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Linear growth in relation to the circulating concentrations of insulin-like growth factor I, parathyroid hormone, and 25-hydroxy vitamin D in children with nutritional rickets before and after treatment: endocrine adaptation to vitamin D deficiency

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Abstract

The objective of the study was to determine the degree of linear growth retardation of patients with vitamin D deficiency rickets at presentation and the magnitude of catch-up growth in relation to their calcium (Ca) homeostasis and hormones affecting it before and after treatment. This prospective study recorded the anthropometric data and measured the circulating 25-hydroxy vitamin D (25-OH-D), insulin-like growth factor I (IGF-I), parathyroid hormone, Ca, phosphate, and alkaline phosphatase concentrations in 46 infants and children with nutritional (vitamin D deficiency) rickets before and 6 months or more after treatment with one intramuscular injection of vitamin D3 megadose (300 000 IU). Forty normal age- and sex-matched children were included as controls for the auxological data. At presentation, patients' mean age = 13.1 ± 1.1 months, length standard deviation scores (LSDS) = −1.5 ± 0.2, and body mass index = 16.3 ± 0.85. They were significantly shorter and had markedly lower growth velocity standard deviation scores (GVSDS) compared with normal controls (LSDS = 0.25 ± 0.18 and 0.31 ± 0.22, respectively). Six months after treatment, the LSDS increased significantly in patients to −0.45 ± 0.13, with a significantly increased GVSDS (2.76 ± 0.45) and body mass index (16.9 ± 0.65). They were still shorter but with significantly higher GVSDS compared with normal controls. Serum Ca and phosphate concentrations increased from 2.07 ± 0.25 and 1.23 ± 0.24 mmol/L, respectively, before treatment to 2.44 ± 0.2 and 1.94 ± 0.2 mmol/L, respectively, after treatment. Serum alkaline phosphatase and parathyroid hormone concentrations decreased from 1183 ± 219 U/L and 294 ± 87 pg/mL, respectively, before treatment to 334 ± 75 U/L and 35.2 ± 15.2 pg/mL, respectively, after treatment. The 25-OH-D level increased from 4.5 ± 0.56 ng/mL before treatment to 44.5 ± 3.7 ng/mL after treatment. Circulating concentrations of IGF-I increased significantly after treatment (52.2 ± 18.9 ng/mL) vs before treatment (26.6 ± 12.8 ng/mL). The 25-OH-D concentrations were correlated significantly with the IGF-I levels before and after treatment (r = 0.603 and r = 0.59, respectively; $P < .001$). The GVSDS after treatment was correlated with the increase of IGF-I and 25-OH-D levels (r = 0.325 and r= 0.314, respectively; $P < .01$). These data denote that the accelerated linear growth after treatment of nutritional vitamin D deficiency is mediated through activation of the growth hormone/IGF-I system and suggests an important role of vitamin D as a link between the proliferating cartilage cells of the growth plate and growth hormone/IGF-I secretion. Three different sequential stages of vitamin D deficiency can be recognized according to the clinical/radiological, biochemical, and hormonal data of patients at presentation.

1. Introduction

Vitamin D is critical for calcium (Ca) homeostasis and for mineralization of the skeleton, especially during the growing years. A deficiency in vitamin D is critical for the pediatric patient because it leads to rickets (a

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mineralization defect at the epiphyseal growth plates and bone tissue) and osteomalacia (a mineralization defect of bone tissue) [1]. The development of clinical vitamin D deficiency rickets is dependent not only on the severity of the vitamin D deficiency (circulating concentrations of 25-hydroxy vitamin D [25-OH-D]) but also on the duration of the deficiency, on the rate of the child's growth (which influences Ca demands), and on the dietary Ca content [1-7].

If vitamin D concentrations are inadequate, Ca absorption from the gut is inadequate; and Ca concentrations begin to decrease. This decrease in serum Ca precedes a decrease in serum phosphate (PO4) concentrations. Parathyroid hormone (PTH) concentrations increase to counteract the decline in serum Ca concentrations. As PTH restores serum Ca concentrations, it increases PO4 loss in urine; and serum PO4 concentrations declines. At this point, clinical features such as rachitic bone changes become apparent on radiographs and on physical examination. In a few weeks to months, Ca salts are mobilized; and bone matrix breakdown begins. As serum Ca levels fall, there is further increased activity of PTH, which promotes Ca loss from the bone. Continued inadequate vitamin D intake eventually is associated with declines in both serum Ca and phosphorus concentrations as mineral absorption becomes inadequate to support normal serum Ca despite elevated PTH concentrations. Rachitic bone changes are usually florid when this occurs. If not recognized and properly treated, vitamin D deficiency may have long-term sequelae [1,2,7-10].

The typical clinical picture of rickets includes growth-plate abnormalities and delayed growth, weakening and bowing of weight-bearing bones, hypoplasia of tooth enamel, and hypocalcemia with muscle hypotonia and even tetany [1,4,7,10].

The basic skeletal lesion is impaired mineralization of the matrix produced by growth-plate chondrocytes or osteoblasts. This zone is characterized by flaring of the ends of the bones and the "rachitic rosary." This entire process occurs within a few months [1-4,10].

Although catch-up growth usually occurs in rachitic children after adequate treatment with vitamin D, the degree of growth retardation at presentation, the magnitude of catch-up growth, and their relation to the changes in Ca homeostasis parameters and the important hormones controlling bone growth and mineralization (insulin-like growth factor I [IGF-I], PTH, and vitamin D) need further clarification.

The objectives of the study were as follows:

1. To determine the degree of linear growth retardation of children with vitamin D deficiency rickets at presentation.
2. To measure the magnitude of catch-up growth for 6 to 12 months after treatment with vitamin D.
3. To measure the circulating concentrations of IGF-I, PTH, and 25-OH-D levels before and after vitamin D therapy and correlate their levels with different growth parameters.
4. To compare growth parameters and biochemical and hormonal data of rachitic patients vs those without hypocalcemia at presentation.

2. Patients and methods

In this prospective study, all infants and children up to and including 3 years of age with vitamin D deficiency (nutritional rickets) attending the Growth Clinic at Hamad General Hospital, Doha, Qatar, between October 2003 and September 2005 (n = 46) were studied. Forty normal age- and sex-matched children attending the vaccination clinic were randomly selected as controls for the auxological data. Qatar has a sunny hot weather all year with no seasonal variation in the incidence of rickets.

Inclusion criteria included clinical manifestations of rickets with the following:

1. Low serum 25-OH-D
2. Elevated serum alkaline phosphatase (ALP)
3. Normal or low serum Ca
4. Normal or low serum PO4
5. High serum PTH (intact molecule)
6. Radiological confirmation of rickets at the distal ulnar or femoral epiphysis.

Exclusion criteria included the following:

1. Vitamin D deficiency rickets associated with underlying disease, such as fat malabsorption, liver disease, and renal insufficiency. Patients with malnutrition or those receiving total parenteral nutrition are also excluded.
2. Vitamin D deficiency secondary to heritable disorders of vitamin D metabolism, including the following:
   - α-Hydroxylase deficiency (pseudo–vitamin D deficiency rickets)
   - Vitamin D receptor (VDR) defects (hypocalcemic vitamin D–resistant rickets
   - Phosphopenic rickets of any etiology (where hypophosphatemia is the primary cause of the rickets, and not due to calcipenic rickets with secondary hyperparathyroidism).

The duration of the study was from October 2003 to September 2005.

2.1. Ethical approval

The Research Ethics Board, Hamad Medical Centre, Doha, Qatar, has approved the protocol of the study; and informed consents were obtained from all the parents of the children included in this study.