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Vitamin D-deficiency in Asia☆

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Abstract

Vitamin D-deficiency rickets is an important disease of childhood in China. It occurs in all regions (20–53°N) but is more prevalent in the north. A survey in Beijing indicated that Vitamin D-deficiency (plasma 25(OH)D concentration <12.5 nmol/l) occurred in more than 40% of adolescent girls in winter. Dietary calcium was often as low as 350 mg per day and a positive correlation was found between this and both bone mineral density (BMD) and Vitamin D status. In a subsequent intervention study with 757 Beijing schoolgirls, a daily supplement of milk, fortified with calcium, was provided on school days for 24 months. From anthropometric and bone density data, it is evident that the increased calcium intake from milk, had significant effects on bone and that deficiencies of both calcium and of Vitamin D had been affecting bone growth and development. In neighboring Mongolia (42°–50°N), rickets is also common, but its prevalence has increased since 1990. A 2-year survey (2000–2002) in Mongolia indicated that, as in China, a low intake of calcium and limited exposure to solar ultraviolet (UV) light in summer were associated with Vitamin D-deficiency. However, over the last decade, malnutrition has become widespread. It now appears that malnutrition impairs the efficiency of the utilization of Vitamin D obtained in summer. Hence, a number of factors need to be addressed to prevent Vitamin D-deficiency during growth.

Keywords: Vitamin D-deficiency; Rickets; Calcium; Malnutrition; China; Mongolia

1. Introduction

For many years, Vitamin D-deficiency rickets has been recognized as a common disease of childhood in China, occurring both in infants [1] and in adolescent children [2]. The prevalence in infants was reported to be about 40% while about 5–15% of adolescents were found to be affected. Vitamin D status in human populations is closely associated with the extent of exposure of skin to ultraviolet (UV) light from the sun [3] rather than from the meager supply of Vitamin D from food. Hence, a limited exposure of skin to sunlight in summer has been presumed to be the cause of Vitamin D-deficiency in China, as has been found in other parts of the world. The reports of a greater prevalence of the disease in the northern regions of China where the intensity of summer UV light is less than in the south, further suggests that Vitamin D-deficiency is simply the consequence of inadequate exposure of skin to the sun.

Yet, in the countries of Europe and North America, at similar latitudes to China, Vitamin D-deficiency in children is much less prevalent. The question therefore arises as to whether other factors than just the amount of exposure of skin to UV light in summer, either environmental or cultural factors, might be contributing to the susceptibility of children in China to deficiency of Vitamin D. To explore whether such factors might exist, a cross-sectional survey of a large number of children in the city of Beijing was undertaken over 2 years in 1995–1996.

2. The Beijing cross-sectional survey

The subjects for this survey were 1277 girls, 12–14 years of age, randomly selected from 13 schools in Beijing and in the surrounding rural area. A range of anthropometric measurements was made on each subject, along with an assessment of their usual daily physical activity. Nutrient intakes were estimated using a validated semi-quantitative food-frequency questionnaire and data from Chinese food composition tables. The daily exposure of each subject to ultraviolet light was estimated using semi-quantitative UV-sensitive badges worn on the shoulder for several days in October 1995 and again in January 1996. The Vitamin D status of each subject was determined in summer and winter by measurement of 25-hydroxyvitamin D in blood plasma. Bone growth and development were assessed by X-ray of

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the hand and wrist and by single photon absorptiometry of the distal radius and ulna [4,5].

The results of this large-scale cross-sectional survey confirmed that Vitamin D-deficiency was a common feature of adolescent girls in Beijing, which lies at a latitude of 40°N. Although no radiological evidence of active rickets was found, limb and thoracic deformities, compatible with rickets in early childhood were observed in up to 19% of subjects. The plasma 25(OH)D concentrations in both winter and summer ranged from 3 to 69 nmol/l but the mean concentration for all children in winter was 12–13 nmol/l whereas in summer the mean value was 25–30 nmol/l. In winter, 45.2% of the subjects had plasma 25(OH)D values of <12.5 nmol/l and while Vitamin D status improved in summer, there were still 6.7% of subjects who had plasma 25(OH)D concentrations of <12.5 nmol/l. As dietary Vitamin D intake was about 1 μg per day (mainly from eggs and some fortified milk), and did not vary with season, it was concluded that, as in other surveys, Vitamin D status was determined mainly by exposure of skin to ultraviolet light in summer. Assessment of UV exposure of each subject from the wearing of UV-sensitive badges also showed that at the latitude of Beijing, significant exposure to UV light occurred only in summer.

The dietary data indicated that the main foods consumed were cereals and vegetables. However, the actual quantity of the very small amounts of dairy products in the diet were found to be positively correlated with bone mineral content, determined as bone mineral density (BMD) and bone width (BW) by single photon absorptiometry. No other dietary component showed any statistical relationship with bone mineral. The individual constituents of milk that gave this statistically significant correlation were Vitamin D, calcium and milk protein. The higher the intake of dairy products, the higher the bone mineral content was found to be [5]. Nevertheless, the mean daily dietary calcium intake was only 356 ± 97 mg, and only 21% of this was derived from dairy products. It is therefore clear that this population of adolescent children not only has a high prevalence of Vitamin D-deficiency but also has a dietary calcium intake which is about half that recommended by the Chinese dietary guidelines. Could it be that there is some causative relationship between the low intake of calcium and the high prevalence of Vitamin D-deficiency in these adolescent children?

A study in experimental rats has shown that a low intake of dietary calcium and the consequent increased production of $1,25(OH)_2D$, is associated with enhanced destruction of 25(OH)D and increased excretion of the metabolic inactivation products in bile [6]. If Vitamin D supply is limited, then Vitamin D-deficiency occurs more rapidly if the experimental rats are also fed a low calcium diet. Could the low intake of calcium by children in Beijing in association with limited exposure of skin to ultraviolet sunlight, be a human example of induced Vitamin D-deficiency by increased metabolic inactivation of 25(OH)D? Certainly, when the subjects under study were divided into a very low calcium intake group (<355 mg per day; mean = 280 mg per day) and a somewhat higher calcium intake group (>355 mg per day; mean = 440 mg per day), those in the low calcium group had a 50% greater chance of being Vitamin D-deficient than those consuming more calcium. Hence, calcium intake was positively correlated not only with bone mineral content but also with Vitamin D status.

To explore further the influence of milk intake on bone growth and Vitamin D status, a 2-year dietary intervention study was carried out with adolescent girls in Beijing.

3. The Beijing 2-year intervention study

A total of 757 girls aged 10 years from nine primary schools in urban Beijing took part in this study. The subjects were assigned at random to three study groups. Group 1 consisted of 238 subjects who were given 330 ml of calcium-fortified UHT milk (containing a total of 560 mg calcium) to drink each school day for 24 months, starting in April 1999. Group 2 consisted of 260 subjects who were given 330 ml of calcium-fortified UHT milk containing also 8 μg Vitamin D. Group 3 consisted of 259 subjects as a non-supplemented control group. Because no milk supplement was consumed on non-school days and during holidays, the calculated daily supply of calcium from the supplementary milk in Groups 1 and 2 averaged over the 24 month study period was 245 mg and the average daily supplement of Vitamin D was 3.33 μg.

The same measurements were made on each subject as in the original cross-sectional survey but in addition, total body bone mineral was determined by dual-energy X-ray absorptiometry. Data were collected at the start of the 2-year intervention period and after 1 year (April 2000) and at the end of the study (April 2001).

Over the 2-year period 59 of the subjects (7.8%) dropped out, so that 698 subjects completed the study. Not unexpectedly, there was a statistically significant increase in Vitamin D status of the Group 2 subjects receiving the milk supplemented with Vitamin D who had a mean plasma 25(OH)D concentration (±S.D.) at the end of the 2-year trial of 47.6 (±23.4) nmol/l compared to 19.4 (±10.2) nmol/l for the Group 3 controls. However, those receiving milk alone, without Vitamin D (Group 1), did not show any increase in 25(OH)D levels (17.9 ± 9.0 nmol/l). Although it is possible that the increase in calcium supply from the milk supplement may not have been as great as the natural difference between high and low calcium intakes in the earlier cross-sectional study, the extra milk certainly had an effect on bone growth and bone mineral content of these subjects.

Compared to the Group 3 controls, there was a significant increase in height of about 1% ($P < 0.0005$) in both milk-supplemented groups and size-adjusted total body bone mineral content was about 2% ($P < 0.0005$) higher than the controls. Thus, milk alone, presumably because of the calcium in milk, appeared to have a positive effect on the

growth of bone. This effect was somewhat higher in Group 2, so adequate Vitamin D status appears to enhance the effect of higher intakes of calcium.

Although this intervention study did not provide evidence that dietary calcium was positively associated with Vitamin D status, it did indicate that even the small daily increase in calcium intake had positive effects on the mineralization of bone.

4. Vitamin D-deficiency in Mongolia

As in China, rickets has been a common disease of childhood in Mongolia. However, the impression was formed amongst public health workers that the prevalence has increased over the past 10 years. In 1992, a national nutritional survey by UNICEF in association with the Mongolian Ministry of Health and Social Welfare found that 45% of young children across the country had skeletal abnormalities of rickets [7]. A further survey by World Vision Mongolia and the Nutrition Research Center of the Public Health Institute in Ulaanbaatar found that in 1997 as many as 70% of children less than 5 years of age had one or more of the clinical signs of rickets [8].

Mongolia is a large, north Asian country lying between western China and Russia at latitudes from approximately 42°N to 50°N. In winter, ultraviolet light intensity from the sun, at wavelengths able to produce Vitamin D is practically negligible. Furthermore, daytime winter temperatures of −20 to −50 °C are a significant disincentive to exposure of skin to sunlight. Nevertheless, during the summer months, the temperatures are comfortable, UV light from the sun is plentiful and the observed outdoor lifestyle of both children and adults at this time would seemingly ensure the build-up of adequate Vitamin D reserves.

Yet, in 1999 when a small-scale survey of Vitamin D status was first conducted, a group of 40 rachitic children was found to have a mean plasma 25(OH)D concentration of 7.09±0.77 nmol/l compared to a mean of 41.3±3.33 nmol/l in 22 apparently healthy children [9]. To identify any special factors that may be promoting Vitamin D-deficiency in Mongolia, the Nutrition Research Center in Ulaanbaatar has conducted a 2-year survey of different population groups, with the financial support of the World Health Organization. This survey was completed in April 2002 and some of the preliminary conclusions are outlined below.

It is evident that Vitamin D-deficiency is a common condition in Mongolian children under 5 years of age. In a cross-sectional survey of groups of 76 children during autumn, winter and spring, between 58 and 65% had plasma 25(OH)D concentrations of less than 18 nmol/l. During the summer months of July to September the prevalence of low Vitamin D status fell to 10.5%. Nevertheless, although the majority of the surveyed children acquired an adequate Vitamin D status during summer, with a mean plasma 25(OH)D concentration of 40.3 ± 2.9 nmol/l, this value had fallen to a mean of 22.4 ± 1.9 nmol/l by autumn, when 58% of the children had values of less than 18 nmol/l.

Once again, the dietary calcium of children under 5 years of age was very low with an average intake in 387 surveyed children of 265 mg per day, which is 46% of the Mongolian recommended daily allowance for this age group. But, perhaps of even greater significance, was the high prevalence of anthropometric signs of malnutrition. In the total study group of 394 children under 5 years of age, 38.8% were stunted, with height-for-age *Z*-score values of less than 2 S.D. and 14.5% of all the children studied were significantly below accepted values for weight-for-age. Furthermore, there was a significant association between the physical signs of malnutrition and Vitamin D status. The children who were underweight or stunted had plasma 25(OH)D values between 8 and 11 nmol/l whereas those who showed normal growth had a 25(OH)D average concentration of 49 nmol/l. There was also a significantly higher incidence of clinical rickets in the malnourished children compared to those with a normal pattern of growth.

Even though rickets and Vitamin D-deficiency were still found in some of the children without signs of malnutrition, the association between malnutrition and low Vitamin D status was clear. During spring and summer the dietary intake of energy, protein and calcium were all significantly lower in children with a plasma 25(OH)D concentration of less than 18 nmol/l compared to all those who had 25(OH)D values above 24 nmol/l. Thus, a tentative conclusion is drawn that malnutrition diminishes the ability of children to conserve Vitamin D acquired during exposure of skin to sunlight in summer.

Another feature of the pattern of Vitamin D-deficiency in Mongolia is the finding that 24% of 120 surveyed children, of less than 12 months of age, were affected with clinical rickets. This raised the question as to whether Vitamin D-deficiency of women during pregnancy may lead to Vitamin D-deficiency of their neonatal infants. Many studies have reported that there is a close relationship between maternal Vitamin D status and that of the child at birth. Animal experiments with rats have shown that there is a quantitative transfer of maternal 25(OH)D into the fetus during the last third of gestation [10]. If the transfer of maternal 25(OH)D across the placenta determines Vitamin D status of infants in the first months after birth then it would follow that low Vitamin D status in pregnant women would result in early Vitamin D-deficiency of their newborn children.

Therefore, a survey of the Vitamin D status of women in the sixth month of pregnancy and again, 3 months later at the time of birth of the child, was carried out at monthly intervals for 12 months in Ulaanbaatar. Maternal Vitamin D status at the sixth month of pregnancy showed the same pattern as in the surveyed Mongolian children, with low plasma 25(OH)D concentrations during autumn, winter and spring (October–June) and adequate levels in summer (July–September). However, at the time of birth of the child, there was no significant seasonal variation in plasma

25(OH)D concentration and the mean value for 57 women was 25.98 ± 1.86 nmol/l over the 12-month survey period. This suggests that transfer of 25(OH)D across the placenta only occurs if maternal 25(OH)D is greater than 25 nmol/l. The women who, in the sixth month of pregnancy, had 25(OH)D values of 60–80 nmol/l in September had values of 20–30 nmol/l at the birth of their children in December. On the other hand, women who had 25(OH)D levels of 20–30 nmol/l at the sixth month of pregnancy in December, had only a small decrease in their Vitamin D status to about 15–20 nmol/l at the birth of their children in March. It is likely, therefore, that very little transfer of 25(OH)D across the placenta could have occurred during these later stages of pregnancy in winter, otherwise maternal Vitamin D status would have fallen to severely deficient levels by the time of childbirth. It appears that maternal Vitamin D status is protected at the expense of that of the fetus. In support of this interpretation, all Mongolian survey results have found that the prevalence of rickets during the first year of life in children born in late winter is much higher than in those born in late summer.

The cause of low Vitamin D status in Mongolian women remains uncertain. There is evidence that adults as well as children may not be adequately fed because of increased poverty during the past 10 years, as Mongolia changes from a centralized to a market economy. The daily intake of calcium by pregnant women was found to be only about 35% of the recommended daily allowance at approximately 400 mg per day. The surveyed women ate diets consisting mainly of flour, rice, potato and meat. Their intake of energy, protein and micronutrients may also have been marginal in comparison to dietary recommendations for pregnancy. Further analysis of dietary data will indicate whether or not maternal nutritional deficiencies are associated with low Vitamin D status of their children of less than 12 months of age.

5. Discussion

The low dietary intakes of calcium by children in both China and Mongolia are associated with Vitamin D-deficiency. Conclusive epidemiological evidence that this might be related to enhanced destruction of 25(OH)D, as demonstrated in rat experiments [6] has not yet been found. However, because a small daily calcium supplement in the form of milk does produce significant positive effects on bone growth in adolescent girls in China, it is likely that at the least, calcium deficiency is contributing to any bone disease caused by Vitamin D-deficiency.

Clinical Vitamin D-deficiency in Mongolia in early childhood is associated not only with an inadequate supply of calcium but also with protein/energy malnutrition. When Vitamin D supply from the ultraviolet irradiation of skin is restricted to the 3 months of summer, any factor that diminishes the efficiency of storing or utilizing Vitamin D will increase the risk of deficiency in winter. The mechanism by which malnutrition might increase the risk of Vitamin D-deficiency requires further investigation. Studies in growing rats have shown that both energy deficiency and protein deficiency cause a decrease in the concentration, relative to albumin, of the specific Vitamin D-binding protein (DBP) in blood plasma [11]. A decrease in DBP concentration would diminish the ability to conserve 25(OH)D. No correlation was found between the concentrations of 25(OH)D and of DBP in the plasma of Mongolian children. However, the DBP concentrations were found to vary over a range of 3–9 mol/l with a mean of about 6.5 mol/l [C.J. Laing, personal communication]. Whether this is normal variation or whether it is related to environmental factors is unknown.

It is of interest to reflect on the pioneering research of Chick et al. [12] that demonstrated that both oral Vitamin D (in cod liver oil) and irradiation of the skin with an ultraviolet lamp would correct the bone disease of rickets in children. This work was done in Vienna from 1919 to 1922, when the prevalence of rickets was noted to be high and there was also a shortage of food following the end of World War I. An association between geographically limited exposure of children to ultraviolet sunlight and malnutrition in the etiology of rickets may indeed have been identified 80 years ago.

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