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An Update on Vitamin D for Clinicians

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Abstract

Purpose of review—The clinical benefits of vitamin D therapy have received substantial attention over the past decade. Recently, several trials looked to clarify the optimal vitamin D dose or serum level needed to promote human health. The purpose of this review is to highlight selected studies published since January 2015.

Recent findings—Several recent trials challenge whether serum vitamin D levels ≥30 ng/mL promote human health. In postmenopausal women with 25(OH)D levels 21±3 ng/mL, high-dose vitamin D for one year increased calcium absorption by 1%, without changes in bone mineral density, physical function, or falls when compared to low-dose vitamin D and placebo. High-dose vitamin D increased risk of falling, in 200 adults 78±5 years old with baseline 25(OH)D levels of ~19±9 ng/mL. High-dose vitamin D in adults increased the number and duration of upper respiratory tract infections, compared to placebo. Asthma patients achieving 25(OH)D levels >30 ng/mL during a trial experienced more respiratory infections than those not achieving such levels.

Summary—Recent studies are congruent with the Institute of Medicine's conclusion that humans are vitamin D replete when their serum 25(OH)D levels are ≥20 ng/mL. Higher levels seem to promote falls and respiratory infections.

Keywords

bone mineral density; colon cancer; falls; respiratory infections; review; vitamin D

Introduction

Vitamin D is a steroid hormone called the "sunshine vitamin," because skin exposure to ultraviolet light coverts provitamin-7-dehydrocholesterol into vitamin D. NHANES 2000–2004 [1] documented that ~75% of adults had vitamin D insufficiency, defined as a serum 25(OH)D levels <30 ng/mL [2]. The epidemic was attributed to a transition from outdoor to indoor work. Blacks and Hispanics had lower 25(OH)D levels than Whites [1], a phenomenon attributed to greater skin melanin causing lower cutaneous vitamin D synthesis.

Measurement of Vitamin D

Vitamin D binding protein (VDBP) transports vitamin D metabolites in serum [3]. Up to 90% of vitamin D is bound to VDBP, ~10% binds to albumin and <1% circulates in the free

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form. The free and albumin-bound vitamin D are considered bioavailable. Thus, VDBP levels could be used to estimate bioavailable vitamin D. VDBP has three major isoforms and two glycosylation patterns, resulting in six configurations that differ in binding affinity and differ by race.

In 2013, researchers reported that racial differences in VDBP explained why Blacks had apparently lower 25(OH)D levels, yet higher bone mineral density, than Whites [4]. In that study, which used a monoclonal assay to measure VDBP, Blacks had lower VDBP levels than Whites. When researchers calculated bioavailable 25(OH)D levels based on VDBP levels, they found that 25(OH)D levels were similar across races. However, a 2016 study [3] concluded that the assay used to measure VDBP in the 2013 study was biased, leading to incorrect conclusions about racial differences in bioactive vitamin D levels.

Three methods of measuring VDBP exist. A recently developed liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay [5] is considered the gold-standard assay. The second and third methods measure VDBP using monoclonal and polyclonal ELISA. Denberg et al. [3] concluded that VDBP levels within individuals vary by the assay utilized. They used all three assays to measure VDBP in 125 older adults with chronic kidney disease. Blacks had lower VDBP using the monoclonal ELISA, compared to the other two methods of measurement. VDBP did not vary by genotype or race when using LC-MS/MS. Therefore, bound and bioactive vitamin D levels were significantly lower in Blacks than Whites. The polyclonal ELISA showed acceptable performance characteristics compared to the LC-MS/MS, representing a less expensive yet accurate method by which to measure VDBP.

For now, clinicians should continue to use serum 25(OH)D levels to assess vitamin D status in patients, regardless of their race. However, the polyclonal ELISA shows potential for future measurement of bioactive vitamin D, in selected circumstances.

Vitamin D supplements during pregnancy

Interventions that increase peak bone mass could potentially reduce an individual's lifetime risk of osteoporosis. Indeed, the skeletal benefits of vitamin D likely have greatest impact in the rapidly growing skeleton. Researchers [6] theorized that vitamin D supplementation during pregnancy might increase neonatal bone mineral content (BMC), and designed a study to test this hypothesis.

The Maternal Vitamin D Osteoporosis Study (MAVIDOS) [6] was a randomized, double-blind, placebo-controlled trial conducted at three United Kingdom sites. Women ≥19 years old with a singleton pregnancy and a serum 25(OH)D level of 10–40 ng/mL were randomized, before 17 weeks' gestation, to placebo or vitamin D_3 1,000 IU once a day until delivery. The primary outcome was neonatal whole body BMC within two weeks of birth.

A total of 1,134 women ages 31 ± 5 years old were randomized into the trial, but 298 (26%) withdrew before measurement of their child's BMC. Additionally, only 737 of 836 (88%) of infants had valid measures of BMC, due to motion artifact. In completers (65% of randomized pregnancies), there was no difference in neonatal BMC between treatment arms.

However, in a planned post-hoc analysis of babes born in winter months (December to February), the vitamin D_3 arm (n=74) had higher whole body BMC than the placebo arm (n=64, 5.5 grams, p=0.004).

In summary, the study did not support widespread use of vitamin D_3 for pregnant women, in order to increase BMC of their infants. However, BMC was approximately 9% higher in babes born in winter. Researchers plan to follow all children in the trial, to evaluate whether such skeletal benefits persist with time.

Optimal serum vitamin D levels in postmenopausal women

Experts have hotly debated the optimal serum vitamin D level needed for human health. The Institute of Medicine [7] concluded that virtually all people were vitamin D replete, with serum 25(OH)D levels ≥20 ng/mL. By contrast, other experts argued that serum levels ≥30 ng/mL indicated optimal status [2]. Such disagreement was possible because prior trials compared vitamin D and calcium to placebo, did not recruit subjects based on initial vitamin D levels, or did not target a high vitamin D level during the trial. Researchers [8] therefore designed a study to directly address ongoing controversy about the optimal serum vitamin D level needed to support musculoskeletal health.

Researchers recruited 230 postmenopausal women with 25(OH)D levels of 14–27 ng/mL into a one-year trial [8]. One-third of subjects received placebo, one-third received low dose vitamin D_3 (800 IU/day) and one-third received a high-dose vitamin D_3 regimen chosen to quickly raise and maintain 25(OH)D levels >30 ng/mL throughout the trial. Because the primary effect of vitamin D is to promote active intestinal calcium absorption, the primary study outcome was the change in calcium absorption, measured using the gold-standard dose-corrected ratio of two stable isotopes in a 24-hour urine collection [9]. Other study outcomes included changes in spine, hip and total body bone mineral density (BMD), Timed-Up-and-Go and 5-Sit-to-Stand test times, muscle mass and falls. Attrition was very low as 226 women (96%) completed the study. Additionally, adherence to study pills approached 100%.

Subjects randomized to high-dose vitamin D experienced a small, but statistically significant increase (1%) in intestinal calcium absorption, compared to subjects randomized to low-dose vitamin D and placebo. However, the small increase in calcium absorption did not translate into changes in BMD, functional status, muscle mass or falls. Study limitations included exclusion of women with osteoporosis, recruitment of predominantly White subjects and short study duration. Although short in duration, based on another trial [10], the study had 90% power to detect a 1% change in mean total hip BMD between the three arms. Thus, the trial did not support the wide-spread clinical practice of correcting serum 25(OH)D to levels ≥30 ng/mL.

Optimal vitamin D dose needed to reduce falls and preserve muscle function

Vitamin D deficiency causes muscle weakness [11]. Several studies reported that vitamin D therapy reduces the risk of falling, with a notable exception [12] in which once-yearly high-dose vitamin D increased the risk of falls. Most researchers have detected vitamin D receptors in muscle cells, providing biologic plausibility that vitamin D favorably affects muscle strength, reducing falls. However, researchers continue to debate the vitamin D dose needed to promote muscle health.

A recent trial [13] directly addressed ongoing controversy about the optimal vitamin D dose needed to reduce risk of falling. Researchers recruited ambulatory adults ≥70 years of age who fell at least once yearly into a clinical trial. Subjects were not recruited based on initial serum 25(OH)D levels, although those taking >800 IU vitamin D daily were excluded. Two-hundred subjects with baseline 25(OH)D levels of ~19±9 ng/mL were randomized to one of three monthly vitamin D regimes for one year: 24,000 IU vitamin D_3, 60,000 IU vitamin D_3, or 24,000 IU vitamin D_2 plus 24,000 IU vitamin D_3. Primary study outcomes were the Short Physical Performance Battery Score and the 25(OH)D level achieved by treatment arm. The secondary outcome was the number of falls, determined by diaries and monthly phone calls.

While 25(OH)D levels increased to the greatest degree in the 48,000 IU/month arm, there was no difference between treatment arms in the Short Physical Performance Battery Score [13]. Moreover, falls were most frequent among subjects randomized to the highest vitamin D dose. The incidence of falls was 48%, 66% and 70% in the 24,000 IU, 60,000 IU, and the 24,000 IU vitamin D_2 plus 24,000 IU vitamin D_3 arms, respectively ($p=0.048$). In summary, higher vitamin D doses given once monthly increased the risk of falling, similar to results of an earlier placebo-controlled trial in which 500,000 IU of vitamin D intramuscular once yearly increased falls [12].

In a second trial [14] researchers studied the effect of vitamin D therapy on muscle strength and lean mass. Brazilian postmenopausal women 50 to 65 years old with ≥1 yearly fall were eligible for the trial. Women with osteopenia, and/or impaired balance, cognition, vision, hearing, and/or use of bone active medications were excluded. Women were randomized to vitamin D_3 1,000 IU or placebo once daily for nine months. The study was powered to detect differences in falls. Other outcomes included changes in handgrip strength, the chair rising test score and lean body mass by whole body BMD.

A total of 160 women ages 59 ± 7 years old with initial 25(OH)D levels 15±8 ng/mL were randomized into the trial [14]. Falls were not reported. The 9-month change in lean mass and handgrip strength were no different between treatment arms, but the chair rising test did improve with vitamin D. Women randomized to vitamin D could perform 3 additional chair rises at 9 months (13 ± 6 chair rises at baseline, 16 ± 5 at nine months, $p<0.001$). By contrast, placebo-treated women experienced no change in chair rises (13 ± 6 at baseline, 13 ± 5 at 9 months, $p=0.773$).

The trials described call for caution when prescribing high-dose vitamin D to improve muscle function or falls, particularly as intermittent bolus doses. It's possible that lower vitamin D levels in the second trial explain improved chair rise tests in that study. Differing bioavailable vitamin D levels by race is a second potential explanation.

Optimal vitamin D dose needed to reduce respiratory infections

Cells of the immune system express the vitamin D receptor [15]. In observational studies, higher vitamin D levels are associated with lower rates of respiratory infection [16]. Thus, investigators [17] hypothesized that vitamin D therapy would reduce the rate of acute respiratory infections (ARI).

Researchers recruited residents living in sheltered housing, and their caregivers, into a one-year clinical trial [17]. Subjects with dementia, asthma, emphysema and those taking >400 IU vitamin D daily were excluded. Vitamin D status was assessed at baseline, but a predefined serum vitamin D level was not required for inclusion.

Residents, and their caregivers within the same housing unit, were randomized together into active or placebo therapy. The housing unit approach to randomization was a key element of the trial, as an infection in one member would likely spread to others sharing the same place. In the high-dose vitamin D arm, residents received vitamin D_3 96,000 IU every two months plus 400 IU vitamin D_3 daily; their caregivers received vitamin D_3 120,000 IU vitamin D3 every two months. In the placebo arm, residents received placebo pills every two months plus 400 IU vitamin D_3 daily; their caregivers received placebo pills every two months. The primary study outcome was time to first ARI; secondary outcomes included rates and duration of upper and lower respiratory tract infections. Researchers used the Jackson criteria to diagnose a cold [18] and cough, fever and myalgia to diagnose influenza; together these events reflected incident upper respiratory infections (URI). The Macfarlane symptom score [19] was used to define lower respiratory tract infections (LRI). ARI included all upper and lower respiratory infections. In a subset of subjects, researchers tested nasopharyngeal secretions for ten common viral infections.

A total of 240 adults were randomized into the one-year trial [17]. Baseline serum 25(OH)D levels were 17±9 and 18±9 ng/mL in the active and placebo arms, respectively, and only 8% of subjects had levels ≥30 ng/mL. Time to first ARI was no different between treatment arms (adjusted hazard ratio 1.18, 95% confidence interval 0.84 to 1.74). However, the high-dose vitamin D arm experienced an increased risk (hazard ratio 1.48, 95% CI 1.02 to 2.16) and greater duration (median of 7 versus 5 days, p=0.005) of URI than the placebo arm.

In another study [20], researchers investigated the effect of vitamin D therapy on risk of URI in adults with mild to moderate asthma and initial 25(OH)D levels <30 ng/mL. The study was a planned post-hoc analysis of the Vitamin D Add-On Therapy Enhances Corticosteroid Responsiveness or "VIDA" trial designed to assess whether vitamin D affected asthma control. Researchers randomized 203 subjects to placebo or vitamin D_3 100,000 IU on day one then 4,000 IU daily for 28 weeks. For the post-hoc analysis, outcomes included the rate

and severity of URI, defined using the validated Wisconsin Upper Respiratory Symptom Survey [21].

A total of 408 adults were randomized into the trial [20]. Baseline 25(OH)D levels were 18 and 20 ng/mL in the vitamin D and placebo arms, respectively. Half of subjects (n=203) experienced ≥1 URI. The cold severity score, judged using a validated scale, was no different between treatment arms. Likewise, rates of infection were no different between treatment arms (1.24 versus 1.48 colds per person-year in the placebo and vitamin D arms, p=0.15). Of concern, Blacks randomized to vitamin D_3 experienced more URI than those assigned to placebo (rate ratio 1.7, 95% CI 1.1 to 2.7). Moreover, subjects achieving 25(OH)D levels >30 ng/mL at 12 weeks experienced more infections than those not achieving such levels (rate 1.4, 95% CI 1.1 to 1.7).

Results contrast with another multi-center trial [22] in which 430 Japanese children aged 6–15 years old were randomized to vitamin D 600 IU twice daily or matching placebo, taken from December 2008 to March 2009. Children randomized to vitamin D experienced lower risk of influenza A (RR 0.58, 95% CI 0.34, 0.99) but no lower risk of influenza B, pneumonia, gastroenteritis or hospitalization. Study limitations included high attrition (22%), high co-morbidity (27%), self-reported adherence and no measurement of serum 25(OH)D.

In summary, the two trials [17,20] in adults conclude that vitamin D does not reduce ARI. Instead, high-dose vitamin D and/or higher serum levels were linked to higher rates and increasing severity of URI. By contrast, wintertime vitamin D therapy seemed to reduce risk of influenza A in children. These contradictory results call for further research, before routine prescription of vitamin D to reduce infections.

Vitamin D and risk of colorectal adenomas

Observational studies have linked higher 25(OH)D levels to lower risk of colon cancer. Researchers therefore hypothesized that vitamin D therapy would reduce the risk of newly identified colon adenomas [23].

Researchers recruited subjects 45–75 years old with a recently detected colon adenoma detected by colonoscopy. Individuals with hyperparathyroidism, nephrolithiasis, osteoporosis, renal disease, abnormal serum calcium or 25(OH)D levels <12 or >90 ng/mL were excluded. Subjects were randomized to vitamin D_3 1,000 IU, calcium carbonate 1200 mg, both supplements or placebo daily until their next colonoscopy 3 to 5 years later. The primary study outcome was the number of adenomas detected on follow up colonoscopy.

A total of 2,259 subjects were randomized into the trial and 2,088 (92%) completed all study visits [23]. Although based on self-report rather than pill counts, 87% of subjects reported at least 80% adherence to study medication. A single pathologist blinded to treatment assignment analyzed all specimens excised during follow up colonoscopy, to confirm reported results of the local pathologist.

The risk ratio for new adenomas was no different across the four treatment arms [23]. Among subjects assigned to vitamin D_3, the risk ratio for new adenomas as 0.99 (95% confidence interval, 0.89 to 1.09) relative to the risk in subjects not taking vitamin D. Likewise, the risk ratio for advanced adenomas with features worrisome for malignancy was 0.99 (95% confidence interval, 0.75 to 1.29), compared to the risk in subjects not assigned to vitamin D. Finally, vitamin D therapy did not reduce the risk of new adenomas among subjects in the lowest quartile for baseline serum 25(OH)D level.

In summary, researchers found no evidence that vitamin D therapy reduced the risk of new adenomas, or advanced adenomas, in adults with pre-existing colon adenomas.

Conclusions

In summary, mounting evidence supports the Institute of Medicine's (IOM) conclusion that vitamin D repletion is defined as a serum 25(OH)D level ≥20 ng/mL. The IOM estimates that repletion can be achieved in nearly all adults by taking the recommended daily allowance for vitamin D (600 IU/day for adults <70 years old and ≥800 IU/day for adults 70 years old). Further research is needed to clarify the value of measuring bioavailable vitamin D levels in clinical practice, whether vitamin D taken during pregnancy provides long-term gains in BMD for children born in winter, or whether vitamin D reduces risk of influenza. Several recent studies show harm (greater risk of falls or respiratory infections) or no benefit from high-dose vitamin D, calling for caution when prescribing high-dose vitamin D to adults.

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Key Points

- In postmenopausal women with 25(OH)D levels around 20 ng/mL at baseline, high-dose vitamin D increased calcium absorption by 1% with no effect on bone mineral density, physical function, or falls compared to low-dose vitamin D or placebo.
- In adults ≥70 years old, high-dose vitamin D promoted falls.
- Vitamin D increased risk and duration of upper respiratory infections in adults.
- Vitamin D had no effect on the risk of new colon adenomas.