Vitamin D-Deficiency Rickets in Northern Europe and Libya

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HISTORY

Rickets has probably been a common disease entity since ancient history (1). Data regarding prevalence of the condition are only available, however, since the latter half of the nineteenth century when epidemic proportions were noted in industrialized countries, including Norway. In 1898 Johannessen quoted prevalence figures of 63–80% among infants and young children of Northern European countries, and reported that 32% of all in- and outpatient children examined at the pediatric department, University of Oslo in the years 1893–1895, suffered from the disease. The condition was most prevalent during the first two years of life, and was diagnosed in 30% of infants less than 6 months, 66% of those between 6 and 12 months, and in 64% of children of 1–2 years of age (2). In the same period Looft observed that 75% of an unselected outpatient population of children less than 2 years in Bergen, Norway, had rickets (3), and on the basis of health reports from various counties Johannessen inferred that the disease was probably similarly common nationwide (2). Johannessen’s communication was published before etiological factors were known and includes a remarkable statement: “It is difficult to estimate the true prevalence of rickets throughout the country because the children are rarely brought to the doctor’s attention since the lay public believes that they can cure the condition with cod liver oil”!

Rickets was also common in Norway in more recent history. In several hamlets in Northern Norway 50% of children less than 2 years of age were found to have active or healing rickets as late as 1929–1930 (4). It is noteworthy that sea fish constituted a major part of the diet after infancy in this region as well as in Bergen. In England 13% of children between 3 and 18 months had clinical signs of rickets in the early 1940s (5). However, in the 1930s and early 1940s most industrialized nations introduced prophylactic programs, and nutritional rickets was almost completely eradicated.

In the Muslim countries and also among the non-Muslim population of India, and in China, rickets is known to be a common disease (6–12). Although historical data
are lacking it is reasonable to assume that vitamin D-deficiency disease among women and infants has been prevalent as long as cultural habits have limited sun exposure.

**RICKETS TODAY**

In Norway vitamin D-deficiency rickets was a "forgotten" disease for several decades when it reemerged as a significant clinical problem at the end of the 1970s (13,14, Table 1). The patients are mainly immigrants from the Mediterranean countries, Africa, and Asia, but some are native Norwegians who have received prolonged breast-feeding or are on strict vegetarian diets (14,15). The breast-fed infants typically present during late winter or early spring at the age of 6–10 months with convulsions due to hypocalcemia, and are commonly admitted with the diagnosis of febrile convulsions. The infants have not received vitamin supplements, and cow's milk and other food items may have been introduced 2–3 weeks before admission. Serum phosphate (P) may be normal or low, alkaline phosphatase (ALP) normal or mildly elevated, and radiographs of the wrist normal or showing moderate rachitic changes. The infants have low serum levels of 25-hydroxyvitamin D (25(OH)D), but 1,25-dihydroxyvitamin D [1,25(OH)₂D] concentrations may be within normal limits. Vitamin D therapy promptly corrects 25(OH)D, Ca, P, and ALP concentrations and radiographic changes, and temporarily results in elevated 1,25(OH)₂D concentrations proving that the cause was simple vitamin D deficiency (14). A typical case history is presented in Figure 1. In these vitamin D-deficient patients hypocalcemia is probably precipitated by the increased phosphate load and by reduced intestinal absorption of Ca secondary to the altered intestinal environment caused by the introduction of cow's milk (16,17). A similar increase in the occurrence of rickets in exclusively breast-fed infants has also been noted in Finland (18). "Immigrant rickets" has, in addition to Norway, been reported from West Germany (19), and particularly among Indian immigrants in Great Britain (20).

**TABLE 1. Number of children diagnosed as having vitamin D-deficiency rickets at Oslo pediatric departments during the period 1951 to 1981**

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number</th>
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<tr>
<td>1951–55</td>
<td>16</td>
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<tr>
<td>1956–60</td>
<td>9</td>
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<tr>
<td>1961–65</td>
<td>7</td>
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<td>1966–70</td>
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<tr>
<td>1976–80</td>
<td>13</td>
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<tr>
<td>1981</td>
<td>8</td>
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*From Seeger-Halvorsen K and Halvorsen S (13).*
Fig. 1. Blood chemistries of a 7½-month-old boy admitted for hypocalcemic convulsions, but no other signs of rickets. He was purely breast-fed until the last few weeks when cereal and cow’s milk were added. Radiographs of the wrist were normal, as were serum P and ALP. Hypocalcemia and a low serum 25(OH)D concentration rapidly became normal on vitamin D treatment. 1,25(OH)₂D was in the low normal range before, and temporarily reached levels above normal after the start of treatment. The bars along the vertical axes indicate normal ranges.

Although rickets is common in Arab countries, prevalence figures are scarce. However, in small towns in Northern Yemen and Tunisia 27% and 17% of infants and young children were found to suffer from the disease (11,12). In Libya, rickets is frequently diagnosed at the El-Fatah Children’s Hospital in Benghazi. The disease is often severe and complicated by pneumonia and other infections. Typically the children have received prolonged breast-feeding and been kept out of sunlight, and the mothers are wearing the traditional veil and are therefore vitamin D deficient (21,22).

In Libya as in Norway, rickets is almost exclusively diagnosed in children less than 2 years of age, and we are not aware of significant long term skeletal deformities. Among the Indian immigrants in Great Britain, however, rickets and osteomalacia have also been found in older children, especially teenagers, and in young adult women (23).

RISK OF VITAMIN D-DEFICIENCY RICKETS

The vitamin D nutritional status of the infant, as judged from serum 25(OH)D levels, is determined by the vitamin D stores acquired in utero, oral vitamin D intake, and exposure to sunshine (Fig. 2). The stores of the newborn are directly related to the mother’s vitamin D intake and exposure to sunshine (Fig. 3).

In the Nordic countries pregnant women who do not take vitamin D supplements tend to be vitamin D deficient during winter (25), while a daily supply of 400 IU gives adequate protection for the woman as well as for her baby at birth (26).

In Libya and other Arab countries pregnant women, and consequently their newborn infants, are commonly severely vitamin D deficient (21,27). Since the vitamin
FIG. 2. Plasma concentrations of 25(OH)D in infants of various ages and at different times of the year (individual values and mean ± SD). The diet consisted of breast milk alone (○), commercial milk formula alone (●), or mixed feeds (▲). *The formula contained 400 IU of vitamin D₃ per liter. From Markestad T (24).

FIG. 3. Relationship between 25(OH)D in maternal and cord serum. The regression equation was $y = 1.73 + 0.58$, $r = 0.93$, $p < 0.0005$. From Markestad T et al. (21).
D content of breast milk is generally low, and directly related to the vitamin D nutritional status of the mother (28,29), the cultural habits leading to vitamin D deficiency in pregnancy will continue to give a highly inadequate nutritional supply of the vitamin to the breast-fed infant.

Even with a relatively large vitamin D supply of 600–1000 IU per day and an adequate serum concentration of 25(OH)D in the mother, exclusively breast-fed infants in countries like Norway and Finland will rapidly deplete their vitamin D stores during winter when sunlight exposure is negligible (30,31). Already by six weeks of age 8 of 12 Norwegian babies breast-fed by mothers receiving 600 IU of vitamin D per day had 25(OH)D levels below 20 nmol/l (30). In our experience infants with such low levels will carry a risk of developing rickets (14). Seven infants from Northern Norway who were on prolonged, un supplementation breast-feeding, all experienced drops in 25(OH)D concentrations to below 20 nmol/l during winter, and there was no apparent effect of providing a vitamin D supplement of 400 IU to the mother (32). During summer, however, the infants rapidly achieved high levels of 25(OH)D. These observations underscore the importance of providing breast-fed infants with either oral vitamin D supplements or skin exposure to ultraviolet light.

Reports at the end of the 1970s suggesting that human milk may contain adequate amounts of vitamin D in a water-soluble form (33), coincided with a growing public interest in unsupplemented and prolonged breast-feeding, and rapidly gained acceptance among the public and health professionals as well. The subsequent apparent increased incidence of rickets among native Norwegian infants, although still a rare disease, was possibly caused by this fallacious reassurance that breast milk of well nourished mothers covers all the nutritional needs of the infant.

Vitamin D supplementation during infancy has for decades been a uniformly honored practice in Norway. The higher prevalence of rickets in the immigrant population is mainly the result of their lack of such traditions. Their darker skin and lesser tendency to expose themselves to sunshine (34,35), and possibly dietary habits (36), may be contributing factors.

The necessity of supplying infants in Northern Europe with additional vitamin D was also recently demonstrated in Germany (37). For many years infants in Germany have received intermittent high doses of vitamin D as a compulsory rickets prevention program. Before the first dose at 4 weeks of age, most of the infants were judged to be vitamin D deficient on the basis of the combined finding of 25(OH)D levels below 20 nmol/l and a significant increase in 1,25(OH)_2D levels following the introduction of vitamin D.

In Libya no food items except infant formulas are enriched with vitamin D, and oral vitamin D supplementation is not generally provided. The limited exposure to sunshine will therefore render the breast-fed babies at considerable risk of rickets. In this country, as in Norway, many cases of vitamin D deficiency and possibly several cases of mild to moderate rickets may occur for each case detected. This can partly be surmised from our studies which showed that one-third of the Norwegian and nearly one-half of the Libyan children already had elevated 1,25(OH)_2D and often other evidence of healing rickets at the time of diagnosis (14,22). Appar-
ently the spring sunshine in Norway and the increased independency of walking and, therefore, the opportunity to get outdoors in Libya, brings about a natural cure.

We found no differences in the regulation of vitamin D metabolism or in safe minimum levels of \(25(OH)D\) between the Norwegian and Libyan children. The latter have, however, darker skin, and may need longer sunshine exposure to obtain an equal dermal synthesis of vitamin D (35).

**PROPHYLAXIS AGAINST RICKETS**

In Norway, margarine is the only food item fortified with vitamin D and is estimated to supply the older child and adult with 100 IU per day. Vitamin D supplements are used almost uniformly during infancy, but probably not widely after the first 2–3 years of life. Limited surveys have indicated, however, that older children, adolescents, and healthy adults maintain adequate \(25(OH)D\) levels even during winter (38). Even this far north, sunshine exposure is obviously the dominating source of vitamin D, and stores acquired during summer seem adequate to bring most people safely through the winter. Oral vitamin D prophylaxis is indicated, however, for young children, pregnant women, and individuals who for some reasons experience limited sun exposure during summer.

For infants and young children the recommended daily allowance of vitamin D of 400 IU per day seems to provide ample protection during winter. In the cross-sectional study referred to earlier (Fig. 2), none of the infants studied at the end of summer had received vitamin D supplements during the previous 4–5 months, but all had high \(25(OH)D\) levels. Exclusively formula-fed infants who received a commercial infant formula containing 400 IU of vitamin D per liter, and thus received approximately 300 IU per day by six weeks, attained similar \(25(OH)D\) levels already at this age without exposure to sunshine. The older infants studied during winter had received a vitamin preparation containing 400 IU of vitamin D per 10 ml. By history they had probably on average only received less than half this dose per day which may explain why their \(25(OH)D\) values were intermediate between those of the infants studied at the end of summer and of the formula-fed infants on one side, and the non-supplemented and non-exposed infants on the other.

In some European countries vitamin D prophylaxis has traditionally been provided as one oral dose of 600,000 IU every 3–4 months during the first 1–2 years of life ("stossprophylaxis,"-37, and see chapter by L. Paunier). Such doses commonly result in serum \(25(OH)D\) levels in the toxic range, and may cause hypercalcemia (37). A similar regime using 100,000–120,000 IU per dose is probably equally effective in preventing rickets (39), but may still be unnecessarily high (Fig. 4). For institutionalized elderly people in Great Britain an oral dose of 100,000 IU twice a year seems to give adequate protection (40), and in Asian immigrants 100,000 IU given in the fall resulted in adequate \(25(OH)D\) levels during winter (41). It would be appropriate to test a similar program for breast-fed babies in countries where the in-
CONCLUSIONS

Sunshine exposure of the skin represents the dominant natural source of vitamin D for all humans, including infants. In Northern Europe nature provides inadequate sunlight to give ample protection to risk groups such as young children during winter, and rickets has reemerged as a significant clinical problem because of the influx of dark skin immigrants who are unaccustomed to take oral vitamin supplements, and because of a more prevalent practice of giving prolonged and unsupplemented breast-feeding and strict vegetarian diets among the native population.

In Libya and many other countries endowed by abundance of sunshine, a high incidence of rickets is a continuing clinical problem because of the cultural habits which severely limit sunlight exposure of pregnant and nursing women as well as of their infants.

In the Northern countries the long time honored practice of providing vitamin D supplements to risk groups should again be encouraged. In the education of the public it is particularly important to emphasize that human milk provides inadequate amounts of vitamin D even in the well nourished mother.

Increased exposure to sunshine seems like the obvious solution in other countries. It must be the responsibility of local health authorities, however, to design prophylactic programs which are socially acceptable to the public and thus have a chance of success.
ACKNOWLEDGMENT

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DISCUSSION

*Dr. Holick:* How do you reconcile the high dietary intake of fish and the significant prevalence of rickets in Norway?

*Dr. Markestad:* Vitamin D deficiency seems to be common during winter, but I would like to emphasize that overt rickets is still uncommon in the native Norwegian population. Furthermore, nutritional rickets is mainly a disease of infancy, when fish is not really a part of the diet. In general terms, however, I think that the vitamin D content of fish doesn’t contribute very much to the total household of vitamin D in the Norwegian population.

*Dr. Holick:* Another explanation is that usually when you eat fish you don’t often eat the liver nor the viscera, where most of the vitamin D is concentrated.

*Dr. Markestad:* Fish liver is considered a delicacy in certain coastal areas, but intake is obviously infrequent and probably does not contribute significantly to the diet.

*Dr. Blanco:* Since we know that all over the world, infant physical and mental health is more correlated to breast-feeding than to any other nutritional consideration, it is particularly important to emphasize that human milk provides inadequate amounts of vitamin D. Inadequate exposure to sunshine is the real problem. In these conditions we have two ways of
preventing rickets: supplementing breast-feeding women and if it is not possible, giving supplemented milk.

Dr. Markestad: I agree with you. The many benefits of prolonged breast-feeding should be stressed. Health workers should, however, be aware of the risk of vitamin D deficiency in areas where the infants are not exposed to sunshine, and take appropriate measures either by educating the public to expose the infants or by providing a simple prophylactic program.

Dr. Guesry: Concerning the comment by Dr. Holick about the content of vitamin D in fish, it is useful to point out that there are two kinds of fish: the fatty fish like mackerel in which fat is in or around the muscles, and lean fish like cod, in which fat is in the liver. Do you know if vitamin D in the fatty fish is with the fat in the muscle? And a corollary to this question is, does anybody know about the rickets incidence in Inuits? Also, do you have any data on the incidence of rickets in Libya?

Dr. Markestad: I cannot comment on the distribution of vitamin D in fish or on the incidence of rickets among Inuits. In Libya rickets is obviously quite common, but there are no incidence figures available. I think the same situation applies to all the Arab countries, namely that incidence figures based on sufficiently large populations are lacking.

Dr. Holick: Inuits do have a common practice of eating polar bear as well as seal liver fresh, which have a very high content, not only of vitamin A but of vitamin D; they also eat a lot of fatty fish, so I do not think that rickets is a problem in that population.

Dr. Marx: The mammals with the highest fish content in their diet are the ocean-dwelling mammals, i.e., whales and seals. Interestingly, their metabolism seems specialized for elimination of vitamin D. Whereas their 25(OH)D levels are similar or modestly higher than those for normal humans, the ocean-going mammals have unusually high serum levels of 24,25(OH)₂D (1).

Dr. Holick: We have analyzed blood specimens from polar bears and found 25(OH)D levels in the range of about 250 ng/ml, whereas 1,25(OH)₂D is about 40 to 60 pg/ml, so it is clear that there is some mechanism for them not to become intoxicated.

Dr. Markestad: In comparing the dietary contribution of vitamin D from fish in humans and seals it is important to be aware that the seal has an enormous consumption of fish compared even with humans who live in a fishing community.

Dr. Delvin: You agreed earlier that you had seen vitamin D intoxication, most probably inadvertently due to the preparations of vitamin D. Does that imply that there is no strict quality control for these vitamin D preparations, not only in Norway but also elsewhere in the world?

Dr. Markestad: This is an important question which is rarely addressed. The pharmaceutical companies have to comply with certain standards, but how exact their methods are I don't know.

Dr. Holick: There are very good methods for determining vitamin D concentrations in a variety of preparations, and I think that most pharmaceutical companies do take great care in monitoring the vitamin D content in their preparations, but in order to maintain a good shelf-life they often will add twice the amount of vitamin D that is actually specified on the label.

Dr. David: You told us that in your country pregnant mothers are taking vitamin D during the last two trimesters of pregnancy. Is it a systematic practice, and how is it done?

Dr. Markestad: In Norway it is common practice to supplement pregnant women with 400 IU of vitamin D per day. This dose is usually taken as one multivitamin tablet or as a spoon of cod-liver oil. In addition margarine is fortified with vitamin D and is estimated to provide the average adult with 100 IU per day.
Dr. Guesry: You said you supplement infants from the age of six weeks with a drop preparation of vitamin D. How much do you give to them? At what age do you stop it?

Dr. Markestad: Vitamin drops are not available in Norway since we fear that misunderstanding regarding the dose may cause vitamin D intoxication. The available liquid multi-vitamin preparations and cod-liver oil contain 400 IU per 5 or 10 ml. Such a daily supplement is provided throughout the first year of life starting at six weeks of age. Parents are also encouraged to provide the same supplement during winter for older children.

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