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Calcium and Vitamin D

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Calcium is required for the bone formation phase of bone remodeling. Typically, about 5 nmol (200 mg) of calcium is removed from the adult skeleton and replaced each day. To supply this amount, one would need to consume about 600 mg of calcium, since calcium is not very efficiently absorbed. Calcium also affects bone mass through its impact on the remodeling rate. An inadequate intake of calcium results in reduced calcium absorption, a lower circulating ionized calcium concentration, and an increased secretion of parathyroid hormone (PTH), a potent bone-resorbing agent. A high remodeling rate leads to bone loss; it is also an independent risk factor for fracture. Dietary calcium at sufficiently high levels, usually 1,000 mg per day or more, lowers the bone remodeling rate by about 10% to 20% in older men and women and the degree of suppression appears to be dose related [1]. The reduction in remodeling rate accounts for the increase in BMD that occurs in the first 12 to 18 months of treatment with calcium.

With aging there is a decline in calcium absorption efficiency in men and women. This may be related to loss of intestinal vitamin D receptors or resistance of these receptors to the action of 1,25-dihydroxyvitamin D. Diet composition, season, and race also influence calcium absorption efficiency.

Vitamin D is acquired from the diet and from skin synthesis, upon exposure to ultraviolet B rays. The best clinical indicator of vitamin D status is the serum 25-hydroxyvitamin D (25OHD) level. Serum 25OHD levels are lower in individuals using sunscreens and in those with more pigmented skin. Season is an important determinant of vitamin D levels. In much of the temperate zone, skin synthesis of vitamin D does not occur during the winter. Consequently, 25OHD levels fall in the winter and early spring. Serum PTH levels vary inversely with 25OHD levels. These cyclic changes are not benign. Bone loss is greater in the winter/spring when 25OHD levels are lowest (and PTH levels are highest) than in the summer/fall when 25OHD levels are highest (and PTH levels are lowest).

Serum 25OHD levels decline with aging for several reasons. There is less efficient skin synthesis of vitamin D with aging as a result of an age-related decline in the amount of 7-dehydrocholesterol, the precursor to vitamin D, in the epidermal layer of skin [2]. Also, older individuals as a group spend less time out-of-doors. There does not appear to be an impairment in the intestinal absorption of vitamin D with aging [3].

IMPACT ON BONE MINERAL DENSITY

Calcium and vitamin D support bone growth in children and adolescents and lower rates of bone loss in adults and the elderly. However, the association of calcium with bone mass appears to be influenced by vitamin D status. In men and women age 20 years and older in National Health and Nutrition Evaluation Survey III (NHANES III), higher calcium intake was associated with higher femoral neck bone mineral density (BMD) at 25OHD levels below 50 nmol/l (or 20 ng/ml) but not at higher

Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism, Eighth Edition. Edited by Clifford J. Rosen.

25OHD levels [4]. A meta-analysis of 15 trials found that calcium alone in adults caused positive mean percentage BMD changes from a baseline of 1.7% at the lumbar spine, 1.6% at the hip, and 1.9% at the distal radius [5]. In one trial, the effects of calcium from food (milk powder) and supplement sources on changes in BMD in older postmenopausal women were compared and found to be similar [6].

Higher serum 25OHD levels have been associated with higher BMD of the hip in young and older adult men and women in NHANES III [4]. This association was present across the full range of 25OHD values. Supplementation with vitamin D also reduces rates of bone loss in older adults [7]. In order to sustain the reduced turnover rate and higher bone mass induced by increased calcium and vitamin D intakes, the higher intakes need to be maintained.

IMPACT ON MUSCLE STRENGTH, BALANCE, AND FALLING

In NHANES III women age 60 and older, higher 25OHD levels were associated with improved lower extremity function (faster walking and sit-to-stand speeds) [8]. Similarly, in 1,234 elderly men and women living in the Netherlands, concentrations of 25(OH)D below 50 nmol/L (or 20 ng/ml) were associated with reduced physical performance [9]. Results of vitamin D intervention studies have been more variable. In a meta-analysis of 17 trials, Stockton and colleagues found that supplemental vitamin D had no significant effect on lower extremity muscle strength except in individuals with low starting serum 25OHD levels, less than 25 nmol/L (or 10 ng/ml) [10]. The mechanism(s) by which vitamin D influences muscle performance and strength are not well established but are likely to involve the nuclear vitamin D receptors known to be present in muscle. Supplementation with 1,000 IU of vitamin D_2 daily over a 2-year period, when compared with placebo, significantly increased the diameter of fast twitch type II muscle fibers in older women who had had a recent stroke [11].

Vitamin D appears to have a favorable effect on balance in older adults. Sway, a measure of balance, is assessed with the subject standing on a force plate that measures the maximum displacement in the anteroposterior and medial-lateral directions, the average speed of displacement, and other parameters [12]. In adults age 60 years and older, the amplitude of sway in the medial–lateral direction was a strong predictor of falling more than once per year [13]. In two independent randomized controlled trials, 800 IU of vitamin D_3 plus 1,000 mg of calcium per day, compared with calcium alone, reduced sway by up to 28% over periods of 2 and 12 months [14, 15]. The mechanisms by which vitamin D affects balance have not been defined.

Vitamin D is recommended by several organizations to lower the risk of falling [16–18]. A meta-analysis of eight randomized placebo-controlled vitamin D intervention trials revealed that the effect of supplementation was dose dependent. Higher dose trials (700–1,000 IU/day) showed a risk reduction, whereas lower dose trials did not [19]. The magnitude of the risk reduction in the higher dose trials averaged 19%, or, when recalculated, 34% [20]. A higher dose of 2,000 IU per day, when compared with 800 IU per day, showed no fall risk reduction in elderly acute hip fracture patients [21], suggesting that 800 IU per day is adequate for this outcome. The serum 25OHD level needed to reduce falls was estimated to be at least 60 nmol/l (or 24 ng/ml) [19]. The impact of vitamin D on falls is likely to be mediated by its effect on muscle strength and balance.

IMPACT ON FRACTURE RATES

Several small studies have examined the impact of supplemental calcium on fracture rates. The Shea meta-analysis of these studies (13) found that calcium alone (versus placebo) tended to lower risk of vertebral fractures [RR 0.77 (CI 0.54–1.09)] but not nonvertebral fractures [RR 0.86 (CI 0.43–1.72)]. The studies in this analysis ranged from 18 months to 4 years in duration. A more recent meta-analysis reached similar conclusions, citing a trend toward a modest reduction in risk of nonvertebral fracture [RR 0.92 (95% CI: 0.81, 1.05)] and no significant effect on hip fracture risk [RR 1.64 (95% CI: 1.02, 2.64)] [22].

The effect of supplemental vitamin D on fracture incidence has been examined in several randomized controlled trials with varying results. A recent meta-analysis of these trials revealed that the response to supplementation was dose dependent. The trials using received doses >400 IU/day per day were positive for nonvertebral fractures [RR 0.80 (0.72–0.89)] and hip fractures [RR 0.82 (0.69–0.97)], whereas those using received doses of less than 400 IU per day were null [23]. Received dose is the product of administered dose and percentage adherence. Serum 25OHD levels were measured in most of these trials and among these, a group mean value of approximately 75 nmol/l (or 30 ng/ml) was needed to lower hip fracture risk [23]. The reduced risk of fracture likely results from effects of vitamin D on muscle, balance, fall risk, and bone metabolism. In many of the higher dose vitamin D trials, calcium was given along with vitamin D; based on this and other evidence, it is reasonable to replete both calcium and vitamin D. Several other meta-analyses have reached different conclusions, at least in part because different specific questions were posed and different selection criteria for study inclusion were applied [24, 25].

ROLE IN PHARMACOTHERAPY

In recent randomized controlled trials testing the antifracture efficacy of the antiresorptive therapies alendro-

nate, risedronate, raloxifene, and calcitonin, and the anabolic drug, PTH 1-34, calcium and vitamin D have been given to both the control and intervention groups. This allows one to define the impact of these drugs in calcium- and vitamin D-replete patients and to conclude that any efficacy of the drugs is beyond that associated with calcium and vitamin D alone. However, one cannot conclude that these drugs would have the same efficacy in calcium- and vitamin D-deficient patients.

INTAKE REQUIREMENTS

Calcium intake recommendations vary enormously worldwide. Recommendations by the Institute of Medicine (IOM) of the U.S. National Academy of Sciences are among the highest. The IOM recommended intakes of calcium are: ages 1–3 years, 500 mg; 4–8 years, mg; 9–18 years, 1,100 mg; 19–50 years, 800 mg; 51–70 years, 800 mg for men and 1,000 mg for women; older than 70 years, 1,000 mg per day [26]. Lower calcium intakes would likely be adequate for populations with lower intakes of salt and protein, two diet components that promote calcium excretion in the urine.

Among females in the U.S., fewer than 1 in 4 meet the calcium requirement through their diets; when calcium from supplement and food sources is considered, about half of U.S. females meet the requirement [26]. Among males, calcium intake from food is somewhat higher and from supplements somewhat lower than among females, with the result that, considering combined calcium sources, about half of U.S. males meet the calcium requirement [26]. Calcium from calcium carbonate, the most commonly used supplement, is better absorbed when taken with a meal [27, 28]. Absorption from all supplements is more efficient in doses up to 500 mg than from higher doses [29]. Thus, individuals requiring more than 500 mg per day from supplements should take it in divided doses.

The vitamin D intake recommendations of the IOM are: for males and females age 1–70 years, 1.5 mcg (600 IU), and for ages older than 70 years, 2 mcg (800 IU) per day [26]. For older adults these recommendations are based on BMD and fracture risk. The IOM concluded that "a 25OHD level of 40 nmol/l was consistent with the intended nature of an average requirement, in that it reflects the desired level for a population median—it meets needs for approximately half of the population" [26]. The IOM recommends a level of 50 nmol/l to meet the need of 97.5% of the population [26]. There is lack of consensus in the professional community about whether the target group mean 25OHD level should be 40, 50, 75 nmol/l or another number. Several organizations recommend 75 nmol/l as the target [16–18].

A vitamin D intake of 800 IU (15 mcg) per day is not adequate to bring more than about half of the elderly population to 25OHD levels of 75 nmol/L (or 30 ng/ml). Older men and women who are at average risk for low 25OHD levels will need an intake of 20 to 25 mcg (800 to 1000 IU) per day to maintain a serum 25OHD level of 75 nmol/L (30 ng/ml). Individuals at increased risk for low serum 25OHD levels, such as those with limited regular skin production of vitamin D (related dark skin, little time out of doors, sunscreen use, protective clothing, high latitude), obesity, malabsorption, and other conditions that limit absorption or alter vitamin D metabolism will need more than 800 to 1,000 IU to maintain a 25OHD level of 75 nmol/l (or 30 ng/ml). The increase in 25OHD with supplementation is inversely related to the starting level. At low starting levels, 1 mcg (40 IU) of vitamin D will increase serum 25OHD by 1.2 nmol/L (or 0.48 ng/ml); at a higher starting level of 70 nmol/L (28 ng/ml), the increase from this dose would be only about 0.7 nmol/L (or 0.28 ng/ml) [30, 31]. Vitamin D is available in two forms: the plant-derived ergocalciferol (D_2) and animal-derived cholecalciferol (D_3). For years these forms were considered to be equipotent in humans but recent evidence indicates that vitamin D_3 increases serum 25OHD levels more efficiently than vitamin D_2 [32]. Moreover, vitamin D_2 is not accurately measured in all 25OHD assays [33]. For these reasons, vitamin D_3, when available, is the preferred form for clinical use.

SAFETY

Recent reports have raised the issue of potential risk associated with excessive calcium supplement use. Bolland and colleagues reported that calcium supplement use without coadministered vitamin D increased risk of myocardial infarction [34]. However, increased risk was not observed in another earlier meta-analysis [35]. A detailed report from the Women's Health Initiative revealed a 17% increase in renal stones in the women treated with calcium and vitamin D as compared to the women treated with placebo [36]. Individuals with high calcium intake from food sources do not share this risk and may in fact have reduced risk of nephrolithiasis [37]. All things considered, it would seem prudent to obtain calcium from food sources to the greatest extent possible and to use supplements only as needed to bring total intake up to recommended levels. The IOM and others have identified no risk associated with serum 25OHD levels up through 125 nmol/l (or 50 ng/ml) [26].

The safe upper limits for calcium set by the IOM are: ages 1–8 years, 2,500 mg; 9–18 years, 3,000 mg; 19–50 years, 2,500 mg; older than 50 years, 2,000 mg per day [26]. The IOM has placed the safe upper limit for vitamin D at: ages 1–3 years, 2,500 IU; ages 4–8 years, 3,000 IU; and ages older than 8 years, 4,000 IU per day [26].

In conclusion, adequate intakes of calcium and vitamin D are essential preventative measures and essential components of any therapeutic regimen for osteoporosis. Many men and women will need supplements to meet the intake requirements. There is no known advantage

but there is potential risk in exceeding current calcium intake recommendations, particularly with use of supplements. Currently, the most common target serum 25OHD levels for musculoskeletal health are 50 nmol/l (20 ng/ml), recommended by the IOM, and 75 nmol/l (30 ng/ml), recommended by many specialty groups and others. There is a consensus that both of these target levels are safe. Additional research is needed to fully define the musculoskeletal and other health effects of different doses of vitamin D and serum 25OHD levels.

REFERENCES

1. Elders PJ, Lips P, Netelenbos JC, et al. 1994. Long-term effect of calcium supplementation on bone loss in perimenopausal women. *J Bone Miner Res* 9(7): 963–970.
2. MacLaughlin J, Holick MF. 1985. Aging decreases the capacity of human skin to produce vitamin D3. *J Clin Invest* 76(4): 1536–1538.
3. Harris SS, Dawson-Hughes B. 2002. Plasma vitamin D and 25OHD responses of young and old men to supplementation with vitamin D3. *J Am Coll Nutr* 21(4): 357–362.
4. Bischoff-Ferrari HA, Kiel DP, Dawson-Hughes B, et al. 2009. Dietary calcium and serum 25-hydroxyvitamin D status in relation to BMD among U.S. adults. *J Bone Miner Res* 24(5): 935–942.
5. Shea B, Wells G, Cranney A, et al. 2002. VII. Meta-analysis of calcium supplementation for the prevention of postmenopausal osteoporosis. *Endocrine Rev* 23(4): 552–559.
6. Prince R, Devine A, Dick I, et al. 1995. The effects of calcium supplementation (milk powder or tablets) and exercise on bone density in postmenopausal women. *J Bone Miner Res* 10(7): 1068–1075.
7. Ooms ME, Roos JC, Bezemer PD, van der Vijgh WJ, Bouter LM, Lips P. 1995. Prevention of bone loss by vitamin D supplementation in elderly women: A randomized double-blind trial. *J Clin Endocrin Metab* 80(4): 1052–1058.
8. Bischoff-Ferrari HA, Dietrich T, Orav EJ, et al. 2004. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged > or =60 y. *Am J Clin Nutr* 80(3): 752–758.
9. Wicherts IS, van Schoor NM, Boeke AJ, et al. 2007. Vitamin D status predicts physical performance and its decline in older persons. *J Clin Endocrinol Metab* 92(6): 2058–2065.
10. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL. 2011. Effect of vitamin D supplementation on muscle strength: A systematic review and meta-analysis. *Osteoporos Int* 22(3): 859–871.
11. Sato Y, Iwamoto J, Kanoko T, Satoh K. 2005. Low-dose vitamin D prevents muscular atrophy and reduces falls and hip fractures in women after stroke: A randomized controlled trial. *Cerebrovasc Dis* 20(3): 187–192.
12. Swanenburg J, de Bruin ED, Favero K, Uebelhart D, Mulder T. 2008. The reliability of postural balance measures in single and dual tasking in elderly fallers and non-fallers. *BMC Musculoskelet Disord* 9: 162.
13. Swanenburg J, de Bruin ED, Uebelhart D, Mulder T. 2010. Falls prediction in elderly people: A 1-year prospective study. *Gait Posture* 31(3): 317–321.
14. Pfeifer M, Begerow B, Minne HW, Abrams C, Nachtigall D, Hansen C. 2000. Effects of a short-term vitamin D and calcium supplementation on body sway and secondary hyperparathyroidism in elderly women. *J Bone Miner Res* 15(6): 1113–1118.
15. Bischoff HA, Stahelin HB, Dick W, et al. 2003. Effects of vitamin D and calcium supplementation on falls: A randomized controlled trial. *J Bone Miner Res* 18(2): 343–351.
16. Michael YL, Whitlock EP, Lin JS, Fu R, O'Connor EA, Gold R. 2010. Primary care-relevant interventions to prevent falling in older adults: A systematic evidence review for the U.S. Preventive Services Task Force. *Ann Intern Med* 153(12): 87–825.
17. Dawson-Hughes B, Mithal A, Bonjour JP, et al. IOF position statement: Vitamin D recommendations for older adults. *Osteoporos Int* 24(4): 1151–1154.
18. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. 2011. Evaluation, treatment, and prevention of vitamin d deficiency: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 96(7): 1911–1930.
19. Bischoff-Ferrari HA, Dawson-Hughes B, Staehelin HB, et al. 2009. Fall prevention with supplemental and active forms of vitamin D: A meta-analysis of randomised controlled trials. *Br Med J* 339: b3692.
20. Bischoff-Ferrari HA, Willett WC, Orav JE, Kiel DP, Dawson-Hughes B. 2011. Fall prevention with vitamin D: Author's reply. *Br Med J* 342: d2608
21. Bischoff-Ferrari HA, Dawson-Hughes B, Platz A, et al. 2010. Effect of high-dosage cholecalciferol and extended physiotherapy on complications after hip fracture: A randomized controlled trial. *Arch Intern Med* 170(9): 813–820.
22. Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. 2007. Calcium intake and hip fracture risk in men and women: A meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 86(6): 1780–1790.
23. Bischoff-Ferrari HA, Willett WC, Wong JB, et al. 2009. Prevention of nonvertebral fractures with oral vitamin D and dose dependency: A meta-analysis of randomized controlled trials. *Arch Intern Med* 169(6): 551–561.
24. 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. [See comment]. *Lancet* 370(9588): 657–666.
25. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P. 2007. Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative meta-analysis of randomized controlled trials. *J Clin Endocrinol Metab* 92(4): 1415–1423.

26. IOM (Institute of Medicine). 2011. *Dietary Reference Intakes for Calcium and Vitamin D*. Washington, DC: The National Academies Press.
27. Heaney RP, Smith KT, Recker RR, Hinders SM. 1989. Meal effects on calcium absorption. *Am J Clin Nutr* 49(2): 372–376.
28. Recker RR. 1985. Calcium absorption and achlorhydria. *N Engl J Med* 313(2): 70–73.
29. Harvey JA, Zobitz MM, Pak CY. 1988. Dose dependency of calcium absorption: A comparison of calcium carbonate and calcium citrate. *J Bone Miner Res* 3(3): 253–258.
30. Vieth R, Ladak Y, Walfish PG. 2003. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab* 88(1): 185–191.
31. Heaney RP, Davies KM, Chen TC, Holick MF, Barger-Lux MJ. 2003. Human serum 25-hydroxycholecalciferol response to extended oral dosing with cholecalciferol. *Am J Clin Nutr* 77(1): 204–210.
32. Heaney RP, Recker RR, Grote J, Horst RL, Armas LA. 2011. Vitamin D(3) is more potent than vitamin D(2) in humans. *J Clin Endocrinol Metab* 96(3): E447–452.
33. Binkley N, Krueger D, Cowgill CS, et al. 2004. Assay variation confounds the diagnosis of hypovitaminosis D: A call for standardization. *J Clin Endocrinol Metab* 89(7): 3152–3157.
34. Bolland MJ, Avenell A, Baron JA, et al. 2010. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: Meta-analysis. *Br Med J* 341: c3691.
35. Wang L, Manson JE, Song Y, Sesso HD. 2010. Systematic review: Vitamin D and calcium supplementation in prevention of cardiovascular events. *Ann Intern Med* 152(5): 315–323.
36. Wallace RB, Wactawski-Wende J, O'Sullivan MJ, et al. 2011. Urinary tract stone occurrence in the Women's Health Initiative (WHI) randomized clinical trial of calcium and vitamin D supplements. *Am J Clin Nutr* 94(1): 270–277.
37. Serio A, Fraioli A. 1999. Epidemiology of nephrolithiasis. *Nephron* 81 Suppl 1: 26–30.