitamin D supplementation. Also, we should consider other health outcomes about vitamin D in addition to fractures and falls. Therefore, we suggest supplementation with vitamin D and calcium for the primary prevention of fractures in elderly people. But for people with a low risk for vitamin D insufficiency are adults below age 50 years without osteoporosis, daily supplementation with greater than 400 IU of vitamin D and greater than 1,000 mg of calcium is not recommended, which was consistent with the USPSTF recommendation (34). There is a need for further studies to address the possible benefits of vitamin D supplements on muscle function, particularly on falls and fractures.

Key recommendations

- Supplements for older adults: for adults over 50 years at high risk of vitamin D deficiency, a minimum daily supplementation of 1,200 mg of calcium and 800 IU of vitamin D is recommended (level 1 evidence, strong recommendation).
- Post-supplementation testing: routine measurement of serum 25[OH]D within 3 months after initiating supplementation is not necessary (level 1 evidence, strong recommendation).

Large clinical trials have shown that supplementation with calcium and vitamin D is not effective for preventing incident fractures in otherwise healthy postmenopausal women, previously mobile elderly people and in healthy midlife and older adults who were not selected for 25[OH]D deficiency, low BMD or osteoporosis (40,43,44). Hence, calcium and vitamin D supplementation should be targeted on individuals with a high risk of fracture and those documented with or at high risk of vitamin D deficiency.

The effects of calcium and vitamin D supplementation on falls have been demonstrated in several clinical RCTs conducted in high-risk individuals. Some randomized trials and meta-analyses found that vitamin D supplementation reduced the risk of falls (45-48). However, a recent RCT in older persons found that vitamin D supplementation at doses of 1,000 IU/d or higher did not prevent falls (49). Two other RCTs documented that high doses of vitamin D may even increase the risk of fall (50,51). Evidence have reached divergent conclusions, possibly because of differences in vitamin D doses, recruitment of participants with vitamin D deficiency or insufficiency, and other design features (52). These findings led to a change in the 2018 USPSTF recommendations, which now do not recommend

vitamin D supplementation to prevent falls in older persons without osteoporosis or vitamin D deficiency (53).

Fracture is the most important outcome of osteoporosis. The effects of calcium and vitamin D on fracture risk have also been studied in the elderly, including ambulatory individuals living in institutions and elderly community residents. These studies found that supplementation with vitamin D and calcium reduced the risk of hip fractures and other nonvertebral fractures among elderly women (54-57). A meta-analysis summarizing eight RCTs (n=30,970) found that a daily combination of vitamin D plus calcium led to a significant 15% reduction of total fractures [relative risk (RR) =0.85; 95% confidence interval (CI): 0.73–0.98] and a 30% reduction of hip fractures (RR =0.70; 95% CI: 0.56–0.87) (5).

In contrast, the efficacy of calcium with vitamin D supplementation for preventing hip and other fractures in the elderly remains equivocal. Recent randomized trials of calcium with vitamin D supplementation found no significant difference in fracture rates for both hip fractures or total fractures between the treatment and placebo groups (40,58). A systematic review and meta-analysis by Bolland *et al.* (n=53,537) (59) found that vitamin D had no effect on total fracture (36 trials; n=44,790; RR =1.00; 95% CI: 0.93–1.07) or hip fracture (20 trials; n=36,655; RR =1.11; 95% CI: 0.97–1.26), which were consistent with the findings of the meta-analysis by Zhao *et al.* (n=51,145) (35). A pooled analysis of 11 trials involving 31,022 participants estimated actual intake of vitamin D in the treatment groups and compared this with those assigned to control groups, found a nonsignificant reduction in the risk of hip fracture and nonvertebral fracture (60). However, the findings by Bolland *et al.* have been challenged because they excluded about 40% of the high-quality trials on the combination of vitamin D and calcium, and there were concerns about the results biased by the dose of vitamin D. In the re-analysis of the Bolland *et al.* meta-analysis, the recommended dosage of 800–1,000 IU of vitamin D with adherence of more than 50% was included, while large trials of annual vitamin D administration were excluded. The results indicated that supplementation of vitamin D could achieve a significant 14% reduction in total fractures (RR =0.86; 95% CI: 0.75–0.98) (61). Furthermore, calcium and vitamin D supplementation is widely recommended in older people who are housebound or living in residential or nursing homes, where vitamin D deficiency and low dietary calcium intake are common (62). Vitamin D supplementation may also reduce the risk of falling, and hip and nonvertebral fractures, but only with a dose of at least 700 IU/d (47,63). A meta-analysis of vitamin D and fracture risk found that anti-fracture efficacy of vitamin D was reached only in trials that gave 700–800 IU/d vitamin D (63). Another meta-analysis of 29 randomized trials (n=63,897) including subjects aged 50 years or older showed that minimum doses of 1,200 mg of calcium and 800 IU of vitamin D had the best therapeutic effect to prevent fracture and osteoporotic bone loss (64). Double-blind RCTs demonstrated that 800 IU/d vitamin D resulted in the improvement of lower extremity strength and body sway (65,66). Previous meta-analysis and international guidelines for older adults (aged ≥65 years) supported a daily dose of 800–1,000 IU of vitamin D, with lower doses being considered ineffective (60,67). In view of these studies, we recommend daily allowance of 1,200 mg calcium and 800 IU vitamin D in adults over 50 years of age with high risk for vitamin D deficiency. Such a threshold is in line with the majority of current vitamin D recommendations in Europe guidelines (62,68), as well as those of the IOM (18).

Serum 25[OH]D can indicate the effectiveness of vitamin D therapy. The half-life of 25[OH]D is 15–20 days and reaches a plateaus after 3–4 months with a standard dose (800–2,000 IU) supplementation (10). Therefore, serum 25[OH]D should be checked no sooner than 3 months after standard dose treatment. Patients taking high doses of vitamin D above "tolerable upper intake level" should have their serum 25[OH]D monitored (69).

Key recommendations

- Fracture prevention: evaluating vitamin D supplementation alone or in conjunction with calcium for primary fracture prevention in community-dwelling adults should consider the balance of potential harms and benefits (level 1 evidence, weak recommendation).

The use of vitamin D in combination with calcium has increased risk of kidney stones in healthy postmenopausal women. The Women's Health Initiative (WHI) trial found that after intake of vitamin D and calcium, the incidence of kidney stones was increased by 17% among healthy postmenopausal women (40). Furthermore, daily supplementation with calcium plus vitamin D for 7 years was associated with an increase in the number of self-reported urinary tract stones (70). A systematic review including 11 RCTs (n=51,419) demonstrated that supplementation with vitamin D alone or with calcium had no significant effect on all-cause mortality, or incidence of

cardiovascular disease or cancer, but was associated with an increased incidence of kidney stones (42).

Single high dose vitamin D supplementation has significant potential to increase the risk of falls and fractures. One clinical trial found that an annual high dose of vitamin D (500,000 IU) supplementation was associated with higher rates of fall-related outcomes (71). Another recent study revealed that high-dose vitamin D supplementation could decrease radial and tibial BMD, which is harmful for bone health (39). Among older community-dwelling women, annual dose of 500,000 IU of vitamin D significantly increased the risk of falls and fractures in women aged 70 years and older (50). Increased risk of falling was observed in a RCT that administrated monthly dosing with 60,000 IU of vitamin D (51). Therefore, high intermittent doses of vitamin D were an undesirable dosing regimen.

To determine the association between cardiovascular disease and serum levels of 25[OH]D, the large Vitamin D Assessment Study administered 100,000 IU of vitamin D monthly for 3.3 years to adults age 50–84 years and found there was no effect on cardiovascular disease events (72), which was consistent with a collaborative meta-analysis in postmenopausal women (73). Meanwhile, many studies have also found that vitamin D supplementation was not associated with reduced major adverse cardiovascular events (74-76).

However, a large observational study demonstrated that serum levels of 25[OH]D were associated with cardiovascular disease in a reverse J-shaped manner, with the highest risk at lower levels (77). Re-analysis the WHI Calcium/Vitamin D Supplementation Study, calcium supplements with or without vitamin D modestly increase the risk of cardiovascular events, especially myocardial infarction (78). Ultimately, the decision to supplement with vitamin D and calcium for fracture prevention should be made on a case-by-case basis with input from healthcare professionals, taking into account an individual's unique health profile and preferences.

Key recommendations

- Calcium and vitamin D status: adequate calcium intake and vitamin D status are essential before initiating anti-resorptive therapy in patients with vitamin D deficiency (level 2 evidence, weak recommendation).

This is particularly important before the administration of potent anti-resorptive agents, such as intravenous bisphosphonates or denosumab, which can produce hypocalcemia in patients with severe vitamin D deficiency. Therefore, intake of calcium and vitamin D should be adequate upon starting intravenous bisphosphonates and denosumab treatment to minimize the risk of hypocalcemia. In postmenopausal women, the increase in lumbar spine and femoral neck BMD was found to be positively correlated with serum 25[OH]D, which revealed that the degree of success of alendronate therapy for osteoporosis may depend on the vitamin D status of patients (79). A study comparing vitamin D-deficient subjects with vitamin D-replete subjects in people treated with bisphosphonate therapy, found that the adjusted odds ratio for incident fractures was 1.77 (95% CI: 1.20–2.59), which demonstrated that optimal vitamin D repletion may be necessary to maximize the response to anti-resorptive agents in terms of both BMD changes and anti-fracture efficacy (80). Study has shown vitamin D repletion or combination of bisphosphonate and calcitriol to be associated with a significantly higher increase in BMD at both spine and femoral neck sites (81). Vitamin D and calcium are necessary for combination therapy of denosumab which could stop the decrease of calcium, inhibit bone resorption and increase BMD (82). The Incidence and Characterization of inadequate clinical Responders in Osteoporosis (ICARO) Study of 880 patients treated with antiresorptive agents for 2 years found that lack of supplementation of calcium and vitamin D was one of major determinants of poor antiresorptive response (83). However, another RCT with 1,000 postmenopausal women found that BMD response to therapy at the hip or spine was not affected by vitamin D status at baseline (84). It was also reported that vitamin D status at initiation of raloxifene therapy did not affect the subsequent BMD response when co-administered with cholecalciferol and calcium (85). Although conflicting data exists, based on physiological plausibility, RCT data, and little harms associated with supplementation, it is the expert panel opinion that adequate calcium intake and vitamin D status is necessary before use of anti-resorptive drugs in patients with vitamin D deficiency. However, further data concerning the efficacy of vitamin D when used with antiresorptive osteoporosis medication are needed, especially from prospective studies.

Appropriate doses of calcium and vitamin D have been shown to be safe and effective in preventing and treating osteoporotic fractures. This expert consensus extensively reviewed the literature on controversial vitamin D topics to better clarify and summarize the measurement, diagnosis and treatment about vitamin D deficiency in different risk populations, especially in patients with osteoporosis.

However, there are some limitations. The recommendations

of the expert consensus are limited by the fact that there were flaws in most of the studies regarding baseline levels of 25[OH]D, dosage of use, the need for coadministration of calcium, and duration of follow-up. Heterogeneity of populations, study designs, and outcomes is also an issue. The large differences in 25[OH]D assays remain to be further clarified. In addition, we excluded non-English-language articles and studies published only in abstract form, and we were unable to assess publication bias due to the small number of studies.

In conclusion, more rigorous methodologies are needed for future RCT studies to reduce assay variability, determine appropriate thresholds for vitamin D deficiency, and identify the efficacy of screening and subpopulations most likely to benefit.

Discussion

The above consensus was reached through discussion among Chinese experts. To gather more extensive views on this issue, we also invite experts outside of China to comment on several controversial questions included in this consensus

Question 1: what is the evidence regarding the effect of supplemental vitamin D doses on non-skeletal health in the treatment of diabetes, cancer, and cardiovascular diseases?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

Associations with low vitamin D and increased risk for diabetes, cancer and cardiovascular disease have been reported. Interventional trials, however; have been inconclusive. The main issue is to exclude reverse causality which remains undefined for each of these non-skeletal effects.

Diabetes: vitamin D receptors are found on beta islet cells and animal models have demonstrated their activation participates in the regulation of insulin secretion, thus there is a plausible physiological association between vitamin D status and glycaemia.

Prospective epidemiological studies have demonstrated an association between low vitamin D status and prevalent diabetes (type 1 and type 2) and others have shown an increased incidence for the development of type 2 diabetes. An inverse relationship between vitamin D levels and glycated hemoglobin (HbA1c) has also been reported. RCT evidence, however, is lacking to support vitamin D and or calcium supplementation with positive and (predominantly) negative trials.

Expert opinion 2: Dr. Dídac Mauricio

I will not refer hereby to the large number of observational studies showing association of vitamin D with these conditions.

Diabetes: to my knowledge, there are no RCTs on prevention of type 1 diabetes. Regarding type 2 diabetes, there is no solid evidence to support the use of vitamin D supplementation to prevent or treat type 2 diabetes (86,87).

Cancer: there is currently insufficient evidence to support the use of vitamin D supplementation aiming at cancer prevention (88-92). The same applies to treatment of subjects with cancer. However, all these subjects with overt vitamin D deficiency (<50 nmol/L) should receive vitamin D supplementation.

Cardiovascular disease: there is no clear effect of vitamin D supplementation on blood pressure (93).

Systematic reviews and meta-analyses did not show an effect of supplementation on cardiovascular disease and/or its risk factors (94-96).

In general, in all these conditions, the principle of treatment of vitamin D deficiency is warranted.

Expert opinion 3: Dr. Andrei P. Sommer

Answer to questions 1 and 2:

What is very important is to assess vitamin D levels prior to application-not only once but as a regular control. Too much vitamin D can cause severe damage to kidneys, and if levels of vitamin D are too high, additional calcium supplementation is likely to amplify potential damage.

During the last several years, and even now during coronavirus disease 2019 (COVID-19), supplementation became very popular. Unfortunately, some physicians, by following obscure advises, recommend to their patients extremely high doses of vitamin D. They believe that they help their patients, but in fact, the opposite is achieved.

Expert opinion 4: Dr. Joshua I. Barzilay

Using PubMed, the following articles show no effect of vitamin D on heart failure. Vitamin D does not prevent diabetes (86,97-103).

Expert opinion 5: Dr. John C. Gallagher

No evidence from prospective trials as of 2020 December.

Expert opinion 6: Dr. David Benaiges

A pathophysiological link can be found between vitamin D deficiency and the development of diabetes, cancer, and cardiovascular diseases. Despite this, there is insufficient evidence from RCT and meta-analysis on the benefits of vitamin D supplementation on the development of diabetes and cardiovascular disease. Currently, there are two ongoing

RCTs [FIND, International Polycap Study 3 (TIPS-3) and Vitamin D and Type 2 Diabetes Study (D2d)] that will shortly provide more robust evidence on the benefits of vitamin D supplementation (104,105).

Regarding the effect on cancer, some possible benefits have been described. The data of the VITAL study, including 25,871 adults randomized to a daily dose of 2,000 IU or placebo with a mean follow-up of 5.3 years, have been recently published. No differences were detected in the incidence of cardiovascular events or cancer, but death from cancer over time was significantly reduced in the vitamin D group with respect to placebo [hazard ratio (HR) 0.79; 95% CI: 0.63 to 0.99] (106).

Question 2: is it necessary to combine vitamin D supplementation with calcium in postmenopausal osteoporosis women? What are the differences between calcium, vitamin D, and co-administered calcium and vitamin D (CaD)?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

Combination calcium and vitamin D supplements are generally recommended for patients with osteoporosis and most RCT's of bone protective agents (antiresorptives and anabolics) have been co-administered with these agents. Combined treatment can reduce the risk of secondary hyperparathyroidism and have been shown to reduce femoral fractures in older individuals residing in nursing homes (64).

Interestingly, calcium and or vitamin D supplementation was not shown to reduce hip fracture incidence in a meta-analysis of 33 randomized trials involving 51,145, mostly community dwelling, participants (35), with similar findings in an updated meta-analysis in 2019 (37).

Important limitations amongst the various studies were the baseline vitamin D levels were usually >50 nmol/L (only 4 trials had baseline measurements <25 nmol/L), and vitamin D was used as monotherapy, rather than combined with calcium where the effects are thought to be greater.

Conversely, calcium supplementation alone has been associated with an increased risk of myocardial infarction (in secondary analysis) raising controversy regarding optimal dosing (78). Additionally, large doses of vitamin D supplementation have also been associated with an increased risk of falls (50).

Expert opinion 2: Dr. Dídac Mauricio

In postmenopausal women with osteoporosis, the recommendation would be to ensure a total daily calcium intake of 1,200 mg (diet plus supplementation; supplements not higher than 1,000 mg) and 600–800 IU of vitamin D, especially to prevent hip fractures. Most clinicians, including myself, would recommend the combination of calcium and vitamin D to treat these women, not any of them alone.

I have not included here the references of the multiple RCTs regarding this matter. In general, absorption of oral vitamin D is not an issue, and we clinicians usually prefer cholecalciferol. Regarding calcium, we usually use calcium carbonate (with meals) or calcium citrate (in the fasting state). The latter is preferred for subjects receiving some medications (e.g., proton pump inhibitors). If calcium supplement higher than 500 mg daily, we recommend divided doses. In our country, clinicians use both combinations or calcium and vitamin D as separate medications.

Expert opinion 3: Dr. Andrei P. Sommer

See please my answer to Question 1.

Expert opinion 4: Dr. Joshua I. Barzilay

It makes sense that the combination is most effective. Yet all the data above indicates no strong recommendation can be made.

Expert opinion 5: Dr. John C. Gallagher

The target should be vitamin D 800 IU + total calcium intake 1,000 mg/daily. Only add calcium elemental if the diet calcium is low. This applies only to Western populations since the data from Asia is insufficient.

Expert opinion 6: Dr. David Benaiges

As shown in different RCT the maximum benefits of vitamin D treatment on BMD and risk of fractures are obtained with the co-administration of calcium and vitamin D.

Question 3: how can vitamin D deficiency be defined when considering variation in age, ethnicity, body mass index, and geography?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

Vitamin deficiency has the same definition (according to serum levels) for each of these categories (generally <50 nmol/L), but there is recognition that insufficiency/deficiency is more common in older individuals, those of African and Asian extraction and with a higher BMI. Recommendations for daily vitamin D intake vary according to age and level of vitamin D insufficiency/deficiency (e.g., in Australia, 1,000–2,000 IU per day for people with mild vitamin D deficiency, 3,000–5,000 IU) per day for 6–12 weeks in moderate to severe deficiency (or 50,000 IU

once a month for 3–6 months). Obesity is associated with vitamin D sequestration in excess adipose tissue and patients may require higher dose supplementation to reach equivalent serum values.

Racial differences may exist due to natural skin barrier to ultraviolet (UV) irradiation in addition potential polymorphisms in the vitamin D receptor. Whether patients of various ethnic groups 'require' various serum levels of vitamin D for optimal health is unclear, and thus adhering to current standard guidelines remains bets practice.

Expert opinion 2: Dr. Dídac Mauricio

For skeletal health, vitamin D deficiency is best defined as 25[OH]D serum concentrations below 50 nmol/L. For other non-skeletal, conditions the evidence is even lower; thus, the optimal level for these other conditions has not been established.

There is very scarce evidence on specific non-Caucasian ethnic groups (dark skin, black subjects) to define a different level, including the issue of the assays available in different regions. There is also little evidence on the effects of vitamin D or calcium in non-Caucasian subjects; here, it should be underlined that provided that there are substantial ethnic differences in mineral metabolism, we may not apply findings from one race/ethnicity to others.

It must be pointed out that the conditions mentioned in this question are among those that may define higher risk of vitamin D insufficiency/deficiency:

- Older population, linked to another strong risk factor, i.e., institutionalized people;
- Obesity;
- Dark skin linked to ethnicity and geographical variations;
- Limited sun exposure also linked to geographical variation.

The usually accepted concentration for definitions of sufficiency/insufficiency/deficiency would be:

- Sufficiency: 25[OH]D >50 nmol/L;
- Insufficiency: 25[OH]D 30–50 nmol/L;
- Deficiency: 25[OH]D <30 nmol/L.

For fracture prevention in clinical trials, the 25[OH]D as a trial endpoint has been defined between 70 to 100 nmol/L, or even higher. However, this should not be used for definition of sufficiency/deficiency.

Expert opinion 3: Dr. Andrei P. Sommer

There is evidence that vitamin D deficiency could be a major public health burden in many parts of the world, mostly because of sun deprivation. Especially during this lockdown era of psychological ice-age, where older people are suggested to stay in the house, we can envisage a major and unprecedented vitamin D deficiency globally, with severe pathological outcomes (osteoporosis, etc.). A widespread global vitamin D insufficiency is reported in a meta-analysis of cross-sectional study (107).

Expert opinion 4: Dr. Joshua I. Barzilay

Heavy people need more vitamin D than thinner people (108-111).

Expert opinion 5: Dr. John C. Gallagher

In Western countries, adults and children, vitamin D deficiency is serum 25[OH]D <25 nmol/L. Vitamin D insufficiency is serum 25[OH]D 27.5–50 nmol/L.

Expert opinion 6: Dr. David Benaiges

Although it is well known that vitamin D levels can be influenced by age, skin tone, adiposity or the degree of sun exposure depending on the latitude, there are no different cut-off levels of 25[OH]D that define vitamin D deficiency for each of these circumstances. Furthermore, there is still controversy surrounding the optimal serum 25[OH]D concentrations in the general population and therefore, there is no consensus on the levels that define vitamin D deficiency. There is also controversy on the evidence used to define the optimal levels of 25[OH]D, whereas some base these recommendations on the effects on bone health, others use indirect factors such as the vitamin D level that increase parathyroid hormone.

Question 4: should vitamin D supplementation for fracture prevention be continued?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

The effects of vitamin D deficiency and adverse bone outcomes are well established. As discussed above, meta-analysis of vitamin D supplementation for fracture prevention have not shown a benefit (however with notable limitations), with most studies including patients with normal baseline values. Most interventional studies in osteoporosis, however, have combined treatment with calcium and vitamin D and thus it would inherently be a sensible aim to replicate trial conditions in order to achieve maximum results. In general, continuation of vitamin D supplementation aiming for levels of 50–75 nmol/L and normal calcium and PTH values would be consistent with the trial data and recommendations from various international societies. Given the low cost, low side effect profile with standard dosing, continuation would appear reasonable.

Expert opinion 2: Dr. Dídac Mauricio

I understand that this question refers to vitamin D

supplementation once a fracture has occurred. Although there is no evidence of an effect of vitamin D on fracture healing, it is important to ensure proper nutrition measures, including an optimal vitamin D status, provided that the prevalence of vitamin D deficiency is high and that doses as high as 1,000 IU/daily have low potential of toxicity. Additionally, in subjects with previous fractures, it is reasonable to maintain the same preventive measures for future fractures.

Expert opinion 3: Dr. Andrei P. Sommer

According to a recent systematic review and meta-analysis, neither intermittent nor daily dosing with standard doses of vitamin D alone was associated with reduced risk of fracture, but daily supplementation with both vitamin D and calcium was a more promising strategy (37).

Expert opinion 4: Dr. Joshua I. Barzilay

The WHI showed a borderline significant reduction in hip fracture if calcium and vitamin D are taken on average for 7 years (112).

Expert opinion 5: Dr. John C. Gallagher

Yes.

Expert opinion 6: Dr. David Benaiges

I think that it makes no sense to answer this question because it is widely discussed in the fifth key recommendation.

Question 5: what dose of vitamin D is needed to achieve adequate 25[OH]D levels in the management of osteoporosis?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

RCT's have varied in their doses of vitamin D supplementation from 400 IU daily to monthly doses of 50–500,000 IU. Increments in serum values were not always reported consistently. From clinical experience, individuals vary in their response to vitamin D supplementation and incrementation of serum values. Important factors in include absorption concerns [inflammatory bowel disease, coeliac disease, and other gastrointestinal (GIT) conditions], co-administration of certain medications known to affect absorption, distribution, or metabolism [e.g., human immunodeficiency virus (HIV) medications, cholestyramine, anti-epileptics, cyclosporin, rifampicin, oral oestrogens] and polymorphisms in the vitamin D receptor.

Expert opinion 2: Dr. Dídac Mauricio

This is a specific question for osteoporosis subjects in whom it is reasonable to determine serum 25[OH]D concentrations. Thereafter, the decision on the dose of vitamin D should be based on this initial assessment. Cholecalciferol is the preferred choice.

- Individuals with concentrations <30 nmol/L, many clinicians would recommend 50,000 IU/week for 6–8 weeks, and then 800 IU/daily thereafter. However, you may find different approaches as the optimal vitamin D treatment schedule is yet to be established and clinician may opt between daily, weekly, or monthly dosing.
- Subjects with 25[OH]D between 30–50 nmol/L: ensure a mean of 800 IU daily, and monitor and titrate, if necessary, upon follow-up results.
- Individuals with concentrations >50 nmol/L, ensure intake of 600–800 IU daily.

Expert opinion 3: Dr. Andrei P. Sommer

There is no agreement on optimal plasma levels of vitamin D, it is apparent that blood 25[OH]D levels seem to be often below recommended ranges for the general population and are particularly low in some subgroups of the population, e.g., who are housebound (113).

Expert opinion 4: Dr. Joshua I. Barzilay

There is no agreement. I would say 1,000–2,000 IU should be OK based on what you wrote above.

Expert opinion 5: Dr. John C. Gallagher

Daily oral intake of 800 IU is appropriate.

Expert opinion 6: Dr. David Benaiges

In case of vitamin D deficiency, a dose of 50,000 IU/week of vitamin D for 8 weeks should be administered, followed by a maintenance dose of 800 to 1,500 IU day orally.

Question 6: does the intake of vitamin D above current reference intakes lead to toxicity?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

There is data indicating adverse effects from over-supplementation of vitamin D. Hypercalcemia and hypercalciuria can occur and lead to established secondary effects (nausea, dehydration, nephrolithiasis and renal toxicity).

As discussed above, high dose vitamin D supplementation was shown to increase the risk of falls in RCTs of older individuals supplemented with high doses of vitamin D.

Of relevance to this issue, a recent trial has shown that supplementing vitamin D above a dose of 200 IU/d does not prevent falls elderly community-dwelling participants. Indeed, in that study a dose of only up to 4,000 IU/d was associated with worse outcomes such as time to hospitalization or death compared to participants who received 1,000 IU/d. Of note, achieved blood levels of

vitamin D were not measure in this study (49).

Expert opinion 2: Dr. Dídac Mauricio

The toxic dose of vitamin D is not clear. It has been defined that the upper tolerable intake is as much of 4,000 IU of vitamin D a day for healthy adults. However, for those with indication of vitamin D replenishment higher doses may be used. In this case, the use of megadoses should be monitored to avoid toxicity. Toxicity usually occurs because of inadequate use of vitamin D. Finally, circulating vitamin D concentrations above which toxicity is a risk are those >220 nmol/L. Therefore, toxicity should not occur at doses usually recommended for management of osteoporosis.

Expert opinion 3: Dr. Andrei P. Sommer

See please my answer to questions 1 and 2.

Expert opinion 4: Dr. Joshua I. Barzilay

One study that I found suggests very little to no risk of toxicity with current doses of vitamin D, even for doses above those recommended (114).

Expert opinion 5: Dr. John C. Gallagher

Doses >4,000 IU daily cause toxicity. Hypercalcemia will only occur when serum 25[OH]D >300–375 nmol/L. New indicators of toxicity are increased bone loss on 4,000 IU, increased falls and increased fractures.

Expert opinion 6: Dr. David Benaiges

There is no evidence that supplementation with a daily dose clearly higher than the recommended one (4,000 IU) is associated with any adverse effect beyond hypercalciuria when administered alone, or kidney stones when administered in combination with oral calcium (115,116).

Question 7: is it necessary to monitor routine vitamin D supplementation by measurement of serum 25[OH]D?

Expert opinion 1: Drs. Richard J. MacIsaac & Jasna Aleksova

In patients with insufficient vitamin D levels where supplementation is prescribed, evaluation of serum levels would be advised to ensure adequate incrementation. This is particularly important in patients at high risk of vitamin D deficiency and or increased risk of fragility fractures. Patients with GIT disturbances and abnormal absorption may not increment serum levels as expected and alternate routes of administration may be sought. Furthermore, dosing requirements are seasonally affected and thus monitoring levels during the winter months and summer months may indicate differences in dosing requirements to achieve optimal serum levels.

Expert opinion 2: Dr. Dídac Mauricio

Monitoring is not necessary in those without insufficiency or deficiency at doses usually recommended of 600–800 IU/d. It is reasonable to monitor (3 to 4 months period) serum vitamin D in those with levels <50 nmol/L, at least until sufficiency is reached.

Expert opinion 3: Dr. Andrei P. Sommer

Absolutely and continuously (see please my answer to questions 1 and 2).

Expert opinion 4: Dr. Joshua I. Barzilay

I would say that initially check every 3–4 months on a certain dose of vitamin D. Once there is a steady level then once a year is enough.

Expert opinion 5: Dr. John C. Gallagher

No need to monitor serum 25[OH]D since a dose of 800 IU will exceed a serum 25[OH]D of 50 nmol/L. Exceptions are patients with GIT problems-bypass, malabsorption.

Expert opinion 6: Dr. David Benaiges

There is no firm evidence on the benefits of monitoring vitamin D levels in patients taking supplements for osteoporosis. With the recommended doses of vitamin D, monitoring cannot be justified to rule out toxicity and it could only be recommended to rule out infra-therapeutic supplementation.

Conclusions

This is a clinical expert consensus that focuses on who and how to evaluate and treat for vitamin D deficiency, especially in osteoporosis. Our recommendations for the use of vitamin D are listed in Box 1. There are still many questions that urgently need to be addressed in future epidemiologic, clinical, and economic studies.

Box 1 Key recommendations for vitamin D supplementation

- Best measurement method: serum 25[OH]D is identified as the optimal method for assessing vitamin D status (level 1 evidence, strong recommendation)
- Standardization issues: in the absence of standardized 25[OH]D assays, serum 25[OH]D levels from different clinical laboratories may not be comparable (level 2 evidence, strong recommendation)
- At-risk patients: measurement of serum 25[OH]D measurement is recommended for patients at risk of vitamin D deficiency (level 2 evidence, strong recommendation)
- Osteoporosis and serum levels: serum 25[OH]D levels should be maintained at ≥75 nmol/L in patients with osteoporosis (level 1 evidence, strong recommendation)
- Low-risk adults: in adults under 50 with a low risk of vitamin D insufficiency, daily supplementation exceeding 400 IU of vitamin D and 1,000 mg of calcium is not recommended (level 1 evidence, weak recommendation)
- Supplements for older adults: for adults over 50 at high risk of vitamin D deficiency, a minimum daily supplementation of 1,200 mg of calcium and 800 IU of vitamin D is recommended (level 1 evidence, strong recommendation)
- Post-supplementation testing: routine measurement of serum 25[OH]D within 3 months of initiating supplementation is not necessary (level 1 evidence, strong recommendation)
- Fracture prevention: evaluating vitamin D supplementation alone or in conjunction with calcium for primary fracture prevention in community-dwelling adults should consider the balance of potential harms and benefits (level 1 evidence, weak recommendation)
- Calcium and vitamin D status: adequate calcium intake and vitamin D status are essential before initiating anti-resorptive therapy in patients with vitamin D deficiency (level 2 evidence, weak recommendation)

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Footnote

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References

1. Kanis JA, Melton LJ 3rd, Christiansen C, et al. The diagnosis of osteoporosis. J Bone Miner Res 1994;9:1137-41.
2. Si L, Winzenberg TM, Chen M, et al. Residual lifetime and 10 year absolute risks of osteoporotic fractures in Chinese men and women. Curr Med Res Opin 2015;31:1149-56.
3. Rizzoli R, Biver E, Brennan-Speranza TC. Nutritional intake and bone health. Lancet Diabetes Endocrinol 2021;9:606-21.

4. Aloia J, Bojadzievski T, Yusupov E, et al. The relative influence of calcium intake and vitamin D status on serum parathyroid hormone and bone turnover biomarkers in a double-blind, placebo-controlled parallel group, longitudinal factorial design. J Clin Endocrinol Metab 2010;95:3216-24.
5. Weaver CM, Alexander DD, Boushey CJ, et al. Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int 2016;27:367-76.
6. Kanis JA, Cooper C, Rizzoli R, et al. Identification and management of patients at increased risk of osteoporotic fracture: outcomes of an ESCEO expert consensus meeting. Osteoporos Int 2017;28:2023-34.
7. Gallagher JC, Rosen CJ. Vitamin D: 100 years of discoveries, yet controversy continues. Lancet Diabetes Endocrinol 2023;11:362-74.
8. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. BMJ 2008;336:1049-51.
9. Piotrowska A, Wierzbicka J, Żmijewski MA. Vitamin D in the skin physiology and pathology. Acta Biochim Pol 2016;63:17-29.
10. Jones G. Pharmacokinetics of vitamin D toxicity. Am J Clin Nutr 2008;88:582S-6S.
11. Prentice A. Vitamin D deficiency: a global perspective. Nutr Rev 2008;66:S153-64.
12. Herrmann M. Assessing vitamin D metabolism - four decades of experience. Clin Chem Lab Med 2023;61:880-94.
13. Wallace AM, Gibson S, de la Hunty A, et al. Measurement of 25-hydroxyvitamin D in the clinical laboratory: current procedures, performance characteristics and limitations. Steroids 2010;75:477-88.
14. Janoušek J, Pilařová V, Macáková K, et al. Vitamin D: sources, physiological role, biokinetics, deficiency, therapeutic use, toxicity, and overview of analytical methods for detection of vitamin D and its metabolites. Crit Rev Clin Lab Sci 2022;59:517-54.
15. Binkley N, Krueger D, Cowgill CS, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab 2004;89:3152-7.
16. Giustina A, Bilezikian JP, Adler RA, et al. Consensus Statement on Vitamin D Status Assessment and Supplementation: Whys, Whens, and Hows. Endocr Rev 2024;45:625-54.
17. Lips P. Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications. Endocr Rev 2001;22:477-501.
18. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. J Clin Endocrinol Metab 2011;96:53-8.
19. Hilger J, Friedel A, Herr R, et al. A systematic review of vitamin D status in populations worldwide. Br J Nutr 2014;111:23-45.
20. Souberbielle JC, Courbebaisse M, Cormier C, et al. When should we measure vitamin D concentration in clinical practice? Scand J Clin Lab Invest Suppl 2012;243:129-35.
21. Charoenngam N, Shirvani A, Holick MF. Vitamin D for skeletal and non-skeletal health: What we should know. J Clin Orthop Trauma 2019;10:1082-93.
22. Binkley N, Wiebe D. Clinical controversies in vitamin D: 25(OH)D measurement, target concentration, and supplementation. J Clin Densitom 2013;16:402-8.
23. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology Clinical Practice Guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. Endocr Pract 2020;26:1-46.
24. Hanley DA, Cranney A, Jones G, et al. Vitamin D in adult health and disease: a review and guideline statement from Osteoporosis Canada. CMAJ 2010;182:E610-8.
25. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911-30.
26. Aspray TJ, Bowring C, Fraser W, et al. National Osteoporosis Society vitamin D guideline summary. Age Ageing 2014;43:592-5.
27. Lips P, Cashman KD, Lamberg-Allardt C, et al. Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: a position statement of the European Calcified Tissue Society. Eur J Endocrinol 2019;180:P23-54.
28. Bischoff-Ferrari HA, Giovannucci E, Willett WC, et al. Estimation of optimal serum concentrations of 25-hydroxyvitamin D for multiple health outcomes. Am J Clin Nutr 2006;84:18-28.
29. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. J Clin Endocrinol Metab 2005;90:3215-24.
30. Bischoff-Ferrari HA, Shao A, Dawson-Hughes B, et al. Benefit-risk assessment of vitamin D supplementation. Osteoporos Int 2010;21:1121-32.
31. Heaney RP, Dowell MS, Hale CA, et al. Calcium

absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr 2003;22:142-6.
32. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266-81.
33. Heaney RP. Functional indices of vitamin D status and ramifications of vitamin D deficiency. Am J Clin Nutr 2004;80:1706S-9S.
34. Moyer VA; U.S. Vitamin D and calcium supplementation to prevent fractures in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2013;158:691-6.
35. Zhao JG, Zeng XT, Wang J, et al. Association Between Calcium or Vitamin D Supplementation and Fracture Incidence in Community-Dwelling Older Adults: A Systematic Review and Meta-analysis. JAMA 2017;318:2466-82.
36. Bolland MJ, Grey A, Gamble GD, et al. The effect of vitamin D supplementation on skeletal, vascular, or cancer outcomes: a trial sequential meta-analysis. Lancet Diabetes Endocrinol 2014;2:307-20.
37. Yao P, Bennett D, Mafham M, et al. Vitamin D and Calcium for the Prevention of Fracture: A Systematic Review and Meta-analysis. JAMA Netw Open 2019;2:e1917789.
38. Méndez-Sánchez L, Clark P, Winzenberg TM, et al. Calcium and vitamin D for increasing bone mineral density in premenopausal women. Cochrane Database Syst Rev 2023;1:CD012664.
39. Burt LA, Billington EO, Rose MS, et al. Effect of High-Dose Vitamin D Supplementation on Volumetric Bone Density and Bone Strength: A Randomized Clinical Trial. JAMA 2019;322:736-45.
40. Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 2006;354:669-83.
41. Emerging Risk Factors Collaboration/EPIC-CVD/ Vitamin D Studies Collaboration. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. Lancet Diabetes Endocrinol 2024;12:e2-e11.
42. Kahwati LC, Weber RP, Pan H, et al. Vitamin D, Calcium, or Combined Supplementation for the Primary Prevention of Fractures in Community-Dwelling Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2018;319:1600-12.
43. Grant AM, Avenell A, Campbell MK, et al. Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. Lancet 2005;365:1621-8.
44. LeBoff MS, Chou SH, Ratliff KA, et al. Supplemental Vitamin D and Incident Fractures in Midlife and Older Adults. N Engl J Med 2022;387:299-309.
45. Bischoff HA, Stähelin HB, Dick W, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res 2003;18:343-51.
46. Flicker L, MacInnis RJ, Stein MS, et al. Should older people in residential care receive vitamin D to prevent falls? Results of a randomized trial. J Am Geriatr Soc 2005;53:1881-8.
47. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials. BMJ 2009;339:b3692.
48. Bischoff-Ferrari HA, Dawson-Hughes B, Willett WC, et al. Effect of Vitamin D on falls: a meta-analysis. JAMA 2004;291:1999-2006.
49. Appel LJ, Michos ED, Mitchell CM, et al. The Effects of Four Doses of Vitamin D Supplements on Falls in Older Adults : A Response-Adaptive, Randomized Clinical Trial. Ann Intern Med 2021;174:145-56.
50. Sanders KM, Stuart AL, Williamson EJ, et al. Annual high-dose oral vitamin D and falls and fractures in older women: a randomized controlled trial. JAMA 2010;303:1815-22.
51. Bischoff-Ferrari HA, Dawson-Hughes B, Orav EJ, et al. Monthly High-Dose Vitamin D Treatment for the Prevention of Functional Decline: A Randomized Clinical Trial. JAMA Intern Med 2016;176:175-83.
52. Tang O, Juraschek SP, Appel LJ. Design Features of Randomized Clinical Trials of Vitamin D and Falls: A Systematic Review. Nutrients 2018;10:964.
53. US Preventive Services Task Force; Grossman DC, Curry SJ, et al. Interventions to Prevent Falls in Community-Dwelling Older Adults: US Preventive Services Task Force Recommendation Statement. JAMA 2018;319:1696-704.
54. Chapuy MC, Arlot ME, Duboeuf F, et al. Vitamin D3 and calcium to prevent hip fractures in elderly women. N Engl J Med 1992;327:1637-42.
55. Chapuy MC, Pamphile R, Paris E, et al. Combined calcium and vitamin D3 supplementation in elderly women: confirmation of reversal of secondary hyperparathyroidism and hip fracture risk: the Decalyos II study. Osteoporos Int 2002;13:257-64.
56. Trivedi DP, Doll R, Khaw KT. Effect of four monthly

oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003;326:469.
57. Larsen ER, Mosekilde L, Foldspang A. Vitamin D and calcium supplementation prevents osteoporotic fractures in elderly community dwelling residents: a pragmatic population-based 3-year intervention study. J Bone Miner Res 2004;19:370-8.
58. Porthouse J, Cockayne S, King C, et al. Randomised controlled trial of calcium and supplementation with cholecalciferol (vitamin D3) for prevention of fractures in primary care. BMJ 2005;330:1003.
59. Bolland MJ, Grey A, Avenell A. Effects of vitamin D supplementation on musculoskeletal health: a systematic review, meta-analysis, and trial sequential analysis. Lancet Diabetes Endocrinol 2018;6:847-58.
60. Bischoff-Ferrari HA, Willett WC, Orav EJ, et al. A pooled analysis of vitamin D dose requirements for fracture prevention. N Engl J Med 2012;367:40-9.
61. Bischoff-Ferrari HA, Orav EJ, Abderhalden L, et al. Vitamin D supplementation and musculoskeletal health. Lancet Diabetes Endocrinol 2019;7:85.
62. Compston J, Bowring C, Cooper A, et al. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas 2013;75:392-6.
63. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 2005;293:2257-64.
64. Tang BM, Eslick GD, Nowson C, et al. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet 2007;370:657-66.
65. Pfeifer M, Begerow B, Minne HW, et al. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. J Bone Miner Res 2000;15:1113-8.
66. Pfeifer M, Begerow B, Minne HW, et al. Effects of a long-term vitamin D and calcium supplementation on falls and parameters of muscle function in community-dwelling older individuals. Osteoporos Int 2009;20:315-22.
67. Compston J, Cooper A, Cooper C, et al. Guidelines for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. Maturitas 2009;62:105-8.
68. Kanis JA, Cooper C, Rizzoli R, et al. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int 2019;30:3-44.
69. Heaney RP, Davies KM, Chen TC, et al. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. Am J Clin Nutr 2003;77:204-10.
70. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, et al. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. Am J Clin Nutr 2011;94:270-7.
71. Guirguis-Blake JM, Michael YL, Perdue LA, et al. Interventions to Prevent Falls in Older Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2018;319:1705-16.
72. Scragg R, Stewart AW, Waayer D, et al. Effect of Monthly High-Dose Vitamin D Supplementation on Cardiovascular Disease in the Vitamin D Assessment Study : A Randomized Clinical Trial. JAMA Cardiol 2017;2:608-16.
73. Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. J Bone Miner Res 2015;30:165-75.
74. Barbarawi M, Kheiri B, Zayed Y, et al. Vitamin D Supplementation and Cardiovascular Disease Risks in More Than 83 000 Individuals in 21 Randomized Clinical Trials: A Meta-analysis. JAMA Cardiol 2019;4:765-76.
75. O'Connor EA, Evans CV, Ivlev I, et al. Vitamin and Mineral Supplements for the Primary Prevention of Cardiovascular Disease and Cancer: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2022;327:2334-47.
76. Kahwati LC, LeBlanc E, Weber RP, et al. Screening for Vitamin D Deficiency in Adults: Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA 2021;325:1443-63.
77. Durup D, Jørgensen HL, Christensen J, et al. A Reverse J-Shaped Association Between Serum 25-Hydroxyvitamin D and Cardiovascular Disease Mortality: The CopD Study. J Clin Endocrinol Metab 2015;100:2339-46.
78. Bolland MJ, Grey A, Avenell A, et al. Calcium supplements with or without vitamin D and risk of cardiovascular events: reanalysis of the Women's Health Initiative limited access dataset and meta-analysis. BMJ 2011;342:d2040.
79. Roux C, Binkley N, Boonen S, et al. Vitamin D status and bone mineral density changes during alendronate treatment in postmenopausal osteoporosis. Calcif Tissue Int 2014;94:153-7.

80. Adami S, Giannini S, Bianchi G, et al. Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 2009;20:239-44.
81. Deane A, Constancio L, Fogelman I, et al. The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation following long-term use in post-menopausal osteoporosis. BMC Musculoskelet Disord 2007;8:3.
82. Nakamura Y, Suzuki T, Kamimura M, et al. Vitamin D and calcium are required at the time of denosumab administration during osteoporosis treatment. Bone Res 2017;5:17021.
83. Adami S, Isaia G, Luisetto G, et al. Fracture incidence and characterization in patients on osteoporosis treatment: the ICARO study. J Bone Miner Res 2006;21:1565-70.
84. Antoniucci DM, Vittinghoff E, Palermo L, et al. Vitamin D insufficiency does not affect response of bone mineral density to alendronate. Osteoporos Int 2009;20:1259-66.
85. Antoniucci DM, Vittinghoff E, Blackwell T, et al. Vitamin D insufficiency does not affect bone mineral density response to raloxifene. J Clin Endocrinol Metab 2005;90:4566-72.
86. Pittas AG, Dawson-Hughes B, Sheehan P, et al. Vitamin D Supplementation and Prevention of Type 2 Diabetes. N Engl J Med 2019;381:520-30.
87. Krul-Poel YH, Ter Wee MM, Lips P, et al. MANAGEMENT OF ENDOCRINE DISEASE: The effect of vitamin D supplementation on glycaemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Eur J Endocrinol 2017;176:R1-R14.
88. Bjelakovic G, Gluud LL, Nikolova D, et al. Vitamin D supplementation for prevention of cancer in adults. Cochrane Database Syst Rev 2014;2014:CD007469.
89. Lappe J, Watson P, Travers-Gustafson D, et al. Effect of Vitamin D and Calcium Supplementation on Cancer Incidence in Older Women: A Randomized Clinical Trial. JAMA 2017;317:1234-43.
90. Manson JE, Cook NR, Lee IM, et al. Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease. N Engl J Med 2019;380:33-44.
91. Scragg R, Khaw KT, Toop L, et al. Monthly High-Dose Vitamin D Supplementation and Cancer Risk: A Post Hoc Analysis of the Vitamin D Assessment Randomized Clinical Trial. JAMA Oncol 2018;4:e182178.
92. Keum N, Lee DH, Greenwood DC, et al. Vitamin D supplementation and total cancer incidence and mortality: a meta-analysis of randomized controlled trials. Ann Oncol 2019;30:733-43.
93. Beveridge LA, Struthers AD, Khan F, et al. Effect of Vitamin D Supplementation on Blood Pressure: A Systematic Review and Meta-analysis Incorporating Individual Patient Data. JAMA Intern Med 2015;175:745-54.
94. Pittas AG, Chung M, Trikalinos T, et al. Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med 2010;152:307-14.
95. Elamin MB, Abu Elnour NO, Elamin KB, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011;96:1931-42.
96. Ford JA, MacLennan GS, Avenell A, et al. Cardiovascular disease and vitamin D supplementation: trial analysis, systematic review, and meta-analysis. Am J Clin Nutr 2014;100:746-55.
97. Busa V, Dardeir A, Marudhai S, et al. Role of Vitamin D Supplementation in Heart Failure Patients With Vitamin D Deficiency and Its Effects on Clinical Outcomes: A Literature Review. Cureus 2020;12:e10840.
98. Zittermann A, Ernst JB, Prokop S, et al. A 3 year post-intervention follow-up on mortality in advanced heart failure (EVITA vitamin D supplementation trial). ESC Heart Fail 2020;7:3754-61.
99. Hopper I, Connell C, Briffa T, et al. Nutraceuticals in Patients With Heart Failure: A Systematic Review. J Card Fail 2020;26:166-79.
100. Zittermann A, Ernst JB, Prokop S, et al. Vitamin D supplementation of 4000 IU daily and cardiac function in patients with advanced heart failure: The EVITA trial. Int J Cardiol 2019;280:117-23.
101. Zittermann A, Ernst JB, Prokop S, et al. Daily Supplementation with 4000 IU Vitamin D3 for Three Years Does Not Modify Cardiovascular Risk Markers in Patients with Advanced Heart Failure: The Effect of Vitamin D on Mortality in Heart Failure Trial. Ann Nutr Metab 2019;74:62-8.
102. Zheng JS, Luan J, Sofianopoulou E, et al. The association between circulating 25-hydroxyvitamin D metabolites and type 2 diabetes in European populations: A meta-analysis and Mendelian randomisation analysis. PLoS Med 2020;17:e1003394.
103. Cangoz S, Chang YY, Chempakaseril SJ, et al. Vitamin D and type 2 diabetes mellitus. J Clin Pharm Ther 2013;38:81-4.
104. Joseph P, Pais P, Dans AL, et al. The International Polycap Study-3 (TIPS-3): Design, baseline characteristics and challenges in conduct. Am Heart J 2018;206:72-9.
105. Pittas AG, Dawson-Hughes B, Sheehan PR, et al.

Rationale and design of the Vitamin D and Type 2 Diabetes (D2d) study: a diabetes prevention trial. Diabetes Care 2014;37:3227-34.
106. Manson JE, Bassuk SS, Lee IM, et al. The VITamin D and OmegA-3 TriaL (VITAL): rationale and design of a large randomized controlled trial of vitamin D and marine omega-3 fatty acid supplements for the primary prevention of cancer and cardiovascular disease. Contemp Clin Trials 2012;33:159-71.
107. Hagenau T, Vest R, Gissel TN, et al. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009;20:133-40.
108. de Oliveira LF, de Azevedo LG, da Mota Santana J, et al. Obesity and overweight decreases the effect of vitamin D supplementation in adults: systematic review and meta-analysis of randomized controlled trials. Rev Endocr Metab Disord 2020;21:67-76.
109. Bassatne A, Chakhtoura M, Saad R, et al. Vitamin D supplementation in obesity and during weight loss: A review of randomized controlled trials. Metabolism 2019;92:193-205.
110. Imga NN, Berker D, Can B, et al. The effects of three regimens of cholecalciferol (vitamin D(3)) supplementation on vitamin D deficiency in non-obese and obese females. Arch Med Sci Atheroscler Dis 2018;3:e60-7.
111. Dhaliwal R, Mikhail M, Feuerman M, et al. The vitamin d dose response in obesity. Endocr Pract 2014;20:1258-64.
112. Prentice RL, Pettinger MB, Jackson RD, et al. Health risks and benefits from calcium and vitamin D supplementation: Women's Health Initiative clinical trial and cohort study. Osteoporos Int 2013;24:567-80.
113. Spiro A, Buttriss JL. Vitamin D: An overview of vitamin D status and intake in Europe. Nutr Bull 2014;39:322-50.
114. Kimball SM, Mirhosseini N, Holick MF. Evaluation of vitamin D3 intakes up to 15,000 international units/day and serum 25-hydroxyvitamin D concentrations up to 300 nmol/L on calcium metabolism in a community setting. Dermatoendocrinol 2017;9:e1300213.
115. Radford LT, Bolland MJ, Mason B, et al. The Auckland calcium study: 5-year post-trial follow-up. Osteoporos Int 2014;25:297-304.
116. Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. The National Academies Collection: Reports funded by National Institutes of Health. In: Ross AC, Taylor CL, Yaktine AL, et al. editors. Dietary Reference Intakes for Calcium and Vitamin D: National Academies Press (US); 2011.

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