Vitamin D and Skeletal Aging

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INTRODUCTION

Vitamin D is required for intestinal absorption of dietary calcium and for normal mineralization of bone. It fulfills the classic definition of a vitamin because it is an essential nutrient provided by natural foodstuffs that is needed in minute amounts to prevent deficiency diseases. Dietary sources are plants, which photosynthesize ergocalciferol (vitamin D_2), fatty fishes such as salmon and mackerel, cod liver oil, and fortified foodstuffs (cereals, cereal bars, and juices).

There are two reasons to consider vitamin D a hormone rather than a vitamin. First, it can be produced by the skin upon exposure to sunlight (Figure 1). Second, because its activity depends upon sequential hydroxylations in the liver and kidney, even dietary vitamin D must be enzymatically activated. The intermediate is 25-hydroxyvitamin D, the major circulating form, and the active metabolite is 1,25-dihydroxyvitamin D (Figure 2).

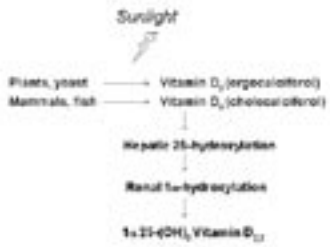

Figure 1

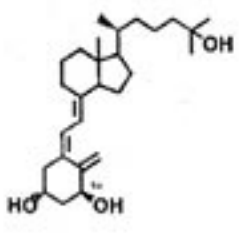

Figure 2

Solar high-energy ultraviolet B photons are absorbed by the precursor of vitamin D, 7-dehydrocholesterol, in the skin, which is converted into cholecalciferol (vitamin D_3). In Boston (42°N), from November through February, the zenith angle of the sun results in more oblique penetration of sunlight and thus more absorption by the ozone layer. Dietary sources and vitamin D supplements become more important during the winter months. Other factors influence the synthesis of vitamin D in the skin. Individuals with a high content of melanin in the skin require longer exposure to sunlight to make adequate amounts of vitamin D. Use of sunscreen with SPF of 8 diminishes production by more than 95%. With aging, there is less 7-dehydrocholesterol in the skin such that elders make 25% of the vitamin D made by younger individuals. Nevertheless, exposure to as little as 5-15 minutes of sunlight to hands, face, and forearms two to three times each week will result in increased blood levels of 25-hydroxyvitamin D in deficient individuals, but even this is often not achieved in many adults. Exposures longer than this need be accompanied by use of sunscreen.

DAILY REQUIREMENT FOR VITAMIN D

According to the Institutes of Medicine (IOM) 1997 review of the daily requirement for vitamin D, an adequate intake of vitamin D is 200 IU/d in children and adults until the age of 50 years. The recommendation is 400 IU/d for adults between the ages of 51 to 70 and 600 IU/d for those older than 71 years. Some physicians treat elders with 1600 IU/day. Elders should avoid taking two multivitamin pills to increase their vitamin D intake because of risk of vitamin A intoxication. The IOM also established the tolerable upper limit of safety as 2000 IU of vitamin D per day for adults. Poor uptake of vitamin D occurs in fat malabsorption syndromes such as Crohn's disease, sprue, Whipple's disease, and hepatobiliary dysfunction. Medications such as phenytoin and phenobarbital inhibit 25-hydroxylation, requiring patients taking those drugs to receive 2-5 times the RDA for vitamin D. Rare inherited hypocalcemic disorders are caused by either a deficiency in renal 1α–hydroxylation (vitamin D-dependent rickets type I) or a defect in the vitamin D receptor (vitamin D-dependent type II).

Alternatives to sun exposure and daily tablets are annual intramuscular injections of 150,000 IU to 300,000 IU of vitamin D. Patients with chronic renal failure cannot 1-hydroxylate the 25-hydoxyvitamin D and require replacement therapy, but treatment with 1,25-dihydoixyvitamin D can produce hypercalcemia. New analogs such as 22-oxacalcitriol (OCT), 1α-OHD2, paricalcitol, and falecalcitriol have lower risk for hypercalcemia than occurs with 1,25-dihydroxyvitamin D and are approved for those patients.

Patients with vitamin D deficiency require immediate aggressive therapy. Pharmacological doses of oral vitamin

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D at 50,000 IU once a week for 8 weeks will rapidly restore D status unless there is ongoing malabsorption. To prevent hypercalcemia or hypercalciuria, medical follow-up of serum calcium, 25-hydroxyvitamin D, and urinary calcium levels are necessary. Vitamin D intoxication can follow the prolonged intake of excessively high levels of vitamin D. Exuberant use of topical calcipotriene (a vitamin D analog) for psoriasis can cause vitamin D intoxication. In patients with vitamin D intoxication, the abnormal calcium metabolism is due to the excessive 25-hydroxyvitamin D and not to 1,25-dihydroxyvitamin D. Values greater than 200 ng/mL 25-hydroxyvitamin D can be encountered. It can manifest with hypercalcemia, hyperosteolysis, azotemia, and anemia. Calcifications of soft tissue, muscle, and vessels may occur. Development of hypercalcemia can lead to headaches, nausea, polyuria, polydipsia, and weakness. Hypercalciuria without hypercalcemia can result in nephrolithiasis. Vitamin D intoxication has occurred due to accidental overfortification of milk by small dairies or due to dietary supplements containing unadvertised high levels of vitamin D.

Vitamin D deficiency is increasingly identified across the lifecycle from adolescents to mature adults. It is important, therefore, to test for the presence of vitamin D deficiency. Vitamin D status is measured by the serum concentration of 25-hydroxyvitamin D. The most abundant metabolite is 25-hydroxyvitamin D, which is tightly bound to vitamin D-binding protein and has a very long half-life in blood. The active metabolite 1,25-dihydroxyvitamin D is less abundant; its normal range is ~16-65 pg/mL. Serum 25-hydroxyvitamin D levels are lower in individuals using sunscreens and in those with more pigmented skin. Values vary with the season[1] and decline with aging. Many laboratories report that values above 9 or 10 ng/mL are within the normal range for the assays. There is ongoing discussion about redefining normal serum levels, especially because it was shown that healthy individuals with serum 25-hydroxyvitamin D levels at the low end of the current reference ranges did not fully absorb calcium from a test meal, compared to those subjects with 25OHD levels of 36 ng/mL.[2] It is notable that the treatment target for vitamin D-sufficiency is ≥ 30 ng/mL, which is established as a level above which secondary rises in PTH do not develop. "Lifeguard" levels of 100 ng/mL are not considered to be vitamin D-intoxication. Intoxication is properly defined as 25-hydroxyvitamin D >125-150 ng/mL, in the face of hypercalcemia. It can be argued that it is not necessary to routinely assay for 25-hydroxyvitamin D because of the cost of the test and because of the low cost and safety in taking 800 IU/day of vitamin D even if sunlight deprived. Because of the very high prevalence of vitamin D deficiency, particularly during the winter months and in the elderly, identification of extreme deficiency is needed to ensure immediate correction.

DAILY CALCIUM REQUIREMENT

Serum concentrations of calcium are tightly regulated between 8.5 to 10.5 mg/dL. Circulating calcium is distributed between bound, ionized, and a small amount complexed to inorganic ions. The ionized, or unbound, form regulates neuromuscular activity, coagulation, and many enzymatic and cellular processes. The hallmark clinical feature of hypocalcemia is neuromuscular irritability. Other manifestations are cardiac and neurological signs and symptoms, smooth muscle involvement, and skin abnormalities.

Calcium-rich foods are dairy products, broccoli, sardines, soy products, and a growing number of fortified products such as juices, cereals, and breakfast bars. The recommended daily intake of calcium is 1000 mg, but growing children between the ages of 9 to 18 require 1300 mg/day and elders require 1200 mg/day. One 8-oz serving of milk or some supplemented orange juices contain 300 mg of calcium and 98 IU of vitamin D. Typical American girls and women have a calcium intake of less than 500 mg, often because of avoidance of dairy products. Because it is difficult for many to meet this requirement, use of supplements is needed. Many forms of calcium supplements are available. Pharmacokinetic analysis of marketed calcium carbonate, encapsulated calcium carbonate, and marketed calcium citrate in vitamin D-replete postmenopausal women showed that they were equally absorbed, and produced the expected depression in serum PTH.[3] Given the equivalent bioavailability of the different forms, a cost/benefit analysis favors the use of the less expensive carbonate products. Use of calcium citrate or calcium phosphate may be associated with fewer gastrointestinal side effects like bloating or constipation in some individuals. Intakes should be divided to 500 to 600 mg per dose as calcium absorption decreases with higher doses.

CONSEQUENCES OF VITAMIN D-DEFICIENCY[4]

Fortification of foods with vitamin D in the United States has dramatically curtailed the occurrence of rickets and osteomalacia. Vitamin D deficiency can be found more commonly in the winter months, especially among African-Americans, those individuals wearing sunblock, or those wearing protective religious clothing.[5]

With vitamin D-deficiency, there is a reduction in intestinal calcium absorption to no more than 10-15% normal. Subsequent decrease in ionized calcium in the blood signals the calcium sensor in the parathyroid glands to increase synthesis and secretion of PTH. Thereupon, PTH increases renal expression of 1α-hydroxylase to increase activation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (see Figure 1). Also in the kidney, PTH increases tubular reabsorption of calcium. In the bone, PTH stimulates osteoclastic bone resorption. The net effect of vitamin D-deficiency is normal serum calcium, elevated PTH, and low level of 25-hydroxyvitamin D in the blood. In extreme cases, hypocalcemia occurs with potential for tetany and generalized weakness, and cardiac arrythmias. The end result of low calcium and vitamin D intake is persistent secondary hyperparathyroidism. Inadequate levels of vitamin D produce a secondary increase in release of parathyroid hormone that stimulates bone resorption and can result in **osteoporosis** and fracture. If coupled with insufficient intake of calcium, vitamin D deficiency results in **osteomalacia**. Deficiency in children results in the bone-forming disease rickets with widening of the epiphyseal plates and deformed long bones,

especially the legs and ribs. After the epiphyseal growth plates of the bones close, deficiency can cause a mineralization defect in bone tissue called osteomalacia, with isolated or generalized bone pain and increased risk of fracture. Muscle pain and weakness, limb pain, and impaired function are also associated with vitamin D deficiency. These problems may limit walking and needed exposure to sunlight. Vitamin D deficiency has also been implicated in falls, colorectal cancers, multiple sclerosis, osteoarthritis, and many other disorders.[6] There may be no radiographic abnormalities in osteomalacia that distinguishes from osteopenia or there may be a coarsening of trabeculae and a blurring of margins. The most specific radiographic abnormalities are Looser's zones (or pseudofractures), ribbon-like zones of rarefaction that are oriented perpendicular to the bone surface. Upon microscopic examination, Looser's zones are seen to be cortical fractures filled in with poorly mineralized callus and fibrous tissue. The axial skeleton is more often affected than the peripheral skeleton.

Osteoporosis is often accompanied by vitamin D deficiency.[7] Low serum 25-hydroxyvitamin D levels have been associated with a reduction in bone mass. There are several reports of a relationship between vitamin D insufficiency and non-vertebral fractures. Many studies, especially those in countries without fortification of foods, indicate reduced fractures in groups of elders supplemented with vitamin D and calcium.

VITAMIN D-DEFICIENCY IN POSTMENOPAUSAL WOMEN WITH HIP FRACTURE

We characterized a series of 30 consenting postmenopausal women who presented to the BWH for reconstruction following hip fracture and had no secondary cause for their osteoporosis.[8] All of them had bone mineral density scores that met the World Health Organization's definition of osteoporosis, i.e. when the bone mineral density by dual x-ray absorptiometry (DXA) is reduced 2.5 or more standard deviations below mean values for young normal individuals. Fifty percent (n=15) of them had deficient 25-hydroxyvitamin D levels ($\leq$12 ng/mL), and 36.7% (n=11) had elevated PTH levels (>65 pg/mL). This study supports the view that the current range for vitamin D sufficiency is inappropriate because several women were identified with 25-hydroxyvitamin D levels between 12 and 22 ng/mL who had elevated levels of parathyroid hormone. With use of the current threshold for vitamin D-deficiency of 15 ng/ml, 57% had vitamin D deficiency. A recent collaborative analysis with another center found that 68% of women with hip fractures had vitamin D deficiency.[9] Referral of hip fracture patients to endocrine specialists is advised in order to determine the cause of the fracture and proper management for each patient. Vitamin D deficiency may explain many cases of osteoporosis, but additional treatments may be indicated for specific patients.

VITAMIN D-DEFICIENCY AND OSTEOPOROSIS IN POSTMENOPAUSAL WOMEN WITH ADVANCED OSTEOARTHRITIS

Postmenopausal women who presented to the BWH for hip arthroplasty for advanced osteoarthritis were recruited as controls for comparison with the osteoporotic hip fracture group.[8] In contrast to the low bone mineral density of osteoporosis, osteoarthritis has often been characterized by radiographic evidence of osteosclerosis in subchondral bone and of bony outgrowths, or osteophytes, at the affected joint. The relationship between these musculoskeletal diseases is of special relevance to the aging population because both diseases increase with age, although the impression is that they do not commonly occur together in the same patient. An oft-quoted retrospective study noted the absence of osteoarthritic changes in radiographs of fractured hips of osteoporotic subjects.[10] A more recent study posited that osteoarthritis protects against osteoporosis.[11] Thus, we expected the women with osteoarthritis to have elevated or normal bone density in comparison with the group with osteoporotic hip fractures.

Of 68 osteoarthritic women, 17 women (25%) had occult osteoporosis. Fifteen of the 68 subjects (22%) had vitamin D deficiency (defined here as 25(OH)D<15 ng/mL), and 3 (4%) had elevated parathyroid hormone. Osteoporosis was systemic in that low bone density was detected by DXA in all sites (hip, spine, and total body) in these women. In addition, this subgroup of women with osteoarthritis and osteoporosis showed significant elevations of markers of bone turnover; urinary N-telopeptides were 2.3-fold greater, serum osteocalcin was 2.1-fold greater, and serum bone-specific alkaline phosphatase was 9% greater than found in the non-osteoporotic osteoarthritic women.[12] These biochemical markers indicate high turnover osteoporosis. Vitamin D-deficiency did not account for the osteoporosis as it was found in both subgroups of osteoarthritic women. Analysis of the relationships of age or years-since-menopause, with bone density or markers of elevated bone turnover showed that osteoporosis was detected throughout the post-menopausal period. The osteoporotic and non-osteoporotic women were well-matched for percent body fat, physical activity, and poor dietary intake of calcium. It happened that all of these study subjects were Caucasian women and the findings may or may not apply to other groups. Occult osteoporosis in osteoarthritic women raises concerns about osteointegration of prosthesis and the need for management of the metabolic disease.

Vitamin D-deficiency was common (22%) in osteoarthritic postmenopausal women. In addition, the findings clearly exclude the hypotheses that all osteoarthritic women are protected against bone loss or that they are protected during the early post-menopausal period. The biochemical evidence of high bone turnover in these women and its occurrence in the early post-menopausal period appears to indicate that the diagnosis of osteoarthritis does not eliminate the risk for accelerated bone loss nor the need for evaluation of bone mineral density in all women with osteoarthritis.

CONCLUSION

With aging, there is reduced photosynthesis of vitamin D in the skin, reduced absorption of vitamin D from the diet, reduced conversion to its active metabolites, and receptor resistance to its action in the intestine and in bone. Vitamin D deficiency is common in the elderly and, to correct the adverse

skeletal effects, it should be diagnosed, treated, and prevented. Adequate intakes of calcium and vitamin D are essential preventive measures and important components of any therapeutic regimen for patients with osteoporosis and those admitted for fractures or joint replacement. Avoidance of, and correction of vitamin D-deficiency is an inexpensive task and may require education of clinicians and important changes in the practice of care for subjects admitted to orthopedic services.

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