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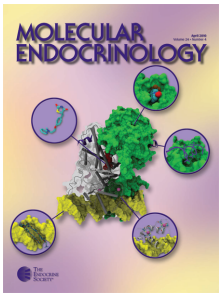

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Vitamin D Insufficiency, Deficiency, and Bone Health

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There has been increasing interest in the potential benefits of vitamin D. Much of the stimulus came from meta-analysis of vitamin D and calcium in osteoporotic fracture studies as well as association studies relating increased prevalence of diseases such as cancer, diabetes, multiple sclerosis, and cardiovascular events with lower levels of serum 25-hydroxyvitamin D (25OHD).

Vitamin D from diet or sun is converted in the liver to 25OHD and then in the kidney to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the active form of vitamin D. Normally, the main source of 1,25$(OH)_2$D is the kidney, and serum 1,25$(OH)_2$D is regulated by changes in serum calcium, phosphorus, fibroblast growth factor-23, and PTH; serum levels are held constant through homeostatic regulation. Circulating 1,25$(OH)_2$D binds to the target tissues in the body that have a vitamin D receptor where it expresses vitamin D-responsive genes.

In addition, many tissues (for example, breast, colon, prostate, bone, and immune cells) express 25OHD-1-α-hydroxylase that converts 25OHD to 1,25-dihydroxyvitamin D locally. These local effects cause decreased proliferation of cells, increased cell differentiation, and cell survival. The importance of the peripheral conversion of 25OHD to 1,25$(OH)_2$D relative to systemic production is difficult to assess, and nothing is known about the level of serum 25OHD when peripheral conversion might be impaired.

It is difficult to define adequate vitamin D nutrition because circulating vitamin D is derived from both dietary sources and sunlight; however, serum 25OHD is stable over weeks and serves as a biomarker of the adequacy of vitamin D supplies. The sunlight effect depends on distance from the equator, so for example in northern countries at 40° latitude, sunlight–or rather UVB radiation–is effective in converting 7-dehydrocholesterol to vitamin D3 in skin for about 7 months of the year and in Sweden at 55–65° latitude, monthly exposure to UVB is 5 months. The length of effective UVB exposure depends on the angle of the sun and atmospheric pollution, and the sun needs to be above 35° to be effective.

With the ready availability of accurate serum 25OHD measurements, results from different countries show a lot of variation in levels, and the discussion centers on the significance of the values. What is a low level? In the past, vitamin D *deficiency* was defined as serum 25OHD below 10 ng/ml because both serum 1,25$(OH)_2$D and calcium absorption declined significantly at this level (1, 2). The World Health Organization (WHO) defined vitamin D *insufficiency* as serum 25OHD below 20 ng/ml (50 nmol/liter) (3). However, others recently started to define vitamin D deficiency as serum 25OHD level below 20 ng/ml and vitamin D insufficiency as less than 30 ng/ml (75 nmol/liter) (4). The primary argument for this change in definition is based on the finding that serum PTH, which is inversely related to serum 25OHD, decreases as serum 25OHD increases and reaches a plateau at a serum 25OHD of approximately 30 ng/ml (75 nmol/liter). This is certainly controversial because numerous studies show a large variation in the plateau level of PTH ranging from a serum 25OHD of 18 ng/ml (45 nmol/liter) (5) to 30 ng/ml (75 nmol/liter) (6).

This change in definition of vitamin D insufficiency actually has major significance because the dose of vitamin D required to increase people to a *minimum* serum 25OHD of 20 ng/ml (50 nmol/liter) is approximately 800 IU daily (7), whereas increasing people to a minimum level of 30 ng/ml (75 nmol/liter) would require approximately 4,000 IU daily (8). Unfortunately, there are no long-term prospective studies of either the efficacy or safety of these larger doses of vitamin D. There are two important questions: what data support recommending a minimum serum 25OHD level of either 20 ng/ml (50 nmol/liter) or 30

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For article see page 2637

Abbreviations: BMD, Bone mineral density; CL, confidence limit; HR, hazard ratio; 1,25$(OH)_2$D, 1,25-dihydroxyvitamin D; 25OHD, 25-hydroxyvitamin D.

ng/ml (75 nmol/liter), and what is the adequate intake required to achieve that level?

A paper published in the current issue of *JCEM* by Melhus *et al.* (9) presents data on the association between serum 25OHD and the incidence of hip fractures and provides some insight into these questions.

Melhus *et al.* (9) describe the results of a prospective, population-based cohort study of 1194 elderly men (mean age, 71 yr) with a median follow-up of 11 yr. The primary outcome was the time to any fracture that was identified using the National Patient and County registries in Sweden. The investigators used an innovative statistical approach to find the optimum category boundary for serum 25OHD. This approach allowed them to divide the cohort into two groups according to serum 25OHD less than and greater than 16 ng/ml (40 nmol/liter). The hazard ratio (HR) for hip fractures in subjects with serum 25OHD below 16 ng/ml (40 nmol/liter) was significantly increased at 1.71 [95% confidence limit (CL), 1.13–2.57], compared with those with serum 25OHD above 16 ng/ml (40 nmol/liter). There was a decrease in risk after adjustment for age, weight, height, cystatin C, blood draw season, and comorbidities to 1.58 (95% CL, 1.04–2.41). This signifies a significant effect of serum 25OHD below 16 ng/ml (40 nmol/liter) on hip fractures, although most of the fractures are due to osteoporosis. Although the study was done in northern Europe, the prevalence of serum 25OHD below 16 ng/ml (40 nmol/liter) was only 5.4% in men so that the relative risk of hip fracture was high but the absolute risk was small. What is surprising is the unexpected low incidence of vitamin D insufficiency in Sweden, which is 55–65° above the equator. Some other studies in Sweden have also shown a low prevalence of serum 25OHD below 20 ng/ml (50 nmol/liter) (10); this may be due to fortification of food and higher vitamin D intake. In other parts of Europe, there is a higher prevalence of serum 25OHD below 20 ng/ml (50 nmol/liter) (10), and in North America the prevalence of serum 25OHD below 20 ng/ml (50 nmol/liter) in men is 23% (11). In areas of vitamin D insufficiency, the absolute number of hip fractures due to vitamin D deficiency should be increased. The authors also analyzed the effect of baseline serum 25OHD on bone mineral density (BMD) and found that the subjects with serum 25OHD below 16 ng/ml (40 nmol/liter) had spine BMD that was 9% lower (1.2 *vs.* 1.32 g/cm^2; $P = 0.04$) compared with those with higher serum 25OHD levels that can be attributed to secondary hyperparathyroidism. There was no difference in hip BMD.

Other recent studies provide similar results. A bone biopsy study in Germany was performed in 675 autopsies after sudden death (12). Autopsies excluded secondary causes of osteoporosis. They found osteomalacia in approximately 24% of cases. Serum 25OHD was measured at autopsy and then correlated with the biopsy findings. Approximately 96.5% of osteomalacia cases occurred at a serum 25OHD level below 20 ng/ml (50 nmol/liter), and approximately 99% occurred at a serum 25OHD below 25 ng/ml (62.5 nmol/liter). There was no difference in the results of men *vs.* women.

A nested case-control study from the Women's Health Initiative (WHI) observation study (mean age, 71 yr) examined hip fracture incidence over 7 yr according to quartiles of serum 25OHD and found a significant increase in hip fractures with an adjusted odds ratio of 1.71 (95% CL, 1.05–2.79) only in the lowest quartile of serum 25OHD of 19 ng/ml (47.5 nmol/liter) or less compared with the highest quartile of at least 28.3 ng/ml (70.75 nmol/liter) (13). In a recent case-cohort study of 436 men with incident nonspine fractures of 1608 men with average follow-up of 5.3 yr (14), the HR for hip fracture incidence was 2.36 (95% CL, 1.08–5.16) in the lowest quartile of total serum 25OHD below 19 ng/ml (47.5 nmol/liter) compared with the highest quartile above 27.9 ng/ml (70 nmol/liter) after adjustment for age, race, clinic, season of blood draw, physical activity, weight, and height. Serum 25OHD was not related to nonspine fracture incidence. In the NHANES study (15), the risk of hip fractures in men and women combined was compared for several categories of serum 25OHD levels: below 16 ng/ml (40 nmol/liter), hip fracture risk was 60% higher; below 20 ng/ml (50 nmol/liter), 45% higher; below 25 ng/ml (62.5 nmol/liter), 36% higher; and below 30 ng/ml (75 nmol/liter), 13% higher (nonsignificant). In a prospective Swedish study, a comparison of hip fracture rates in ambulatory, elderly women (age 75 yr) showed a 2-fold increase with a serum 25OHD below 20 ng/ml (50 nmol/liter) (16). However, three small studies found no associations between fractures and serum 25OHD (17–19), but there were some caveats—younger subjects in one study (53 yr), high dropout rate and lack of adjustment for confounders in the second, and old technology for measuring serum 25OHD in the third.

In looking at other outcomes, a longitudinal study of bone loss over 4.4 yr in the Osteoporotic Fractures in Men (MrOS) study compared rates of bone loss in quartiles of serum 25OHD (11). The rate of bone loss in the hip was as follows: serum 25OHD below 15 ng/ml (37.5 nmol/liter), 0.59%/yr; 15–20 ng/ml (37.5–50 nmol/liter), 0.54%/yr; 20–30 ng/ml (50–75 nmol/liter), 0.35%/yr; and above 30 ng/ml (75 nmol/liter), 0.37%/yr; thus, the higher rates of bone loss occurred in the groups with serum 25OHD below 20 ng/ml (50 nmol/liter). This relationship was more apparent for the older men in the study, *i.e.* age 75+ yr. One other study in women of hip bone loss and

serum 25OHD did find an association with serum 25OHD levels (20).

What are the recommendations for populations with vitamin D insufficiency with serum 25OHD below 20 ng/ml (50 nmol/liter)? To determine the optimum dose of vitamin D for treatment of bone loss and fractures, it is necessary to perform dose-response studies. In osteoporosis trials, study design tries to find a noneffective dose, a minimum effective dose, and an optimum dose for benefit/risk because higher doses often come with more adverse events. These types of trials have never been done for vitamin D, and so it is difficult to determine a threshold level of serum 25OHD for efficacy from published data. Consequently, one has to use an indirect approach and try to estimate from serum 25OHD measurements a threshold for efficacy. Usually, the calculation of the recommended daily allowance for vitamin D is based on achieving the efficacy end point in 97.5% of the treated group. If those data are not available, then an adequate intake is estimated for 50% of the population. Because of the lack of suitably designed clinical trials, efficacy has to be estimated from meta-analysis of osteoporosis studies. Complicating the picture is the fact that most vitamin D studies also include calcium supplements that may have an interaction with vitamin D.

The best single-dose study is the placebo-controlled WHI trial of vitamin D 400 IU plus calcium 1g/d (21). Baseline vitamin D intake of 365 IU increased the total daily dose to approximately 765 IU, and baseline calcium intake of 1150 mg/d increased the total intake to 2150 mg/d. In the intent-to-treat analysis, there was no significant effect on any fracture, but a complier analysis (≥80% of study medication used) showed a significant effect on hip fracture reduction (HR, 0.71; 95% CL, 0.52–0.97). In a subset of women, serum 25OHD at baseline was 18.8 ng/ml (47 nmol/liter) and increased 28% to 24 ng/ml (60 nmol/liter) on vitamin D. To prevent one hip fracture, the number needed to treat was 5045 for all postmenopausal women and 1914 for women above age 60 yrs. Of concern was the small but significant increase in renal stones in the intent-to-treat analysis (HR, 1.17; 95% CL, 1.02–1.34); it was not dependent on baseline calcium intake, suggesting that adding vitamin D increased the risk. In the WHI trial, there was no decrease in all-cause mortality on vitamin D plus calcium.

Two high-quality meta-analyses (22, 23) with slightly different inclusion criteria included 68,517 and 46,108 men and women from mostly vitamin D-insufficient areas. The conclusions were similar in that vitamin D alone is not effective for fracture prevention (HR, 1.01; 95% CL, 0.92–1.12) (22), but vitamin D intake of at least 800 IU/d combined with a calcium intake of 1000–1200 mg/d is effective for fracture prevention: HR, 0.92; 95% CL, 0.86–0.99 (22); and relative risk, 0.87; 95% CL, 0.77–0.97 (23).

In summary, a convergence of the data suggests that an optimal serum level of 25OHD for bone health is above 20 ng/ml (50 nmol/liter) and that treatment with a small dose of vitamin D 800 IU plus a total calcium intake of 1200 mg/d can reduce fractures. Vitamin D and calcium have a small effect on fracture risk reduction and are best used as an adjunctive therapy with other osteoporosis drugs.

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References

1. **Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK** 1987 Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency. Am J Clin Nutr 45:755–763
2. **Need AG, O'Loughlin PD, Morris HA, Coates PS, Horowitz M, Nordin BE** 2008 Vitamin D metabolites and calcium absorption in severe vitamin D deficiency. J Bone Miner Res 23:1859–1863
3. **WHO Scientific Group on the Prevention and Management of Osteoporosis** 2003 Prevention and management of osteoporosis: report of a WHO scientific group. Geneva: World Health Organization
4. **Holick MF** 2007 Vitamin D deficiency. N Engl J Med 357:266–281
5. **Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G** 2005 Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. JAMA 294:2336–2341
6. **Chapuy MC, Preziosi P, Maamer M, Arnaud S, Galan P, Hercberg S, Meunier PJ** 1997 Prevalence of vitamin D insufficiency in an adult normal population. Osteoporos Int 7:439–443
7. **Harwood RH, Sahota O, Gaynor K, Masud T, Hosking DJ** 2004 Nottingham Neck of Femur (NONOF) Study. A randomised, controlled comparison of different calcium and vitamin D supplementation regimens in elderly women after hip fracture: The Nottingham Neck of Femur (NONOF) Study. Age Ageing 33:45–51
8. **Aloia JF, Patel M, Dimaano R, Li-Ng M, Talwar SA, Mikhail M, Pollack S, Yeh JK** 2008 Vitamin D intake to attain a desired serum 25-hydroxyvitamin D concentration. Am J Clin Nutr 87:1952–1958
9. **Melhus H, Snellman G, Gedeborg R, Byberg L, Berglund L, Mallmin H, Hellman P, Blomhoff R, Hagström E, Arnlöv J, Michaëlsson K** 2010 Plasma 25-hydroxyvitamin D levels and fracture risk in a community-based cohort of elderly men in Sweden. J Clin Endocrinol Metab 95:2637–2645
10. **Lips P, Duong T, Oleksik A, Black D, Cummings S, Cox D, Nickelsen T** 2001 A global study of vitamin D status and parathyroid function in

postmenopausal women with osteoporosis: baseline data from the multiple outcomes of raloxifene evaluation clinical trial. J Clin Endocrinol Metab 86:1212–1221

11. **Ensrud KE, Taylor BC, Paudel ML, Cauley JA, Cawthon PM, Cummings SR, Fink HA, Barrett-Connor E, Zmuda JM, Shikany JM, Orwoll ES, Osteoporotic Fractures in Men Study Group** 2009 Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Clin Endocrinol Metab 94:2773–2780
12. **Priemel M, von Domarus C, Klatte TO, Kessler S, Schlie J, Meier S, Proksch N, Pastor F, Netter C, Streichert T, Püschel K, Amling M** 2010 Bone mineralization defects and vitamin D deficiency: histomorphometric analysis of iliac crest bone biopsies and circulating 25-hydroxyvitamin D in 675 patients. J Bone Miner Res 25:305–312
13. **Cauley JA, Lacroix AZ, Wu L, Horwitz M, Danielson ME, Bauer DC, Lee JS, Jackson RD, Robbins JA, Wu C, Stanczyk FZ, LeBoff MS, Wactawski-Wende J, Sarto G, Ockene J, Cummings SR** 2008 Serum 25-hydroxyvitamin D concentrations and risk for hip fractures. Ann Intern Med 149:242–250
14. **Cauley JA, Parimi N, Ensrud KE, Bauer DC, Cawthon PM, Cummings SR, Hoffman AR, Shikany JM, Barrett-Connor E, Orwoll E; for the Osteoporotic Fractures in Men (MrOS) Research Group** 2010 Serum 25 hydroxyvitamin D and the risk of hip and non-spine fractures in older men. J Bone Miner Res 25:545–553
15. **Looker AC, Mussolino ME** 2008 Serum 25-hydroxyvitamin D and hip fracture risk in older U.S. white adults. J Bone Miner Res 23: 143–150
16. **Gerdhem P, Ringsberg KA, Obrant KJ, Akesson K** 2005 Association between 25-hydroxy vitamin D levels, physical activity, muscle strength and fractures in the prospective population-based OPRA study of elderly women. Osteoporos Int 16:1425–1431
17. **Roddam AW, Neale R, Appleby P, Allen NE, Tipper S, Key TJ** 2007 Association between plasma 25-hydroxyvitamin D levels and fracture risk: the EPIC-Oxford study. Am J Epidemiol 166:1327–1336
18. **Woo J, Lau E, Swaminathan R, Pang CP, MacDonald D** 1990 Biochemical predictors for osteoporotic fractures in elderly Chinese—a longitudinal study. Gerontology 36:55–58
19. **Cummings SR, Browner WS, Bauer D, Stone K, Ensrud K, Jamal S, Ettinger B** 1998 Endogenous hormones and the risk of hip and vertebral fractures among older women. Study of Osteoporotic Fractures Research Group. N Engl J Med 339:733–738
20. **Stone K, Bauer DC, Black DM, Sklarin P, Ensrud KE, Cummings SR** 1998 Hormonal predictors of bone loss in elderly women: a prospective study. The Study of Osteoporotic Fractures Research Group. J Bone Miner Res 13:1167–1174
21. **Jackson RD, LaCroix AZ, Gass M, Wallace RB, Robbins J, Lewis CE, Bassford T, Beresford SA, Black HR, Blanchette P, Bonds DE, Brunner RL, Brzyski RG, Caan B, Cauley JA, Chlebowski RT, Cummings SR, Granek I, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Johnson KC, Judd H, Kotchen JM, Kuller LH, Langer RD, Lasser NL, Limacher MC, Ludlam S, Manson JE, Margolis KL, McGowan J, Ockene JK, O'Sullivan MJ, Phillips L, Prentice RL, Sarto GE, Stefanick ML, Van Horn L, Wactawski-Wende J, Whitlock E, Anderson GL, Assaf AR, Barad D, Women's Health Initiative Investigators** 2006 Calcium plus vitamin D supplementation and the risk of fractures. N Engl J Med 354:669–683
22. **DIPART (Vitamin D Individual Patient Analysis of Randomized Trials) Group** 2010 Patient level pooled analysis of 68,500 patients from seven major vitamin D fracture trials in US and Europe. BMJ 340:b5463
23. **Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A** 2007 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 370:657–666