16. Vitamin D

Physiology and metabolism

The two major forms of vitamin D are the secosteroids cholecalciferol (vitamin D_3), derived from cholesterol and of animal origin, and ergocalciferol (vitamin D_2), derived from the plant sterol, ergosterol. Since vitamins D_2 and D_3 have roughly the same activity in man, the term vitamin D will be used here to refer to both D_2 and D_3. Amounts of vitamin D are usually expressed in terms of weight, but the older International Unit (IU) is still in use (1 IU = 0.025 µg vitamin D).

Sources

Vitamin D is not strictly a vitamin as most of it is formed in the body by the action of sunlight converting 7-dehydrocholesterol in the skin to previtamin D_3 [1]. This endogenous synthesis depends on the thickness and pigmentation of the skin and on the quality (290-315 nm) and intensity of the ultraviolet irradiation; the lowest UVB radiation that produces a significant increase in serum vitamin D_3 is 18 mJ/cm^2 in untanned white subjects [2]. As in North America [2,3], this threshold level may not be reached in Northern Europe for a large part of the year. For example in Paris (48°N) only between late spring and early autumn is there sufficient UVB solar radiation to produce vitamin D. Even so, the amount produced during that limited season appears to be adequate to cover the needs of healthy adults living at latitudes between 35°N and 60°N, provided that the time in sunlight (10-15 min/d) and the amount of skin exposed (30%) to optimal UV irradiation are sufficient [3,4] and that atmospheric pollution is not excessive [5]. Vitamin D synthesis also depends on the age of the subject, being decreased in elderly people [3].

The diet is a much less important source of vitamin D. Only a few foods (fatty fish, eggs, butter, liver and certain types of meat) contain significant amounts of the vitamin and average daily intakes are too small to influence vitamin D status significantly, unless fortified food products are eaten regularly, e.g. margarine, milk, cereals. Dietary practices, such as vegetarianism [6], macrobiotic diets [7], or just low calcium intakes [8], may decrease the availability of exogenous vitamin D or increase its catabolism.

Metabolism

In the blood vitamin D is bound to a specific vitamin D-binding protein, DBP, and is transported to the liver, where it undergoes a first hydroxylation into 25-hydroxyvitamin D (25-(OH)D). This formation of 25-(OH)D in the liver is not tightly regulated and after inadvertent administration of excessive doses of vitamin D circulating levels of this metabolite increase up a hundred fold higher than those found in healthy populations. In its turn 25-(OH)D is transported, bound to the same DBP, to the renal proximal tubule, where it is converted into 1,25-dihydroxyvitamin D ($1,25\text{-}(OH)_2D$) [9].

The renal proximal tubule is the major contributor to the circulating pool of $1,25\text{-}(OH)_2D$ in healthy non-pregnant subjects, 0.3-1 µg/d being formed [10]. During pregnancy, the fetoplacental unit is a second major source of the circulating $1,25\text{-}(OH)_2D$. Unlike its precursor, 25-(OH)D, the circulating levels of $1,25\text{-}(OH)_2D$ are not influenced by vitamin D status except in situations of severe vitamin D deficiency. In contrast, the synthesis of $25\text{-}(OH)_2D$ is tightly feedback regulated by $1,25\text{-}(OH)_2D$ itself and depends mainly upon the calcium and phosphate needs of the body [9,11,12].

Actions

$1,25\text{-}(OH)_2D$ is the form of vitamin D responsible for calcium and phosphate absorption from the intestine, and for various actions on bone, kidneys, parathyroid glands and muscle, leading to the maintenance of phosphate homoeostasis in the extracellular fluid, to an increase in the extracellular concentration of calcium and to adequate mineralization of the skeleton [11,12]. In addition, $1,25\text{-}(OH)_2D$ may be directly involved in a variety of different processes unrelated to calcium and phosphate homoeostasis, but the physiological relevance, if any, of these latter actions remains to be evaluated.

Deficiency and excess

The early signs of vitamin D deficiency are infraclinical: decreased serum concentrations of calcium and phosphate, resulting from depressed absorption of calcium and phosphate from the intestine, secondary hyperparathyroidism and increased serum alkaline phosphatase activity. Hypocalcemic convulsions may occur at this stage. Later signs are inadequate skeletal mineralization (rickets or osteomalacia), bone pains, severe bone deformities, and alterations in muscle metabolism and respiratory function.

Signs of acute and chronic vitamin D intoxication include nausea, diarrhoea, polyuria, weight loss, hypercalcaemia, hypercalciuria, and eventually nephrocalcinosis, decreased renal function, or calcification of soft tissues. Signs of vitamin D intoxication have been found after prolonged administration of 250-1250 µg/d [13], although short term administration (7 weeks) of 250 µg/d to healthy adults had no detectable effects on the serum and urinary calcium and phosphate concentrations, and did not increase 25-(OH)D concentrations above levels spontaneously reached after daily total body exposure to UV irradiation [14].

Hypercalcaemia has been shown to occur occasionally in infant populations receiving periodic administration of very high doses of vitamin D (15 mg, every 6 months) as a prophylaxis against rickets, and 25-(OH)D levels in the blood of these infants reach values similar to those found in patients with obvious vitamin D intoxication [1,5].

It was claimed that prolonged daily intakes of 100 µg/d by infants increased the incidence of hypercalcaemia [16], but no reliable assessments of vitamin D intake could be made at that time. Doses of 50 µg/d do not appear to be harmful to infants as they do not affect statural growth [17].

Requirements

Assessment of vitamin D status

The most reliable marker of vitamin D status is the circulating level of 25-(OH)D. Healthy adults who do not expose themselves to sunshine, or live in countries with only a short season of useful UV irradiation, may have 25-(OH)D values as low as 6-8 ng/ml (15-20 nmol/L). Subclinical signs of vitamin D deficiency have been found in some of these otherwise healthy adults with 25-(OH)D levels below 10 ng/ml. At the other end of the scale, 25-(OH)D levels as high as 80 ng/ml (200 nmol/L) are found in healthy adults living in tropical countries or in southern Europe after prolonged sunbathing. Patients with clear signs of vitamin D intoxication usually have 25-(OH)D levels above 100 ng/ml. Thus a desirable range for 25-(OH)D could be 10-40 ng/ml (25-100 nmol/L). The vitamin D requirement is therefore being considered as that necessary to maintain circulating 25-(OH)D concentrations in that range.

Dietary recommendations

The problem in trying to give a dietary requirement for vitamin D is that many individuals maintain their circulating 25-(OH)D concentrations in the desirable range by endogenous synthesis of vitamin D, and so need none in the diet.

Those that do not produce sufficient vitamin D by endogenous synthesis need some dietary supply. The intake necessary will depend on the shortfall of exposure to effective UV radiation and perhaps on inadequacy of calcium and phosphate intakes. There will thus be considerable variation between different geographical regions in Europe (latitude, climate and air pollution) and perhaps between social and ethnic groups in a given geographical region (calcium and phosphate intake, exposure to sunlight).

In such circumstances, precise recommendations are hard to give; for some groups it would be pointless to try to do so, notably for adults, where most have no dietary requirement.

In all groups of the population however some individuals will need some dietary vitamin D, and a range of values is suggested that would meet the needs of all members of the group, even those with minimal endogenous production of vitamin D.

Some population groups may have difficulty in obtaining their needs by endogenous synthesis, either because of inadequate exposure to sunlight (e.g. the elderly) or of a physiologically raised requirement (e.g. in pregnancy and lactation) or both (e.g. very young children). Substantial numbers in these groups will need dietary vitamin D, and there is a sizeable risk of an individual becoming deficient. In these groups, as a matter of prudence, a minimum value for intake is given, i.e. it is recommended that all members of the group receive that amount. In practice this will call for the consumption of supplements or fortified foodstuffs.

Adults

On the basis of their 25-(OH)D levels, dietary intakes of vitamin D do not appear essential for healthy adults, adequately supplied with calcium and phosphate, unless they are confined indoors [4].

No information is available on the effects of dietary vitamin D on 25-(OH)D levels of non-pregnant younger adults, but from studies on elderly people [18,19], it appears that daily intakes of 10 µg/d would bring 25-(OH)D concentrations into the desired range, even if endogenous synthesis were minimal.

It is suggested that the requirements of all adults would met by dietary intakes of 0-10 µg/d.

Children

There is a substantial incidence of rickets in infants not given vitamin D supplements. Studies on the 25-(OH)D levels of infants supplemented or not supplemented with vitamin D confirm that infants have a high requirement [20,21].

In order to maintain circulating 25-(OH)D levels in the desired range it is recommended that the dietary intake of infants 6-11m should not be less than 10 µg/d. It is possible that the requirement may be higher in some infants, perhaps up to 25 µg/d [21].

Infants and children are vulnerable to vitamin D deficiency because calcium is being laid down in bone at a high rate. As children in the 1-3 y group may not get adequate exposure to sunlight it is recommended that their intake should not be less than 10 µg.

Older children still have a high requirement for vitamin D, and adolescents, who have to reach adult bone mass at a time of accelerated skeletal growth, have a particularly high requirement for calcium and thus for vitamin D. Most children of 4 years and over and most adolescents should however get enough exposure to sunlight to make adequate amounts themselves.

Those belonging to social or ethnic groups with insufficient exposure to the sun, or on not wholly satisfactory diets, are at risk of vitamin D deficiency, and attention should be paid to adolescents in northern Europe. The ranges of dietary vitamin D are 0-10 µg/d for 4-10 y and 0-15 µg/d for 11-17 y.

Pregnancy and lactation

Pregnant and lactating women have higher requirements for vitamin D than do non-pregnant women along with their need for high amounts of calcium and phosphate for the mineralization of the growing skeleton of the fetus and infant; lactating women also have to provide vitamin D in the milk. Numerous studies on 25-(OH)D levels have shown that customary exposure to sunlight in Europe may be insufficient to cover the needs for vitamin D, especially during the last trimester of pregnancy, and notably at the end of the winter. The ensuing vitamin D deficiency will affect not only the mother but also the newborn, whose vitamin D reserves are very dependent on those of the mother. To maintain 25-(OH)D levels, 10 µg/d is recommended [22,23].

The elderly and institutionalized individuals

Because of lack of exposure to sunlight, and the decline with age of the ability to synthesize vitamin D_3, elderly and institutionalized people are prone to develop D deficiency. To maintain circulating 25-(OH)D values between 10 and 20 ng/ml, elderly and institutionalized people should receive 10 µg/d [18,19].

Summary

Requirements

A range of values up from zero indicates that all members of the group should be able to produce adequate vitamin D for themselves by exposure to sunlight, and most will, with no need for a dietary supply. The higher end of the range is the estimated dietary requirement of an individual with minimal endogenous synthesis.

In other groups a single value indicates that it is prudent for the whole group to be supplemented to avoid occurrence of vitamin D deficiency.

Age group	PRI (µg/d)
6 - 11 m	10-25
1 - 3 y	10
4 - 6 y	0-10
7 - 10 y	0-10
11-14 y	0-15
15-17 y	0-15
18-64 y	0-10
65 + y	10
Pregnancy	10
Lactation	10

Higher intakes

Intakes of 250 µg/d have been reported as harmful [13]; the lowest level at which ill effects appear is not known. Intakes of 50 µg/d appear safe [17]. There seems no benefit to be obtained by healthy individuals from higher regular intakes. It would be prudent not to exceed 50 µg/d in habitual intake.

References

1. Webb AR, Holick MF. (1988). The role of sunlight in the cutaneous production of vitamin D_3. *Ann Rev Nutr*, **8:** 375-399.

2. Matsuoka LY, Wortsman J, Haddad JG, Hollis BW. (1989). *In vivo* threshold for cutaneous synthesis of vitamin D_3. *J Lab Clin Med*, **114:** 301-305.

3. Holick MF. (1986). Vitamin D requirements for the elderly. *Clin Nutr*, **5:**121-129.

4. Markestad T, Elzouki AY. (1991). Vitamin D-deficiency rickets in northern Europe and Libya. In: Glorieux F, ed. *Rickets*. Nestlé Nutrition Workshop Series, **21**. New York: Raven Press 203-213.

5. Loomis WF. (1970). Rickets. *Scientific Amer*, **223 (6):**76-91.

6. Henderson JB, Dunnigan MG, McIntosh WB, Motaal AA, Hole D. (1990). Asian osteomalacia is determined by dietary factors when exposure to ultraviolet radiation is restricted: a risk factor model . *Q J Med*, **76:** 923-933.

7. Dagnelie PC, Vergote FJVRA, van Staveren WA, van Den Berg H, Dingjan PG, Hautvast JGAJ. (1990). High prevalence of rickets in infants on macrobiotic diets. *Am J Clin Nutr*, **51:**202-208.

8. Clements MR, Johnson L, Fraser DR. (1987). A new mechanism for induced vitamin D deficiency in calcium deprivation. *Nature*, **327:**62-65.

9. Fraser DR. (1980). Regulation of the metabolism of vitamin D. *Physiol Rev*, **60:** 551-613.

10. Gray RW, Caldas AE, Wilz DR, Lemann J, Smith GA, DeLuca HF. (1978). Metabolism and excretion of ^{3}H-1,25-$(OH)_2$-vitamin D_3 in healthy adults. *J Clin Endocrinol Metab*, **46:**756-765.

11. Kumar R. (1986). The metabolism and mechanism of action of 1,25-dihydroxyvitamin D_3. *Kidney Int*, **30:**793-803.

12. Reichel H, Koeffler HP, Norman AW. (1989). The role of the vitamin D endocrine system in health and disease. *N Engl J Med*, **320:**980-991.

13. Anning ST, Dawson J, Dolby DE, Ingram JT. (1948). The toxic effect of calciferol. *Q J Med*, **17**:203-228.

14. Berlin T, Emtestam L, Björkhem I. (1986). Studies on the relationship between vitamin D_3 status and urinary excretion of calcium in healthy subjects: effects of increased levels of 25-hydroxyvitamin D_3. *Scand J Clin Lab Invest*, **46:** 723-729.

15. Markestadt T, Hesse V, Siebenhuner M, Jahreis G, Aksnes L, Plenert W, Aarskog D. (1987). Intermittent high-dose vitamin D prophylaxis during infancy: effect on vitamin D metabolites, calcium and phosphorus. *Am J Clin Nutr*, **46:** 652-658.

16. Fraser D, Kidd BSL, Kooh SW, Paunier L. (1966). A new look at infantile hypercalcemia. *Pediatr Clin North Am*, **13:** 503-525.

17. Fomon SJ, Younoszai MK, Thomas LN. (1966). Influence of vitamin D on linear growth of normal full-term infants. *J Nutr*, **88:**345-350.

18. MacLennan WJ, Hamilton JC. (1977). Vitamin D supplements and 25-hydroxyvitamin D concentrations in the elderly. *Br Med J*, **2:**859-861.

19. Toss G, Larsson L, Lindgren S. (1983). Serum levels of 25-hydroxyvitamin D in adults and elderly humans after a prophylactic dose of vitamin D_2. *Scand J Clin Lab Invest*, **43:**329-332.

20. Poskitt EME, Cole TJ, Lawson DEM. (1979). Diet, sunlight and 25-hydroxyvitamin D in healthy children and adults. *Br Med J*, **1:**221-223.

21. Garabédian M, Zeghoud F, Rossignol C. (1991). Les besoins en vitamine D du nourrisson vivant en France. In: Journées Parisiennes de Pédiatrie. Médecine-Sciences, Flammarion, Paris, 51-57.

22. Cockburn F, Belton NR, Purvis RJ, Giles MM, Brown JK, Turner TL *et al.* (1980). Maternal vitamin D intake and mineral metabolism in mothers and their new-born infants. *Br Med J*, **281:**11-14.

23. Greer FR, Searcy JE, Levin RS, Steichen JJ, Asch PS, Tsang RC. (1981). Bone mineral content and 25-hydroxyvitamin D concentration in breast-fed infants with and without supplemental vitamin D. *J Pediatr*, **98:**696-701.