

Vitamin D-deficient Rickets #58; A Multifactorial Disease
[Nutrition Grand Rounds]. Fitzpatrick, S; Sheard, N; Clark, N; Ritter, M.
Nutrition Reviews. #169; July 2000 International Life Sciences Institute. Vol
58(7): 218-222

Ms. Fitzpatrick is with the Department of Nutrition and Food Sciences, Dr. Sheard is with the Departments of Nutrition and Food Sciences and Medicine, Dr. Clark is with the Departments of Nutrition and Food Sciences, Medicine, and Pediatrics, and Ms. Ritter is with the Department of Pediatrics, University of Vermont, Burlington, VT 05401, USA.

Outline

- Abstract
- Introduction
- Case Report
- Discussion
- Vitamin D Metabolism
- Impact of Breast-feeding on Vitamin D Status
- Role of Sunlight
- Conclusion

Graphics

- Figure 1
- Table 1
- Table 2

Abstract

We present a case of an African-American child with vitamin D-deficient rickets. In addition to being solely breast-fed for the period of 1 year, he resided in New England, where exposure to ultraviolet light is limited owing to its northern latitude and long cold winters. He presented with classical signs of nutritional rickets and was immediately responsive to treatment with vitamin D supplementation.

Introduction

Total vitamin D intake is a sum of that derived from both dietary intake and synthesis in the skin owing to ultraviolet (UV) light exposure. Both of these sources of vitamin D have equal biologic potency.^{1,2} Therefore, if either source is lacking, the body can compensate by using the other. A problem arises, however, when both sun exposure and vitamin D-containing foods are inadequate. In infancy and childhood, this lack of vitamin D leads to one of the many forms of rickets.

We describe a case of an African-American child living in Vermont who presented with vitamin D-deficient rickets. The biochemical indicators of rickets (serum levels of 25-hydroxyvitamin D, alkaline phosphatase, parathyroid hormone, and

calcium)^{3,4} responded quickly to vitamin D supplementation and the addition of cow's milk formula to the diet. This clinical case represents an example of a relatively uncommon disorder that still affects children today, and exemplifies the role that multiple factors play in its etiology.

Case Report

AA is an African-American male born to a 22-year-old African-American, Islamic woman. Mother and son had recently moved to the area from New York City to escape an abusive relationship (in which the child was reportedly not physically involved). Prior to their relocation to Vermont, neither the mother nor the child was permitted to leave the home, except on very few occasions. Thus, neither received significant exposure to sunlight. In addition, because of her Islamic beliefs, the mother wore clothing that limited skin exposure. Mother and son had been living in Vermont for approximately 3 months prior to AA's diagnosis in February 1999.

At 13 months of age, AA presented to his primary care provider with an upper respiratory infection. The provider noted that he had slight frontal bossing, bilateral flared radii, visible moderate bow-leggedness in a standing position, and bilateral flared distal tibiae. The mother reported that AA was not yet able to walk on his own and that he had had bowed legs since birth. At this time, AA was breast-fed approximately 10 times per day and consumed limited table foods, which included applesauce, fruit, pasta, rice, and beans. These foods were introduced at approximately 1 year of age. The physical exam, along with the dietary and social history, led to the suspicion of rickets.

Consequently, x-rays of the wrists were obtained, as were laboratory tests, including measurements of 25-hydroxyvitamin D, alkaline phosphatase, calcium, phosphorus, and parathyroid hormone (PTH). The x-rays revealed metaphyseal cupping, flaring, and frayed edges of the distal radius and ulna, along with decreased cortical bone density (Figure 1). These radiologic findings were consistent with the suspected diagnosis of rickets. Laboratory values revealed an elevated alkaline phosphatase level and low levels of both serum calcium and phosphorus (Table 1). Laboratory studies (drawn before vitamin D supplementation was begun) disclosed an elevated concentration of C terminal PTH, a depressed level of 25-hydroxyvitamin D, and a normal concentration of 1,25-dihydroxyvitamin D (Table 1). All were consistent with a diagnosis of vitamin D-deficient rickets.

Figure 1. Radiographs of a wrist of the case study, AA, at diagnosis revealed metaphyseal cupping, flaring, and frayed edges of the distal radius and ulna, along with decreased cortical bone density, all consistent with a diagnosis of rickets. A, anterior-posterior view; B, lateral view.

Table 1. Laboratory Values of the Case Study, AA

Following diagnosis, AA began oral vitamin D supplementation by taking 4000 international units (IU) per day and also took 250 milligrams of calcium (Tums) per day. He was also started on Similac[®]: 8 fluid ounces twice per day. The diagnosis of rickets was discussed at length with the mother, and she was provided with written educational materials. The mother was also referred to the

local Women, Infants, and Children program.

Radiologic examination of the legs 3 months later revealed mild bowing of the distal aspect of the femur bilaterally but no evidence of frayed metaphyses or increased epiphyseal spaces, which are usual findings in rickets cases. Blood tests were repeated and indicated that the alkaline phosphatase and PTH levels had decreased and that the concentration of calcium and 25-hydroxyvitamin D had returned to normal (Table 1). Although it had been recommended that AA consume 16 fluid ounces of Similac[®] per day, he was taking approximately half that amount. The mother was also having difficulty with persuading AA to take the calcium supplement.

During a visit to his primary care provider approximately 1 year after the initial diagnosis of rickets, alkaline phosphatase and 25-hydroxyvitamin D levels were within normal limits and calcium and 1,25-dihydroxyvitamin D values were above the normal range (Table 1).

Discussion

The case described illustrates many of the classical signs of and risk factors for vitamin D-deficient rickets: radiologic, serologic, dietary, demographic, and racial. The etiology of AA's rickets is multifactorial and includes a low intake of vitamin D, minimal exposure to sunlight, and his racial heritage. The vitamin D content of breast milk (AA's predominant source of nutrients) is low, and other sources of vitamin D were lacking in the diet. Minimal exposure to sunlight owing to geographic region, climate, and social history, coupled with his dark pigmented skin, compounded this lack of dietary intake, resulting in the development of rickets.

AA presented with some of the most common as well as most striking features of rickets, including a low serum concentration of 25-hydroxyvitamin D, an increase in plasma alkaline phosphatase (400% above normal) secondary to increasing but ineffective osteoblast activity, and bone changes.³⁻⁵ In addition, he was hypocalcemic, hypophosphatemic, and markedly hyperparathyroid. Supplementation with vitamin D (4000 IU/day) lowered his alkaline phosphatase level, increased his 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels, and returned his levels of calcium, phosphorus, and parathyroid hormone to normal within 3 months.

Vitamin D Metabolism

Vitamin D is found in the diet in one of two forms: D₂ (ergocalciferol, from plants) or D₃ (cholecalciferol, from animal products). Few food sources contain a significant amount of vitamin D naturally; most vitamin D derived from the diet comes from foods that are fortified with this nutrient (e.g., milk). Vitamin D₃ is also synthesized in the skin through the action of UV light.^{1,2,6,7}

Vitamin D (a combination of D₂ and D₃) enters the circulation and is bound to a vitamin D-binding protein.^{1,2,7} This complex is taken up by the liver and hydroxylated to produce 25-hydroxyvitamin D, the major circulating form of vitamin D.^{1,2,6} It is this form that is measured in the blood to determine vitamin D status because the major storage pool of this nutrient is in the circulation.⁸ Once 25-hydroxyvitamin D is made by the liver, the majority is bound to vitamin D-binding protein.^{1,2,7} Unbound 25-hydroxyvitamin D enters the kidney, where it is hydroxylated to form 1,25-dihydroxyvitamin D.^{1,2,6} This vitamin D metabolite is the biologically active form, carrying out most of vitamin D's biologic functions.⁹ The serum concentration of this metabolite is

tightly regulated.⁹

In the case of AA, 25-hydroxyvitamin D was significantly depressed at the time of diagnosis and quickly returned to a normal level following supplementation. Other abnormal laboratory findings (serum calcium, alkaline phosphatase, parathyroid hormone) also normalized following treatment with vitamin D, supporting the diagnosis of vitamin D deficiency. The concentration of 1,25-dihydroxyvitamin D, which fell within the normal range initially, exceeded the upper limit of normal following supplementation. This finding is consistent with previous case reports of rickets.^{3,4,10} Rosen and Chesney⁴ have suggested that this seemingly paradoxical result may be secondary to the dramatic increase in parathyroid hormone, an important modulator of 1,25-dihydroxyvitamin D synthesis in the kidney, that occurs in rickets.

Impact of Breast-feeding on Vitamin D Status

The American Academy of Pediatrics (AAP) recommends that infants be exclusively breast-fed for at least the first 6 months of life.¹¹ In a position statement issued in 1997, the AAP stated that human breast milk is the preferred feeding for all infants and that exclusive breast-feeding is sufficient to support optimal growth and development for the first 6 months of life.¹¹ Despite the nutritional quality of human breast milk, supplementation of both iron and vitamin D may be needed in certain groups of infants.¹² The vitamin D content of human milk is low (15-75 IU/L) (Table 2),¹²⁻¹⁶ and supplementation with 400 IU/day (10 μ g/day) is recommended in infants receiving breast milk as their sole source of nutrition, if the mother is vitamin D deficient or if the infant has inadequate exposure to sunlight.^{11,12} Because the synthesis of vitamin D is dependent on geographic location and skin pigmentation, high-risk populations include infants living in northern regions of the United States and those with dark skin pigmentation.^{11,12,17} Indeed, immediately following birth, African-American infants have a lower serum 25-hydroxyvitamin D concentration than their season-matched Caucasian infant counterparts.¹⁸ In addition, the vitamin D content of breast milk in African-American women in the United States is less than that of Caucasian women.¹⁹ Thus, African-American infants who are breast-fed are likely to require supplementation to achieve adequate vitamin D levels.^{11,12} Both commercial infant formulas (400 IU/L) (Table 2) and cow's milk (400 IU/quart) are enriched with vitamin D, so the addition of these foods to the diet in sufficient quantities removes the need for therapeutic supplementation.¹²

Table 2. Composition of Milk Products

Role of Sunlight

The other major contributing factor to vitamin D content of both breast milk^{13,20} and body stores^{1,2} is direct exposure to sunlight. Exposure of the face alone to UV light has been shown to supply approximately 400 IU of vitamin D per day.²¹ The time of day, season of the year, and latitude, however, influence the amount of UV radiation that reaches the earth.^{1,2} One study conducted in Boston concluded that for middle-aged and older adults, exposure of the hands, face, and arms to moderate doses of sunlight (~5-30 minutes/day) two to three times per week during the summer months was sufficient to provide adequate vitamin D synthesis.²¹ Little vitamin D synthesis in the skin occurs, however, during the period from November through February in Boston.^{22,23} Adequate exposure to UV

light can be even more difficult at more northern latitudes, such as in upper New England and Canada.²³ Thus, it becomes important in certain geographic regions, especially for susceptible children and vegans, to be exposed to ample sunlight in the summertime.^{12,17} Because vitamin D₃ can be stored in the body in adipose tissue, what is produced in the spring and summer months can be released from storage and used during the winter, when the UV light is not strong enough to promote vitamin D₃ synthesis in the skin.^{3,9} Both the use of sunscreen, which blocks ultraviolet-B radiation, and clothing, however, decrease the efficiency of the conversion of 7-dehydrocholesterol to previtamin D in the skin.^{24,25}

The degree of melanin pigmentation also influences vitamin D synthesis in the skin.²⁶⁻²⁹ Black persons with very dark skin pigment required sixfold longer exposure to sunlight to make the same amount of vitamin D as light-skinned Caucasians.²⁷ This explains, in part, why African-Americans have lower circulating levels of both vitamin D and 25-hydroxyvitamin D and are more likely to develop rickets.

Conclusion

This case demonstrates the occurrence of a vitamin deficiency that is considered uncommon today, especially in industrialized countries. When a number of risk factors associated with rickets occur concurrently, however, the development of this disorder is more likely. The combination of dark pigmented skin, lack of exposure to sunlight, and decreased intake of vitamin D-rich foods in the diet can lead to the onset of nutritional rickets. Certain cultural practices may also add to the risk of developing vitamin D-deficient rickets, e.g., draping garments to cover the body in observance of some religions. Physicians should therefore consider vitamin D supplementation for any infant with dark skin living in areas with limited sunlight, any infant who is exclusively breast-fed for longer than 6 months, and any breast-fed infant whose mother may lack adequate vitamin D intake or synthesis. Vitamin D-deficient rickets is readily treated with the addition of this nutrient to the diet, and the reversal of both the biochemical and skeletal changes is rapid.

1. Holick MF. Vitamin D-new horizons for the 21st century. *Am J Clin Nutr* 1994;60:619-30 [Medline Link] [CINAHL Link] [BIOSIS Previews Link]
2. Norman AW. Sunlight, season, skin pigmentation, vitamin D, and 25-hydroxyvitamin D: integral components of the vitamin D endocrine system. *Am J Clin Nutr* 1998;67:1108-10 [Medline Link]
3. Chesney RW, Zimmerman J, Hamstra A, et al. Vitamin D metabolite concentrations in vitamin D deficiency. *Am J Dis Child* 1981;135:1025-8 [Medline Link]
4. Rosen JF, Chesney RW. Circulating calcitriol concentrations in health and disease. *J Pediatr* 1983;103:1-17 [Medline Link]
5. Pitt MJ. Rickets and osteomalacia are still around. *Radiol Clin North Am* 1991;29(1):105-6 [Medline Link]
6. Bouillon R, Okamura WH, Norman AW. Structure-function relationships in the vitamin D endocrine system. *Endocr Rev* 1995;16:200-57 [Medline Link] [BIOSIS Previews Link]
7. Holick MF, MacLaughlin JA, Clark MB, et al. Photosynthesis of previtamin D in

- human skin and the physiologic consequences. *Science* 1980;210:203-5 [Medline Link]
8. Holick MF. The use and interpretation of assays for vitamin D and its metabolites. *J Nutr* 1990;120:1464-9 [Medline Link]
 9. Holick MF, Potts JR, Krane SM. Calcium, phosphorus and bone metabolism. In: Isselbacher K, Braunwald E, Wilson JD, et al., eds. *Harrison's principles of internal medicine*. New York: McGraw Hill, 1990;2137-51
 10. Venkataraman PS, Tsang RC, Buckley DD, et al. Elevation of serum 1,25-dihydroxyvitamin D in response to physiologic doses of vitamin D in vitamin D-deficient infants. *J Pediatr* 1983;103:416-9 [Medline Link]
 11. American Academy of Pediatrics (AAP). Breastfeeding and the use of human milk. *Pediatrics* 1997;100:1035-9 [Medline Link]
 12. AAP, Committee on Nutrition. Vitamin and mineral supplement needs in normal children in the United States. *Pediatrics* 1980;60:1010-20
 13. Reeve LE, Chesney RW, DeLuca HF. Vitamin D of human milk: identification of biologically active forms. *Am J Clin Nutr* 1982;36:122-6 [Medline Link]
 14. Hollis BW, Roos BA, Draper HH, Lambert PW. Vitamin D and its metabolites in human and bovine milk. *J Nutr* 1981;111:1240-8 [Medline Link]
 15. Leerbeck E, Sondergaard H. The total content of vitamin D in human milk and cow's milk. *Br J Nutr* 1980;44:7-12 [Medline Link]
 16. Makin HLJ, Seamark DA, Trafford DJH. Vitamin D and its metabolites in human breast milk. *Arch Dis Child* 1983;58:750-3 [Medline Link]
 17. Backrach S, Fisher J, Parks JS. An outbreak of vitamin D deficiency rickets in a susceptible population. *Pediatrics* 1979;6:871-7
 18. Hollis BW, Pittard WB. Evaluation of the total fetomaternal vitamin D relationships at term: evidence for racial differences. *J Clin Endocrinol Metab* 1986;59:652-7
 19. Specker BL, Tsang RC, Hollis BW. Effect of race and diet on human-milk vitamin D and 25-hydroxyvitamin D. *Am J Dis Child* 1985;139:1134-7 [Medline Link]
 20. Hollis BW. Individual quantitation of vitamin D₂, vitamin D₃, 25-hydroxyvitamin D₂ and 25-hydroxyvitamin D₃ in human milk. *Ann Bioch* 1983;131:211-9
 21. Holick MF. Vitamin D requirements for the elderly. *Clin Nutr* 1986;5:129-31
 22. Webb AR, Kline L, Holick MF. Influence of season and latitude on the cutaneous synthesis of vitamin D: exposure to winter sunlight in Boston and Edmonton will not promote vitamin D synthesis in human skin. *J Clin Endocrinol Metab* 1988;67:373-8 [Medline Link]
 23. Lu Z, Chen TC, Kline L, et al. Photosynthesis of previtamin D in cities around the world. In: Holick MF, Kligman A, eds. *Proceedings of the Biologic*

Effects of Light Symposium. Berlin: Walter DeGruyter & Co, 1992;48-52

24. Matsuoka LY, Ide L, Wortsman J, et al. Sunscreens suppress cutaneous vitamin D synthesis. *J Clin Endocrinol Metab* 1987;64:1165-8 [Medline Link]

25. Matsuoka LY, Wortsman J, Dannenberg MJ, et al. Clothing prevents ultraviolet-B radiation-dependent photosynthesis of vitamin D. *J Clin Endocrinol Metab* 1992;75:1099-103 [Medline Link] [BIOSIS Previews Link]

26. Holick MF, MacLaughlin JA, Doppelt SH. Factors that influence the cutaneous photosynthesis of previtamin D. *Science* 1981;211:590-3 [Medline Link]

27. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of the skin to synthesize vitamin D. *Lancet* 1982;1:74-6

28. Matsuoka LY, Wortsman J, Haddad JH, et al. Racial pigmentation and the cutaneous synthesis of vitamin D. *Arch Dermatol* 1991;127:536-8 [Medline Link]

29. Harris SS, Dawson-Hughes B. Seasonal changes in plasma 25-hydroxyvitamin D concentrations of young American black and white women. *Am J Clin Nutr* 1998;67:1232-6 [Medline Link] [CINAHL Link] [BIOSIS Previews Link]
