

Research Article

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Dr. Deepak Viswanath*

Professor, Department of
Pedodontics and Preventive
Dentistry, Krishnadevaraya
College of Dental Sciences,
Hunasamaranahalli, Bangalore,
India

Correspondence:

Dr. Deepak Viswanath

Professor, Department of
Pedodontics and Preventive
Dentistry, Krishnadevaraya College
of Dental Sciences,
Hunasamaranahalli, Bangalore,
India- 562157

Tel: +91-9480226226

E-mail: pedodons@gmail.com

Dietary Reference Intakes for Calcium and Vitamin D

Dr. Deepak Viswanath

Abstract

Calcium and vitamin D are the two essential nutrients which are known for their vital role in the health of bones. But over the last few years, the general public has heard conflicting reviews over the benefits of these nutrients- especially vitamin D- and also about how much calcium and vitamin D needs to be taken in order to stay healthy. To help and clarify this pertinent issue, major steps were drawn with the help of U.S and Canadian Governments and also by the European Commission to set a dietary reference value and also set the Tolerance upper intake level of both these nutrients. The purpose of this article is to cover exhaustively the potential health outcomes of these essential nutrients not just in bone health but also in overall health condition of an individual.

Keywords: Calcium, Vitamin D, Dietary reference, Intake level, Hypercalcaemia

1. Introduction

The principal physiological function of vitamin D in all vertebrates including humans is to maintain serum calcium and phosphorus concentrations in a range which maintains and supports the cellular processes, neuromuscular functioning and mainly bone ossification. Vitamin D also has other important functions in tissues which are not primarily related to mineral metabolism.^{1,2} Typical example being its active role in the modulation of renal production of rennin and its role in insulin secretion. The active metabolite, 1, 25(OH)₂D, regulates the transcription of a large number of genes through binding to a transcription factor, the vitamin D receptor.

In 2003, the Scientific Committee on Food established a Tolerable Upper Intake Level (UL) of vitamin D for adults, including the pregnant and also lactating mothers. This Upper Limit was based on the increased risk of hypercalcaemia observed after intakes of around 100µg vitamin D/day in the highest dose group in a study reported by Narang et al.³ For infants and young children aged 0-24 months, the Upper Limit was set at 25µg/day based on the absence of hypercalcaemia attributable to intervention with Vitamin D in a couple of studies where breast-fed or infant formula fed-infants received 25µg vitamin D/day for some months. The Upper Limit for children aged between 3 to 10 years was set at 25µg/day and for adolescents aged 11-17 years at 50µg/day.

In 2011, the American Institute of Medicine published an overall re-assessment of the Upper Limit for vitamin D and considered an intake of 250µg vitamin D/day as a no observed adverse effect level (NOAFL). The Upper Limit for adults, including pregnant and lactating women, was set at 100µg/day.

The same Upper Limit was also set for children and adolescents aged 9 to 18 years, while the value was scaled down for young children. For infants aged 0 to 6 months, an Upper Limit of 25µg/day was set based on the normal growth in infants receiving a mean of 45µg vitamin D/day.

The adequate dietary intake of calcium and vitamin D in children is important to guarantee normal bone mineralization and for rickets prevention. Bone is the main store of Calcium and it is a reserve for the homeostasis of serum-calcium concentration, which varies within narrow limits around 10 mg/dL. Calcium apart from its structural role, is also important in coagulation cascade, in neuromuscular excitability and contraction, in enzyme hormones and growth factors activity, in secretion of hormones and in cell growth and differentiation.⁴ Dietary Recommended Intake (DRI) for Calcium is 700 mg/day for children aged 1–3 years, 1000 mg/day for children aged 4–8 years, and 1300 mg/day for children aged 9–10 year and adolescents.⁵ The metabolism of Calcium closely depends on Vitamin D, parathormone and calcitonin levels. Vitamin D stimulates intestinal absorption of Ca²⁺ and phosphorus, and regulates serum Ca²⁺ levels maintaining an adequate mineralization of the skeleton.⁵

2. Dietary intakes of calcium and vitamin D

The Dietary Reference Intakes are intended to serve not only as a guide, but also provide the basis for the development of nutrient guidelines both in United States and Canada. On an average, 500mg of calcium per day meets the requirements of children aged between 1 to 3 years and 800 milligrams is adequate for children between 4 to 8 years. Adolescents require higher levels to meet and support bone growth; 1300 milligrams per day meets the necessary requirements of most of the adolescents. Women aged from 19 to 50 and men aged upto 70 years require on an average 800 milligrams per day and women over 50 and also men and women above the age of 70 require around 1000 milligrams per day.

Determining the intake levels of vitamin D is somewhat more complicated; vitamin D levels in the body may not only come from exposure to sunlight but also from various dietary sources. Table 1 gives a detailed explanation about the Dietary Reference Intakes for calcium and vitamin D.⁶

Table 1: Dietary reference intakes for Calcium and Vitamin D

Life Stage Group	Calcium			Vitamin D		
	Estimated average requirement (mg/day)	Recommended dietary allowance (mg/day)	Upper level intake (mg/day)	Estimated average requirement (mg/day)	Recommended dietary allowance (mg/day)	Upper level intake (mg/day)
Infants 0 to 6 months	#	#	1000	##	##	1000
Infants 6 to 12 months	#	#	1500	##	##	1500
1 to 3 year olds	500	700	2500	400	600	2500
4 to 8 year olds	800	1000	2500	400	600	3000
9 to 13 year olds	1100	1300	3000	400	600	4000
14 to 18 year olds	1100	1300	2500	400	600	4000
19 to 30 year olds	800	1000	2500	400	600	4000
31 to 50 year olds	800	1000	2500	400	600	4000

51 to 70 year old males	800	1000	2000	400	600	4000
51 to 70 year old females	1000	1200	2000	400	600	4000
Above 70 year old	1000	1200	2000	400	600	4000
14 to 18 years old, pregnant/lactating	1100	1300	3000	400	600	4000
19 to 50 year old, pregnant/lactating	800	1000	2500	400	600	4000

- for infants, adequate intake is 200 mg/day for 0 to 6 months of age and 260 mg/day for 6 to 12 months of age

##- for infants, adequate intake is 400 IU/day for 0 to 6 months of age and 400 IU/day for 6 to 12 months of age

3. Physiology of Vitamin D

The source of vitamin D is not just from diet, but also from sunlight. It is synthesized in the skin from 7-dehydrocholesterol under the influence of UV radiation (290-315nm wavelengths), leading to the formation of previtamin D3. Previtamin D3 thermally isomerises to vitamin D3 immediately after formation; sunlight itself acting as a regulator in the production. The dietary intake of vitamin D increases 25(OH)D concentrations without an equivalent regulatory mechanism, with a linear relationship between vitamin D intakes and serum 25(OH)D concentrations well into the high dose range.² The 24-hydroxylase catabolises 25(OH)D to 24,25(OH)2D to prevent its eventual activation to 1,25(OH)2D.⁷ Following the supplementation of vitamin D, 24-hydroxylase is upregulated, though this adaptation occurs with a lag of several weeks.⁸

Both 25- and 1 α -hydroxylation of vitamin D are needed to form the active metabolite 1,25(OH)2D. At least four enzymes, namely CYP2DH, CYP2D25, CYP3A4 and CYP2R1 can accomplish the 25-hydroxylation of vitamin D in the hepatocytes. Serum 1,25(OH)2D, the active metabolite is synthesized in the kidneys where the activity of the enzyme 25(OH)D-1 α -hydroxylase (CYP27B1) is regulated by calcium and phosphate, as well as by their regulating hormones like calcium, calcitonin, parathormone, growth hormone and insulin-like growth factor I being the positive regulators and phosphates, fibroblast growth factors and even 1,25(OH)2D being the negative regulators.

The principal function of the active metabolite i.e., 1,25(OH)2D is to maintain intracellular and extracellular calcium concentrations within a physiologically acceptable

range and this is accomplished by enhancing the efficiency of small intestine in absorbing dietary calcium and phosphorus, and by mobilising calcium and phosphorus from the bone.

4. Biomarkers of vitamin D intake, status and activity

The concentration of 25(OH)D in plasma or serum can only be used as a biomarker of vitamin D intake in people with low exposure to sunlight. After initiation of vitamin D supplementation, a new steady state is reached after 6 to 8 weeks in adults.⁹ It was suggested that vitamin D2 and vitamin D3 equally increases 25(OH)D concentrations when they are supplemented daily and vitamin D3 may raise 25(OH)D concentrations more than vitamin D2.¹⁰ Because of its slow turnover in the body, the half-life being 2 months,¹¹ vitamin D is often administered weekly in equivalent doses. The main determinants of vitamin D status are skin pigmentation and sunlight exposure. The concentrations of 25(OH)D varies according to the season, with the lowest concentrations occurring at the winter and the highest during summer.¹² The latitude of the residence and also the time of the day plays an equally important role; for example, below a latitude of approximately 35°North, the ultra-violet radiation is sufficient for vitamin D3 synthesis all-round the year. In Rome, where the latitude is 41.9°North, cutaneous vitamin D3 synthesis is not possible from November through February. Following extended exposure to sunlight during summer, median 25(OH)D concentrations in late summer were 122 nmol/L in 26 young adults for whom sun exposure was the principal source of vitamin D, with the highest concentration being 211 nmol/L. The median seasonal difference in 25(OH)D concentration between late summer and late winter was 49nmol/L.¹³ Further determinants of vitamin D status are age and body mass, with lower

25(OH)D concentrations observed in older aged people, and in obese people.^{2, 12, 14- 16}

5. Toxicity and adverse effects of excess vitamin D intake

Following ingestion of large doses of vitamin D, the concentration of 25(OH)D increases in the serum, while that of the active metabolite 1,25(OH)₂D remains unchanged,¹¹ but at high concentrations, the binding capacity of the binding protein may exceed, leading to the release of unbound 25(OH)D and 1,25(OH)₂D. It has been hypothesised that these free forms enter the target cells and directly stimulate gene transcription.¹ Very high serum 25(OH)D concentrations may lead to hypercalcaemia.^{2, 6, 17} The clinical symptoms associated with hypercalcaemia (serum calcium concentrations of 11mg/dL) are fatigue, muscle weakness, anorexia, nausea, vomiting, constipation, tachycardic arrhythmia, soft tissue calcification, failure to thrive and weight loss. Hypercalcaemia may also lead to hypercalciuria, which is defined by a calcium excretion of >0.3mg/mg creatinine in 24-hour urine of adults, or as a calcium excretion >250mg/day in women and >275-300mg/day in men. Sustained hypercalcaemia causes nephrolithiasis (kidney stones), nephrocalcinosis and also a decrease in kidney function.

5.1 Adverse effects in pregnant and lactating women

De-Regil¹⁸ and his co-workers in a systematic search evaluated the effect of supplementation with vitamin D alone or in combination with calcium on women during pregnancy; the dose of vitamin D used in routine daily supplementation ranged from 20-30µg and these studies reported on pre-eclampsia, nephritic syndrome, still births or neonatal deaths. Hollis et al¹⁹ randomly assigned pregnant women to receive either 10µg, 50µg or 100µg vitamin D₃/day from 12-16 weeks of gestation until delivery; the primary focus of the research being changes in maternal serum 25(OH)D concentrations. The study also addressed the safety of vitamin D supplementation and pregnancy outcomes. The authors concluded from their study that no adverse event was attributed to vitamin D supplementation or serum 25(OH)D concentrations.

5.2 Adverse effects of vitamin D in infants

In infants, hypercalcaemia has been associated with single large dose therapies of vitamin D (commonly known as Stoss Therapy). There are many studies which have documented the lower daily doses of vitamin D. Hypponen

et al²⁰ reported that there was no association of vitamin D dose (<50µg/day, n=66; 50µg/day according to the Finnish recommendations at that time, where n=8,100; and >50µg/day, n=407) in regularly supplemented infants with body measurements of length measured at one year, at 14 years where it was self-reported and in adulthood both self-reported as well as measured. Further there was no difference in height between the groups which was classified according to the frequency of supplementation. In another study from Finland, Ala-Houhala²¹ supplemented breast-fed infants with 0, 10 or 25µg vitamin D₂/day for 20 weeks; the mothers of infants not taking vitamin D received around 25µg/day. Two studies were then carried, one in January and the other in July; the mean serum calcium concentrations in infants did not appear to increase throughout the study in both the groups. In another randomized study²², infants and toddlers with hypovitaminosis D aged between 9-23 months were treated for 6 weeks with either 50µg vitamin D₂ daily or 50µg vitamin D₃ daily and both groups received 50mg calcium/kg body weight per day. There was small changes in serum calcium concentrations in the groups; -3% for vitamin D₂ daily, +3% for vitamin D₂ weekly and +1% for vitamin D₃ daily; as well as a higher overall incidence of mild hypercalcaemia at baseline compared to after treatment. Further, all the subjects with hypercalcaemia were reported to be asymptomatic.

5.3 Hypercalcaemia in children and adolescents

In a study by Maalouf et al²³, healthy girls (n=168) and boys (n=172) aged 10-17 years from Beirut randomly received weekly either 35µg vitamin D₃, 350µg vitamin D₃ or placebo for one year. The author reported primary changes in lean mass, bone mineral density and also in bone mineral content. Further hypercalcaemia did not occur in the girls who received vitamin D₃; hypercalcaemia occurred in active and non-active treatment groups, but were not related to supplementation of vitamin D. Thus it was concluded that vitamin D intakes at doses upto 50µg/day did not lead hypercalcaemia in children and adolescents aged 10-17 years.

6. Tolerable Upper Intake Level

6.1 Adults, pregnant and lactating women

There is no evidence that pregnancy or lactation increases the susceptibility for adverse effects of vitamin D intake. An Upper Limit of 100µg/day for adults also applies to pregnant and lactating women. This Upper Limit is supported by two studies in pregnant and lactating women,

both using doses of vitamin D2 or D3 upto 100µg/day for several weeks to months.^{19,23}

6.2 Infants, children and adolescents

There is a paucity of data on which to base a NOAEL or a lowest observed adverse effect level (LOAEL) in infants. Considering this, the Upper Limit of 25µg vitamin D/day for 0-12 months is recommended. For children 1-10 years, an Upper Limit of 50µg/day is recommended and 100µg/day for adolescents aged between 11-17 years.

7. Calcium intakes versus recommendations and the role of Health Professional

The majority of children and adolescents do not consume enough dietary calcium on a daily basis. It is estimated that 9/10 girls and 6/10 boys aged 12-19 years do not consume adequate calcium.²⁴ Children aged 9-19 years need 1300mg of calcium for optimal growth of long bones. The American Academy of Pediatrics recommends three 8-ounce glasses of milk a day, or its equivalent, for children 4-8 years of age and four glasses for adolescents.²⁵

Pediatricians, Pediatric Dentists and other health professionals dealing with children are in an ideal position to monitor and assess calcium status and future issues with osteopenia and osteoporosis. The following are considered:

- Children need 2-3 servings of nutrient-rich food sources from dairy and dairy products; adolescents need 3-4 servings.
- Calcium intake should be assessed atleast three times during childhood and adolescence.
- Many dairy foods can be supplemented to children and adolescents as they are a rich source of bone-building nutrients like vitamin D, magnesium, phosphorus and proteins.
- Cheese and yogurt can be given during snack time; other calcium-rich foods such as beans, green leafy vegetables and nuts are recommended for optimal bone health.
- Assess the physical activity levels in children and adolescents, emphasizing on running, jumping or walking to enhance bone health.
- To identify children with bone defects, check bone mineral density against age, race and sex.

8. Meeting Vitamin D recommendations and the role of Health Professional

Vitamin D has to be supplemented from various sources, but these supplements not only leads to over consumption, but also there is an “incomplete” package of nutrients. Multivitamin supplements generally provides 200-400 IU/tablet; single vitamin D supplements provides upto 2000 IU.

The Health Professional is in an ideal position to monitor and assess vitamin D status in all age groups. While evaluating vitamin D status;

- Consider skin pigmentation, use of sunscreen, time spent out/indoors.
- Assess calcium intake simultaneously for its impact on bone health.
- Recommend a vitamin D test; use the IOM value of 20ng/ml to assess status.
- Check for any complaints of bone pain or muscle pain.
- Encourage food and fortified food sources of vitamin D first, then followed by supplements.

Conclusion

The Upper Limit for vitamin D for adults, including pregnant and lactating women, has been established at 100µg/day. For children and adolescents, the Upper Limit has been set at 50µg/day for ages 1-10 years and at 100µg/day for ages 11-17 years. For infants up to 1 year of age, the Upper Limit is 25µg/day.

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