

Vitamin D in Infancy, Childhood and Adolescence



Christopher Kovacs, MD, FRCPC, FACP

Professor of Medicine (Endocrinology)

Memorial University of Newfoundland

ckovacs@mun.ca

Disclosure

- I am currently serving on the Institute of Medicine's committee which is charged with reviewing data in order to revise the Dietary Reference Intakes for Calcium and Vitamin D. Please do not consider the following to be a preview of the report or a hint of the committee's conclusions. The committee has not yet completed its deliberations. More importantly, the opinions expressed herein are my own.

Confounding in Associational Studies

It Applies to Infants, Children, and Adolescents Too

- Adults who have higher vitamin D intakes or 25-D levels are also more likely to:
 - ◆ Be lean (not overweight or obese)
 - ◆ Exercise and spend more time outdoors
 - ◆ Consume dairy products and other vitamins
 - ◆ Have other indicators of healthier lifestyle
 - ◆ Have higher socioeconomic status
 - ◆ Be non-smokers, have low alcohol consumption, etc.
- Associational studies of vitamin D may be confounded by comparing healthier to less healthy individuals
 - ◆ c.f. associational studies of estrogen replacement and anti-oxidants versus subsequent clinical trials

The Infant

Infant Skeletal Outcomes

Animal Models

- In animal models of severe vitamin D deficiency, absence of the 1-alpha-hydroxylase, or absence of the vitamin D receptor, the fetal blood calcium, skeletal lengths, and mineralization are normal at term
- It is around the time of weaning – when intestinal calcium absorption becomes calcitriol-dependent – that the animal begins to develop rickets
 - ◆ A high-calcium prevents rickets by bypassing the need for calcitriol to stimulate active calcium absorption

Halloran BP. *Arch Biochem Biophys* 1981;209:7-14; Halloran BP. *Science* 1979;204:73-4; Miller SC. *Calcif Tissue Int* 1983;35:455-60; Lachenmaier-Currle U. *J Perinat Med* 1989;17:127-36; Kovacs CS. *Am J Physiol Endo Metab* 2005;289:E133-44.

Natural History of Rickets in Humans

- Normal serum calcium and skeleton at birth even with very low 25-D but some signs (larger fontanelle) may be recognized after first few weeks
- Deficiency is present months before skeletal effects are noticeable
- Peak incidence of rickets at 3-18 months
- A UK retrospective review found two presentations:
 - ◆ Hypocalcemia during periods of rapid growth
 - ◆ 17/29 had no radiological evidence of rickets
 - ◆ Chronic skeletal effects of rickets and demineralization
 - ◆ Bow legs, pain, swollen joints, other bone abnormalities
 - ◆ All had 25-D levels < 15 nmol/l

Infant Skeletal Outcomes

Observational Studies

- Born with a 25-hydroxyvitamin D (25-D) level about equal to the mother's because it readily crosses the placenta
- Vitamin D and 25-D content of human milk is usually very low
- Typical doses of vitamin D given to the mother do not increase 25-D levels of the suckling infant
- Breastfed infants will develop low 25-D levels unless directly supplemented with vitamin D or exposed to sunlight
- Infant formulas in North America are supplemented with vitamin D

Rachitic Threshold of 25-D?

Observational Studies

- Most cases of rickets occurred in infants and children with 25-D levels less than 30 nmol/l, especially < 20 nmol/l
- If calcium intake is adequate (as in most North American children) then a 25-D level > 30 nmol/l will prevent rickets
- Where dietary calcium intake is very low (as in studies from Nigeria, India, and Middle East) and intake of phytate (calcium inhibitors) is high, rickets has been observed with 25-D levels as high as 50 nmol/l
- But if the calcium intake is very low it may be more important to fix the calcium intake than to raise the 25-D level to > 50 nmol/l
 - ◆ If there's little or no calcium in the diet, no amount of vitamin D will prevent rickets

Prevalence of Low Vitamin D in Infants and Toddlers

■ Boston:¹

- ◆ < 20 nmol/l: 1.9%
- ◆ < 50 nmol/l : 12.1%
- ◆ < 75 nmol/l : 40.0%

■ St. John's, Newfoundland:²

- ◆ < 25 nmol/l : 3.6%
- ◆ < 50 nmol/l : 12.7%
- ◆ < 75 nmol/l : 54.5%

¹Gordon CM. *Arch Pediatr Adolesc Med* 2008;162:505-12.

²Unpublished hospital laboratory data, 2008

Risk Factors for Low Vitamin D in Infants and Toddlers

- Study of 380 infants and toddlers in Boston
- Infants:
 - ◆ Breastfed with no vitamin D supplement given to baby
- Toddlers
 - ◆ Low milk consumption
 - ◆ Higher body mass index

Canadian Risk Factors for Rickets

- 94% of children with rickets were breastfed
- Additional risk factors include:
 - ◆ dark skin
 - ◆ living in far North
 - ◆ born of mother who took no vitamin supplements
 - ◆ limited sun exposure
 - ◆ emigrated from a region where vitamin D deficiency is endemic
 - ◆ delayed initiation of solid foods
- Incidence 2.9 per 100,000 cases in Canada
- Mean age at diagnosis 1.4 years (range 2 weeks to 6.3 years)

Vitamin D Supplementation in Infants

- 300 or 400 IU per day resulted in mean 25-D levels >75 nmol/l¹⁻³

¹Greer FR. *J Pediatr* 1982;100:919-22

²Greer FR. *J Pediatr* 1989;114:204-12

³Wagner CL. *Breastfeeding Med* 2006;1:59-70.

Upper Limit - Infants

- Current upper limit is 1,000 IU per day in infants
- 300 to 400 IU per day gives 25-D levels 75-100 nmol/l during first six months
- Consensus opinion asserts that 25-D > 50 nmol/l (or possibly > 75 nmol/l) may be ideal; there are no data to support that even higher levels would be beneficial
- 1,400 IU per day caused toxicity in an infant at Yale (dose was 500 IU per kg) in an unpublished report
 - ◆ Earlier reports of toxicity with 1,800-2,000 IU in infants
- The current limit of 1,000 IU per day in infants may be reasonable

Infant Skeletal Outcomes

Treatment Studies

- All breastfed infants had 25-D levels > 75 nmol/l by supplementing mothers with 6,400 IU per day¹
 - ◆ Babies given 300 IU directly achieved the same 25-D level¹
- No objective benefits of this approach have been established other than achieving an arbitrary 25-D value
 - ◆ It certainly doesn't affect the milk calcium content
 - ◆ It is assumed to be safe but objective data on short and long-term safety for mothers and babies are also lacking

¹Wagner CL. *Breastfeeding Med* 2006;1:59-70.

Infant Skeletal Outcomes

Treatment Studies

- Beyond preventing rickets, only a transient benefit on bone mass has been seen
- Study of 18 healthy term infants randomized to receive 400 IU or placebo
 - ◆ At 12 weeks of age, higher BMC and 25-D levels observed in the 9 infants receiving vitamin D¹
 - ◆ At 25 weeks, the BMC was identical between the two groups²
- Study of 46 healthy breastfed infants randomized to receive 400 IU vitamin D or placebo
 - ◆ No difference in BMC at 3 or 6 months of age³

¹Greer FR. *J Pediatr* 1981;98:696-701

²Greer FR. *J Pediatr* 1982;100:919-22

³Greer FR. *J Pediatr* 1989;114:204-12.

Infant Skeletal Outcomes

Long-term Observational Studies

- 596 pregnant women; 160 had 25-D levels measured during 3rd trimester; 178 children later assessed at age 8.9 yr
- Women sorted post-hoc by 25-D status: low (< 27.5 nmol/l or 11 ng/ml), insufficient (27.5-49.9 nmol/l), and sufficient (> 49.9 nmol/l or 20 ng/ml)
 - ◆ No association with weight, length, head circumference, arm circumference at birth or 9 months
 - ◆ No association with weight, height, head circumference, BMI, lean or fat mass, neuro and IQ scores at age 9 yr
 - ◆ Low maternal 25-D associated with slightly lower BMC at age 9 yr
 - ◆ 1.04 ± 0.16 vs. 1.14 ± 0.17 vs. 1.16 ± 0.17 kg ($p < 0.02$ of low versus sufficient)

Infant Non-Skeletal Outcomes

Observational Studies

- Many extra-skeletal benefits of vitamin D have been proposed for the adult; presumably these benefits could be conferred beginning *in utero* or early postnatal life
- These include protection against autoimmune diseases (type 1 diabetes), multiple sclerosis, cardiovascular disease, cancer, etc.
- For most of these outcomes there are no data pertaining to fetal or neonatal vitamin D status
- The risk of type 1 diabetes has drawn the most attention on the basis of associational studies but, as yet, no clinical trials

Vitamin D and Type 1 Diabetes

- 10,366 children born in Finland in 1966
- 1967: (12 months) mothers were asked if a 2,000 IU vitamin D supplement was given to infants in the prior year
- 1998: incidence of type 1 diabetes assessed
- “Conclusion” regular vitamin D use: 0.22 RR of diabetes

	Type 1 diabetes	Time at risk (years)	Incidence per 100 000 years at risk	RR (95% CI)	Adjusted RR (95% CI)*
Use of vitamin D supplements					
None	2	981	204	1 (reference)	1 (reference)
Irregularly	12	36 143	33	0.16 (0.04–0.72)	0.16 (0.04–0.74)
Regularly	67	276 235	24	0.12 (0.03–0.47)	0.12 (0.03–0.51)
Dose of vitamin D†					
Low	2	2 093	96	1 (reference)	1 (reference)
Recommended	63	259 779	24	0.20 (0.05–0.84)	0.22 (0.05–0.89)
High	2	13 245	15	0.14 (0.02–0.97)	0.14 (0.02–1.01)
Suspected rickets‡					
No	77	306 945	25	1 (reference)	1 (reference)
Yes	4	6 414	62	2.6 (1.0–7.2)	3.0 (1.0–9.0)

*Adjusted for sex, neonatal (parity, gestational and maternal age), length of maternal education, social status, and standardised birth weight, and growth rate in infancy (suspected rickets adjusted in addition to the increased dose of vitamin D); †In children receiving vitamin D supplementation regularly.

The Child

Childhood (age 2-8)

- An interval of relatively slow bone growth compared to fetus, infant and adolescent
- There are no prospective data that define what the optimal 25-D level of children should be
 - ◆ > 30 nmol/l is considered protective against rickets based on the experience with infants and toddlers
 - ◆ > 50 nmol/l provides a secure margin over the rachitic threshold
 - ◆ > 75 nmol/l is considered by some the target to be consistent with the commonly-held adult target

Childhood (age 2-8)

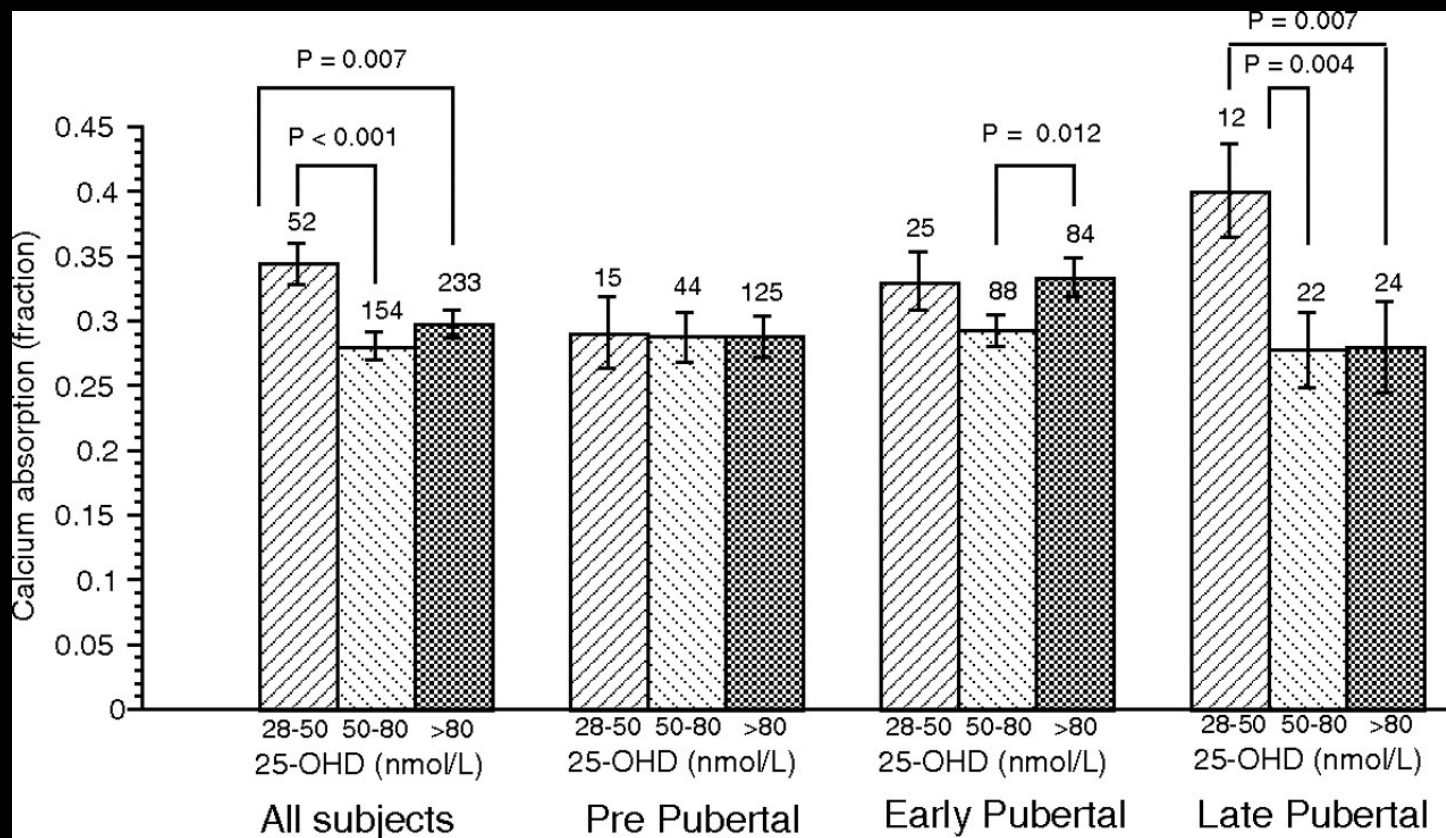
- Current recommendations are 200 IU per day (IOM) and 400 IU per day (AAP and CPS)
- There are no data about dose-response (vitamin D intake to achieved 25-D level) in this age group
- Increasing size/weight/adiposity increases the amount of vitamin D required to maintain a particular 25-D level
- A dose of 400 IU per day will likely achieve 25-D levels > 50 nmol/l in most children; 1,000 IU per day may be needed for a target of > 75 nmol/l

The Adolescent

Adolescence (age 9-18)

- An interval of rapid bone growth
- Average weight is 5-10 times the amount of an infant
- There are no prospective data that define what the optimal 25-D level of children should be
- Intestinal calcium absorption does not show a dose-response to increasing 25-D level

Intestinal Calcium Absorption



Adolescence (age 9-18)

- Current recommendation is still 200 IU per day (IOM) and 400 IU per day (AAP)
- There are insufficient data on dose-response relationships in this age group
- A dose of 600 IU per day may be needed for a target of > 50 nmol/l
- A dose of 1,000 IU per day may be needed for a target of > 75 nmol/l

Sunlight Exposure

- 10-15 minutes of full body exposure in a light-skinned adult will generate 10,000-20,000 IU of vitamin D over the following 12-24 hours
 - ◆ Reduced by darker skin pigmentation, latitudes further from the equator, season, pollution, cloud cover, amount of skin exposed, sunscreen, age, etc.
- Similar studies on time requirements have not been done in infants or children but vitamin D sufficiency can easily be maintained by adequate sunlight exposure
- Avoidance of sun exposure to reduce cancer risk necessitates the use of vitamin D supplements and fortified food sources

Prevalence of Low Vitamin D in Adolescents

■ Boston¹

- ◆ < 20 nmol/l : 4.6%
- ◆ < 50 nmol/l : 42.0%
- ◆ < 75 nmol/l : not quoted

■ St. John's, Newfoundland²

- ◆ < 25 nmol/l : 2.7%
- ◆ < 50 nmol/l : 32.5%
- ◆ < 75 nmol/l : 76.6%

¹Gordon CM. *Arch Pediatr Adolesc Med* 2004;158:531-7.

²Unpublished hospital laboratory data, 2008

Risk Factors for Low Vitamin D in Adolescents

- Study of 307 adolescents in Boston (ages 11-18)
- Higher consumption of soft drinks, fruit juice, iced tea
- Low consumption of milk
- Low consumption of cold cereal
- No multivitamin use
- Higher body mass index
- Dark skin (African American>Hispanic>Asian or Caucasian)

Effect of Low Vitamin D in Adolescents

- Significantly lower cortical BMD of the distal radius and tibial shaft in pubertal and prepubertal Finnish girls with 25-D levels <25 nmol/l¹
- Femur BMD increased by 14.3% and 17.2% versus placebo in Finnish adolescents (ages 11-12) who received 200 IU or 400 IU daily for 12 months²
- Other studies suggest that vitamin D replenishment will increase BMD but the effect is not sustained

¹Cheng S. *Am J Clin Nutr* 2003;78:489-92.

²Viljakainen HT. *J Bone Miner Res* 2006;21:836-55

Upper Limit - Children and Adolescents

- Current upper limit is 2,000 IU per day in children and adolescents
- There are no specific data on safety of particular doses in older children; adult data suggest >50,000 IU per day and 25-D levels > 500 nmol/l are needed for true toxicity
- More vitamin D is required to achieve a target 25-D level as weight and body size increase
- For children age 1-8, an upper limit of 2 to 3,000 IU may be reasonable
- For adolescents age 9-18, an upper limit of 5,000 IU or more per day may be reasonable

Conclusions

- A maternal and neonatal 25-D level > 30 nmol/l (12 ng/ml) protects against neonatal hypocalcemia and rickets
- Whether a higher 25-D level confers additional benefits in the fetus, infant or child is unproven
- Breastfed babies need 300-400 IU daily administered directly or that their mothers consume 6,400 IU daily
- The dose required to maintain a given 25-D level increases with age and body size
- Proposed long-term skeletal and extra-skeletal benefits of higher 25-D levels are based on possibly confounded observational data and require confirmation by randomized, controlled trials