Prevention of Rickets

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Although it has been known for over 40 years that vitamin D is essential for maintenance of normal calcium and phosphorus metabolism in human beings, the daily amount of vitamin D needed by an infant for protection from rickets is still far from being precisely established. The problem is complex since dietary supply is not the only source of vitamin D. Other factors include prenatal storage of vitamin D and minerals, vitamin D status of the lactating mother, and the availability of ultraviolet irradiation. Furthermore genetic and racial factors as well as the occurrence of chronic diseases possibly interfere with vitamin D absorption and metabolism. During the last 30 years rickets due to vitamin D deficiency has almost disappeared from North America and Western Europe. However it is still present in certain groups at risk, such as migrant workers especially if they come from Southern countries or if they have a pigmented skin (1,2), or in people with peculiar beliefs and food habits such as strict vegetarians (3). Vitamin D-deficiency rickets still exists in numerous countries and is often associated with other nutritional deficiencies like protein-caloric malnutrition. Rickets disappeared from the industrialized countries because, over the years, great efforts have been made by health authorities toward establishing an adequate vitamin D intake throughout the population. Education programs have stressed the need for vitamin D made available through provision of vitamin supplements and enrichment of common food.

Subsequently, a clearer understanding of vitamin D physiology occurred with the development of methods allowing the measurement of vitamin D metabolites and calcitrophic hormones in blood and biological materials. To devise a strategy to eradicate rickets is not easy. Measures and recommendations directed toward providing an adequate amount of vitamin D have to be adapted to the psychology, the way of life, the food habits, and the customs of the various populations where rickets is still prevalent.

REQUIREMENTS OF VITAMIN D

For the normal full term infant the current recommended daily allowance for vitamin D in most countries is 400 IU/day (4). This requirement is based on studies
completed during the 1930s (5). Term infants fed cow's milk containing 135 IU of vitamin D per quart did not develop rickets. However infants given 300–400 IU per quart grew somewhat faster. More recently in Great Britain, Poskitt et al. (6) have shown that a daily intake of 100 IU/day was too low to be fully effective and that with such an intake children require exposure to the sun and ultraviolet radiation to have normal 25-hydroxyvitamin D serum levels. Moderate overdosages of vitamin D do not interfere with the rate of growth of normal infants. Two groups of normal full term infants fed on evaporated milk formula received either 350–550 IU/day or 1380–2200 IU/day of vitamin D. A third group was breast-fed and received 300 IU/day of vitamin D. Rates of growth, gains in weight, and serum calcium concentrations were similar in the 3 groups (7).

The vitamin D requirements of the premature infants were more difficult to establish than for full term infants. Preterm infants have the ability to 25-hydroxylate vitamin D in the liver and 1 \( \alpha \)-hydroxylate vitamin D in the kidney early in life (8–10). Other clinical studies in which large groups of formula-fed premature infants were observed clinically, roentgenographically, and biochemically, indicated that rickets could be prevented and normal calcium and phosphorus homeostasis maintained with vitamin D intakes as low as 100 to 200 IU/day (11). Rates of growth in body length have been as rapid with vitamin D intakes of 100 to 200 IU daily as with intakes of 400 to 1200 IU daily (11). Prematures given 1000–1500 IU of vitamin D per day have, during the first 3 months of life, adequate serum levels of \( \text{25(OH)D} \) and \( \text{1,25(OH)}_2\text{D} \) (8). Thus premature infants should receive amounts of vitamin D between 400 and 1000 IU/day.

**MATERNAL VITAMIN D STATUS**

During pregnancy vitamin D, \( \text{25(OH)D} \), and \( \text{24,25(OH)}_2\text{D} \) easily cross the placenta. There is an enhancement of the placental transport of vitamin D during the last third of the gestation period in the rat. Vitamin D and its metabolites are accumulated and stored in fetal tissues mainly in muscles where they are readily available for neonatal requirements (12). The fetus depends on the maternal supply for \( \text{25(OH)D} \) and \( \text{24,25(OH)}_2\text{D} \) but the feto-placental unit synthesizes \( \text{1,25(OH)}_2\text{D} \) according to fetal needs (13,14). There is no direct relationship between maternal and fetal levels of \( \text{1,25(OH)}_2\text{D} \) and each compartment appears to be autonomous.

Concentration of \( \text{1,25(OH)}_2\text{D} \) in the fetal circulation is usually lower than in that of the mother and depends mostly on endogenous renal synthesis (13,14). Newborns from mothers supplemented from the sixth month of gestation with 1000 IU of vitamin D daily were compared with a control group not having received vitamin D. In the infants born from the supplemented mothers, venous cord blood \( \text{25(OH)D} \) levels were higher and at 4 days serum calcium dropped to a lesser extent (15). Four-day-old term infants from mothers with a suboptimal vitamin D intake (<150 IU/day) have lower serum calcium levels than those born from mothers whose intake was >500 IU/day (16).
Infants born from vitamin D-deficient mothers may exhibit congenital or very early rickets (17–19). Thus the vitamin D status of the pregnant woman is important for the fetus and the newborn to build a normal bone mass and maintain normal calcium–phosphorus homeostasis.

MATERNAL-INFANT VITAMIN D RELATIONSHIP DURING BREAST-FEEDING

It was known for many years that breast-feeding had a protective effect against rickets. For instance in a large epidemiological study in Greece, Lapatsanis et al. (20) demonstrated that there was a significant difference in the incidence of rickets between the breast-fed and the artificially-fed infants not receiving vitamin D. But it was also known that this protection was only relative and depended upon maternal vitamin D status; most cases of rickets reported in the literature occurs in breast-fed infants, since the artificially-fed infants are protected by the addition of vitamin D to the infants formulas or the cow’s milk (21–23). In breast milk, the amount of vitamin D and its metabolites appear to be less than the minimum (100 IU) required for maintenance of normal calcium homeostasis and skeletal development in the suckling infant (24). In a double-blind randomized prospective study of breast-fed infants, Greer et al. (25) found that at 3 months of age, bone mineral content and serum 25(OH)D concentrations were significantly lower in the infants not receiving vitamin D than in a supplemented group receiving 400 IU/day. At 6 months 25(OH)D serum concentration had fallen further in unsupplemented infants and several had no detectable serum 25(OH)D. At 1 year, the unsupplemented infants were significantly shorter than infants given supplements and when compared to a third group fed with a cow’s milk formula (26).

Cancela et al. (27) have demonstrated that there was a significant correlation between the 25(OH)D content of maternal milk and the serum levels of this vitamin D metabolite in paired breast-fed infants after 1 month of lactation. In winter, infants breast-fed by mothers receiving a supplement of 2000 IU/day had the same serum 25(OH)D as did infants receiving a supplement of 400 IU/day (28). Even in a population living in a favorable climate like South Africa, the transfer of vitamin D by the milk from the mother to the infant is low and does not fully protect against rickets (29). Thus even if the Committee on Nutrition of the American Academy of Pediatrics (30) did not give clear recommendations about vitamin D supplementation during breast-feeding, it is necessary to continue to recommend routine daily supplementation of 400 IU of vitamin D for breast-fed infants (31). In this respect it is interesting to cite the result of a survey of vitamin supplementation practices among general pediatricians who are members of the American Academy of Pediatrics. A supplement of vitamin D was prescribed for breast-fed infants by 71% of the responding pediatricians, but of those in pediatric practice for less than 10 years 45% did not prescribe supplements for breast-fed infants (21).
PHOTOSYNTHESIS OF VITAMIN D IN THE SKIN

Natural exposure to sunlight is responsible for maintaining adequate vitamin D status for most of the population of the world. During the past 15 years significant progress have been made in our knowledge of the photobiologic mechanisms that result in the synthesis of vitamin D₃ production in the skin (32). Repeated exposure to sunlight does not necessarily increase the total cutaneous production of vitamin D₃ since, once formed, vitamin D₃ is also photodegraded (33). This phenomenon prevents vitamin D intoxication in persons heavily exposed to sun irradiation. Thomson (34) studied the role of pigmentation and thickness of the epidermis protecting the skin of Europeans and Africans against solar ultraviolet irradiation. Transmission of ultraviolet radiation through skin was affected by skin pigmentation. Later, Clemens et al. demonstrated that melanin pigmentation reduces cutaneous synthesis of vitamin D₃ (35).

There is no precise recommendations for adequate sunlight exposure to prevent rickets in a child. Such recommendations should take into account the time of the year, the geographical location, the quality of the atmospheric air, and the thickness and the pigmentation of the skin. In the elderly, Holick has estimated that for a white person living in Boston, exposing the hands, face, and arms to the sun on a clear summer day for 10–15 minutes should be sufficient to maintain a normal vitamin D status (36). During the summer, infants in Cincinnati (37) or in Beijing (38) had to be exposed approximately 100 minutes per week to sunlight with face and hands uncovered to maintain serum 25(OH) levels above 11 ng/ml, which is acknowledged to be the lower limit of the normal range.

TOXIC DOSES OF VITAMIN D

Hypercalcemia does not ordinarily occur unless vitamin D intake is in the order of 10,000 to 20,000 IU/day (39,40) an amount approximately 25 times the recommended prophylactic dose of 400 IU/day. Epidemiological studies of the hypercalcemic syndrome in infants (41), which were conducted in Great Britain in the 1950s, led many to believe that some individuals might be more sensitive to vitamin D than others. In the period 1953–1955, nutrition surveys indicated that the normal British infant could ingest from various sources as much as 4,000 IU of vitamin D per day. This was coincident with numerous cases of infantile hypercalcemia mainly of the mild form. In the following years the food enrichment policies were changed and subsequently the incidence of infantile hypercalcemia fell (42). However there was still some doubt about a direct relationship between the magnitude of vitamin D intake and the prevalence of hypercalcemia since the two were not exactly chronologically related. Von Sydow and Hedvail (43) studied the potential toxicity of vitamin D in premature babies. 162 babies weighing between 1510 and 2000 g at birth were nursed on breast milk and divided into 3 groups given 450, 2250, and 10,000 IU of vitamin D daily from the eighth day of life. After one month there was no
difference between the groups concerning weight increase, and serum concentrations of calcium, inorganic phosphorus, and alkaline phosphatase. Since this study extended over a short period of time it has to be taken with some reservation. It can, however, be concluded that doses up to 2000 IU/day of vitamin D are unlikely to cause damages.

OSTEOPATHY OF PREMATURITY

Rickets and/or osteopenia is known to occur despite vitamin D supplementation in very-low-birthweight infants (44). Recent studies (9,44) have shown that with a vitamin D intake comprised between 500 and 1000 IU/day, premature babies have normal serum levels of 25(OH)D and 1,25(OH)₂D. Thus the main cause of metabolic bone disease of prematurity is mineral deficiency, phosphate in particular. Breast-fed premature infants may have extremely low concentration of plasma phosphate but normal or high concentrations of plasma calcium and raised urinary calcium excretion (45). The special formula for preterm babies brings 40 mg of phosphorus for 100 ml. Various ways of supplementing breast-milk with phosphate have been proposed (46,47). Phosphorus can be given as buffered sodium phosphate added to the milk to give an extra 10–15 mg phosphorus per 100 ml feed. This supplement is continued until the infant reaches 2000 g (44). Vitamin D supplementation is recommended at 500 to 1000 IU/day.

PRACTICAL PROBLEMS FOR PREVENTION OF RICKETS

Vitamin D supplements are currently recommended since the average diet contains little vitamin D and since many people do not receive enough ultraviolet irradiation from the sun to synthesize sufficient natural vitamin D in their skin. These vitamin D supplements can be provided in different ways.

Prescription of a Daily Dose of 400–1000 IU of Vitamin D

This is the simplest, the safest, and the more physiological way to administer the vitamin to a child who does not receive vitamin D from other sources, in particular to breast-fed infants. However it implies a good compliance from the mother and the availability of adequate pharmaceutical forms of vitamin D. These two conditions are not always met in developing countries.

Periodic Administration of High Doses of Vitamin D (Stoss therapy)

This form of prophylaxis is still in use in certain European and African countries: 5 to 15 mg of vitamin D are given every 3 months, amounting to 20–60 mg a year. The capsule of vitamin D is given to the child during a visit to the pediatrician or a
health service facility and its intake controlled. In this way there is no problem of compliance.

In the literature, there is little information on the effectiveness or on the dangers of such high doses of vitamin D. Wolf and Del Solar (48) observed in Germany 13 cases of rickets in infants having received 5 mg of vitamin D once during the first year of life, 5 cases having received 5 mg twice, and 5 cases having received 5 mg three times during the first year.

It is likely that in some children the dose of vitamin D is not fully absorbed. The same authors (49) studied the effects of 5 mg of vitamin D, given as a single dose during the second day of life to normal newborns. On the fifth day of life, mean serum calcium concentration was 10.4 mg/100 ml (2.6 mmol/l) compared to 9.35 mg/100 ml (2.33 mmol/l) \( (p < 0.001) \) in control infants having received 400 IU of vitamin D daily. Serum phosphorus concentration was also significantly higher in the infants after the high dose of vitamin D. Thus prophylaxis of rickets with intermittent high doses of vitamin D is not very effective. It may cause serious side effects especially if doses as high as 15 mg of vitamin D (50) are given. Some children may develop hypercalcemia. The people who still use this form of prevention should be encouraged to properly evaluate it for both its effectiveness and its side effects.

**Food Enrichment**

There is no doubt that rickets almost totally disappeared from the industrialized countries as soon as milk and various food products were enriched with vitamin D. This strategy is efficient if appropriate to the economic status and food habits of the population concerned. Pietrek et al. (51) have demonstrated that rickets disappeared from the Pakistani communities in England when the flour utilized to make a traditional food, chupatty, had been enriched with vitamin D. The enrichment should be limited to one or a few types of food. In the 1950s in England in an overenthusiasm for prevention of rickets, children were receiving oral vitamin D from proprietary concentrates and from various food products: numerous cases of infantile hypercalcemia resulted. In 1957 the amount of vitamin D added to dried milk and cereals and contained in cod-liver oil was reduced and a subsequent survey made in 1960 showed that the children took an average of 424–740 IU of vitamin D daily (52). During this period, infantile hypercalcemia disappeared from England.

These observations show that the proper enrichment of food is a very delicate process which must take into account the food habits of the population concerned.

**CONCLUSIONS**

1. Fetus and breast-fed infants are entirely dependent on their mothers' vitamin D status. Pregnant and lactating mothers should be given 500–1000 IU of vitamin D daily and/or encouraged to expose themselves to sun. Breast-fed infants should for safety receive 500 IU of vitamin D daily.
2. Premature babies are able to normally metabolize vitamin D. They should receive 500–1000 IU of vitamin D/day as a supplement or in their formula. To prevent the bone disease of very-low-birthweight infants, special attention has to be given to calcium and phosphorus intake.

3. Every child should receive around 500 IU of vitamin D daily. This is particularly important during the period of rapid growth of the first year of life. The enrichment of food is the best way to eradicate rickets from a population if this measure is carefully planned by the health authorities.

4. Appropriate measures of prevention will remain difficult in countries where some people are not exposed to the sun and where the economic situation prevents a good delivery of medical care to each individual. In these countries prevention of rickets should make use of all possible ways and means: education, enrichment of food, and distribution of vitamin D. “Stoss-therapy” which constitutes a possibility should be more precisely evaluated, and its pros and cons carefully weighed in a given population before large scale implementation.

REFERENCES

DISCUSSION

**Dr. Holick:** Regarding the recommended daily allowance for vitamin D, I quite agree that there are really no satisfactory studies that have definitely set what is the lower limit of required vitamin D intake. We did a study in submariners, and we do know, that in the absence of any sunlight, 600 IU/day are necessary to maintain serum 25-hydroxyvitamin D levels at the same level throughout the entire voyage. So the 400 IU that has been recommended is pretty reasonable, especially if children are exposed to some sunlight. Concerning breast milk and the concept of putative water-soluble forms of vitamin D, let me say the following. I have proposed that there was, in the milk a vitamin D sulfate that even if not biologically active, could be broken down by a sulfatase present in the intestine of neonates and therefore, release vitamin D. We now know that that is not the case. Even if vitamin D sulfate did exist in human milk, it would have no biologic activity.

**Dr. Pettifor:** The one point I would like to make again is that if one recommends vitamin D supplementation for breast-fed infants only, one may well detract from breast-feeding; and mothers will feel that there is something wrong with breast milk. If one makes a general policy that all infants under the age of one year should receive 400 IU in the form of either vitamin D drops or as a multivitamin preparation, you get away from this problem of the difference between breast milk and infant formula or cow’s milk.

**Dr. Paunier:** I agree with you. It is more appropriate to supplement every child, either breast or bottle-fed. If the formula is already enriched with vitamin D, I do not think that the baby will suffer if receiving an extra 400 IU of vitamin D per day.

**Dr. Guesry:** All vitamin recommendations are given by kilogram body weight or per one hundred kilocalories except vitamin D. It is an interesting difference. Is there any reason why the level of vitamin D supplementation should remain stable from birth to death?

**Dr. Paunier:** The ultraviolet irradiation being the main source of vitamin D, the skin surface area exposed is one of the major factors influencing the production of vitamin D, and this obviously changes with age.

**Dr. Markestad:** In Norway we recommend giving vitamin D to all breast-fed babies, but not to infants fed a commercial formula containing 400–500 IU per liter. Babies receiving such a formula will rapidly attain high 25(OH)D levels within the first few weeks of life and at a time when the total intake is only 200–300 IU per day (1). Although additional amounts of the vitamin are probably safe, it is obviously superfluous, and I would be a bit concerned about providing more vitamin D to an already vitamin D replete individual.

**Dr. Paunier:** How do you explain that the children who receive 600,000 IU of vitamin D
four times during a year return to practically normal 25(OH)D levels 3 months after such a large dose?

**Dr. Markestad:** I think that we have a tremendous capacity to detoxify vitamin D. There is a close linear relationship between serum concentrations of 25(OH)D and 24,25(OH)₂D and 25,26(OH)₂D, and probably many other vitamin D metabolites indicating that the higher the 25(OH)D, the more of it is rapidly converted to metabolites other than the active 1,25(OH)₂D (1). In the liver there also seems to be a concentration-dependent conversion of vitamin D and 25(OH)D to water-soluble products which are excreted in the bile (2). After a large vitamin D dose serum 25(OH)D levels therefore decrease in an exponential fashion.

**Dr. Elidrissy:** I have been using high doses of vitamin D for treatment for quite time, but lately I have abandoned this, because the availability of these very high doses create the risk of uncontrolled administration, that might lead to vitamin D intoxication. So, now, we feel that it is better to give small doses for treatment.

**Dr. Paunier:** I certainly agree with you that the prevention with large doses of vitamin D may be dangerous and I personally do not like this form of prevention. However, in certain countries it is practically the only form of prevention which can be used. People produce and eat their own food so you cannot enrich it, and they receive only occasional medical care. In this situation, the best way to prevent rickets is to give to the infant 200,000 IU of vitamin D each time he comes to the clinic for a vaccination for instance. These doses have to be properly recorded to avoid overdose.

**Dr. Coates:** What, in your opinion, is the best time for exposure to sunshine, since ultra-violet rays are seemingly more abundant in the morning. In terms of vitamin D synthesis, would it be better to recommend exposure to sunshine early in the morning for a shorter while than it would be necessary later in the day?

**Dr. Paunier:** Dr. Holick will answer this question.

**Dr. Holick:** In the summertime, in Boston, exposure as early as nine o’clock in the morning is quite sufficient, but you need a longer period of time for that exposure. But later in the season, in the fall, exposure to sunlight at nine o’clock in the morning will not promote any vitamin D synthesis.

**Dr. Mautalen:** Perhaps we should recommend to the pharmaceutical industry to manufacture ampules of vitamin D containing at the most 5 mg, instead of the traditional dose of 15 mg, which might produce vitamin D intoxication more frequently.

**Dr. Paunier:** I fully agree with that.

**Dr. Markestad:** I think that we should not disregard intermittent high dose vitamin D prophylaxis ("stoss therapy"), since this is an attractive mode in parts of the world where the incidence of rickets is high and other programs are deemed inefficient because of poor compliance. It is a question of determining an appropriate dose and schedule of treatment. Such a program could be combined with, i.e., immunization programs.

**Dr. Paunier:** Yes, that is quite correct, but again I would say that we need good scientific information about the amount of vitamin D that can be given safely and with efficiency. We know very little about this important question.

**REFERENCES**