Rickets due to Maternal and Infant Micronutrient Deficiencies

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Introduction

Typically nutritional rickets and osteomalacia are problems associated with the extremes of life. In both groups they are the consequence of an inability to obtain adequate exposure to ultraviolet radiation as a result of their dependence on others to get out of doors into sunlight. Despite our understanding of its pathogenesis and the availability of cheap and effective methods of prevention, nutritional rickets remains a major public health problem in a number of developing countries and is showing a resurgence in incidence in certain communities within developed countries. In this chapter, I shall review the factors responsible for the development of rickets in young infants, provide a global perspective of the incidence of the disease in various communities, comment on its presentation, and discuss the difficulties in establishing the prevalence of active rickets in developing countries. Finally I shall discuss various methods of treating and preventing the development of the disease.

Historical Perspective

Although rickets as a disease was possibly reported some 2,000 years ago, it was the superb clinical descriptions by Francis Glisson and Daniel Whistler in the middle of the 17th century that drew attention to the prevalence of the condition in infants and young children in England. With the onset of the industrial revolution in Europe, the rapid movement of families from the open
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farmlands to the overcrowded, squalid and smog-laden towns and cities occurred, resulting in rickets becoming almost universal in toddlers and children. Several studies have documented that rickets was not only a problem in England but in most of northern Europe during the 19th century.

During the first quarter of the 20th century, rapid progress was made in establishing the roles of sunlight and dietary vitamin D in the pathogenesis of the disease. It thus became possible to offer practical, cheap and effective ways of preventing rickets in communities. Within a generation, rickets had been conquered as a public health problem in most developed countries through a combination of the vitamin D fortification of foods, the provision of vitamin D supplements or health education. However, over the last 20 years, there has been an increasing awareness of the persistence or increasing prevalence of rickets in certain communities within developed countries, and the disease remains a major problem in a number of developing countries.

Rickets in the Young Infant

Vitamin D Deficiency

The newborn infant derives its stores of vitamin D from the transplacental passage of vitamin D metabolites during in utero life. The major metabolite to cross the placenta is 25-hydroxyvitamin D (25-OHD) with cord levels being approximately two thirds of those found in the mother [1]. The dihydroxylated metabolites, 1,25-dihydroxyvitamin D (1,25-(OH)₂D) and 24,25-dihydroxyvitamin D, are thought to be derived mainly from fetal and/or placental synthesis. The parent compound, vitamin D, probably crosses the placenta in only limited quantities as circulating levels in the mother are generally very low. Thus unless an exogenous source of vitamin D is provided, the infant in the first few months of life is dependent on the maternally derived 25-OHD to maintain vitamin D sufficiency. 25-OHD has a relatively short half-life of approximately 3–4 weeks, thus serum levels drop rapidly after birth. In a study conducted in Johannesburg during the winter months, 25-OHD levels reached very low levels within 6 weeks of birth in those infants who did not receive a vitamin D supplement and who were being exclusively breast-fed [2].

Maternal vitamin D status thus has a major effect on the vitamin D status of the newborn infant and on the duration for which the infant will be able to maintain normal calcium homeostasis after delivery without an exogenous source of vitamin D. Although congenital rickets is an unusual consequence of maternal vitamin D deficiency, it does occur and is reported most commonly from those communities in which maternal vitamin D deficiency is common.

Breast milk contains relatively small quantities of vitamin D and its metabolites, and under normal circumstances the amount supplied in breast
milk is insufficient to meet the needs of the growing infant. It has been estimated that breast milk contains between 20 and 60 IU vitamin D activity/1 [3, 4], unless the mother is vitamin D supplemented. Thus an infant drinking approximately 700 ml/day will only receive 15–45 IU/day, the recommended intake being approximately 200 IU/day if no sunlight exposure is guaranteed. Studies in the USA have shown that circulating levels of 25-OHD in the infant are much more closely related to sunlight exposure than they are to breast milk concentrations. The now classical studies of Specker et al. [5] showed that breast-fed infants were able to maintain vitamin D sufficiency if, wearing a nappy only, they were exposed to sunlight for 30 min/week, or if fully clothed but not wearing a hat, they had 2 h/week of sunshine during the summer months in Cincinnati.

In a number of epidemiological studies, breast-fed infants have been found to be relatively protected from vitamin D deficiency compared to those fed cow’s milk-based substitutes. It was suggested that the vitamin D content of breast milk had been under-estimated [6], as the presence of water-soluble vitamin D sulfate had not been considered [7]. However this suggestion has not been substantiated, and the reason for the lower incidence of rickets in breast-fed infants probably reflects a better balance of calcium and phosphorus in breast milk compared to cow’s milk and the almost complete absence of vitamin D in cow’s milk unless fortified. Since specifically designed breast-milk substitutes have replaced cow’s milk in the feeding of non-breast-fed infants, it is now breast-fed infants who more commonly develop rickets as all breast-milk substitutes are vitamin D-fortified.

A Global Perspective

As discussed in the introduction, vitamin D deficiency rickets was almost universal in young children in many parts of northern Europe at the turn of the 20th century. The discovery of the role of vitamin D and sunlight in the prevention of vitamin D deficiency resulted in programs in a number of countries to reduce the incidence of the disease. Thus through a combination of food fortification, vitamin D supplementation and health education vitamin D deficiency was effectively controlled in North America and a number of other developed countries. Nevertheless, vitamin D deficiency rickets remains a public health problem in certain communities within industrialized countries and in a number of developing countries. Accurate figures of the prevalence of vitamin D deficiency globally are not available. Most of the statistics are derived from studies which have assessed the prevalence of clinical signs of rickets within a community or studies conducted in selected in-hospital or outpatient-based samples. Despite the obvious biases associated with these studies, they do give an indication of the severity of the problem in various countries. In China and Tibet [8], for example, about 50% of young children have clinical features suggestive of rickets, while in Ethiopia and the Yemen over 40% of children admitted with pneumonia had radiologically confirmed rickets. In a number of other countries, studies have assessed the prevalence
at over 10% in certain areas or communities, for example, Greece [9], Turkey, Saudi Arabia [10] and Iran [11]. Worrying reports have appeared recently of an increase in the incidence of rickets in the African-American community in the USA [12], and in New Zealand [13], Australia, and a number of northern European countries [14] rickets is being recognized more frequently in the immigrant population.

The factors responsible for the development of vitamin D deficiency rickets in the young infant relate to reduced endogenous vitamin D synthesis in the skin due to a lack of ultraviolet B irradiation from sunlight or to a lack of supply of exogenous vitamin D to the infant. Thus both maternal and infant factors are important.

Factors in the mother resulting in poor vitamin D stores in the neonate include:

1. Vegetarianism in the mother resulting in a poor vitamin D intake [15]: in climates with adequate ultraviolet irradiation, skin synthesis of vitamin D should adequately compensate for poor dietary intakes, thus vitamin D insufficiency in the mother is only a problem in communities living at high latitudes or where other factors such as clothing coverage preclude vitamin D synthesis.

2. Dark-skinned mothers living in countries of high latitude: poor vitamin D synthesis is only a problem in dark-skinned individuals when the amount of ultraviolet irradiation reaching the skin is limited as occurs in the Asian community in the United Kingdom.

3. Lack of sunlight exposure of the mother during pregnancy and lactation due to complete skin coverage by clothing or as a result of social or religious customs, which discourage sunlight exposure.

Factors in the infant:

1. Infants living in countries at high latitudes, which are associated with long cold winters.

2. Exclusively breast-fed infants without adequate sunlight exposure as a result of clothing or cultural and social customs or without vitamin D supplementation.

3. The belief that breast-milk contains all the essential nutrients for a growing infant, thus discouraging mothers from providing vitamin D supplements.

4. Living in high-rise apartment blocks in inner cities or in crowded polluted informal settlements.

In developing countries, such as Ethiopia and the Yemen, it is unclear whether the pathogenesis of rickets in young children is due solely to vitamin D deficiency as a result of prolonged breast-feeding and lack of sunlight exposure or whether low dietary calcium intakes aggravate the condition by increasing the catabolism of vitamin D [16].

It is clear that despite effective and cheap methods of prevention, vitamin D deficiency remains a problem not only in certain developing countries but also in minority communities within developed countries.
Clinical Presentation

The peak incidence of clinical rickets occurs in the second 6 months of life and by 18 months of age the incidence starts to fall off sharply [11]. The clinical disease is uncommon in infants under 3 months of age, however in countries where vitamin D deficiency has a high prevalence, no age group is immune.

The classical features of rickets are well known to clinicians and will not be discussed in detail. The presentation is as a result of the effects of vitamin D deficiency on calcium and phosphorus homeostasis, on the mineralization of the growth plate and osteoid formed during bone turnover and remodeling, and on the muscular and immune systems. Perhaps insufficienly appreciated is the fact that vitamin D deficiency may present as apneic attacks, convulsions, stridor or tetany in the young infant without other features of rickets. These clinical signs of hypocalcemia may occur in the early stages of vitamin D deficiency, are most common in the young infant (often less than 3 months of age) and may be precipitated by acute infection [17].

Of considerable interest to public health planners is the role that vitamin D deficiency might play in contributing to the morbidity and mortality associated with infections in the young child, particularly in developing countries. It has been suggested that vitamin D deficiency is associated with an increased risk of both respiratory and gastrointestinal infections [18]. In Ethiopia, rickets was found to be 13 times more common in children with pneumonia than controls [19], with 42% of pneumonic children having rickets. In the Yemen, rickets together with anemia and malnutrition were associated with an increase in mortality in children with pneumonia [20].

The increased mortality associated with pneumonia could possibly be explained on purely mechanical grounds, as a result of the inability to clear pulmonary secretions because of muscle weakness and the softening of the ribs leading to chest deformities and the compression of underlying lung by the enlarged costochondral junctions. However mechanical mechanisms are unlikely to account for the increase in gastrointestinal infections. Good evidence exists concerning the role of 1,25-(OH)2D in immune modulation [21], and impaired phagocytosis and neutrophil mobility have been described in vitamin D deficiency. Thus it is possible that vitamin D deficiency through its effects on immune function might predispose infants to an increase in the frequency and severity of infections. However no controlled studies have been performed to test the effect of vitamin D supplementation on morbidity and mortality from infections in infants and young children living in communities with a high prevalence of vitamin D deficiency. These studies are urgently needed.

Another area, which has been poorly researched, is the effect of maternal vitamin D deficiency on fetal and neonatal well-being. Although it appears that the fetus is able to maintain calcium homeostasis in the face of maternal vitamin D deficiency, neonatal calcium homeostasis is impaired and an
increased incidence of both early and late neonatal hypocalcemia has been reported, as well as a delay in fetal ossification and tooth enamel formation [22]. It has also been suggested that both intrauterine and postnatal growth is affected [23].

**What Is Vitamin D Sufficiency in Infancy?**

The characteristic biochemical feature of vitamin D deficiency is a low circulating level of 25-OHD, the major circulating form of the vitamin. However what represents vitamin D sufficiency is unclear. As vitamin D, and more specifically 1,25-(OH)₂D, is central to ensuring adequate intestinal calcium absorption to meet the needs of the individual, it is rational to believe that vitamin D requirements might vary depending not only on factors such as the calcium demands of the individual and on the calcium content of the diet, but also on the ability of the kidney to synthesize 1,25-(OH)₂D. Little is known about the latter, except that neonates are able to increase 1,25-(OH)₂D levels very adequately in response to calcium stress [24].

Of considerable interest, but with no clearcut answers, is the definition of vitamin D sufficiency. Should vitamin D sufficiency be defined by the absence of clinical disease, or by the absence of changes in parathyroid hormone or 1,25-(OH)₂D levels when 25-OHD levels are increased by vitamin D administration? Furthermore, should we be looking at the effect of differing 25-OHD levels on the immune function in children?

There is little information on these questions not only in infants but also in children. Those studies, which have been conducted, would suggest that at present with our current information serum 25-OHD levels should be maintained above 12 ng/ml (30 nmol/l) [25]. Whether higher levels in infants and young children would be beneficial is unclear.

**The Diagnosis of Rickets**

The diagnosis of vitamin D deficiency rickets is not difficult on an individual basis when X-rays and biochemical assessments are available. However at a community level the assessment of the prevalence of active rickets is much more difficult, especially as it is inappropriate to X-ray every infant included in a survey and it may be difficult to obtain blood for analysis. In communities in which rickets has a high prevalence, clinically based assessments may be of some value but as the prevalence of the disease falls in a community so the usefulness of these signs declines. In Mongolia, where rickets in young infants is thought to be very common, a combination of the following signs has been used: craniotabes, occipital alopecia, excessive sweating, muscular hypotonia, enlarged fontanel, rachitic rosary, Harrison's
groove, bowed legs, large forehead, and spinal deformities (E Kudlova, personal communication). It is clear that a combination of two or more of these signs is likely to be present in a well-established case of rickets, but the individual signs are not particularly helpful by themselves or in combinations to pick up an early case of rickets, as has been shown, for example in South Africa, where the presence of craniotabes in 3-month-old infants did not differentiate those with from those without rickets [26]. Furthermore, the use of bowlegs or knock-knees as signs of active rickets might overestimate the prevalence as not only are there other causes of these deformities but also the deformities may persist for some time after active rickets has responded to treatment.

Thus, there is an urgent need to establish whether the prevalence of active rickets in a community can be established using clinical features alone, or whether they must be combined with simple biochemical tests such as alkaline phosphatase estimations. At a public health level, it is essential that reasonably accurate reflections of the degree of severity of rickets within a community can be readily obtained so as to determine the need for community-directed interventions.

**Prevention and Treatment of Vitamin D Deficiency**

The recommended intake for vitamin D is dependent on the amount of ultraviolet irradiation to which individuals are exposed. In sunny tropical climates, a vitamin D intake is unnecessary unless for cultural or social reasons exposure to sunlight is limited. In temperate climates, dietary intakes are usually recommended. The United Kingdom recommends a reference nutrient intake of 8.5 μg/day (340 IU/day) for infants less than 6 months of age and 7 μg/day (280 IU/day) for toddlers between 6 months and 3 years [27]. The reason for the reduction in recommended intake with age is because it is assumed that the child is exposed to more sunlight with increasing age. In North America an adequate intake of 200 IU/day (5 μg/day) has been set for children between 0 and 18 years [28].

In the infant age group it is those who are exclusively breast-fed who are at risk from vitamin D deficiency, as those not breast-fed are usually fed vitamin D-fortified breast-milk substitutes. Thus, the Department of Health in the United Kingdom suggests that routine vitamin D supplementation would provide an effective safety net for those groups at risk. However, in the US, the American Academy of Pediatrics suggests that only those infants in risk groups should be considered for vitamin D supplementation. The lack of a clearcut recommendation may well be responsible for the apparent increase in vitamin D deficiency rickets in breast-fed infants in the USA. Certainly in countries such as Tibet and China where vitamin D deficiency remains a significant public health problem, routine vitamin D supplementation of breast-fed infants
should be recommended. Despite the ease and inexpensiveness of vitamin D supplementation, the effectiveness of daily supplementation at a national level may not be good due to coverage and compliance problems. To circumvent these issues, intermittent high-dose therapy (‘Stosstherapie’) has been used in some European countries. However the safety and effectiveness of this type of intervention has not been well documented, and concerns have been raised about the risk of hypercalcemia [29].

Treatment of vitamin D deficiency rickets is effectively achieved using daily doses of either vitamin D<sub>2</sub> or D<sub>3</sub>. The usually recommended dose is between 5,000 and 15,000 IU daily for 4–8 weeks. Biochemical improvement is generally seen within 2–3 weeks, although alkaline phosphatase values remain elevated for several months. As most young rachitic infants are on an adequate calcium intake because of being either breast-fed or on breast-milk substitutes, it is probably unnecessary to provide additional calcium supplements during the initial healing phase, unless symptomatic hypocalcemia has occurred. Furthermore, there appears to be no advantage in using the more expensive vitamin D metabolites or analogues, 1,25-(OH)<sub>2</sub>D or 1α-hydroxycholecalciferol, as serum 1,25-(OH)<sub>2</sub>D levels rise rapidly on treatment with the parent vitamin D [30].

References


Discussion

Dr. Endres: Concerning the toxicity, I think that the ‘Stoss’ therapy is a German invention, and I never experienced such high doses in the 1960s. 100,000 and 200,000 units on a daily basis have been used only for vitamin D-resistant rickets. But with the ‘Stoss’ therapy which actually was a preventive measure – only 5 or sometimes 10 mg vitamin D were used over a time period of several weeks. With these doses we rarely saw some side effects such as fever, constipation, elevated transaminases and an increased renal excretion of cystathionine probably due to an impaired catabolism of methionine. Due to these side effects the ‘Stoss’ therapy was abandoned in the early 1970s. The reason for using the ‘Stoss’ therapy instead of a daily application of low amounts of vitamin D was that there many Turkish guest workers in Germany who were not able to understand the instructions for the daily application. Therefore, their infants received during the first weeks of life twice 2.5 mg vitamin D; this procedure was repeated after 4–6 weeks.
**Dr. Pettifor:** The initial study by Markestad et al. [1] was not done in Germany, it was in another European country, and it was the recommended therapy in Eastern Europe as well. I think your information is right that toxicity is a major problem. The issue though is how do we address the problem in developing communities where daily prophylaxis is unlikely to work because of compliance problems. I think it is very difficult to give children medication or treatment everyday.

**Dr. Endres:** I think it is a health care issue to inform the public that sunlight is very important.

**Dr. Pettifor:** Tibet is interesting. Tibetan infants were actually exposed to sunlight and oil was rubbed on their skin, but that tradition has disappeared. So it may well be that changes in traditions are influencing the prevalence of vitamin D deficiency.

**Dr. West:** I am just wondering about areas such as Nepal, about whether there is seasonality in mountain regions like that in, for example, vitamin D production. There is a great deal of cloud cover there during the monsoon season but then during the winter season there is the long shadow of the mountains that restricts villagers who live in valleys from being exposed to adequate ultraviolet (UV) light. The actual amount of UV light exposure to sunlight during the winter months is really quite minimal, even though there is no cloud cover. So you can actually construct reasons for there being continuously low levels of vitamin D production in such areas.

**Dr. Pettifor:** The cloud cover does not necessarily prevent UV light from coming through, so you may have quite severe UV light burn when there is substantial cloud cover. I don't think it necessarily means that there is no UV light reaching them. It is the issue of the sun's incident angle to the earth, which probably cuts out the vast majority of the UV light.

**Dr. Abu Libdeh:** I have two questions. The first one is whether exposure to sunlight indoors passing through clear glass can affect the utilization of UV light and the making of vitamin D? The second is, in my country we almost routinely give all children, especially breast-fed babies, vitamin D supplementation. I have seen pediatricians who, when they find the fontanel to be of a small size, stop vitamin D saying that it will promote or facilitate closure of the fontanel. I don't think there is a scientific basis for that. What is your opinion about that?

**Dr. Pettifor:** The answer to the first question, can you be adequately exposed to UV light indoors if you have windows and the sun comes in through the glass? That is a major problem, UV light is blocked by glass, so very little UV light penetrates through the glass and reaches the infant even if the infant is in the sunlight. So that is a major problem. The issue of the fontanel is an interesting concept because it is partially right, as with vitamin D toxicity the fontanel may well be small but in the sort of doses that one is giving that is not an issue. It is just that perhaps those infants that are vitamin D-deficient have larger fontanels than those that are vitamin D-replete.

**Dr. Delange:** I was also surprised by your figures from Tibet because sunlight occurs there. What I remember from my trip over there, in the northern part of Nepal, even during the periods of sunlight what impressed me was that rarely clothes are taken off. I wondered whether these infants were washed occasionally, so I really think that exposure to sunlight must be minimal because of this practice. That is the dirtiest population of children I have ever seen in my life. Now I have a very innocent question. How do you measure the hourly production of vitamin D?

**Dr. Pettifor:** We have vials of 7-dehydrocholesterol which we put out in the sun every hour and then measure the conversion of 7-dehydrocholesterol to vitamin D.

**Dr. Bozo:** What do you think about the French modality to give 200,000 IU every 6 months for the prevention of vitamin D deficiency? The Committee of Nutrition of the American Academy of Pediatrics recommends giving vitamin D to all breast-fed infants. What is your view on that?
Dr. Pettifor: The first issue of the 200,000 IU every 6 months: the data from Zeghoud et al. [2] show that the problem is that relatively high levels of 25-hydroxyvitamin D are produced, not in the toxic range but certainly very much higher than the normal range, soon after giving that dose. If you look at the levels 6 months later the 25-hydroxyvitamin D levels are in the lower range of normal in many of the children. A number of children are in the vitamin D-insufficient range. So it is probably not frequent enough, and that is why they recommend 100,000 IU every 3 months because those enormous peaks that are seen if the bigger dose is given every 6 months are prevented. I thought the Committee of Pediatrics’ recommendation was only for the at-risk population suggesting that it should be considered in at-risk groups, not for all breast-fed infants. I may be wrong, that was a statement that I saw a year or 2 back.

Dr. Bozo: I am talking about the recommendations published by the Committee of Nutrition in 1998.

Dr. Pettifor: The American Academy of Pediatrics’ recommendations [3] I am quoting were published in 1997, and they are suggesting it only in at-risk groups. But I agree, I think it should be given to all breast-fed infants. I think it is a cheap, effective, safe prevention of vitamin D deficiency, and it should be given until the child is a year old and getting out into the sun, or until breast-feeding stops and the child is drinking or eating vitamin D-supplemented fortified products.

Dr. Zlotkin: The Canadian Pediatric Society Committee on Nutrition recommends vitamin D supplementation for all exclusively breast-fed infants and the published dose is 400 IU/day although there is some debate as to whether we are going to change that to 200 IU/day. But the Canadian Pediatric Society Nutrition Committee, of which I was the chairperson, recommends that all exclusively breast-fed babies should receive a vitamin D supplement in Canada.

Dr. Fawzi: The issue of vitamin D deficiency and infection is very interesting. There are a couple of studies that I am aware of that looked at vitamin D-deficiency rickets, particularly in pneumonia. There was a case-control study from Ethiopia, and then studies on vitamin D deficiency in Tibet. How relevant is this discussion for sub-Saharan Africa where there is adequate sunlight? Do we know much about the prevalence of vitamin D deficiency in these populations? Another question, there are some studies also perhaps mostly in vitro studies that suggest that vitamin D analogs could be associated with immune suppression. Could you comment on that? That is not necessarily always protective.

Dr. Pettifor: The first issue of the role of vitamin D deficiency in immune modulation and perhaps increasing the severity or the frequency of infections, I don't think it has been fully answered. The problem in sub-Saharan Africa I think is going to be relatively small, although we don't know at what serum level we need to maximize immune function. Is it only the vitamin D-deficient individual who has very low vitamin D levels that is going to run the risk of impaired immune deficiency or impaired immune function? The problem is that the vitamin D system in the bone marrow cells is not regulated like that of the calcium homeostatic function, in which 1,25-dihydroxyvitamin D is regulated very clearly by the kidney and parathyroid hormone, but macrophage production of 1,25-dihydroxyvitamin D is not regulated by parathyroid hormone but appears to be dose-dependent. So as you increase 25-hydroxyvitamin D levels the 1,25-dihydroxyvitamin D production by the macrophage increases almost linearly, and that is the problem for instance with tuberculosis or sarcoidosis where the increase in 1,25-dihydroxyvitamin D levels is not suppressed by changes in calcium homeostasis. So I don't think we have an answer to the question that you are asking. You are asking whether it can be a problem in sub-Saharan Africa, I can't give you an answer to that and I don't know what level we should be aiming for as far as vitamin D sufficiency is concerned. But vitamin D deficiency rickets is a
relatively uncommon problem as far as I am aware in the vast majority of sub-Saharan Africa. I am much more worried about dietary calcium deficiency in the older age groups in that community.

Dr. Allen: Please comment on calcium deficiency rickets, and particularly what happens when children make the transition from breast milk to complementary foods that contain almost no calcium, which is typical in developing countries.

Dr. Pettifor: I didn’t discuss that issue because I am dealing with the first 6 months of life but the information we have is that certainly in South Africa, where the problem was first described, it occurs in the older children around the age of 9, 10, and 11. I thought this was due to the increase in growth rates around that time when calcium would be required maximally. But in the studies that we have been doing in Nigeria the data suggest that it is occurring much earlier, the mean age at presentation is around 4 years of age, but many of those children are developing symptoms somewhere just after weaning (around 18 months to 2 years) with the mother first noticing bowed legs or the child stopping to walk. It is interesting that Dr. Carpenter (personal communication) from New England looked at children presenting with rickets, who were mainly African-Americans. What he showed was that it may well be that those infants are not vitamin D-deficient although they may have relative vitamin D deficiency as well, but there may well be dietary calcium deficiency related to the changes from a calcium content in breast milk to a weaning diet which contains almost no calcium. Thus dietary calcium deficiency may well be a problem that we are not as well aware of as we should be. I think the issue is that we shouldn’t be looking at dietary calcium deficiency on one hand and vitamin D deficiency on the other hand, but the two act synergistically to regulate the situation. If you are relatively calcium-deficient you require more vitamin D as you increase the vitamin D catabolism and therefore the vitamin D requirements. So I think you should always be aware of the synergism between the two problems.

Dr. Mousa: We used to diagnose rickets radiologically by doing X-rays of the wrist. My question is which site of the body would be suitable to X-ray to look for findings in the first 2 months of life, the wrist or the knee?

Dr. Pettifor: Sites for X-ray of rickets, I tend to use the wrist more than the knee because of the problem of getting radiographers to position the knee adequately for a decent interpretation, the wrist is much easier. The issue is that it should be bones that are growing rapidly and obviously the wrist is one part that grows rapidly, but the knee also grows very rapidly. I don’t have a major issue as to which one uses. Certainly using a chest X-ray to look at the costochondral junctions is a major problem. We did a study with our radiologist who used to diagnose rickets on looking at the cupping of the costochondral junctions. We gave her the chest X-rays blinded and I did 25-hydroxyvitamin D and an X-ray of the wrist at the same time. There was no correlation between what she called rickets at the costochondral junctions and the 25-hydroxyvitamin D levels or the changes that occur at the wrist. 25-Hydroxyvitamin D levels correlated well with the ricketic changes at the wrist but there was no relationship with her so-called diagnosed rickets at the costochondral junctions.

Dr. Mousa: I have a few patients in the neonatal unit, and in my own experience they have the ricketic changes in the knee more than in the wrist, I don’t know why.

Dr. Pettifor: It relates to the rate of growth of that growth plate, so if the child is growing reasonably well you are going to see good changes and the knee is probably the best place, yes.

Dr. Endres: In a study you showed that a relatively high percentage of infants with rickets do not have craniotabes. Would you agree that a high percentage of those infants where you find craniotabes don’t have rickets?

Dr. Pettifor: Absolutely. If craniotabes is present in a 6- or 9-month-old child then I would suspect rickets. There are very few other things that cause craniotabes at that
age, but in the younger infant I think the use of craniotabes is a major problem, as it may be normal.

Dr. Endres: I have a second question concerning the daily amount of vitamin D. Some concerns have been raised that if you add the 400 units which are recommended in 1 liter of infant formula, and in addition vitamin D complementary food and then capsules or tablets, that can amount to up to about 1,500 IU/day. There are some people, for example in the Nutrition Committee in Norway, who had some concern about that. I personally don't believe that this is harmful regarding the toxicity. What is your opinion about that?

Dr. Pettifor: I think that there is a push for reevaluating the safe limits of vitamin D. It appears that adults can take very much bigger doses than we generally recommended previously. In children I am not sure. The issue of the problems in the postwar in Britain I think made people a little bit worried about the combination of vitamin D supplementation as well as food fortification. Although the evidence in the data is very dubious about the relationship between hypercalcemia that occurred postwar and the vitamin D supplements in Britain, I think people are still concerned that it might be a possibility. I have not seen vitamin D toxicity in children at all except in children who ate food cooked in a vitamin D concentrate which was being sold as cooking oil. We had whole families going down with vitamin D toxicity. But they had enormous intakes, the 25-hydroxyvitamin D level was quite high. So these are very different situations.

Dr. Al Awar: My question regards the table in which you showed the studies on mothers who had vitamin D supplements, and about parathyroid hormone. I think one study was in 1990 and the other one was around 1980–1985. In the newborn period there are many babies with hypocalcemia and also primary transient hypoparathyroidism which is related to that, but there was no difference in parathyroid hormone in these children. The second question is in regard to the same thing on vitamin D intoxication based on the studies which you have done in Iran and in Kuwait. Do you recommend that in these areas vitamin D supplement should be given routinely, and in this case, we know that in this area the sunlight is truly sufficient, is there a possibility of vitamin D intoxication?

Dr. Pettifor: I think there is very little risk of vitamin D toxicity in mothers who are exposed to sunlight, or in the infants for that matter, although the amount of vitamin that can be produced in the skin has been estimated to be up to 2,000 IU/day if you expose large parts of the skin to UV light. But I think the major issue is getting children and mothers to believe that they should be getting sunlight exposure anyway. The issue of your first question was the hypocalcemia and the transient hypoparathyroidism. I think there is evidence that this is aggravated by vitamin D deficiency, and if one can maintain an adequate vitamin D status in that neonatal period the problems of transient hypocalcemia, transient hypoparathyroidism are reduced dramatically.

References