

Review

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Vitamin D Revisited: Impact on Osteoporosis

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ABBREVIATIONS: IOM: Institute of Medicine; ANZBMS: Australian and New Zealand Bone and Mineral Society and Osteoporosis Australia; RDA: Recommended Dietary Allowance; UVB: Ultra Violet B; SIGN: Scottish Intercollegiate Guidelines Network.

INTRODUCTION

With the now widespread recognition that the prevention and treatment of osteoporosis has a major impact on healthcare, the various components and contributing factors to this condition is the subject of many recent and ongoing studies. One of these contributing factors is vitamin D, and it is obvious from a review of the literature that there is no scarcity of research on this topic. This vitamin is the subject of many studies even in areas other than bone health. The Institute of Medicine (IOM) expert committee found inconsistent evidence of the alleged role of vitamin D in conditions such as cancer, cardiovascular disease, diabetes, and immunity. They found that the evidence existing to date is inconsistent and does not demonstrate a cause-and-effect relationship. A quick look at just only one of the websites on vitamin D, that of the Vitamin D Council, shows the following issues highlighted during the month of February 2013:

- Alaska State legislator is sponsoring the House Bill to test the vitamin D levels of all newborns in Alaska.
- According to a study published in the Pediatric Infectious Diseases Journal, vitamin D supplementation may be needed in children with HIV.
- Professional ballerinas have a high incidence of vitamin D deficiency, improving slightly during summer months. Dancers also are more likely to get injured during the winter, according to research published in the Journal of Science and Medicine in Sport.
- Sunshine is good, according to new guidelines set by the Australian and New Zealand Bone and Mineral Society and Osteoporosis Australia (ANZBMS).
- Researchers at the Chaim Sheba Medical Center in Israel recently reviewed the evidence that vitamin D is involved in autoimmune disorders.
- Researchers in Iran wanted to know if treating patients with vitamin D and calcium would improve their chronic pain.
- By taking 5,000 IU vitamin D every day, do you absorb enough calcium from your diet without having to rely on supplements?
- Researchers in Mexico report that vitamin D levels among young children are surprisingly sufficient compared to their United States neighbors.

Of all the possible roles of vitamin D and its implication in various fields of medicine, its role in bone health is the only one that is based on ample scientific evidence. This review is

a concise summary of the properties of vitamin D with emphasis on its role in the prevention and treatment of osteoporosis and osteoporotic fractures.

IMPORTANCE OF VITAMIN D IN OSTEOPOROSIS

Vitamin D enhances calcium absorption in the gastrointestinal tract and balances plasma calcium and phosphate concentrations to ensure proper bone mineralization. In addition, it is important for proper remodeling by osteoblasts and osteoclasts.

It is well recognized that the vast majority of studies on anti-osteoporosis agents have been on subjects maintained on calcium and vitamin D supplements. As such, adequate calcium and vitamin D intake is part and parcel of osteoporosis prevention and management.

Vitamin D deficiency causes rickets in children and will precipitate and exacerbate osteopenia, osteoporosis, and fractures in adults.

A low level of serum vitamin D is an independent predictor of incident falls¹ and many authors recommend that older people, especially those in residential care, should receive vitamin D in order to prevent falls.²

In men and women ≥ 65 years of age, calcium and vitamin D maintained better hip and spinal BMD and protected against non-vertebral fractures.^{3,4}

In a pooled analysis of more than 70,000 patients, Rejnmark, et al. showed that vitamin D with calcium reduces mortality.⁵ Although, vitamin D has been reported to play a role in cancer, autoimmune diseases, hypertension, multiple sclerosis, infectious diseases and other numerous conditions, the best evi-

dence of benefit is for bone health.

SOURCES OF VITAMIN D

Vitamin D is a fat-soluble vitamin that is present naturally in only very few foods such as fatty fish, fish liver oils, and some sun-enriched mushrooms. In some countries (e.g. USA and Canada) some products, such as milk and cereals, are fortified with vitamin D and these may constitute a good source of vitamin D. However, in most countries in the world these natural foods and those fortified with vitamin D are not consumed in large enough amounts to label them as adequate sources of vitamin D. Endogenous cutaneous vitamin D triggered by sunlight remains the major source of vitamin D, and moderate exposure to sunlight is still the best route to get vitamin D.⁶

Vitamin D is present in an inactive form as 7-dehydrocholesterol (provitamin D₃) in the two deepest layers of the dermis, the stratum spinosum and stratum basale. Under the influence of sunlight's Ultra Violet B (UVB) waves at wavelengths between 270-290 nm, provitamin D₃ is doubly hydroxylated by the liver and kidneys into calcitriol. This active form then binds to its protein in the plasma and is transported to its vitamin D receptors in the nuclei of the target cells. (Figure 1).

RECOMMENDED VITAMIN D INTAKE IN POSTMENOPAUSAL WOMEN

Dietary vitamin D is measured in micrograms (mcg) or International Units (I.U), with the following conversions:

1 mcg = 40 I.U

1 I.U = 0.025 mcg

There is no consensus on the exact daily vitamin D

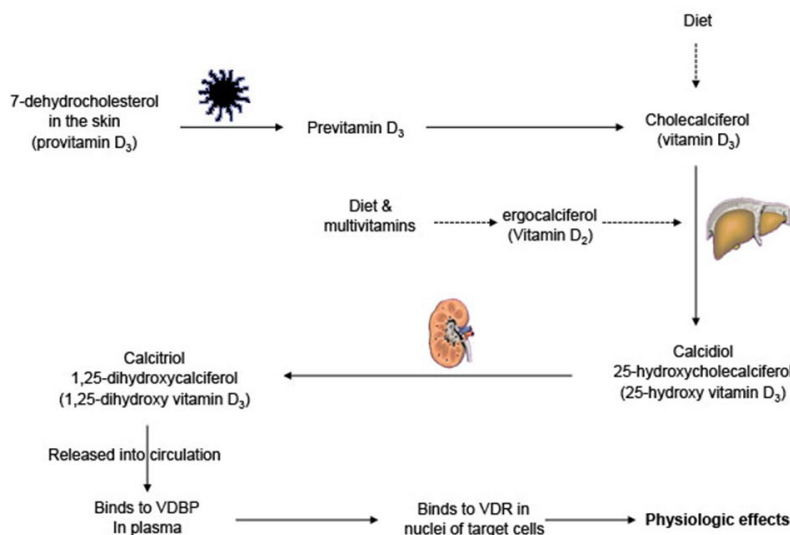


Figure 1: Vitamin D synthesis (VDBP: Vitamin D Binding Protein; VDR: Vitamin D Receptor).

requirements in postmenopausal osteoporotic women. Even if there is, it is very difficult to make an exact estimate of how much vitamin D a woman is getting out of the various foods or supplements she is taking, or the amount of endogenous vitamin D she is getting out of exposure to sunlight.

The Recommended Dietary Allowance (RDA) is now the accepted reference for the adequacy of dietary vitamin D intake; the reason for excluding the endogenous source of vitamin D that is triggered by exposure to sunlight is because of concern issues about the safety of Ultra Violet B (UVB) rays with regard to skin cancer. Another reason for sunlight exclusion is that the extent of UVB ray penetration of the skin cannot be gauged properly because of variable factors affecting this penetration, such as clouds and air pollution, shade, sunscreens, skin color, latitude, altitude, season, obesity, degree of clothing, malabsorption, gastric bypass, some medications, and age.⁷

So these RDAs are set at levels to ensure that sun exposure is not necessary in order to obtain enough vitamin D. The Institute of Medicine's latest RDA for postmenopausal osteoporotic women ≤ 70 years is 600 I.U./day and for those >70 years is 800 I.U. For postmenopausal women of all ages, the tolerable upper intake level is 4000 I.U. There is no additional benefit if the intake is higher than the RDA.

RECOMMENDED SERUM LEVELS OF VITAMIN D

The classical unit measurements of serum vitamin D are ng/ml and nMol/L, and have the following conversion relationship:

$$1 \text{ ng/ml} = 2.5 \text{ nmol/L}$$

$$1 \text{ nmol/L} = 0.4 \text{ ng/ml}$$

The same controversy exists regarding the acceptable serum level of vitamin D required to maintain bone health.

Serum calcidiol [25(OH)D] concentration is classically accepted as the best indicator for vitamin D levels in the body. The terms "inadequate", "insufficient", "deficient", "low", and "high" have been used by different authors to mean different things, and it is probably wise to avoid using most of them.

What we need to know is whether a postmenopausal woman needs treatment with vitamin D supplements or not, and to do so we need only know if she has acceptable serum levels or not. What is "acceptable" has also been controversial, some going as far as saying that serum 25(OH)D₃ concentrations of <80 nmol/L are associated with reduced calcium absorption, osteoporosis, and increased fracture risk.⁸

The IOM expert committee suggests that almost all people are vitamin D sufficient at serum calcidiol concentration ≥ 50 nmol/L and are deficient at levels <30 nmol/L. Those

between 30-50 nmol/L are at risk of having inadequate levels. Levels above 125 nmol/L may put patients at risk of vitamin D toxicity.

WIDESPREAD VITAMIN D DEFICIENCY

One of the missing links in the inconsistency of the beneficial effects of antiresorptive agents is the recognition that many of these patients are vitamin D deficient. With the recent doubling of the daily allowance of vitamin D, even those who were thought to be on adequate vitamin D supplementation according to international guidelines were actually falling below the newly introduced requirements. More than half of North American women receiving therapy to treat or prevent osteoporosis have vitamin D inadequacy.⁹

The prevalence of inadequate vitamin D levels appears to be high in post-menopausal women, especially in those with osteoporosis and history of fracture. Vitamin D supplementation in this group is required to prevent falls and fracture, especially in elderly and osteoporotic populations,^{10,11} and black women are at an even higher risk than are white women.¹² Because vitamin D deficiency is preventable, heightened awareness is necessary to ensure adequate vitamin D intake, particularly in northern latitudes.¹³

MEASUREMENT OF VITAMIN D

The serum concentration of the singly hydroxylated [25(OH)D] vitamin D (calcidiol) is the best indicator of vitamin D status; it reflects total vitamin D input, both exogenous and endogenous. Though it is inactive, it is easy to measure because it has a long half-life (15 days). The doubly hydroxylated [1,25(OH)D] biologically active vitamin D (calcitriol) is not a good biomarker of vitamin D status because it has a short half-life (15 hours), and its level is regulated by PTH, calcium, and phosphate.

The most common assays used to measure serum vitamin D levels are: Competitive protein binding, high-performance liquid chromatography, and radioimmunoassay. However, there are many problems in clinical measurement of serum vitamin among patients, and one should be very careful in interpreting the results.⁸ Without proper cross calibration. Interlaboratory variations and differences among different assays may give false results.¹⁴

A drawback of measuring calcidiol rather than calcitriol is that an osteoporotic patient with a kidney disease may have adequate levels of the inactive vitamin D and yet be depleted of the active form because of lack of hydroxylation by the kidneys. In patients with kidney disease, it is advisable to give alfacalcidol, instead of regular vitamin D, because it is doubly hydroxylated into the active form without passing through the kidneys. Inadequate metabolism of 25-OH-D to 1,25(OH)2D contributes significantly to decreased calcium absorption in os-

teoporotic and even in elderly normal women. In osteoporotic women this abnormality could be due to their decreased parathyroid hormone secretion and increased serum phosphate, and in these elderly subjects there may even be a primary abnormality in the metabolism of 25-OH-D to 1,25(OH)₂D.¹⁵

TREATMENT OF VITAMIN D DEFICIENCY

Many specialists in the field of osteoporosis have now opted to give their patients enough vitamin D in doses above the recommended daily requirements, without resorting to laboratory determination of serum vitamin D levels. This is based on the fact that serum vitamin D tests are quite expensive in many countries, vitamin D deficiency is widespread in many countries, even those blessed with a lot of sun, lab results are inconsistent even when performed in the same lab, there are imperfections in many of the methods that measure serum vitamin D levels, and finally vitamin D toxicity is quite uncommon. This rare toxicity is partly due to the fact that increased calcitriol levels inhibit PTH, causing calcitriol production in the kidney to decrease. Renal 24-hydroxylase activity further limits the availability of calcitriol by creating inert metabolites of both calcitriol and calcidiol. The 24-hydroxylase gene is under the transcriptional control of calcitriol, thereby providing tight negative feedback.¹⁶

It is reasonable to say that natural and fortified foods are not enough to treat vitamin D deficiency, let alone maintain normal vitamin D serum levels. In people with suspicious skin lesions, such as melanomas, and in those at risk of developing skin cancer, the safest and cheapest way of treating deficiency is through vitamin D supplements. The problem with this is the lack of expert agreement on which to base firm recommendations. Scottish Intercollegiate Guidelines Network (SIGN) in their 2003 guideline on osteoporosis recommend a vitamin D supplement as low as 800 IU for deficient patients¹⁷ compared to Pearce and Cheetham who recommend a loading dose of 20 000 IU per week for 8-12 weeks if serum vitamin D <25 nmol/L, followed by maintenance at 1000-2000 IU daily.¹⁸ A common practice is to start with a loading dose of 50,000 IU weekly for 3 months, followed by serum level determination; if this is normal, a maintenance dose equal to the recommended RDA is given with close monitoring. If the serum level is still below 50 nmol/L (20 ng/ml) the same protocol is repeated. Note that higher doses may be required in obese individuals because of sequestration of vitamin D in adipose tissue. Another protocol is to give 4,000 IU vitamin D₃ daily or 30,000 IU weekly, then maintain at daily 2000 IU.¹⁹

A Mega intramuscular doses of vitamin D have recently been advocated.²⁰⁻²² Many physicians have started giving high doses of vitamin D empirically without resorting to blood tests. Is this acceptable? We will have to wait and see.

CONCLUSIONS

Vitamin D is an intriguing vitamin; so much so that

there is barely any disease with which it has not reportedly been associated. Its most important role, however, is in bone health. The recommended daily requirements and the desirable serum levels, though mostly standardized, are ever changing. Vitamin D serum level measurements are sometimes erratic, and better methods need to be sought. The ever-changing treatment protocols of vitamin D deficiency will probably keep changing as long as the whole scope of the role of vitamin D is yet to be discovered.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

REFERENCES

1. Flicker L, Mead K, MacInnis RJ, et al. Serum Vitamin D and falls in older women in residential care in Australia. *Journal of the American Geriatrics Society*. 2003; 51: 1533-1538. doi: [10.1046/j.1532-5415.2003.51510.x](https://doi.org/10.1046/j.1532-5415.2003.51510.x)
2. 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. *Journal of the American Geriatrics Society*. 2005; 53: 1881-1888. doi: [10.1111/j.1532-5415.2005.00468.x](https://doi.org/10.1111/j.1532-5415.2005.00468.x)
3. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE. Effect of calcium and vitamin D supplementation on bone density in men and women 65 years of age or older. *N Engl J Med*. 1997; 337: 670-676. doi: [10.1056/NEJM199709043371003](https://doi.org/10.1056/NEJM199709043371003)
4. Ott SM. ACP Journal Club. Review: Vitamin D with calcium reduces fractures in adults. *Ann Intern Med*. 2012; 156: JC6-JC7. doi: [10.7326/0003-4819-156-12-201206190-02007](https://doi.org/10.7326/0003-4819-156-12-201206190-02007)
5. Rejnmark L, Avenell A, Masud T, et al. Vitamin D with calcium reduces mortality: patient level pooled analysis of 70,528 patients from eight major vitamin D trials. *J Clin Endocrinol Metab*. 2012; 97: 2670-2681. doi: [10.1210/jc.2011-3328](https://doi.org/10.1210/jc.2011-3328)
6. Holick FM, Chen TC. Vitamin D deficiency: a worldwide problem with health consequences. *Am J Clin Nutr*. 2008; 87: 1080S-1086S.
7. Bell NH, Greene A, Epstein S, et al. Evidence for alteration of the vitamin D-endocrine system in blacks. *J Clin Invest*. 1985; 76: 470-473. doi: [10.1172/JCI111995](https://doi.org/10.1172/JCI111995)
8. Heaney R. Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am J Clin Nutr*. 2004; 80: 1706S-1709S.
9. Holick MF, Siris ES, Binkley N, et al. Prevalence of Vitamin D inadequacy among postmenopausal North American women receiving osteoporosis therapy. *The Journal of Clinical Endocrinology & Metabolism*. 2005; 90: 3215-3224. doi: [10.1210/](https://doi.org/10.1210/)

[jc.2004-2364](#)min D deficient/insufficient elderly. *Maturitas*. 2012; 72: 332-338. doi: [10.1016/j.maturitas.2012.04.011](https://doi.org/10.1016/j.maturitas.2012.04.011)

10. Gaugris S, Heaney RP, Boonen S, et al. Vitamin D inadequacy among post-menopausal women: a systematic review. *QJM*. 2005; 98: 667-676. doi: [10.1093/qjmed/hci096](https://doi.org/10.1093/qjmed/hci096)

11. Lips P, Hosking D, Lippuner K, et al. The prevalence of vitamin D inadequacy amongst women with osteoporosis: an international epidemiological investigation. *Journal of Internal Medicine*. 2006; 260: 245-254. doi: [10.1111/j.1365-2796.2006.01685.x](https://doi.org/10.1111/j.1365-2796.2006.01685.x)

12. Semba RD, Garrett E, Johnson BA, Guralnik JM, Fried LP. Vitamin D deficiency among older women with and without disability. *Am J Clin Nutr*. 2000; 72: 1529-1534.

13. LeBoff MS, Kohlmeier L, Hurwitz S, et al. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *JAMA*. 1999; 281: 1505-1511. doi: [10.1001/jama.281.16.1505](https://doi.org/10.1001/jama.281.16.1505)

14. Lips P, Chapuy MC, Dawson-Hughes B, Pols HA, Holick MF. An international comparison of serum 25-Hydroxy vitamin D measurements. *Osteoporosis International*. 1999; 9: 394-397.

15. Gallagher JC, Riggs BL, Eisman J, et al. Intestinal calcium absorption and serum vitamin d metabolites in normal subjects and osteoporotic patients. *J Clin Invest*. 1979; 64: 729-736. doi: [10.1172/JCI109516](https://doi.org/10.1172/JCI109516)

16. Kennel K, Drake M, Hurley D. Vitamin D deficiency in adults: When to test and how to treat. *Mayo Clin Proc*. 2010; 85: 752-758. doi: [10.4065/mcp.2010.0138](https://doi.org/10.4065/mcp.2010.0138)

17. SIGN. Guideline 71. Management of osteoporosis. Edinburgh: Royal College of Physicians. 2003.

18. Pearce S, Cheetham T. Diagnosis and management of vitamin D deficiency. *BMJ*. 2010; 340: 142-147. doi: [10.1136/bmj.b5664](https://doi.org/10.1136/bmj.b5664)

19. Khan Q, Fabian C. How i treat vitamin D deficiency. *JOP*. 2010; 6: 97-101. doi: [10.1200/JOP.091087](https://doi.org/10.1200/JOP.091087)

20. Khan AH, Rohra DK, Saghir SA, Udani SK, Wood R. Response of a single 'mega intramuscular dose' of vitamin D on serum 25OHD and parathyroid hormone levels. *J Coll Physicians Surg Pak*. 2012; 22: 207-212. doi: [04.2012/JCPSP.207212](https://doi.org/10.2012/JCPSP.207212)

21. Carnes J, Quinn S, Nelson M, Jones G, Winzenberg T. Intermittent high-dose vitamin D corrects vitamin D deficiency in adolescents: a pilot study. *Eur J Clin Nutr*. 2012 ; 66 : 530-532. doi: [10.1038/ejcn.2011.204](https://doi.org/10.1038/ejcn.2011.204)

22. Tellioglu A, Basaran S, Guzel R, Seydaoglu G. Efficacy and safety of high dose intramuscular or oral cholecalciferol in vita-