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Clinical Medicine Insights: Women's Health

# The Role of Vitamin D Supplements in Women's Health

Tiffany M. Bohon[1] and Marci A. Goolsby[2]

[1]Department of Family Medicine and Department of Orthopedics, University of Missouri, Columbia, MO, USA. [2]Department of Medicine, Hospital for Special Surgery, New York, NY, USA.

**ABSTRACT:** Vitamin D is pivotal to the absorption of calcium and maximizing bone health. Women suffer great morbidity and mortality related to osteoporosis and fractures, which may be decreased by interventions such as vitamin D. In addition, extraskeletal benefits of vitamin D have been postulated including positive effects on cancer. Both the classical and nonclassical functions of vitamin D will be discussed here, with a focus on women.

**KEYWORDS:** vitamin D, women's health, fracture, cancer

**CITATION:** Bohon and Goolsby. The Role of Vitamin D Supplements in Women's Health. *Clinical Medicine Insights: Women's Health* 2013:6 67–70 doi:10.4137/CMWH.S11067.

**TYPE:** Review

**FUNDING:** Authors disclose no funding sources.

**COMPETING INTERESTS:** Authors disclose no potential conflicts of interest.



**CORRESPONDENCE:** goolsbym@hss.edu

## Introduction

Although vitamin D deficiency is currently a hot topic of discussion, the debate started long ago. Initially identified as a vitamin in the 1900s, scientists now define it as a prohormone.[1] The first major documentation of vitamin D deficiency occurred during the industrial revolution when children in urban environments demonstrated growth retardation and skeletal deformities, termed rickets.[2] The link was made in the early 1900s between sunlight and improvement in rickets. By 1930, food and drinks were being fortified, but it was not well monitored, and children experienced toxicity, causing many countries to stop fortification.[2]

After the initial discovery of vitamin D's influence on the skeletal system, further research showed vitamin D's pivotal role in calcium absorption.[3] In addition, there is recent research on nonclassical functions of vitamin D, which include its possible role in the prevention or treatment of cancer, autoimmune diseases, heart disease, and infections.[1,4] Both the classical and nonclassical functions of vitamin D can affect men and women, but the focus of this article is the impact of vitamin D on women's health.

## Physiology and Definitions

It has been estimated that humans get 80% of their vitamin D from ultraviolet B rays via the skin and 20% from their diet.[5] In the skin, sunlight transforms 7-dehydrocholesterol into previtamin $D_3$, which is then isomerized to vitamin $D_3$. The vitamin D is taken to the liver where it's transformed into 25-hydroxyvitamin D (25[OH]D or calcidiol), which is the major circulating metabolite. From the liver, the 25(OH)D travels to the kidneys where it is converted into 1,25-dihydroxyvitamin D (1,25$[OH]_2$D or calcitriol), which is the active form of vitamin D.[4,6] This renal conversion is regulated by plasma parathyroid hormone levels, as well as serum calcium and phosphorus levels.[4] The inactive metabolite 25(OH)D is currently the preferred serum level to obtain, as it is a more accurate indication of the vitamin D status than 1,25(OH)D.[2]

Vitamin D deficiency is defined most commonly as a 25(OH)D level $< 20$ ng/mL. Vitamin D insufficiency is defined as 21 to 29 ng/mL, while anyone with a vitamin D $\geq 30$ ng/mL is considered sufficient.[4] Vitamin D intoxication can occur with a 25(OH)D level $> 150$ ng/mL.[4]

## Prevalence

Using Holick's above definitions, approximately 1 billion people worldwide have vitamin D deficiency or insufficiency.[4] The National Health and Nutrition Examination Survey (NHANES) data collected from 2001–2004 showed a decrease in American vitamin D levels when compared with the 1988–1994 population. Specifically, 97% of non-Hispanic blacks and 90% of Mexican Americans had vitamin D insufficiency or deficiency according to the most recent NHANES study. More than 50% of the white population studied had vitamin D deficiency or insufficiency as well.[5,7]

## Risk Factors

Many factors contribute to vitamin D deficiency. Reduced skin synthesis is related to sunscreen use, darker skin pigmentation, aging, winter months, early or late time of day exposure, residing at a latitude >35 degrees, and skin grafts for burns.[4] Decreased bioavailabity is secondary to malabsorption from gastrointestinal diseases or procedures (eg, celiac disease, Crohn's disease, gastric bypass surgery) as well as obesity, because vitamin D is fat-soluble and gets sequestered in the fat cells.[4] Increased catabolism becomes a risk factor for those taking medications such as anticonvulsants, glucocorticoids, HIV medications, and antirejection medications because they break down vitamin D to its inactive forms. There is insufficient vitamin D content in a mother's milk, so breast-fed infants need supplementation. Finally, diseases of the kidneys and liver affect vitamin D levels by disrupting synthesis.[4]

## Effects of Vitamin D on Musculoskeletal System

Annually, there are 1.5 million people in the United States who sustain an osteoporotic fracture.[3] Estimates show that 47% of women and 22% of men ≥ 50 years old will experience an osteoporotic fracture in their lifetime.[4] During the first 3 months following a hip fracture, the mortality risk increases 2.8 to 4 times.[3] Thus, it is critical that further measures are taken to decrease future morbidity and mortality with medical interventions such as vitamin D. Vitamin D is known to affect bone physiology with its impact on calcium and phosphorus levels. Only 10% to 15% of dietary calcium and about 60% of phosphorus is absorbed without vitamin D.[4] Vitamin D decreases parathyroid hormone levels and secondarily affects bone turnover.[5]

Studies have been done evaluating the effect of vitamin D on fractures, falls, and muscle strength. The Women's Health Initiative (WHI) trials included a subset evaluation of 36,282 American women between the ages of 50 and 79[8,9] to evaluate the effects of calcium and vitamin D supplementation on fracture prevention (primary outcome) and colorectal cancer (secondary outcome).[8,10] Half of the women received 400 IU of vitamin D and 1000 mg of calcium while the other half received a placebo. The results showed no statistically significant reduction in hip fractures or total fractures.[3] Based on this, the US Preventive Services Task Force (USPSTF) recommends against daily supplementation with 400 IU or less of vitamin $D_3$ and 1000 mg or less of calcium for the primary prevention of fractures in noninstitutionalized postmenopausal women.[3] In interpreting the results, one must consider the fact that all participants were allowed to supplement with up to 1000 mg of calcium and 600 IU of vitamin D per day.[11] Compliance was poor, with 41% of the intervention group not taking their supplements as directed.[8] Finally, it is important to note that the WHI trial was looking at supplementation with vitamin D and calcium, so it is difficult to draw conclusions on vitamin D alone.

Following the WHI trial, another study entitled Randomised Evaluation of Calcium or vitamin D (RECORD) was done in the United Kingdom to further investigate these supplements' effects on low-energy fractures.[12] In this trial, 5292 men and women age 70 and older were randomly assigned to 1 of 4 groups: 800 IU vitamin $D_3$ daily, 1000 mg calcium daily, 800 IU vitamin $D_3$ plus 1000 mg calcium daily, or placebo.[12] Their results showed no statistical advantage of one group over another, but the mean concentration of 25(OH)D only increased from 15.2 ng/mL to 24.8 ng/mL, which is still below the threshold thought to provide fracture protection.[4,12] However, although the assigned intake for vitamin D was 800 IU daily, the true vitamin D intake was actually only 539 IU daily in the vitamin D plus calcium group and 613 IU daily in the vitamin D only group.[13] Also, at 24 months, only 60% of those who returned their questionnaires were still taking their assigned pills.[12]

Bischoff-Ferrari et al pooled data from 11 double-blind, randomized controlled trials of men and women ≥ 65 years old who were assigned to 1 of 4 groups: vitamin D, calcium, vitamin D plus calcium, or placebo.[13] They concluded that high-dose vitamin D (≥800 IU daily) appears to help reduce the risk of hip fracture and any nonvertebral fracture in persons ≥ 65 years old.[13] One limitation is that all of the trials that used higher doses of vitamin D and appeared to show a decreased fracture risk also included high doses of calcium.[13] The Vitamin D Individual Patient Analysis of Randomized Trials (DIPART) Group analyzed pooled data on 68,500 patients from 7 major vitamin D fracture trials in the United States and Europe.[14] The DIPART group concluded that vitamin D alone in low doses (400 IU–800 IU) does not prevent fractures, but giving vitamin D and calcium together can reduce total fractures.[14] The authors admit that the analysis unfortunately did not allow for a direct comparison of vitamin D and vitamin D with calcium.[14]

In addition to risk of fractures, correlation between vitamin D and falls has been investigated. A study by Sanders et al evaluated 2256 community-dwelling women ≥ 70 years old who were considered to be at high risk for fracture. Their data showed that high-dose vitamin $D_3$ (500,000 IU of oral vitamin $D_3$ once per year) actually resulted in an increased risk

of falls and fractures (by 15% and 26%, respectively), which was highest in the first few months following administration.[15] Broe et al also researched the effect of vitamin D supplementation on falls in 124 nursing home residents given either vitamin D in the dose of 200 IU, 400 IU, 600 IU, 800 IU, or a placebo pill.[16] Only those taking the highest dose of vitamin D (800 IU) fell less. One downside of this study is the smaller sample size.[16]

Although the above results can be difficult to interpret, it is important to note that the benefits or harms of vitamin D supplementation may be dose related and need to be studied separately from calcium. Further large randomized controlled trials are needed to shed light on the inconsistent results.

## Nonclassical Effects of Vitamin D

In addition to the classical musculoskeletal functions, vitamin D has been found to possibly exert influence on nonclassical sites,[1] such as the brain, prostate, breast, and colon.[4] Disease processes such as cancer, autoimmune disease, cardiovascular disease, infections, endocrine/reproductive diseases, and others have been linked to low vitamin D levels as well as living at higher latitudes, specifically above 37° latitude.[4,17,18] The proposed mechanism by which vitamin D reduces the incidence of cancer is by inhibiting tumor angiogenesis.[18] With 25(OH)D levels above 30 ng/mL, the risk of some cancers is reduced.[4,19] Epidemiologic studies show that if levels of 25(OH)D are <20 ng/mL, there is a 30% to 50% increased risk of colon, prostate, and breast cancer.[4] In addition to the higher risk of developing cancer, this population has a higher mortality rate from the cancer.[4] Conversely, the WHI trial showed there was no effect from daily supplementation of 1000 mg calcium and 400 IU vitamin D on the incidence of colorectal cancer among postmenopausal women. A possible issue with this trial was that follow-up was 7 years, but the latency for developing colon cancer is 10 to 20 years.[10]

Garland et al looked at 30 studies with vitamin D and colon cancer, finding 20 with a statistically significant benefit of vitamin D, its metabolites, or sunlight exposure; 5 with borderline statistically significant benefit; and 5 with no association.[18] This review also examined 13 studies of breast cancer, with 9 showing a favorable association of vitamin D markers or sunlight with decreased cancer risk, 1 showing benefit of borderline significance, and 3 without association.[18] They evaluated 7 studies of ovarian cancer, 5 of which showed higher mortality with lower vitamin D intake or lower sun exposure.[18]

In addition to a possible anticarcinogenic effect of vitamin D, autoimmune diseases such as type 1 diabetes mellitus, multiple sclerosis, and Crohn's disease may be linked to vitamin D, as those living at higher latitudes are once again at increased risk.[4] Women who ingested >400 IU of vitamin D per day showed a decreased risk of developing multiple sclerosis.[4] In terms of cardiovascular disease, living at higher latitudes increases the risk of hypertension and heart disease.[4] Other medical issues linked to vitamin D deficiency include infections such as tuberculosis, depression, and schizophrenia.[4]

Vitamin D has also been a point of discussion in reproductive and endocrine fields. A high rate of vitamin D deficiency has been found in women with polycystic ovarian syndrome (PCOS). There have been cross-sectional studies showing a possible association between low vitamin D and menstrual dysfunction, infertility, hirsutism, obesity, and insulin resistance in patients with PCOS. However, there is a paucity of evidence proving causality; thus, further research is needed.[20] In addition, there may be an association with low vitamin D and adverse pregnancy outcomes, specifically a higher rate of preeclampsia, preterm birth, small of gestational age infants, bacterial vaginosis, and gestational diabetes.[21,22] However, a Cochrane review concluded that the number of high quality trials and outcomes reported is too limited to draw conclusions on the usefulness and safety of vitamin D taken during pregnancy.[23] Currently, the American College of Obstetrics and Gynecology has the same recommendations as the Institute of Medicine of 600 IU of vitamin D daily for pregnant women. They do not feel there is sufficient evidence for screening all pregnant women, but, if a deficiency is identified, most experts agree that 1000 to 2000 IU per day is safe.[24]

## Treatment/Replacement Strategies

Many clinicians suggest the optimal serum 25(OH)D is 30 ng/mL, at which point the parathyroid hormone is adequately suppressed, fracture risk is reduced, and health outcomes are improved.[5,19] Others argue the majority of the population can meet their vitamin D needs when their 25(OH)D level is 20 ng/mL and that a level > 30 ng/mL is not associated with potential health benefits. Further, they feel there are risks when the 25(OH)D level is >50 ng/mL.[25] In addition, it is difficult to define the recommended dietary allowance (RDA) because of the dual source of vitamin D, from sunlight and dietary intake.[1] Also, there are factors that affect how much vitamin D one actually absorbs.

The current RDA is 600 IU daily for those ages 1 to 70 and 800 IU daily for those >70 years old.[25] Since an RDA has not been established for infants, the adequate intake (AI) reference value is 400 IU daily.[25] Naturally occurring vitamin D rich foods include fatty/oily ocean fish, irradiated mushrooms, and cod liver oil.[5] Food and drinks sometimes fortified with vitamin D include milk, yogurt, orange juice, margarine, breakfast cereals, and infant formula.[1,5] Oral supplements are available as vitamin $D_2$ or $D_3$ in varying dosages. To get vitamin D from sunlight, exposing arms and legs for 5 to 30 minutes between the hours of 10 AM and 3 PM is usually sufficient but depends on skin pigmentation, time of day, latitude, and season.[4]

## Toxicity

Being a fat-soluble vitamin, vitamin D toxicity is a concern, but fortunately it is an extremely rare occurrence.[4] The most liberal definition of vitamin D intoxication is a 25(OH)D level > 150 ng/mL with associated hypercalcemia.[4,12] Some feel 25(OH)D levels > 50 ng/mL are concerning, and recent observational studies show an association between 25(OH)D levels > 60 ng/mL and an increased risk of pancreatic cancer, vascular calcification, and death from any cause.[17,25] Translating the toxicity levels into the daily tolerable upper intake level (UL), the Institute of Medicine recommends no more than 4000 IU/day.[17,25] However, some studies even show that 10,000 IU/day for up to 5 months does not cause toxicity.[4,5] Signs and symptoms of vitamin D toxicity are mainly secondary to hypercalcemia and include headache, irritability, metallic taste, vascular calcinosis, nephrocalcinosis, hypercalciuria, renal failure, pancreatitis, dehydration, nausea, and vomiting.[5,18]

## Conclusion

Researchers and clinicians over the years have shown that too little and too much vitamin D can have negative health consequences. Unfortunately, we still do not have clear insight as to exactly how much vitamin D is best. Confounders such as skin pigmentation, latitude of residence, obesity, and others make standardizing and simplifying the recommendations difficult. Further randomized controlled trials are needed with a large diverse population supplementing with vitamin D alone. Specifically for women, further research is needed for osteoporosis and fracture prevention, cancer incidence, pregnancy outcomes, and PCOS treatment. Factors that may impact vitamin D absorption and availability such as gastrointestinal issues and body mass index need to be adjusted for in the studies. For now, clinicians should take into consideration individual variables when recommending vitamin D supplementation.

## Author Contributions

Conceived the concept: TB, MG. Analyzed the data: TB, MG. Wrote the first draft of the manuscript: TB. Contributed to the writing of the manuscript: TB, MG. Agree with manuscript results and conclusions: TB, MG. Jointly developed the structure and arguments for the paper: TB, MG. Made critical revisions and approved final version: TB, MG. All authors reviewed and approved of the final manuscript.

**DISCLOSURES AND ETHICS**

As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests. Provenance: the authors were invited to submit this paper.

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