Commentary

Effect of Vitamin D and Calcium on Periodontitis

Charles F. Hildebolt*

The anthropological record indicates that we are exposed to considerably less ultraviolet radiation (required for the synthesis of vitamin D) and consume considerably less calcium than did our early ancestors. Most U.S. citizens have calcium intakes and serum levels of vitamin D far below recommended values. This is despite there having been extensive evidence that optimal calcium and vitamin D intakes not only benefit our postcranial bone health but also have many other health benefits. Numerous articles indicate that vitamin D and calcium deficiencies result in bone loss and increased inflammation, which are well recognized symptoms of periodontal disease. For more than 40 years, investigators have suggested that calcium intake may be associated with alveolar bone resorption, and more recently there have been a number of studies in which investigators have suggested that calcium and vitamin D may benefit periodontal health, and it has been suggested that calcium deficiency may be a risk factor for periodontal disease. There has not, however, been a vitamin-D-calcium-periodontitis clinical trial in which randomization and masking were carefully controlled, the periodontal disease status of patients known, periodontal disease measures were the primary outcomes, and levels of intake optimized to produce maximal effects. Such research might demonstrate that calcium and vitamin D are important adjuncts to standard treatments for preventing and treating periodontal disease. J Periodontol 2005;76:1576-1587.

KEY WORDS

Alveolar bone loss/etiology; calcium/therapeutic use; diet; nutrition; periodontal diseases/prevention and control; sunlight/therapeutic use; tooth loss/prevention and control; vitamin D.

* Department of Radiology, Washington University School of Medicine, St. Louis, MO.

Humans have a multi-million year evolutionary history, during which genetic adaptations occurred; however, since about 10,000 years ago, with the domestication of plants and animals, culture change has far outpaced genetic adaptation.[1] We are genetically almost identical to our Paleolithic ancestors and, because of this, our nutritional adaptations are nearly identical to theirs, and Paleolithic diets are good models for our diets.[1] The estimated Paleolithic intake of calcium was 1,492 to 1,956 mg/day.[1,2] The current recommendation for calcium intake is 1,200 mg/day for ages over 50.[3] In the U.S., the median calcium intake for men 50 to 70 years of age is 708 mg/day and for women 571 mg/day. Over the age of 70, the respective median intakes are 702 and 517 mg/day.

We obtain most (90% to 100%) of our vitamin D from sunshine.[4] It is now generally accepted that humans evolved in equatorial Africa,[5] where exposure to sunshine would have been common rather than rare. Today there are, however, many things that reduce sunlight exposure.[6,7] These include sunscreen, clothing, age, pollution, the zenith angle of the sun, and limited outdoor activity. Because of these factors, people today receive minimal exposure to ultraviolet radiation. There is growing concern that recent studies have identified high prevalences of vitamin D insufficiency in otherwise healthy adults.[8,9]

CALCIUM: AN ESSENTIAL MINERAL

Skeletal bone mass increases throughout infancy, childhood, and adolescence to achieve a genetically determined peak bone mass in early adulthood. Thereafter, the skeleton loses bone mass. The rate of both increase and loss is dependent upon heredity and the availability of calcium. At different stages in our lives, even if the levels of calcium are sufficient, there are threshold values of calcium intake above which increased intakes are not utilized (Fig. 1). These threshold values are, in essence, saturation intakes that assure maximal availability of calcium for skeletal needs.[11,12] Put another way, these are the lowest values that will sustain bone mass. If calcium intakes are not at or above threshold values, skeletal calcium is resorbed to maintain the body's calcium homeostasis, which is essential for life-sustaining processes – such as blood clotting, muscle contraction, and nerve excitability. More specifically, extracellular-fluid levels of calcium are tightly controlled within a narrow range, required for normal physiological

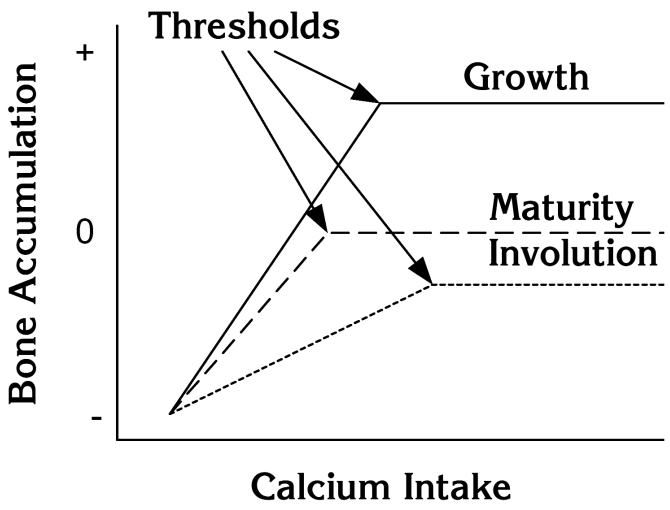

Figure 1.
Threshold behavior of calcium. Below the threshold, bone gain is a linear function of intake. Above the threshold, bone gain is no longer related to intake. Bone accumulation is greatest during growth, zero at maturity, and negative during involution. During involution, there is reduced retention and a greater demand for calcium intakes, as indicated by the low slope of the line and the threshold being located further to the right. During involution, some bone loss may occur because of non-dietary reasons and this loss is exacerbated by inadequate calcium intakes. (Adapted from Heaney.[10])

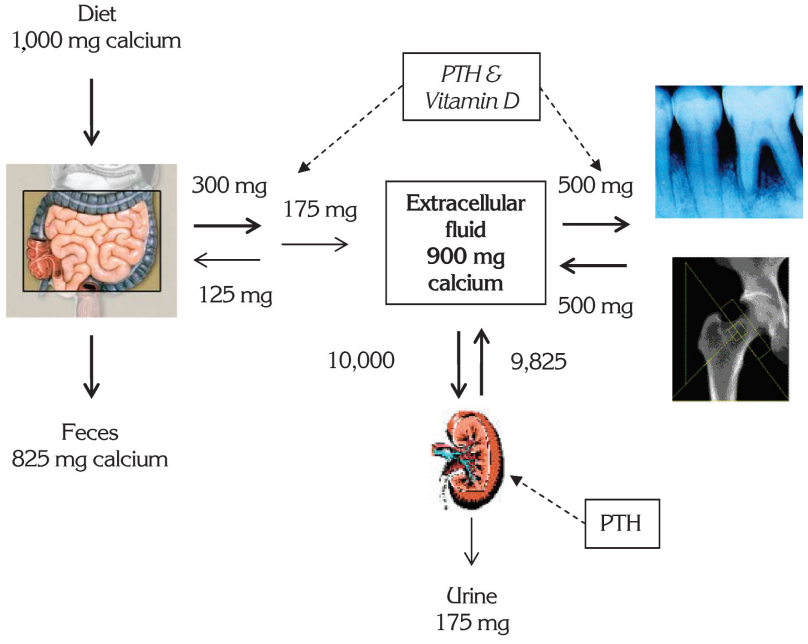

Figure 2.
Calcium metabolism. A person in good health and calcium homeostatis has an intake of approximately 1,000 mg of calcium/day. Of this, approximately 175 mg is absorbed by the gut. Of the approximately 1 kg of calcium in an adult, 99% is in the bones and teeth, with approximately 500 mg/day being resorbed and deposited. Of the 10,000 mg of calcium that passes through the kidneys, about 175 mg is excreted in the urine. These processes are mostly controlled by PTH and vitamin D. (Adapted from Broadus[13] and Bruder et al.[15]) Thicker arrows indicate a larger transfer.

function.[13] This control is mediated by two calciotropic hormones (parathyroid hormone [PTH] and vitamin D), which are discussed below.[14] These hormones act on the gut, kidney, and bone (Fig. 2). Although the extracellular fluid calcium (900 mg, which represents about 1% of the body's calcium) is tightly controlled, there are enormous fluxes in calcium levels that take place during calcium metabolism. The kidney filters approximately 10,000 mg of calcium per day and reabsorbs about 97% of what it filters, but about 175 mg is lost through sweat, gastrointestinal secretions, and cell sloughing. If calcium levels drop below this range, the result is hypocalcemia.[15] This loss is balanced by what is absorbed by the intestine, and in zero balance, the amount of bone resorption and deposition is equivalent (500 mg/day). Bone contains about 99% of the body's calcium and not only plays a structural role but also acts as a calcium reserve.[15] If the dietary intake of calcium is insufficient, bone is resorbed to prevent hypocalcemia. The bone reserve of calcium is large enough to support normal physiologic function for months to years. The result of bone resorption, however, can be osteoporosis, which for women is defined as bone mineral density values (BMD) more than 2.5 standard deviations below those for young adult women. Osteoporosis occurs in about 21% of Caucasian women, and osteopenia (BMD 1 to 2.5 standard deviations below those for young adult women) occurs in 38% of women aged 50 and over.[16,17] Women over the age of 50 also have a 50% chance of having an osteoporotic fracture before they die.[10,18] In Caucasian women, the risk of hip fracture is equal to the combined risks of developing breast, uterine, and ovarian cancer. In 1995, the estimated health-care costs of osteoporotic fracture was $13.8 billion.[19]

VITAMIN D: AN ESSENTIAL HORMONE

Vitamin D enters the circulation from the skin or diet (Fig. 3).[20] Within several hours, it accumulates in the liver where it undergoes hydroxylation to form 25(OH)D (calcidiol). This form of vitamin D is fairly stable in the body and is, therefore, a good indicator of vitamin deficiency or toxicity. In the kidney, 25(OH)D undergoes another hydroxylation to become the biologically active hormone $1,25(OH)_2D$ (calcitriol), whose major function is to maintain serum calcium and phosphorus concentrations within normal ranges, by controlling absorption in the small intestine.[21] When serum calcium levels drop below the body's needs, parathyroid hormone (PTH) increases the synthesis of $1,25(OH)_2D$, which increases the absorption of calcium

from the intestine and along with PTH increases osteoclastic activity in bone to release stored calcium to the circulation.

Among elderly patients with hip fractures, 30% to 40% are vitamin D insufficient or deficient[6] As recently pointed out in a review article, there is a transient loss of spinal bone mineral density in females during the winter, during which season hip fracture rates are the highest.[22] It was also pointed out that the highest hip fracture rates are in Northern Europe; that hip fractures occur most often in women who have 25[OH]D levels below 50 nmol/l; that spinal and femoral bone mineral loss have been prevented with daily supplements of 700 IU vitamin D and 500 mg calcium; and that non-vertebral fractures have been prevented with daily supplements of 800 IU vitamin D and 1200 mg calcium.

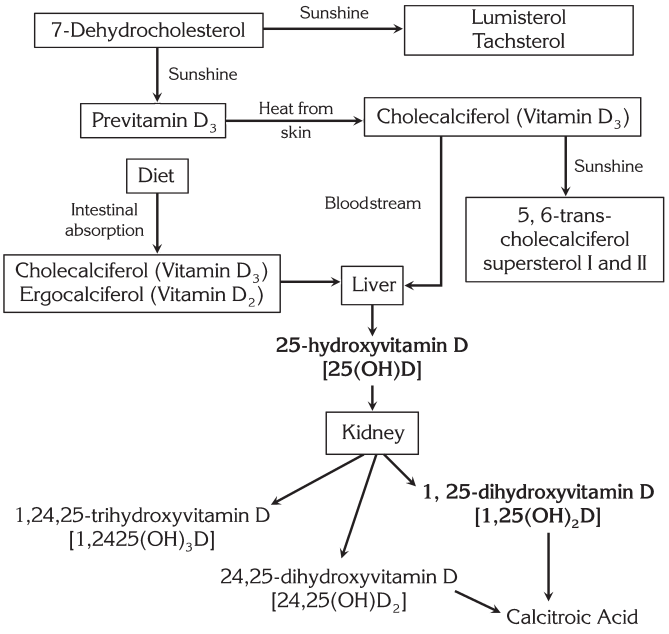

Figure 3.
Metabolic pathways of vitamin D (adapted from Holick[6,20]). Sunlight penetrates the skin and causes conversion of 7-dehydrocholesterol into previtamin D_3 or biologically inactive lumisterol and tachysterol.[6] No matter how much sunshine a person gets, only about 15% of the available 7-dehydrocholesterol is converted into previtamin D_3. Previtamin D_3, with heat from the skin, is converted into cholecalciferol, which is photolabile; what does not enter the circulation is converted into 5, 6-trans-cholecalciferol, supersterol I, and supersterol II. Sunlight, thus, appears to regulate the cutaneous production of cholecalciferol and may account for there never having been a reported case of vitamin D intoxication from overexposure to sunlight in a healthy person.[6] Cholecalciferol and ergocalciferol (vitamin D_2) can also be ingested. Cholecalciferol and ergocalciferol are commonly referred to as vitamin D/calciferol. Ergocalciferol originates in yeast and plant sterol.[3] In humans, 90% to 100% of our vitamin D requirement is attributable to sunlight.[4] Both cholecalciferol and ergocalciferol are biologically inert and require two hydroxylations to become a biologically active hormone.[21] The first hydroxylation occurs in the liver where vitamin D-25-hydroxylase creates 25-hydroxyvitamin D [25(OH)D], which has a half-life from 10 days to 3 weeks. The circulating level of 25(0H)D is, therefore, a good indication of sunlight exposure and ingestion of vitamin D.[3] To become biologically active at physiologic concentrations, 25(OH)D must undergo a further hydroxylation [caused by 25(OH)D-1α-hydroxylase] to become 1,25$(OH)_2$D. This hydroxylation occurs in the kidney and is homeostatically controlled by PTH which, in turn, is controlled by serum calcium levels. Both 25(OH)D and 1,25$(OH)_2$D can undergo further hydroxylations to become 1,24,25-trihydroxyvitamin D [1,24,25$(OH)_3$D] and 24,25-dihydroxyvitamin D [24,25$(OH)_2$D], which can be further degraded to calcitroic acid. The half-life of 1,25$(OH)_2$D in the circulation is 4 to 6 hours.

CURRENT RECOMMENDED INTAKES OF VITAMIN D AND CALCIUM

Exactly how much vitamin D and calcium supplementation people should receive has not been resolved. Since 1941, the Food and Nutrition Board (FNB) of the Institute of Medicine has published the well-known recommended dietary allowances (RDA) – the latest of which was published in 1989. In 1997, the FNB published a new set of reference values to replace the RDA.[3] These values consist of four types of daily intakes that can be used in assessing diets of individuals or groups (Fig. 4): 1) Estimated average requirement (EAR) is the intake that meets the needs of 50% of individuals. 2) Recommended dietary allowance (RDA) is the intake that meets the needs of 97% to 98% of individuals. 3) Adequate intake (AI) is the intake that appears to sustain normal health. 4) Upper level (UL) is the highest level of intake that poses no adverse effects.

Because there were insufficient data to establish EAR and RDA for calcium and vitamin D, AIs were established, with the assumption that the AIs are at or above the RDAs. At the time the AIs were created, there was no sound basis for establishing separate intake values

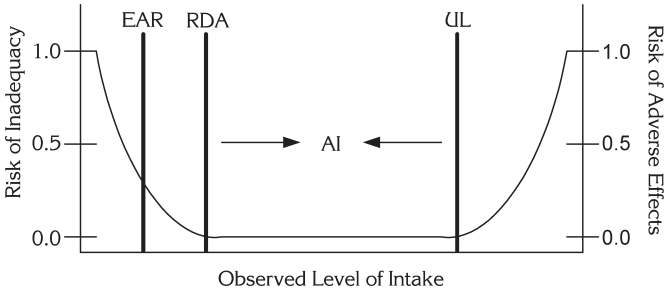

Figure 4.
Dietary reference intakes. The RDA is set such that it is sufficient to meet the nutrient needs of 97% to 98% of the individuals of a group and is based on the EAR, such that the RDA is two standard deviations above the EAR. Thus the intake based on RDA is higher than that based on EAR. The AI is set instead of the RDA when there is not enough scientific evidence to set the EAR, as is the case for calcium and vitamin D. It is assumed that the AI is at or above the RDA (if the RDA could be calculated) and below the upper level (UL, the highest level of intake that poses no adverse effects). The AI thus has risks of inadequacy and excess close to 0. (Adapted from the Food and Nutrition Board.[3])

for males and females nor for different racial/ethnic groups. A single set of AI values was, therefore, used to cover all individuals in the various categories. For calcium the AI was based on calcium balance studies, factorial modeling based on bone mineral accretion, and clinical trials. AIs of 1,000 mg/day of calcium and 5.0 µg (200 IU)/day of vitamin D were set for adults aged 19 to 50 and 1,200 mg/day of calcium and 10.0 µg (400 IU)/day of vitamin D for ages 50 to 70. For adults older than 70, AIs were set at 1,200 mg/day of calcium and 15.0 µg (600 IU)/day of vitamin D.

The ULs for these adults were set at 2,500 mg/day for calcium and 50 µg (2,000 IU)/day for vitamin D. According to the FNB, at intakes above the UL, the risk of adverse effects (hypercalcemia) may increase, but adverse events are unlikely unless intakes of calcium reach 4 gm per day and intakes of vitamin D exceed 250 to 1,250 µg (10,000 to 50,000 IU) per day.[3] Symptoms of hypercalcemia include constipation, thirst, and malaise and can be exacerbated by cancer and hyperparathroidism.[23] AIs and ULs for all ages are given in Dietary Reference Intakes.[3]

PREVENTION OF INDEX DISEASES OF VITAMIN D AND CALCIUM DEFICIENCIES IS NOT ENOUGH

The current recommended intake of vitamin D is intended to prevent the index diseases of rickets and osteomalacia, and the current recommended intake of calcium is intended to prevent the index disease of osteoporosis – just as thiamine, niacin, and iodine are intended to prevent beriberi, pellagra, and goiter.[24] Low intake levels of vitamin D and calcium have, however, far more reaching consequences. Calcium that is not absorbed in the intestine binds with food oxalate, fatty acids, and bile acids. Calcium's binding with food oxalate reduces the risk of calcium oxalate (kidney) stones.[24] This is a short-term effect. A more long-term effect is that of calcium's binding with unabsorbed fatty acids and bile acids. In the bound states, these acids cause less chronic, colon-mucosa irritation, which in time can result in cancer. As discussed below, obtaining adequate vitamin D from food is problematic. There are, however, many foods that are rich in calcium (Table 1), and it is therefore recommended that calcium be obtained from natural food sources whenever possible, with milk and other dairy products as the primary sources of calcium.[3] (Additional information is also available at http://www.nichd.nih.gov/milk/whycal/sources.cfm).

The $1,25(OH)_2D$ that is produced in the kidneys in response to low serum calcium levels is transported to the small intestine and bone (its main target organs), where it interacts with vitamin D receptors (VDRs) to increase calcium absorption in the intestine and to release calcium from bone. The $1,25(OH)_2D$ also travels to various tissues where it binds to membrane receptors

Table 1.

Food Sources of Calcium*†

Serving Size	Food Item	Calcium (mg)	% Daily Value
1 cup	Plain yogurt, fat-free	450	45%
2 oz.	American cheese	350	35%
1 cup	Yogurt with fruit (low-fat or fat-free)	315	31%
8 oz.	Milk (fat-free, low-fat, or whole)	300	30%
6-8 nachos	Nachos with cheese	272	25%
1 slice	Cheese pizza	220	22%
1 oz.	Cheddar cheese	204	20%
1/2 cup	Macaroni and cheese	180	18%
1 cup	Cottage cheese	138	10%
1/2 cup	Ice cream, soft serve	118	10%
1 oz.	Cooked dried white beans	161	15%
1/2 cup	Spinach	122	10%
1/2 cup	Turnip greens	99	8%
1/2 cup	Soybeans, cooked	90	8%
1 cup	Broccoli, cooked or fresh	90	8%
1/2 cup	Bok choy, cooked or fresh	80	8%
1 cup	Garbanzo beans	80	8%
3	Corn tortillas (lime-treated)	132	10%
1 oz.	Dry roasted almonds	80	8%
1 slice	Bread, white or whole wheat	30	2%
1/2 cup	Frozen yogurt, fat-free, calcium added	450	45%
8 fluid oz.	Calcium fortified orange juice	300	30%
1 cup	Soy milk, calcium added	250-300	25-30%
1/2 cup	Tofu made with calcium	260	25%

Calcium content in many foods varies depending on ingredients. Check the food labels to get exact content.
* Adapted from reference 25.
† Information also available at http://www.nichd.nih.gov/milk/whycal/sources.cfm.

and opens calcium channels. This in turn can result in obesity and hypertension.[24]

The consequences of having intake levels of vitamin D that are adequate for preventing only rickets and osteomalacia can be insidious. As recently pointed out, by increasing 25[OH]D levels from ≈50 nmol/l to ≈80 nmol/l, calcium absorption can be increased by two-thirds and osteoporotic fracture risk decreased by one-third.[24] Osteoporosis that results from chronic low vitamin D intakes has a long latency period. Other effects caused by low intake levels of vitamin D may not have such long latency periods. More than 30 tissues have been identified that have vitamin D receptors (VDRs).[22] Many of these tissues can express 25(OH)D-1α-hydroxylase, which converts 25(OH)D to $1,25(OH)_2D$. Monocytes have vitamin D receptors and $1,25(OH)_2D$ can induce monocytes to differentiate into macrophages, which can express 25(OH)D-1α-hydroxylase and can make $1,25(OH)_2D$, which increases lysosomal enzyme activity and phagocytosis.[22] Infectious diseases such as acute respiratory infections and pneumonia have been found to be more prevalent in children with rickets [low levels of 25(OH)D], and vitamin D status seems to be implicated in tuberculosis.[22] Conversely, the in vitro synthesis of macrophage mRNA for interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-α has been shown to be inhibited by $1,25(OH)_2D$, with the implication being that threshold serum levels of 25(OH)D can result in suppression of cytokine synthesis. Because of these relationships, it has been suggested that vitamin D deficiency may play roles in rheumatoid arthritis, inflammatory bowel diseases, multiple sclerosis, and hypertension – all of whose morbidities are associated with proinflammatory cytokines.[22] In addition, proinflammatory cytokines and vitamin D have been implicated in cardiovascular diseases and diabetes mellitus.[22]

PERIODONTAL DISEASE, CYTOKINE, VITAMIN D INTERCONNECTIONS

Periodontitis can be considered an abnormal inflammatory response to periodontal flora, in which hard and soft tissues are destroyed by auto-degradative mechanisms.[26,27] As part of this process, monocytes respond to bacteria invasion and secrete cytokines, which in turn cause lymphocytic infiltration, bone resorption, and dissolution of the extracellular matrix. Cytokines (cell proteins) regulate the body's inflammatory response by transmitting signals between cells. Cytokines such as IL-1, IL-6, and TNF-α are potent osteoclastogenic signaling agents, which result in the resorption of alveolar bone.[26,28] IL-1 also stimulates the release of metalloproteinases (MMP), which degrade the extracellular matrix and prostaglandin E_2 (PGE_2), which causes vasodilation, edema, and bone resorption. In Type I diabetes (formerly called juvenile diabetes or insulin-dependent diabetes), there is also upregulation of the expression of IL-1, PGE_2, and TNF-α.[29,30] In addition, these agents appear to be up regulated in cardiovascular disease and preterm low birthweight babies.[31-33]

It has also been suggested that periodontal disease and proinflammatory cytokines are associated with diabetes mellitus, cardiovascular diseases, and preterm low birthweight babies.[22,31-35] In addition, hypertension, diabetes mellitus, cardiovascular diseases, and periodontal diseases are associated with obesity and, because vitamin D and 25(OH)D are stored in adipose tissue, obese subjects have low serum levels of 25(OH)D.[22,36] Moreover, specific vitamin D-receptor genotypes have been shown to be associated with localized aggressive periodontal disease, with oral bone loss, clinical attachment loss, and tooth loss.[37,38]

OPTIMAL SERUM LEVELS OF VITAMIN D

Rickets and osteomalacia, which recommended levels of supplementation are intended to prevent, occur at serum 25(OH)D levels <12.5 nmol/l (5 ng/ml), but a number of investigators convincingly argue that serum 25(OH)D levels <80 mnol/l are deficient (Fig. 5).[7,22,39] Perhaps the best argument in support of this is that people who live close to the equator or who are exposed to a lot of sunshine (sunbathers and people who work outdoors) have serum 25(OH)D levels from about 100 to 160 nmol/l, with the highest level (225 nmol/l) found in a Puerto Rican

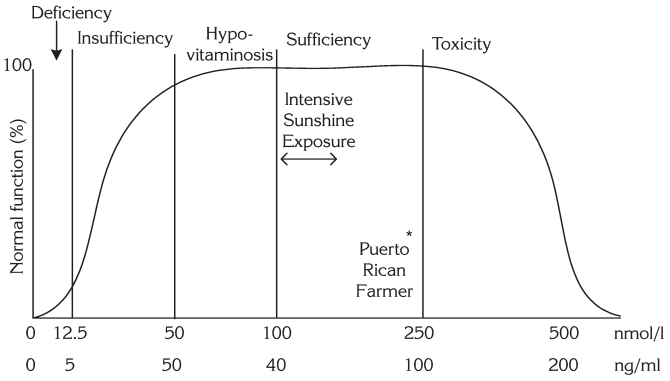

Figure 5.
*Serum 25(OH)D concentrations. There is no consensus with regard to threshold values of serum 25(OH)D for deficiency, insufficiency, hypovitaminosis, sufficiency, and toxicity. Blood levels below 12.5 nmol/l result in rickets and osteomalacia. Below 50 nmol/l can result in mild hyperparathyroidism and decreased bone density. Toxic levels of 25(OH)D can result in hypercalcemia. Intensive exposure to sunshine results in serum 25(OH)D levels of from 100 to 160 nmol/l. The highest serum level from sunshine was recorded in a Puerto Rican farmer (225 nmol/l). One ng/ml of 25(OH)D is equal to 2.5 nmol/l. (Adapted from Zittermann.[22]) *Indicates approximate serum level of vitamin D for farmer.*

farmer.[22,40] There has never been a report of vitamin D intoxication caused by sunlight exposure in a healthy person. The serum levels of 25(OH)D (100 to 160 nmol/l) that result from intensive sunlight exposure can, therefore, be regarded as the upper safe levels.[22] In addition, with 25(OH)D serum levels below ~80 nmol/l, there is decreased calcium absorption and increased PTH secretion, and it is speculated that the threshold for optimal calcium absorption and minimal PTH secretion occurs at 25(OH)D levels of ~80 to 90 nmol/l.[39]

OBTAINING VITAMIN D FROM ORAL SUPPLEMENTATION

Although it is possible to reach these levels with vitamin D supplementation, the doses would have to be high, as indicated in Table 2. The changes in serum 25(OH)D levels, however, are nonlinear and vary by some inverse function of baseline serum levels.[42] In an attempt to determine the amounts of vitamin D inputs needed to achieve or maintain serum 25(OH)D levels, a study of men (mean age = 39 years) was conducted in Omaha, Nebraska, during the winter.[39] For this population, serum 25(OH)D levels increased ~0.70 nmol/l for each µg (40 IU) of vitamin D supplementation. To maintain base levels of 25(OH)D (70.1 nmol/l), a supplementation of 12.5 µg (500 IU)/day would be required. At zero level of supplementation, serum levels decreased by 12.4 nmol/l, and with 25 µg (1000 IU)/day of supplementation, serum levels increased 12.0 nmol/l. Moreover, it was calculated that a supplementation of 10 µg (400 IU)/day would elevate serum levels by 7.0 nmol/l, a level that would probably not be detectable in an individual, and 600 IU/day of supplementation in a 70-year old would result in a serum level 12.5 nmol/l, if this were the person's only source of vitamin D. As commented by the investigators, "Thus, the recommendations of the FNB with respect to oral vitamin D input fall into a curious zone between irrelevance and inadequacy."[39]

Table 2.

Increases in Serum Levels of 25(OH)D With Vitamin D Supplementation*

Vitamin D Supplementation per Day	Increases in 25(OH)D
5 µg (200 IU)	~10 nmol/l
10 to 20 µg (400 to 800 IU)	~37 nmol/l
25 to 50 µg (1,000 to 2,000 IU)	~47 nmol/l
100 µg (4,000 IU)	~56 nmol/l
250 µg (10,000 IU)	~112 nmol/l

* Data compiled from references 22, 40, and 41.

FOOD SOURCES OF VITAMIN D

There are a few natural foods and fortified foods that contain vitamin D (Table 3). The levels of vitamin D, however, vary depending upon the time of year food is harvested, and levels of food fortification are highly variable, with some fortified foods containing no vitamin D. Because of this, it is exceedingly difficult to obtain adequate vitamin D requirement from food.[43-46] The median intake of vitamin D from food was estimated to be 2.3 µg (90 IU)/day in older women.[47]

VITAMIN D INTOXICATION

Although vitamin D intoxication can cause hypercalcemia, in all cases of vitamin D intoxication, the levels of 25(OH) were >200 nmol/l.[22] In these cases, the vitamin D doses were ≥1,000 µg (40,000 IU)/day. There has been one case for which hypercalcemia resulted from an average vitamin D supplementation of 250 µg (10,000 IU)/day; however, this person received the vitamin D in a single dose of 7,550 µg (300,000 IU). Vitamin D intoxication has been caused

Table 3.

Food Sources of Vitamin D*

	International Units
Cod liver oil, 1 tbs.	1,360 IU
Salmon, cooked, 3.5 oz.	360 IU
Mackerel, cooked, 3.5 oz.	345 IU
Sardines, canned in oil, drained, 3.5 oz.	270 IU
Eel, cooked, 3.5 oz.	200 IU
Milk, non-fat, reduced fat, and whole, vitamin D fortified, 1 cup	98 IU
Margarine, fortified, 1 tbs.	60 IU
Cereal grain bars, fortified w/10% of the DV, 1 each	50 IU
Pudding, 1/2 cup prepared from mix and made with vitamin D fortified milk	50 IU
Dry cereal, vit D fortified w/10%† of DV, 3/4 cup †Other cereals may be fortified with more or less vitamin D	40-50 IU
Liver, beef, cooked, 3.5 oz.	30 IU
Egg, 1 whole (vitamin D is present in the yolk)	25 IU

* The table was developed by the Clinical Nutrition Service, Warren Grant Magnuson Clinical Center, National Institutes of Health (NIH), Bethesda, MD, in conjunction with the Office of Dietary Supplements (ODS) in the Office of the Director of NIH and is available at http://www.cc.nih.gov/ccc/supplements/vitd.html#food.

† DV = daily value, which for the purposes of this table is equal to 400 IU of vitamin D and a 2,000-calorie diet.

by accidental excessive fortification of foods (such as milk) and excessive intakes of vitamin D.[22,41] In arguing that the UL of 50 µg (2,000 IU)/day for vitamin D set by the FNB in 1997 should be increased, one investigator summarized his review by stating, "If there is published evidence of toxicity in adults from intake of 250 µg (10,000 IU)/day, and that is verified by the 25(OH)D concentration, I have yet to find it."[41] Other investigators have also argued that the UL is set far too low.[22,24] Although hypersensitivity to vitamin D occurs with some conditions (most notably hyperparathyroidism), this is not a good reason for setting low intake levels for vitamin D because before the condition (hyperparathyroidism) develops, the vitamin D would be preventive in that it would lower parathyroid secretion and reduce the risk of developing parathyroid hyperplasia.[41] It has been suggested that for adults daily supplementation with vitamin D at levels of 25 and 100 µg (1,000 and 4,000 IU)/day are beneficial to health and safe, and that the FNB needs to raise AI and UL for vitamin D.[8,22,24,39-42,44,48]

BEST SOURCE OF VITAMIN D

The best means of obtaining vitamin D requirement is from sunshine. A person wearing a bathing suit, who receives a sub-erythemal (slight redness of the skin) dose of sunshine will produce 250 µg (10,000 IU) of vitamin D.[41,49] It is, therefore, possible for adults to obtain their body's vitamin D requirements by exposing their hands, arms, and face to a third to a half of a suberythemal dose of sunshine two to three times per week.[49] In Boston, during the spring, summer, and fall, for a light- to medium-skin-colored person, each exposure, if obtained about noon, would require about 5 minutes of exposure time and would result in about 15 to 25 µg (600 to 1,000 IU) of vitamin D, which would be adequate for vitamin D needs. People who stay outdoors longer should apply a sunscreen (SPF ≥15).

EFFECT OF VITAMIN D AND CALCIUM SUPPLEMENTATION ON POSTCRANIAL BONE

Vitamin D and calcium supplementation counteract deficiencies, and reduce bone resorption and fracture rates.[50-54] Vitamin D supplementation (10 µg [400 IU/day]) and adjusted calcium intakes of 1,000 mg/day increased vertebral bone density and total body calcium in postmenopausal women,[55] and serum vitamin D levels have been demonstrated to be directly related to femoral bone mineral densities.[56] Maximum bone gains occur after 2 years of supplementation in both the femur and lumbar spine and are maintained for at least 4 years.[57] In a 2002 review of 180 articles on calcium intake and bone status, 70 studies were "investigator-controlled," which is generally recognized as the only research design capable of establishing a causal connection between exposure and outcome.[58] Sixty-eight of the 70 studies (97%) found that calcium supplementation results in either greater gains in bone during growth, less loss of bone with age, and/or reduced fracture risk, relative to unsupplemented individuals. Of the 110 observational studies, 85 (77%) reported positive effects for calcium supplementation. These findings are in keeping with other reviews.[59-63] Moreover, vitamin D has its greatest effect when combined with calcium supplementation[64] and, although vitamin D supplementation alone can result in bone gain, most studies have used a combination of vitamin D and calcium.[65,66]

EFFECT OF VITAMIN D AND CALCIUM ON TOOTH LOSS

Tooth loss was studied in a double-masked, randomized, placebo-controlled trial of the effects of calcium and vitamin D supplementation on bone loss from the hip.[67] Subjects (N = 82) who received 500 mg of calcium and 700 IU of vitamin D per day for 3 years had a 60% lower risk of tooth loss than did those who took placebos.[67] These patients were followed for an additional 2 years during which time subjects who consumed at least 1,000 mg/day of calcium also had a 60% lower risk of tooth loss than subjects who took less calcium. Although some data were collected on the periodontal disease status of the patients at the end of the study, corresponding data at baseline were not available. The major limitation of this investigation was that tooth loss was a secondary outcome in the study, and tooth counts were based on self-reports by subjects who completed the study.

EFFECT OF VITAMIN D AND CALCIUM ON RESIDUAL ALVEOLAR RIDGE RESORPTION

In a cross-sectional study, low consumptions of milk and milk products were attributed to more severe residual alveolar ridge resorption in 44 edentulous subjects who completed 14-day dietary surveys.[68] The 14 subjects who had minimal ridge resorption on panoramic radiographs had a mean intake of calcium of 933 mg/day whereas the 30 subjects who had severe resorption had a mean intake of 533 mg/day. A subsequent 1-year, randomized, double-masked, placebo-controlled clinical trial of 60 subjects who received immediate dentures was performed.[69] Subjects received either placebos or 750 mg calcium and 375 IU vitamin D per day. Bone resorption over the 1-year period was measured with panoramic radiographs. Seven-day dietary records for 13 supplemented subjects and 19 placebo subjects were used to estimate calcium consumption. Details were provided on randomization, masking, methods, and reasons for dropout. Although data were not analyzed on an intention-to-treat basis, those subjects who completed the study and received supplementation (N = 23) had 36% less bone loss than did subjects

who received placebo. In a cross-sectional study of 11 healthy post-menopausal women who required complete-denture replacements, the mean dietary intake of calcium was 800 mg/day and the mean serum level of vitamin D was 18.8 ng/ml.[70] The investigators suggested that these low levels contributed to low mandibular bone densities in these subjects. In another cross-sectional study, subjects were divided into five groups, based on age and number of remaining teeth.[71] The highest percentage of subjects with calcium deficient diets was in edentulous geriatric patients. Eleven edentulous patients with severe ridge atrophy underwent comprehensive biochemical and histomorphological testing prior to ridge augmentation procedures.[72] The investigators concluded that the ridge resorption was consistent with metabolic bone loss resulting from secondary hyperparathyroidism, resulting from insufficient calcium intakes. Combining these 11 subjects with 63 other subjects (total 74), the same investigators used gonial-angle thickness as a parameter for metabolic bone loss.[73] In the subjects with the thinnest gonial angles, resorption surfaces and osteoid volume and seam thickness were consistent with low calcium intakes and hyperparathyroidism.

EFFECT OF VITAMIN D AND CALCIUM ON ALVEOLAR BONE

In a 1960 cross-sectional study, two groups of 24 subjects each were followed.[74] One group had periodontal disease and the other group did not have periodontal disease. The severe radiographic alveolar bone resorption in the subjects with periodontal disease was attributed to past histories of low calcium intakes (350 to 555 mg/day), which the investigators suggested was caused by low milk ingestion. Low intakes of milk and cheese were also attributed to low dietary calcium levels (325 mg/day) in another study in which 10 subjects with periodontal disease received 1,000 mg/day of calcium supplementation and were followed for 6 months.[75] Little detail on methods is provided in this 1972 study. The investigators reported that at the end of 6 months of treatment, gingival inflammation was improved, probing depth and tooth mobility decreased, and new bone appeared to have formed as observed radiographically. In a similar study, these same investigators followed for 6 months a cohort of 10 subjects who received 1,000 mg/day of calcium.[76] No detail is provided concerning methodology. The investigators reported decreases in gingivitis, probing depth, and tooth mobility, and increases in alveolar crest bone. These investigators also followed 90 patients for one year.[76,77] Subjects received one of three forms of calcium (1,000 mg/day) or a placebo. No detail is provided on masking, randomization, or methodology. The investigators reported that there were increases in radiographic mandibular bone density for the subjects, who received supplemental calcium. The first study (1972)[75] in this series was repeated by two other investigators in 1984.[78] Contrary to the earlier findings, no significant differences between the calcium-supplemented group and the placebo group were determined for plaque and gingival index scores or probing depths. It was also reported that radiographs studied with a magnifying glass "failed to show any changes in marginal bone level or density."[78] No data were provided for radiographic assessments. In none of these studies does it appear that standard periodontal therapies (such as dental prophylaxes or scaling and root planing) were provided. Standard periodontal therapy was provided, however, in a double-masked placebo controlled trial of 40 subjects, who received either calcium (750 mg/day) and vitamin D (375 IU/day) or placebo.[79] Thirty-three subjects finished 1 year of treatment. Nine of 15 subjects (60%) who received supplementation had improved periodontal health, whereas only three of 18 subjects (3%) who received placebos had improved periodontal health, (P <0.01). Although radiographs were obtained, they were not analyzed. Little information is provided regarding the assessment of periodontal health, so it is difficult to interpret these results.

In an examination of data on 12,000 adults who took part in the Third National Health and Nutrition Examination Survey (NHANES III), it was found that lower dietary intake of calcium increased attachment loss in a dose-dependent fashion.[80] The investigators suggested that the increased risk of periodontal disease could be related to decreased alveolar bone density associated with inadequate calcium intake. The major limitations of the study are that it was cross-sectional and lacked exact data on calcium supplementation. Other investigators used the NHANES III data to examine the association between serum vitamin D levels and attachment loss and found an inverse relationship: the lower the levels of vitamin D the more attachment loss, with the association being independent of factors such as smoking habit and diabetes.[81] They suggested that this inverse relationship might be attributable to the anti-inflammatory effects of vitamin D. The limitations of this study are that it was cross-sectional and serum levels of vitamin D were determined at only one point. In another study, dietary surveys were conducted and alveolar crest height measurements made on 550 male subjects.[82] A subject was considered to have low alveolar bone loss if the distance from the cemento-enamel junction (CEJ) to the alveolar crest on periapical radiographs was ≤20% of the distance from the CEJ to the root tip. High bone loss was defined as having a value >20%. The number of subjects who progressed from low to high alveolar bone loss was 30% higher in subjects who consumed less than 1,000 mg/day of calcium over a 7-year period than in those who consumed more than 1,000 mg/day.

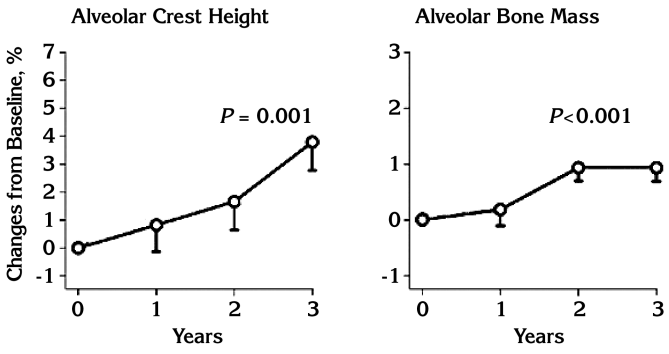

Figure 6.
Alveolar bone gain in periodontally healthy post-menopausal women who received 1,000 mg calcium and 400 IU vitamin D per day. (Adapted from Civitelli et al.[84])

The limitation of the study is that 40% of the teeth did not have detectable alveolar bone loss at baseline.

Eighty-five post-menopausal women received 400 IU per day of vitamin D and increased calcium intake to 1,000 mg per day.[83] Women were also randomized to receive either calcitriol or a placebo. After two years, 83% of the women either maintained or gained mandibular bone mass although no significant difference was attributable to calcitriol alone. The major limitations of this study are that 20% of the subjects were edentulous and data on periodontal disease status were not given. The results of this study are similar to those found in a more recent 3-year hormone replacement study in which 67 periodontally healthy post-menopausal women received only 1,000 mg of calcium and 400 IU of vitamin D per day (Fig. 6).[84] Over a 3-year period, there were significant increases in both alveolar bone mass and alveolar crest height (Fig. 6). The apparent increase in crestal bone height was attributed to a reduction or complete refilling of the remodeling space. After 3 years, this increase in crestal density (decrease in crestal porosity) would have been most pronounced in subjects with vitamin D deficiency and radiographically would appear as an increase in alveolar crest height. The limitations of this study are that the women were periodontally healthy and there was no control arm for which women received only placebo.

LIMITATIONS OF STUDIES ON THE EFFECT OF VITAMIN D AND CALCIUM ON PERIODONTAL HEALTH

All of the above investigations had limitations. Most were observational. In some, dental measurements were secondary outcomes and in others procedures for randomization, masking, and data collection were not presented. Some studies lacked data on the cause of tooth loss and/or the periodontal-disease status of the patients. Often no data on exact amounts of supplementation were available. There was also a great deal of variation among the studies with regard to the amounts of supplementation and the monitoring of intakes. In many instances, supplementation/intakes were below recommended intakes and, therefore, may have been too small to produce effects, particularly for vitamin D, for which there is growing concern that current recommended intakes are too low. For the effects of vitamin D and calcium on periodontitis, there has never been a clinical trial in which randomization and blinding were carefully controlled, the periodontal disease status of patients known, periodontal disease measures were the primary outcomes, and levels of supplementation/intake optimized to produce maximal effects.

SUMMARY

As of 2002, there had been 70 randomized clinical trials of the effects of calcium and vitamin D on the postcranial skeleton, and 68 of these studies (97%) reported positive effects for supplementation.[58] Based upon a systematic review and meta-analysis of 15 of these trials (1,806 patients), it was determined that 2 or more years of supplementations resulted in 1.66% less bone loss at the lumbar spine and 1.64% less loss at the hip.[66] This may not seem to be a large benefit, but if this benefit were to be extended over decades or the lifetime of an individual, the benefit could be enormous, particularly in a patient with periodontal disease, which is generally considered to be a long-term, chronic condition. In a recent article in which osteoporotic, bone-fragility fractures were discussed, it was pointed out that a rate of calcium depletion (bone loss) of 3%/year would have a measurable effect on bone strength; yet clinically the depletion would not be detectable for, at least, 10 years, and at lower (more typical) rates of loss, the clinical manifestation of the disease might take 30 years.[24] The long latency period of the disease does not, however, decrease its health importance.

Moreover, low levels of calcium intake and particularly vitamin D intake result in a low serum level of calcium that stimulates the parathyroid gland to produce PTH, which results in osteoclastogenesis. Periodontal disease results in the production of proinflammatory cytokines, which also result in osteoclastogenesis. It follows that alveolar bone in patients with periodontal disease and low levels of vitamin D and calcium should be under a heavier osteoclastic load than are bones such as the femur and spine. A number of infectious diseases have been linked with low levels of vitamin D, and it has been demonstrated that vitamin D can suppress cytokine production.[22] Because of periodontal disease's unique periodontal-pathogen, hard-tissue environment, it may be that the effect of vitamin D and calcium on alveolar bone is more pronounced than its effects in the spine and hip.

Bacteria are necessary but not sufficient for periodontal disease, which is multifactorial. The belief that

all disease was caused by external invaders (bacteria or toxic) was a hurtle that nutritional scientists had to overcome, with the concept that people could become sick because of something lacking in their diets being inconceivable.[24] Numerous articles indicate that vitamin D and calcium deficiencies result in bone loss and increased inflammation, which are well recognized symptoms of periodontal disease. It has been suggested that calcium deficiency may be a risk factor for periodontal disease.[80] Perhaps vitamin D deficiency should also be considered as a risk factor in studies of the etiology of periodontal disease. Further research is needed to clearly define the health risks (including periodontal disease) associated with inadequate levels of vitamin D and calcium intake.[82,85]

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Correspondence: Dr. Charles F. Hildebolt, Department of Radiology, Washington University School of Medicine, 510 S. Kingshighway, St. Louis, MO 63110. Fax: 314/362-6971; e-mail: hildeboltc@mir.wustl.edu.

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