Treatment of vitamin D insufficiency in postmenopausal women: desirable levels of vitamin D and supplementation

In a recent article in *JAMA*, Hansen and colleagues presented a randomized clinical trial of treatment of vitamin D insufficiency in postmenopausal women [1]. The trial compared the effects of placebo, low-dose cholecalciferol, and high-dose cholecalciferol on 1-year changes in total fractional calcium absorption, bone mineral density (BMD), timed-up-and-go and five sit-to-stand tests, and muscle mass in postmenopausal women with vitamin D insufficiency. This randomized, double-blind, placebo-controlled trial studied a total of 230 postmenopausal women 75 years or younger with baseline levels of 25-hydroxyvitamin D or 25(OH)D of 14–27 ng/ml and no osteoporosis. Outcome measures were 1-year change in total fractional calcium absorption using two stable isotopes, BMD and muscle mass, using dual-energy X-ray absorptiometry. After baseline absorption was controlled for, calcium absorption increased by 1% (10 mg/day) in the high-dose arm but decreased by 2% in the low-dose arm ($p = 0.005$ vs. high-dose arm) and 1.3% in the placebo arm ($p = 0.03$ vs. high-dose arm). We found no between-arm changes in spine, mean total hip, mean femoral neck, or total body BMD, trabecular bone score, muscle mass, and timed-up-and-go or five sit-to-stand test scores. Likewise, we found no between-arm differences for number of falls, number of fallers, physical activity, or functional status.

High-dose cholecalciferol therapy increased calcium absorption, but the effect was small and did not translate into beneficial effects on BMD, muscle function, muscle mass, or falls. We found no data to support experts' recommendations to maintain serum 25(OH)D levels of 30 ng/ml or higher in postmenopausal women. Instead, we found that low- and high-dose cholecalciferol were equivalent to placebo in their effects on bone and muscle outcomes in this cohort of postmenopausal women with 25(OH)D levels less than 30 ng/ml.

Comment

In the US National Library of Medicine [2], we can read that vitamin D includes both cholecalciferol and ergocalciferol. Vitamin D is a hormone since it is formed in the skin by action of ultraviolet rays upon the precursors, 7-dehydrocholesterol and ergosterol, and acts on vitamin D receptors to regulate calcium in opposition to parathyroid hormone (PTH). But, because in our times, exposure to sunlight is so difficult, vitamin D is really a vitamin, as we need take vitamin D with meals; however, we have another problem: a diet does not usually contain a sufficient amount of vitamin D, as it is present in very few foods.

This is the reason why many people need vitamin D supplementation, so the question is then in what dose? If we think only of the function of bone metabolism, vitamin D promotes calcium absorption in the gut and maintains adequate serum calcium and phosphate concentrations to enable normal mineralization of bone. Vitamin D is also needed for bone growth, bone remodeling and to prevent hypocalcemia. Vitamin D prevents rickets in children and osteomalacia in adults. Together with calcium, vitamin D also helps protect older adults from osteoporosis [3].

Measurement of the serum level 25(OH)D is the best way to know the status of vitamin D; if the level is less than 50 nmol/l or 20 ng/ml, it is considered inadequate for bone and overall health in healthy individuals. If it is > 125 nmol/l (> 50 ng/ml) it may be harmful. Then we have a therapeutic window, and we need to supplement adequately [3].

Hansen and colleagues [1] reinforce the concept that 20 ng/ml may be enough for bone health. They did not find clinically significant differences in calcium absorption and no differences in BMD, trabecular bone score, muscle mass, timed-up-and-go or five sit-to-stand test scores, number of falls, number of fallers, physical activity, or functional status, between high-dose vs. low-dose vitamin D supplementation.

But, will we need to prescribe vitamin D to reach a level of 20 ng/ml in any case? First, the desirable level is probably not the same in all people. There are racial differences in the relationship between vitamin D, BMD, and PTH. Optimal ranges for vitamin D between whites and blacks may not be the same; in blacks, significant reductions in PTH with supplementation of vitamin D occur only when the concentration on 25(OH)D is < 17 ng/ml [4].

Second, vitamin D is not only important for bone health but its deficiency has been associated with several chronic diseases like autoimmunity, cancer and cardiovascular disease. Then, we need to know the vitamin D level for prevention of these conditions [5]. But the evidence is not complete and occasionally controversial.

The relationship between vitamin D and autoimmunity works in its ability to inhibit T lymphocyte proliferation and cytokine production, particularly of the Th1 arm. Vitamin D decreases secretion of interleukin (IL)-2 and IFN-γ by CD4 T cells, attenuates dendritic cell maturation and modulates macrophage responses. Vitamin D may play a role in type 1 diabetes mellitus, inflammatory bowel disease, autoimmune thyroiditis, systemic lupus erythematosus and multiple sclerosis [6]. In multiple sclerosis, levels of 25(OH)D ≥ 75 nmol/l (30 ng/ml) were associated with a decreased risk [7].

Rossi found that dietary intake of vitamin D was inversely associated with breast cancer risk [8], and Kermani showed that the median level of 25(OH)D was significantly higher in patients with metastases (27.7 vs. 12.0 ng/ml; p = 0.03) [9]. In men, a 25(OH)D increment of 25 nmol/l (10 ng/ml) was associated with a 17% reduction in total cancer incidence, a 29% reduction in total cancer mortality, a 43% reduction in total gastrointestinal cancer

incidence and 45% reduction in gastrointestinal cancer mortality [10]. Then, considering protection against cancer, the desirable 25(OH)D level should be at least 30 ng/ml [11]; to reach this level, we need a vitamin D daily intake of 800–1000 IU.

Low serum 25(OH)D levels are associated with increased incidence, prevalence and risk factors for cardiovascular disease, and evidence suggests that increasing serum 25(OH)D levels to at least 30 ng/ml will reduce the risk [12].

In conclusion, for good bone health we need to supplement vitamin D to maintain a 25(OH)D level of 20 ng/ml, but, because vitamin D has extra-osseous activity, it is probably better supplement vitamin D to reach a level of 30 ng/ml.

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References

1. Hansen KE, Johnson RE, Chambers KR, et al. Treatment of vitamin D insufficiency in postmenopausal women a randomized clinical trial. JAMA Intern Med 2015;175:1612-21 http://www.ncbi.nlm.nih.gov/pubmed/26237520
2. US National Library of Medicine http://www.ncbi.nlm.nih.gov/mesh/?term=vitamin+d
3. Vitamin D Fact Sheet for Health Professionals https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/
4. Warden SJ, Hill KM, Ferira AJ, et al. Racial differences in the relationship between vitamin D, bone mineral density, and parathyroid hormone in the National Health and Nutrition Examination Survey. Osteoporos Int 2011;22:1745–53 http://www.ncbi.nlm.nih.gov/pubmed/23093348
5. Holick MF. Vitamin D: important for prevention of osteoporosis, cardiovascular heart disease, type 1 diabetes, autoimmune diseases, and some cancers. South Med J 2005;98:1024-7 http://www.ncbi.nlm.nih.gov/pubmed/16295817
6. Arnson Y, Amital H, Shoenfeld Y. Vitamin D and autoimmunity: new aetiological and therapeutic considerations. Ann Rheum Dis 2007;66:1137–42 http://www.ncbi.nlm.nih.gov/pubmed/17557889
7. Salzer J, Hallmans G, Nyström M, Stenlund H, Wadell G, Sundström P. Vitamin D as a protective factor in multiple sclerosis. Neurology 2012;79:2140-5 http://www.ncbi.nlm.nih.gov/pubmed/23170011
8. Rossi M, McLaughlin JK, Lagiou P, et al. Vitamin D intake and breast cancer risk: a case-control study in Italy. Ann Oncol 2009;20:374-8 http://www.ncbi.nlm.nih.gov/pubmed/18711029
9. Kermani IA, Kojidi HT, Gharamaleki JV, et al. Association of serum level of 25 hydroxy-vitamin D with prognostic factors for breast cancer. Asian Pac J Cancer Prev 2011;12:1381-4 http://www.ncbi.nlm.nih.gov/pubmed/22126468
10. Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst 2006;98:451-9 http://www.ncbi.nlm.nih.gov/pubmed/16595781
11. Garland CF, Garland FC, Gorham ED, et al. The role of vitamin D in cancer prevention. Am J Public Health 2006;96:252-61 http://www.ncbi.nlm.nih.gov/pubmed/16380576
12. Weyland PG, Grant WB, Howie-Esquivel J. Does sufficient evidence exist to support a causal association between vitamin D status and cardiovascular disease risk? An assessment using Hill's criteria for causality. Nutrients 2014;6:3403-30 http://www.ncbi.nlm.nih.gov/pubmed/25184368