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Vitamin D and Cancer Mini-Symposium: The Risk of Additional Vitamin D

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Any benefit of vitamin D needs to be balanced against the risk of toxicity, which is characterized by hypercalcemia. Daily brief, suberythemal exposure of a substantial area of the skin to ultraviolet light, climate allowing, provides adults with a safe, physiologic amount of vitamin D, equivalent to an oral intake of about 10,000 IU vitamin D_3 per day, with the plasma 25-hydroxyvitamin D (25(OH)D) concentration potentially reaching 220 nmol/L (88 ng/mL). The incremental consumption of 40 IU/d of vitamin D_3 raises plasma 25(OH)D by about 1 nmol/L (0.4 ng/mL). High doses of vitamin D may cause hypercalcemia once the 25(OH)D concentration is well above the top of the physiologic range. The physiological buffer for vitamin D safety is the capacity of plasma vitamin D–binding protein to bind the total of circulating 25(OH)D, vitamin D, and 1,25-dihydroxyvitamin D [1,25(OH)2D]. Hypercalcemia occurs when the free concentration is inappropriately high because vitamin D and its other metabolites have displaced 1,25(OH)2D from vitamin D–binding protein. Evidence from clinical trials shows, with a wide margin of confidence, that a prolonged intake of 10,000 IU/d of vitamin D_3 poses no risk of adverse effects for adults, even if this is added to a rather high physiologic background level of vitamin D.
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Most of the evidence relating vitamin D to cancer suggests that higher vitamin D nutritional status is beneficial. However, benefit needs to be balanced against risk. Vitamin D may be unique in terms of nutritional and environmental inputs because there is an objective laboratory assay for it that reflects exposure during several months preceding the time a sample of blood is taken. The serum or plasma concentration of 25-hydroxyvitamin D (25(OH)D) is the generally accepted measure of vitamin D nutritional status (1). The dermatology community has generally discouraged a strategy of maintaining high 25(OH)D concentrations through exposure of skin to ultraviolet light because of concerns about risk of skin damage or cancer (2, 3). It is very unlikely that anyone following current advice regarding protection of the skin from solar ultraviolet (2) could achieve a serum 25(OH)D concentration greater than 75 nmol/L (30 ng/mL) without taking a vitamin D supplement. However, most epidemiological studies have found that 25(OH)D concentrations greater than 75 nmol/L are needed to substantially reduce incidence of invasive cancers and several other serious diseases. The purpose of this review is to address the risk-related consequences of vitamin D supplementation for adults.

THE BIOLOGY OF HIGH 25(OH)D AND CALCIUM

Any agent that can elicit a biological effect will be harmful if the amount taken is sufficiently high. Although vitamin D has a long history of safe clinical applications in humans and many animals, it can be toxic. High concentrations of vitamin D are toxic to rats and have been used to poison them (40,000 IU can kill a rat, which is the equivalent, on a weight basis, of approximately 7–10 million IU in a 70-kg human) (4, 5). There is no toxic mechanism known for vitamin D other than through calcium. Hypercalcemia can be fatal because it causes neuromuscular impairment, polyuria, and ensuing dehydration. If animals survive the acute phase of vitamin D excess, the hypercalcemia also leads to calcification of the soft tissues and vasculature (6). Hypercalcemia is harmful through at least three mechanisms: 1) Calcium combines with inorganic phosphate; calcium and phosphate crystallize as hydroxyapatite in soft tissues. 2) Ionized calcium binds to the phosphate in phospholipid bilayers of cell membranes, making neuromuscular tissues more difficult to depolarize (7), thereby suppressing cardiac and brain function that can lead to death. 3) Hypercalcemia acts like a diuretic by inhibiting antidiuretic hormone (vasopressin), causing dehydration and renal

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impairment through diminished vascular perfusion of the kidney (8, 9).

The potential risk of vitamin D supplementation should be considered in the context of the serum 25(OH)D concentration achieved. The physiologic limit for serum 25(OH)D concentrations in humans appears to be approximately 220 nmol/L (88 ng/mL) because this approximates the top of the range of values reported for humans who are well exposed to ultraviolet light (10). From a teleological perspective, humans are designed through natural selection to live in a tropical environment, with regular exposure of full skin surface to sunshine. This perspective implies that the upper end of the physiological concentration range for 25(OH)D is not only safe, but optimal, because the Paleolithic concept of nutrition regards the conditions of our evolution as a reference point for modern nutrition standards (11). The safety of solar-derived vitamin D is generally accepted because vitamin D toxicity due to solar exposure has not, to my knowledge, been reported, although this has not been addressed experimentally. Skin exhibits a limited capacity to generate vitamin D in response to ultraviolet light because the skin provides a self-limited supply of vitamin D that is determined by the concentration of its precursor, 7-dehydrocholesterol, in skin. Equilibrium is achieved after about one minimal erythemal dose of ultraviolet B (UVB), when further biosynthesis of new pre-vitamin D is counteracted by photodegradation (2, 12).

Fig. 1 (12–19) shows the effect of ultraviolet exposure on adults, with the initial and final serum concentrations of 25(OH)D after various exposure regimens (10). Added to the published data are the mean initial and final 25(OH)D concentrations for one male and two female municipal lifeguards in Toronto (43°N latitude). Despite the implementation of sun-safe practices that included compulsory use of sunscreen lotion, long-sleeved shirts, and umbrellas, the 25(OH)D concentrations increased substantially during the June–August season. This confirms with contemporary data the 25(OH)D concentrations of lifeguards reported in previous decades.

The weight of published evidence relating to vitamin D toxicity shows that the lowest 25(OH)D concentration causing hypercalcemia is greater than 500 nmol/L (200 ng/mL) (Fig. 2 [20–24]) (25). Patients exhibiting hypercalcemia with a 25(OH)D concentration less than 500 nmol/L were taking vitamin D as infrequent but extreme doses. For example, in Fig. 2, the hypercalcemic patient with the lowest 25(OH)D concentration was taking vitamin D as a 600,000-IU dose once weekly. Under these circumstances the unmetabolized vitamin D itself contributes to the hypercalcemia, as explained below. Few studies have looked at effects of high doses of vitamin D on urinary calcium, which is a more sensitive harbinger of vitamin D excess. The effect of 25(OH)D on intestinal calcium absorption

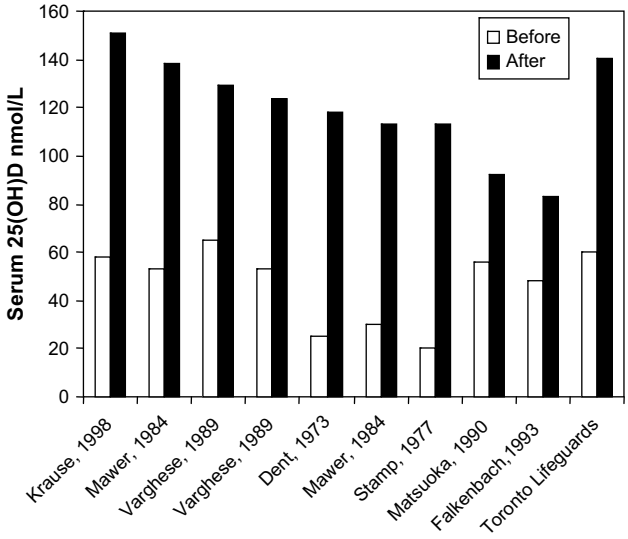

FIGURE 1. Effect of exposure of skin to ultraviolet light on serum 25(OH)D concentrations. The *open bars* show mean values before exposure, and the *solid bars* show mean values after exposure. The results show the effect of work at an outdoor municipal swimming pool in Toronto, Canada, during June–August on 3 young adults (at far right). Also shown are mean results of published studies in which near-full-skin surface are was exposed from once to several times per week for periods of treatment that were typically 2 weeks; these are sorted according to the final 25(OH)D concentration that was achieved (13–19).

generally reaches a plateau at a serum 25(OH)D concentration of about 80 nmol/L (26–28). (Intestinal calcium absorption implicitly equates to urinary calcium. Adults are essentially at equilibrium for total body calcium; therefore virtually all of the net amount of calcium absorbed daily by the gut is excreted daily into the urine.) The evidence is very strong that there is no hypercalcemia, and no hypercalcinuria, associated with supplementary vitamin D intakes of at least 10,000 IU per day, in addition to the background vitamin D that healthy North American adults acquire through the usual course of modern life.

An epidemiologic analysis of a community population of about 11,000 households that were provided milk that contained, on average, 30 times the appropriate 400 IU vitamin D per quart offers helpful insight. A home-delivery dairy had produced milk that for 4 years averaged 12,000 IU vitamin D per quart, but because of defective measuring equipment, the dose ranged from none to over 100,000 IU per quart (21, 29). Blank et al. (21) concluded that the situation contributed to the deaths of two susceptible elderly individuals. Incidence of hypercalcemia was rare. The group most susceptible to the excess vitamin D was women over age 65. The average 25(OH)D concentration of the confirmed cases of vitamin D toxicity was 535 nmol/L (214 ng/mL) (11) (see Fig. 2).

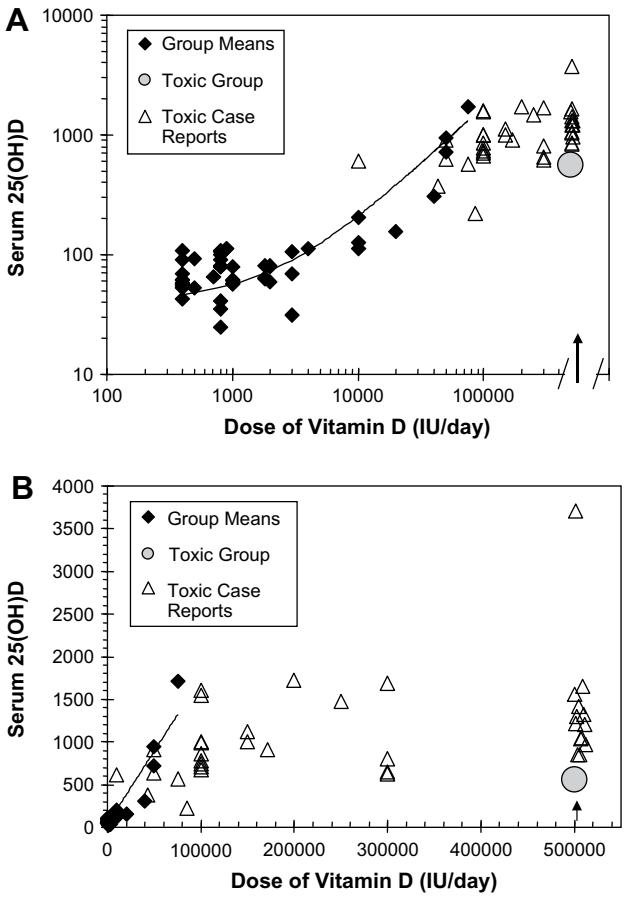

FIGURE 2. Relationships between vitamin D dose, and serum or plasma 25(OH)D concentration in healthy subjects and in vitamin D toxicity. *Black diamonds* show mean 25(OH)D concentrations for groups of healthy adult subjects as shown previously (10), updated with additional data (20), along with the calculated linear-regression line for data represented by *black diamonds*. *Large gray circle* shows mean 25(OH)D of 35 members of the public who were hypercalcemic because of unknowingly consuming excessive vitamin D in milk over a period of years (21). *Open diamonds* show values for individual patients who became hypercalcemic with known high doses of vitamin D as shown previously (10) updated with additional data (9, 22–24). The dose of vitamin D was not reliably known for patients intoxicated accidentally with vitamin D; for them, the 25(OH)D results are clustered at the right side of the figure, indicated with an *arrow* (9, 21–24). A, log scales; B, linear scales.

People with abundant exposure to sunlight can easily exhibit a serum 25(OH)D greater than 150 nmol/L (60 ng/mL) (see Fig. 1). Such 25(OH)D concentrations reflect a pre-supplement oral intake or biosynthesis of vitamin D equivalent to more than 4,000 IU per day (30). An additional oral intake of 4,000 IU per day of vitamin D would still be far less than the dose of 50,000 IU per day that was reported to be non-hypercalcemic in clinical trials (20, 28).

Amounts of vitamin D much greater than physiologic levels, specifically greater than 10,000 IU per day, eventually become toxic once they occupy a meaningful proportion of circulating vitamin D–binding protein (DBP). High circulating concentrations of vitamin D metabolites displace $1,25(OH)_2D$ into the unbound, free phase that enters target tissues (5, 6). At toxic doses, the freely circulating vitamin D and its metabolites accumulate not just in adipose tissue (19) but also in muscle (13, 16). Supplementation with 4,000 IU per day of vitamin D in adults should be regarded as physiologic and comparable to the amount of vitamin D acquired through natural sun exposure—and far below the concentration required to cause physiochemical displacement of metabolites from vitamin DBP (30). The average capacity of human plasma DBP to bind vitamin D and its metabolites is 4,700 nmol/L (30); this concentration exceeds by 20 times the physiologic total concentration of its vitamin D–derived ligands, and DBP is the saturable factor that limits the safe range for vitamin D dosing in most adults.

VITAMIN D EXCESS AND ITS METABOLISM

The classic reason to supplement with vitamin D is its role as a bone-anabolic agent. For this role in calcium homeostasis, vitamin D is the initial substrate in a two-stage process, where the liver hydroxylates vitamin D to 25(OH)D, and the kidney further hydroxylates it to produce $1,25(OH)_2D$ that stimulates active transport of calcium across intestinal mucosa. A clear understanding of vitamin D biology requires an appreciation that the biochemistry of vitamin D endocrinology differs from the biochemistry of other cholesterol-based steroid-hormone systems. Unlike all other fat-soluble signaling systems, the substrate for hormone production, 25(OH)D, is rate limiting. For example, to produce sex steroid hormones, the cholesterol substrate circulates in the millimolar range; these concentrations are so high that the substrate supply has no practical, rate-limiting effect on the production of sex steroid hormones. In contrast, 25(OH)D circulates at concentrations in the order of a million-fold lower than cholesterol. With such a low substrate concentration, the activity of each unit of every enzyme in the pathway metabolizing vitamin D is determined by availability of substrate. As vitamin D supply increases, so does the liver increase its rate of 25-hydroxylation of vitamin D molecules to produce 25(OH)D (5). As the plasma 25(OH)D concentration increases, the 25(OH)D-1-alpha-hydroxylase (CYP27A2) within the kidney produces ever more $1,25(OH)_2D$ per unit of enzyme protein (31). Over time, after the plasma 25(OH)D concentration increases in vivo, the plasma concentration of $1,25(OH)_2D$ is regulated to a fairly constant level that is independent of 25(OH)D because the amount of 25(OH)D-1-alpha-hydroxylase protein in the kidney

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decreases, and the concentration of the 25(OH)D-24-hydroxylase enzyme increases.

The 24-hydroxylase can cleave the side-chains of both $1,25(OH)_2D$ and 25(OH)D (32). As 25(OH)D concentrations continue to rise to several times the top of their physiological range, a limit is reached beyond which the substrate-driven output of $1,25(OH)_2D$ can no longer be regulated through adjustments to its synthetic and catabolic enzymes. When the vitamin D system is driven to excess, hypercalcemia is produced because of increased intestinal calcium absorption, and increased bone resorption (33, 34).

In vitamin D excess the high bone resorption is opposite to the relationship between bone resorption when vitamin D supplies are insufficient: the low and high extremes in 25(OH)D concentration are the opposite ends of a U-shaped relationship with bone resorption (34, 35). The classic symptoms of vitamin D toxicity are entirely associated with hypercalcemia, and they include nausea, dehydration, and lethargy (21, 22). Without laboratory testing, these signs of hypercalcemia have been mistaken for gastroenteritis (9).

The average whole-body half-life for vitamin D molecules is about 2 months, based on the disappearance of radioactivity after radioactively labeled vitamin D_3 was injected into 60 adults (36) and the effect of acute sun-deprivation on serum 25(OH)D concentrations (10). Although concentrations of $1,25(OH)_2D$ are not appreciably increased in vitamin D intoxication, toxicity is the result of excessive levels of free $1,25(OH)_2D$ displaced from DBP, due to vast excess of other vitamin D metabolites (23, 30). This excess has been demonstrated by using centrifugal ultrafiltration isodialysis to measure the free $1,25(OH)_2D$ concentrations in vitamin D–intoxicated individuals (23). The physiochemical saturation of plasma vitamin D–binding capacity is also confirmed by the high total vitamin D and 25(OH)D concentrations (19,500 nmol/L and 7,800 ng/mL, respectively) in patients intoxicated after consuming over one million IU of vitamin D daily for many months (35).

In laboratory rats, hypercalcemia is detected only once the total of all vitamin D metabolites exceeds about 20% of the binding capacity of DBP—when the total of serum 25(OH)D plus unmetabolized vitamin D exceeds 2000 nmol/L (5). A similar observation has been reported in humans (9). The background presence of vitamin D after a large occasional one-time dose of vitamin D explains why the measured 25(OH)D concentration can range widely in clinical reports of hypercalcemia; this is because the high plasma concentration of unmetabolized vitamin D after an extreme dose of vitamin D is not reflected in assays that measure 25(OH)D, yet the vitamin D can displace circulating $1,25(OH)_2D$ into the free form that is accessible to tissues.

CONCLUSION

The results of well-conducted trials of vitamin D lead to the conclusion that the current U.S. National Academy of Sciences–Institute of Medicine upper limit for vitamin D intake of 2000 IU per day (1, 37) is excessively conservative. That intake would raise serum 25(OH)D by an average of about 50 nmol/L (20 ng/mL), well within the safe range of serum 25(OH)D concentrations that extends to 500 nmol/L (200 ng/mL). Intake of 4,000 IU per day would raise serum 25(OH)D by an average of about 100 nmol/L (40 ng/mL). Even prolonged physiologic-replacement intake of 10,000 IU per day of vitamin D_3 would pose no known risk of adverse effects in virtually all adults (25).

Dr. Vieth serves as a consultant for the following companies: Cytochroma, DiaSorin, D Drops, Merck, Novartis, Wyeth, Yoplait.

REFERENCES

1. Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes: calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academy Press; 1997.
2. Gilchrest BA. Sun protection and Vitamin D: three dimensions of obfuscation. J Steroid Biochem Mol Biol. 2007;103:655–663.
3. Lim HW, Gilchrest BA, Cooper KD, Bischoff-Ferrari HA, Rigel DS, Cyr WH, et al. Sunlight, tanning booths, and vitamin D. J Am Acad Dermatol. 2005;52:868–876.
4. Murphy MJ. Rodenticides. Vet Clin North Am Small Anim Pract. 2002;32:469–484 viii.
5. Shephard RM, DeLuca HF. Plasma concentrations of vitamin D3 and its metabolites in the rat as influenced by vitamin D3 or 25-hydroxyvitamin D3 intakes. Arch Biochem Biophys. 1980;202:43–53.
6. Thorin E, Henrion D, Oster L, Thorin-Trescases N, Capdeville C, Martin JA, et al. Vascular calcium overload produced by administration of vitamin D3 and nicotine in rats. Changes in tissue calcium levels, blood pressure, and pressor responses to electrical stimulation or norepinephrine in vivo. J Cardiovasc Pharmacol. 1990;16:257–266.
7. Stein RB. Ionic currents in nerve and muscle. In: Nerve and muscle. New York: Plenum Press; 1980. p. 45–63.
8. Robinson BG, Clifton-Bligh P, Posen S, Morris BJ. Plasma vasopressin in hypercalcaemic states. Aust N Z J Med. 1983;13:5–7.
9. Vieth R, Pinto T, Reen BS, Wong MM. Vitamin D poisoning by table sugar. Lancet. 2002;359:672.
10. Vieth R. Vitamin D supplementation, 25-hydroxyvitamin D concentrations, and safety. Am J Clin Nutr. 1999;69:842–856.
11. Eaton SB. The ancestral human diet: what was it and should it be a paradigm for contemporary nutrition? Proc Nutr Soc. 2006;65:1–6.
12. Webb AR, DeCosta BR, Holick MF. Sunlight regulates the cutaneous production of vitamin D3 by causing its photodegradation. J Clin Endocrinol Metab. 1989;68:882–887.
13. Dent CE, Round JM, Rowe DJ, Stamp TC. Effect of chapattis and ultraviolet irradiation on nutritional rickets in an Indian immigrant. Lancet. 1973;1:1282–1284.
14. Falkenbach A, Unkelbach U, Boehm BO, Regeniter A, Stein J, Seiffert U, et al. Bone metabolism before and after irradiation with ultraviolet light. Eur J Appl Physiol. 1993;66:55–59.
15. Krause R, Buhring M, Hopfenmuller W, Holick MF, Sharma AM. Ultraviolet B and blood pressure [letter]. Lancet. 1998;352:709–710.

16. Matsuoka LY, Wortsman J, Hollis BW. Suntanning and cutaneous synthesis of vitamin D3. J Lab Clin Med. 1990;116:87–90.
17. Mawer EB, Berry JL, Sommer-Tsilenis E, Beykirch W, Kuhlwein A, Rohde BT. Ultraviolet irradiation increases serum 1,25-dihydroxyvitamin D in vitamin-D-replete adults. Miner Electrolyte Metab. 1984;10:117–121.
18. Stamp TC, Haddad JG, Twigg CA. Comparison of oral 25-hydroxycholecalciferol, vitamin D, and ultraviolet light as determinants of circulating 25-hydroxyvitamin D. Lancet. 1977;1:1341–1343.
19. arghese M, Rodman JS, Williams JJ, Brown A, Carter DM, Zerwekh JE, et al. The effect of ultraviolet B radiation treatments on calcium excretion and vitamin D metabolites in kidney stone formers. Clin Nephrol. 1989;31:225–231.
20. Barger-Lux MJ, Heaney RP, Dowell S, Chen TC, Holick MF. Vitamin D and its major metabolites: serum levels after graded oral dosing in healthy men. Osteoporos Int. 1998;8:222–230.
21. Blank S, Scanlon KS, Sinks TH, Lett S, Falk H. An outbreak of hypervitaminosis D associated with the overfortification of milk from a home-delivery dairy. Am J Public Health. 1995;85:656–659.
22. Koutkia P, Chen TC, Holick MF. Vitamin D intoxication associated with an over-the-counter supplement. N Engl J Med. 2001;345:66–67.
23. Pettifor JM, Bikle DD, Cavaleros M, Zachen D, Kamdar MC, Ross FP. Serum levels of free 1,25-dihydroxyvitamin D in vitamin D toxicity. Ann Intern Med. 1995;122:511–513.
24. Vieth R, Rao DS. Inaccuracies in relating 25-hydroxyvitamin D to ischemic heart disease. Eur J Epidemiol. 2003;18:461–462.
25. Hathcock J, Shao A, Vieth R, Heaney R. A risk assessment for vitamin D. Am J Clin Nutr. 2007;85:6–18.
26. Heaney RP, Dowell MS, Hale CA, Bendich A. Calcium absorption varies within the reference range for serum 25-hydroxyvitamin D. J Am Coll Nutr. 2003;22:142–146.
27. Heaney RP, Weaver CM. Calcium and vitamin D. Endocrinol Metab Clin North Am. 2003;32:181–194. vii–viii.
28. Ursell MR, Vieth R, O'Connor PW, Gray B, Kimball S. A phase I dose-escalation study of vitamin D3 with calcium supplementation in patients with multiple sclerosis. Presented as a poster (P667) at the 21st Congress of the European Committee for the Treatment and Research in Multiple Sclerosis. September 28–October 1, 2005. Thessaloniki, Greece. Ref Type: Conference Proceeding
29. Jacobus CH, Holick MF, Shao Q, Chen TC, Holm IA, Kolodny JM, et al. Hypervitaminosis D associated with drinking milk. N Engl J Med. 1992;326:1173–1177 Comment in: N Engl J Med. 1992;326:1213–1215.
30. Vieth R. The mechanisms of vitamin D toxicity. Bone Miner. 1990;11:267–272.
31. ieth R, McCarten K, Norwich KH. Role of 25-hydroxyvitamin D3 dose in determining rat 1,25-dihydroxyvitamin D3 production. Am J Physiol. 1990;258:E780–E789.
32. Prosser DE, Jones G. Enzymes involved in the activation and inactivation of vitamin D. Trends Biochem Sci. 2004;29:664–673.
33. Selby PL, Davies M, Marks JS, Mawer EB. Vitamin D intoxication causes hypercalcaemia by increased bone resorption which responds to pamidronate. Clin Endocrinol (Oxf). 1995;43:531–536.
34. Suda T, Ueno Y, Fujii K, Shinki T. Vitamin D and bone. J Cell Biochem. 2003;88:259–266.
35. Jesudason D, Need AG, Horowitz M, O'Loughlin PD, Morris HA, Nordin BE. Relationship between serum 25-hydroxyvitamin D and bone resorption markers in vitamin D insufficiency. Bone. 2002;31:626–630.
36. Mawer EB, Backhouse J, Holman CA, Lumb GA, Stanbury SW. The distribution and storage of vitamin D and its metabolites in human tissues. Clin Sci. 1972;43:413–431.
37. HEALTH & CONSUMER PROTECTION DIRECTORATE-GENERAL. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Vitamin D. EUROPEAN COMMISSION. Available at: http://europa.eu.int/comm/food/fs/sc/scf/out157_en.pdf. Accessed August 11, 2003. 2002. Brussels, Belgium. 1-10-0030. Ref Type: Report.