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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.

2.2. Methods

All patients attended our research clinic at baseline and every 3 months for at least 6 months and were subjected to the following:

1. Detailed history taking including nutritional intake and exposure to sun.
2. Physical examination including clinical manifestations of rickets.
3. Anthropometric measurements including weight, length, and head circumference. Length was measured with an infant/child height/length measuring board: This board has a 130-cm capacity (collapses to 75 cm) and has 0.1-cm increments, with the sliding head-foot piece. (Shorr Productions, Olney, MD). The standard deviation of the difference between blind triplicate height measurements of 20 children was 0.12 cm. Weight (child lightly clothed) was measured using an electronic baby scale with digital display.
4. Length standard deviation scores (LSDS), length growth velocity standard deviation scores (GVSDS), and body mass index (BMI) were calculated prospectively before and at least 6 months or more after treatment. Annualized length velocity (GV) was calculated from length measurements taken 6 months apart. Standard deviation scores were calculated for length and length velocity (using the standards of Cameron [11] and of Tanner et al [12]) and BMI (using the standards of Cole et al [13]).
5. Biochemical investigations included measurement of serum creatinine, bicarbonate, Ca, PO4, albumin, ALP, PTH, IGF-I, and 25-OH-D concentrations. Serum Ca was corrected for individual variations in serum albumin using the following formula: corrected serum Ca (in millimoles per liter) = measured serum Ca (in millimoles per liter) + 0.02 × [40 − measured albumin (in grams per liter)]. Children with plasma 25-OH-D levels less than 10 ng/mL were considered to have vitamin D deficiency. Insulin-like growth factor I, PTH, and 25-OH-D were measured by radioimmunometric assay using reagents purchased from Mediagnost (Reutlingen, Germany). Intraassay coefficients of variation were 5.6%, 6.9%, and 5.8%, respectively; and interassay coefficient of variations were 7.9%, 8.9%, and 8.2%, respectively. Results were expressed as the mean ± SD and analyzed by paired Student *t* test to compare growth parameters and analyte concentrations before vs after treatment. A nonpaired Student *t* test was used to compare growth parameters and analyte concentrations between normocalcemic and hypocalcemic groups. Correlation and linear regression analyses were used to investigate the relation between growth parameters and the other variables. For ethical reasons, hormonal and analyte concentrations for normal controls were not measured.

The presence or absence of radiological evidence of rickets was determined from routine radiological reports.

3. Results

Anthropometric and biochemical data of rachitic patients (Table 1) show that after 6 months or more of therapy (300 000 U of vitamin D3 intramuscularly), the LSDS increased significantly from −1.5 ± 0.2 to −0.45 ± 0.13, with an annualized growth velocity = 16.3 ± 0.85 cm/y. Their high GVSDS (2.76 ± 0.45) denoted a significant growth spurt. Before treatment, patients were significantly shorter and had markedly lower GVSDS compared with normal controls. Six months after treatment, patients had significantly higher GVSDS compared with controls but were still significantly shorter.

After treatment, serum Ca and PO4 concentrations increased significantly from 2.07 ± 0.25 and 1.23 ± 0.24 mmol/L, respectively, to 2.44 ± 0.2 and 1.94 ± 0.2 mmol/L, respectively. Circulating concentrations of ALP and PTH decreased significantly after treatment compared with values before treatment. After treatment, circulating 25-OH-D and IGF-I concentrations increased significantly vs before treatment.

Comparing rachitic patients presenting with hypocalcemia with those with normocalcemia (Table 2) revealed that

Table 1
Anthropometric and biochemical data of rachitic children before vs after treatment with vitamin D

		Age (mo)	LSDS	GVSDS	BMI (kg/m^2)	Ca (mmol/L)	PO4 (mmol/L)	ALP (U/L)	25-OH-D (ng/mL)	PTH (pg/mL)	IGF-I (ng/mL)
Patients before treatment (n = 46)	Mean	13.1	(−)1.5 *	(−)1.25 *	16.3	2.07	1.23	1183	4.5	294	26.6
	SD	1.1	0.2	0.34	0.85	0.25	0.24	219	0.56	87	12.8
Patients 6 mo after treatment	Mean	21.88	(−)0.45 *,†	2.76 *,†	16.9	2.44 †	1.94 †	334 †	44.5 †	35.2 †	52.2 †
	SD	1.5	0.13	0.31	0.65	0.2	0.2	75	3.7	15.2	18.9
Controls (n = 40)	Mean	14.3	0.25	0.22	16.3						
	SD	2.2	0.18	0.18	1.5						
Controls after 6 mo (n = 40)	Mean	21.5	0.32	0.42	16.5						
	SD	1.9	0.19	0.24	1.7						

* $P < .05$ patients vs controls.
† $P < .05$ before vs after 6 months.

Table 2
Comparison between normocalcemic (adapted) and hypocalcemic (dysadapted) rachitic children

	Hypocalcemic group (dysadapted)	Normocalcemic groups (adapted)
n	14	32
Birth length (cm)	49.9 ± 1.5	49.6 ± 1.9
Age at Dx (mo)	12.4 ± 7.9	13.4 ± 8
Age at end of study	22 ± 10.7	21.6 ± 9.5
LSDS at Dx	(−) 1.87 ± 0.9	(−) 1.05 ± 0.7 *
LSDS at end of study	(−) 0.74 ± 0.26	(−) 0.32 ± 0.14
GVSDS at Dx	(−) 1.6 ± 0.4	(−) 1.05 ± 0.2 *
GVSDS at end of study	2.5 ± 0.5	2.9 ± 0.4 *
BMI at Dx	16.5 ± 1.8	17.3 ± 1.8
BMI at end of study	17.3 ± 1.4	17.5 ± 1.9
Ca at Dx (mmol/L)	1.67 ± 0.04	2.24 ± 0.26 *
Ca at end of study (mmol/L)	2.46 ± 0.2	2.44 ± 0.3
PO4 at Dx (mmol/L)	1.03 ± 0.2	1.24 ± 0.3 *
PO4 at end of study (mmol/L)	1.93 ± 0.2	1.9 ± 0.25
ALP at Dx (U/L)	1356 ± 229	1032 ± 208 *
ALP at end of study (U/L)	355 ± 46	326 ± 151
PTH at Dx (pg/mL)	326 ± 98	237 ± 47 *
PTH at end of study (pg/mL)	34 ± 15.8	35.8 ± 21
25-OH-D at Dx (ng/mL)	2.8 ± 1.6	7.6 ± 2.6 *
25-OH-D at end of study (ng/mL)	43.3 ± 13.8	47.5 ± 21
IGF-I at Dx (ng/mL)	21 ± 12	31.8 ± 11 *
IGF-I at end of study (ng/mL)	48.7 ± 15	56 ± 24

Dx indicates diagnosis.
* $P < .05$, (mean ± SD).

the hypocalcemic group was significantly shorter with significantly lower GVSDS. They had significantly lower serum PO4, 25-OH-D, and IGF-I concentrations and significantly higher PTH and ALP concentrations compared with normocalcemic patients. Although both groups had significantly increased GVSDS after treatment, the GVSDS of the hypocalcemic group was significantly lower than that of the normocalcemic group. Six months after treatment, the LSDS of the group presenting with hypocalcemia was not significantly lower vs the normocalcemic group.

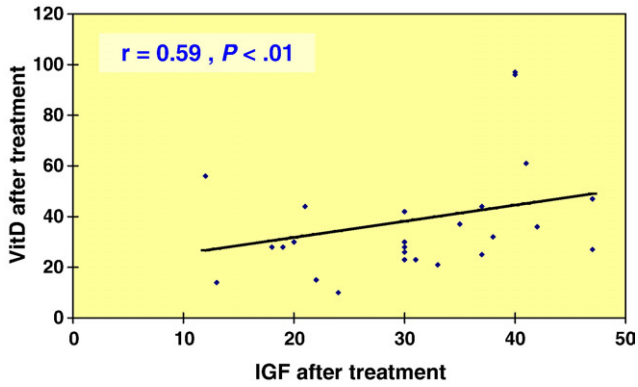

Fig. 1. Regression line plot of IGF and vitamin D concentrations after treatment ($r = 0.59$, $P < .01$).

Table 3 presents the correlations between IGF-I and 25-OH-D concentrations before and after 6 months of treatment (Fig. 1). After treatment, serum concentrations of IGF-I was correlated significantly with the percentage of increment of 25-OH-D concentrations ($r = 0.443$, $P < .01$).

The GVSDS after treatment were correlated with IGF-I concentration and with the percentage of increment of IGF-I level ($r = 0.339$ and 0.325, respectively; $P < .01$) as well as with 25-OH-D concentration and percentage of increment of 25-OH-D concentration ($r = 0.34$ and 0.31, respectively; $P < .01$) but not with Ca or PO4 concentrations (Table 4). Alkaline phosphatase levels were significantly correlated with serum PO4 concentrations before and after treatment ($r = 0.55$ and 0.43, $P < .001$) but not with serum Ca concentrations.

Analysis of the radiological findings of patients in relation to their biochemical data revealed 3 radiological stages, as follows: (1) Patients with low 25-OH-D but normal serum Ca and PO4 concentrations had mild broadening of the joint space, near-normal epiphyseal and metaphyseal calcification without cupping or fraying, and normal diaphyseal thickness (Figs. 2A and 3A). (2) Patients with low 25-OH-D, normal serum Ca, but low serum PO4 concentrations had irregular/faint (fraying) line of ossification at metaphyseal front with excessive osteoid (cupping) and some metaphyseal and

Table 3
Correlation between 25-OH-D and IGF-I concentrations before and after treatment with vitamin D

	25-OH-D-b	25-OH-D-a	Increment of 25-OH-D	IGF-I-b	IGF-I-a	Increment of IGF-I
25-OH-D-b	1.000					
25-OH-D-a	0.321	1.000				
Increment of 25-OH-D	0.170	0.983	1.000			
IGF-I-b	0.603 *	0.622	0.522	1.000		
IGF-I-a	0.712	0.589 *	0.443 *	0.865	1.000	
Increment of IGF-I	0.441	−0.058	0.211	0.322	0.754	1.000

b indicates before vitamin D treatment; a, after vitamin D treatment.
* $P < .001$.

Table 4
Correlations between growth data and biochemical variables

	LSDS-b	GVSDS-b	LSDS-a	GVSDS-a
Ca-b	−0.039	0.139	0.174	0.040
Ca-a	−0.143	−0.146	0.107	0.157
Ca % change	−0.181	−0.325	−0.001	0.077
PO4-b	0.208	0.270	0.266	−0.315
PO4-a	0.193	0.222	−0.001	−0.080
PO4 % change	0.182	0.207	−0.001	−0.078
PTH-b	−0.027	−0.078	−0.003	−0.334 *
PTH-a	−0.131	−0.182	0.078	−0.385 *
PTH % change	−0.006	0.113	−0.130	0.255 *
25-OH-D-b	−0.185	−0.027	0.007	−0.012
25-OH-D-a	−0.097	−0.139	0.099	0.340 *
25-OH-D % change	0.194	−0.020	0.248 *	0.314 *
IGF-I-b	−0.246	−0.230	0.303 *	−0.141
IGF-I-a	0.012	0.034	0.334 *	0.339 *
IGF-I % change	−0.529	−0.033	0.195	0.326 *

b indicates before treatment; a, after treatment.
* $P < .05$.

diaphyseal demineralization (Figs. 2B and 3B). (3) Patients with low 25-OH-D, Ca, and PO4 concentrations (dysadapted) had absent line of ossification at metaphyseal front, excessive osteoid deposition (very wide wrist space) with cupping, marked decalcification of the metaphysis, and diaphysis of long bones (very thin cortex) with subperiosteal erosion of the shafts (Figs. 2C and 3C).

4. Discussion

In this study, infants and children with vitamin D deficiency rickets (n = 46, younger than 3 years) presented with short stature (LSDS = −1.5 ± 0.7) because of the lack of the effect/s of vitamin D on their linear growth. Marked improvement in their LSDS was achieved 6 months or more after treatment with vitamin D (LSDS = −0.45 ± 0.13), with a period of significant catch-up growth evidenced by GVSDS = 2.76 ± 0.45 during recovery. This growth spurt appeared to compensate adequately for the period of growth retardation during vitamin D deficiency in most of the patients.

Many factors can contribute to impaired linear growth in these children, including the following: (1) defective mineralization and increased size of the hypertrophic layer of the growth plate with the deposition of excessive osteoid; (2) deformities of the long bones of the lower limbs with bowing of both femur and tibia due to weakening of the shafts; (3) hypotonia of the back muscles and ligaments with tendency to postural kyphosis or kyphoscoliosis; (4) a possible effect of vitamin D deficiency on growth hormone (GH)/IGF-I axis; and (5) repeated infections that might be due to the lack of vitamin D effect on the immune system with subsequent effect on the nutritional status of the infant [1-10].

In our rachitic children, circulating IGF-I concentrations increased significantly after vs before treatment with vitamin D. The GVSDS after treatment were correlated significantly

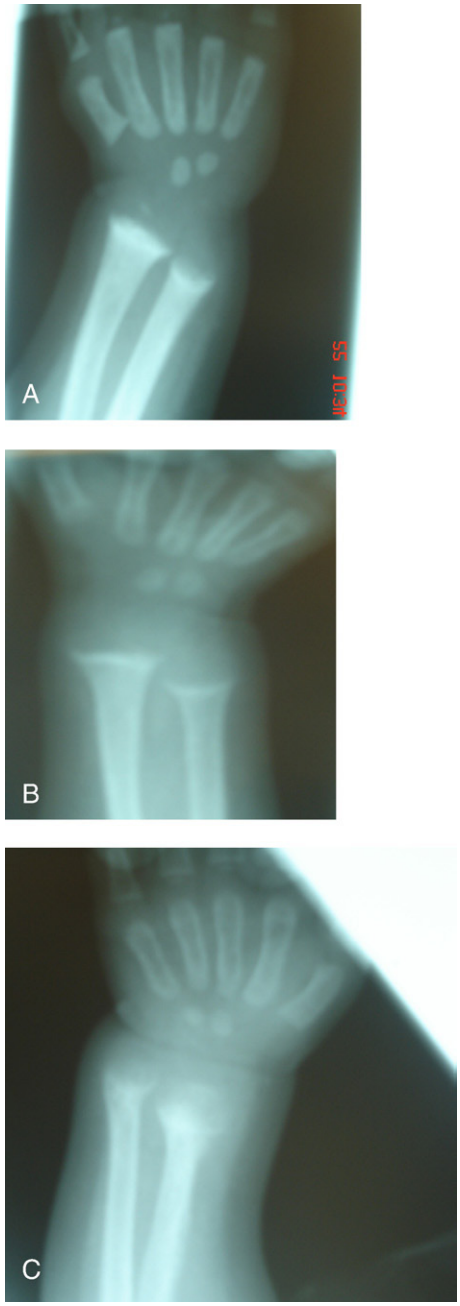

Fig. 2. A, Stage I (adapted). Normal serum Ca and PO4 concentrations and high PTH and ALP concentrations. Near-normal epiphyseal and metaphyseal calcification without cupping or fraying with mild broadening of the joint space. Normal diaphyseal thickness. B, Stage II (adapted). Normal serum Ca, low serum PO4 concentrations, high PTH and ALP (markedly lower than in stage III), and low IGF-I (higher than in stage III) concentration. Clear line of ossification at metaphyseal front but irregular/faint (fraying) with excessive osteoid (cupping) and improvement of metaphyseal and diaphyseal calcification. Linear GVSDS = 3.1. C, Stage III (dysadapted). Low serum Ca and PO4 concentrations and higher PTH and ALP concentrations. Absent line of ossification at metaphyseal front, excessive osteoid deposition (very wide wrist space) with cupping, decalcification of the metaphysis, and shafts of long bones (very thin cortex) with subperiosteal erosion of the shafts.

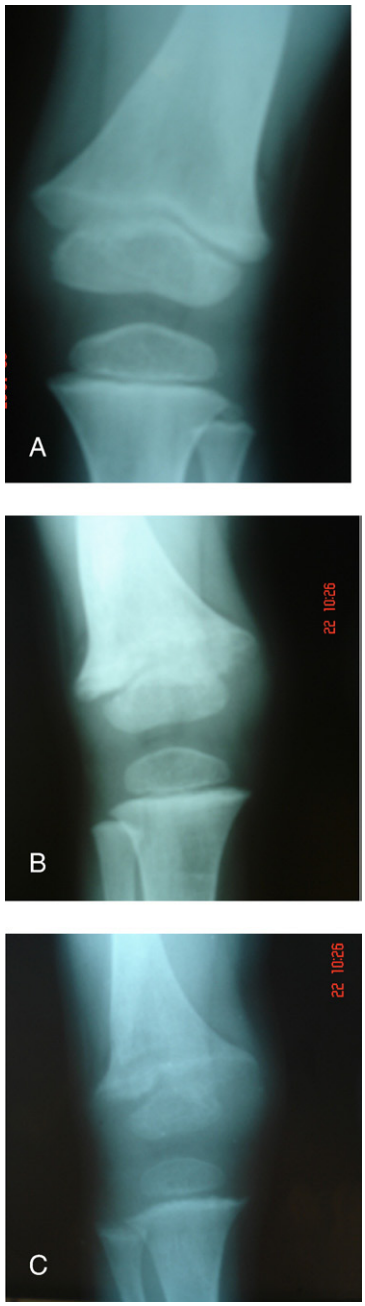

Fig. 3. A, Stage I (adapted). Normal serum Ca and PO4 concentrations and high PTH and ALP concentrations. Near-normal epiphyseal and metaphyseal calcification without cupping or fraying with mild broadening of the joint space. Normal diaphyseal thickness. B, Stage II (adapted). Normal serum Ca, low serum PO4 concentrations, high PTH and ALP (markedly lower than in stage III), and low IGF-I (higher than in stage III) concentration. Clear line of ossification at metaphyseal front but irregular/faint (fraying) with excessive osteoid (cupping) and improvement of metaphyseal and diaphyseal calcification. Linear GVSDS = 2.8. C, Stage III (dysadapted). Low serum Ca and PO4 concentrations and higher PTH and ALP concentrations. Absent line of ossification at metaphyseal front, excessive osteoid deposition (very wide wrist space) with cupping, decalcification of the metaphysis, and shafts of long bones (very thin cortex) with subperiosteal erosion of the shafts.

with both IGF-I and 25-OH-D concentrations as well as their increments. The LSDS were correlated significantly with IGF-I concentration before and after treatment. In addition, IGF-I concentrations were correlated significantly with the 25-OH-D concentrations both before and after treatment. These findings support the view that the attained growth spurt after treatment is mediated through increased IGF-I synthesis (stimulation of GH/IGF-I axis).

There are some good evidence that vitamin D may regulate pituitary function. The VDR messenger RNA (mRNA) expression has been demonstrated in the human pituitary gland, suggesting the possibility that, like in the rat pituitary, VDR may regulate the human pituitary gene expression and hormone secretion [14,15].

Selective effects of 1,25-dihydroxyvitamin D3 (1,25-[OH]2D3) have been shown on gene expression and thyroid-stimulating hormone release in normal rat pituitary cells in vitro. These data and others [16,17] further support a permissive or regulatory role of vitamin D in the normal pituitary gland and suggest that 1,25-(OH)2D3 may act to increase GH secretion in our rachitic patients with subsequent increase in IGF-I synthesis and secretion after treatment with vitamin D.

Systemically, IGF-I stimulates the production of 1,25-(OH)2D3 by kidney cells independently of GH in vitro. In GH-deficient patients, there is evidence that IGF-I mediates the stimulatory effect of GH on 1,25-(OH)2D3 production independently of circulating PTH [18-21].

The stimulatory effects of IGF-I on bone formation in GH-deficient patients suggest an intrinsic action of this peptide on osteoblasts. In fact, IGF-I has been shown to support proliferation, differentiation, and matrix synthesis in cultures of osteoblast-like cells and bone organ cultures. In vitro, IGF-I is a potent stimulator of the production of type I collagen, the main structural protein of bone. Insulin-like growth factor I has also been found to increase procollagen$_{\alpha 1}$ (I) mRNA expression both in osteoblasts in vitro and in bone in vivo [22-24].

In epiphyseal chondrocytes, 1,25-(OH)2D3 potentiates IGF-I synthesis and stimulates cell differentiation as judged by ALP activity, collagen X mRNA, and matrix calcification in long-term experiments. 1,25-(OH)2D3 stimulates chondrocytes proliferation and cell differentiation. This proliferative effect is mediated by local IGF-I synthesis [25]. Thus, locally synthesized IGF-I may decrease in vitamin D–deficient children and cause growth deceleration. Infusion of GH or IGF-I shortens stem and proliferating cell cycle time in the growth plate of hypophysectomized rats and decreases the duration of the hypertrophic differentiation phase [26]. Hence, decreased circulating and locally produced IGF-I concentrations may explain in part the defective matrix calcification, the irregular maturation of chondrocytes, and the large irregular hypertrophic zone found in the growth plate of rachitic children. The large hypertrophic zone can be explained by the prolongation of the cell cycle time, defective maturation, and impaired calcification due to the

effect of high level of PTH (stimulates proliferation of chondrocytes) in the presence of low IGF-I (delays maturation and calcification of chondrocytes) [25,26]. In addition, low IGF-I may also decrease the anabolic effect of PTH on bones, adding further weakness to these developing bones [27,28].

In vitro studies showed that IGF-I and 1α,25(OH)2D3 mutually up-regulate their respective receptors in growth-plate chondrocytes. In parallel, they have additive effects on cell proliferation and colony formation, suggesting independent effector pathways. After injection of vitamin D, increased 1α,25(OH)2D3 increases the IGF-I receptors on chondrocytes and increases its growth-promoting actions [26]. In rachitic rats, 1,25-(OH)2D appears to play a major role in bone healing and exerts a direct effect on bone cells. This effect might be due to increased IGF-I secretion and/or IGF-I receptor expression [29]. Increased circulating and locally produced IGF-I as well as IGF-I receptors in the bones can explain the fast growth velocity and significant catch-up growth in our rachitic patients after treatment with vitamin D. The significant correlation between IGF-I and vitamin D levels on the one hand and between GVSDS and IGF-I on the other hand supports this view.

It is well appreciated that overt cases of rickets represent only the tip of the iceberg of infants and children with vitamin D deficiency [30,31]. Decreased circulating and locally produced IGF-I in rachitic children appears to be a gradual adaptive process to inhibit linear growth (in growth plate) and bone mineral accretion (diaphysis) during vitamin D deficiency. This process conserves bone minerals and proteins to maintain normal serum Ca concentration and slows down the breakdown of the already formed bones instead of using them in forming new bones.

Comparing growth and the biochemical and radiological data of rachitic patients presenting with hypocalcemia vs those with normocalcemia supported this view. During the early stages, mild to moderate decrease in IGF-I production slows down linear growth at the epiphyseal plate through slowing down chondrocyte maturation to the hypertrophic stage, slowing down calcification, and economizing the use of Ca, whereas moderate and/or intermittent increase of PTH stimulates the production of 1α(OH)2D3, increases Ca absorption from the gut, and ensures maintenance of normal serum Ca concentration important for adaptive stage. It was shown that intermittent high PTH is anabolic for bone [32,33]. At this stage, only mild radiological manifestations can be seen. With longer and/or more severe vitamin D deficiency, IGF-I decreases further with more slowing of bone growth; and the persistently high PTH mediates significant osteoclastic activity on the bones to maintain normal serum Ca concentration. Low IGF-I decreases the anabolic effect of PTH on bone cells favoring its catabolic actions. Hypophosphatemia may occur because of the phosphaturic effect of continuously elevated PTH, which further compromises mineralization of the growth plate and bones. This stage is usually associated with significant radiological manifestations. In the late/terminal stage, failure of these adaptive mechanisms (low IGF-I, very slow or arrested bone growth, and high PTH) and significant exhaustion of bone hydroxyapatite lead to hypocalcemia. In this stage, severe radiological manifestations including deformities and fractures occur. It appears that hormonal adaptation to vitamin D deficiency is effective and explains the lower incidence of symptomatic disease despite the higher prevalence of vitamin D deficiency in our population [34].

In one study, the age of children presenting with symptomatic hypocalcemia correlated well with the periods of rapid growth, suggesting that growth rate is an important factor in determining the onset of hypocalcemia (failure of adaptation) because of the increased metabolic demands of rapid growth during these periods [35]. In this study, the mean age of patients with hypocalcemia and those with normocalcemia did not differ. In addition, there was no clustering of patients with severe disease (evidenced by hypocalcemia and severe radiological signs) at any specific season.

In summary, accelerated linear growth after treatment of nutritional vitamin D deficiency appears to be mediated through activation of the GH/IGF-I system and suggests an important role of vitamin D as a link between the proliferating cartilage cells of the growth plate and GH/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; the first 2 of them reflect significant adaptation to vitamin D deficiency.

References

[1] Root AW, Diamond FB. Calcium metabolism, normal homeostasis and disorders of calcium metabolism in the child and adolescent. In: Sperling MA, editor. Pediatric endocrinology. 2nd ed. Philadelphia: Saunders; 2002. p. 65-110.
[2] Thomas MK, Demay MB. Vitamin D deficiency and disorders of vitamin D metabolism. Endocrinol Metab Clin North Am 2000;29: 611-27.
[3] Key Jr LL. Nutritional rickets. Trends Endocrinol Metab 1991;2:81-5.
[4] Mughal MZ, Salama H, Laing I, et al. Florid rickets associated with prolonged breast feeding without vitamin D supplementation. BMJ 1999;318:39-40.
[5] Joiner TA, Foster C, Shope T. The many faces of vitamin D deficiency rickets. Pediatr Rev 2000;21:296-302.
[6] Cosgrove L, Dietrich A. Nutritional rickets in breast-fed infants. J Fam Pract 1985;21:205-9.
[7] El A, Hag I, Karrar ZA. Nutritional vitamin D deficiency rickets in Sudanese children. Ann Trop Paediatr 1995;15:69-76.
[8] Hanley DA, Davison KS. Vitamin D insufficiency in North America. J Nutr 2005;135:332-7.
[9] Prentice A. Micronutrients and the bone mineral content of the mother, fetus and newborn. J Nutr 2003;133:1693S-9S.
[10] Blok BH, Grant CC, McNeil AR, Reid IR. Characteristics of children with florid vitamin D deficient rickets in the Auckland region in 1998. N Z Med J 2000;113:374-6.
[11] Cameron N. The methods of auxological anthropometry. In: Falkner F, Tanner JM, editors. Human growth, Vol 3, 2nd ed. New York: Plenum; 1986. p. 3-46.

[12] Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight, height velocity and weight velocity: British children 1965. Arch Dis Child 1966;41:454-71, 613-35.
[13] Cole TJ, Freeman JV, Preece MA. Body mass index reference curves for the UK, 1990. Arch Dis Child 1995;73:25-9.
[14] Perez-Fernandez R, Alonso M, Segura C, Munoz I, Garcia-Caballero T, Diguez C. Vitamin D receptor gene expression in human pituitary gland. Life Sci 1997;60:35-42.
[15] d'Emden MC, Wark JD. Vitamin D–enhanced thyrotrophin release from rat pituitary cells: effects of Ca2+, dihydropyridines and ionomycin. J Endocrinol 1989;121:441-50.
[16] Wark JD, Gurtler V. Vitamin D induction of secretory responses in rat pituitary tumor (GH4C1) cells. J Endocrinol 117:293-8.
[17] Seoane S, Perez-Fernandez R. The vitamin D receptor represses transcription of the pituitary transcription factor pit-1 gene without involvement of the retinoid X receptor. Mol Endocrinol 2005;10:0253.
[18] Bianda T, Glatz Y, Bouillon R, Froesch ER, Schmid C. Effects of short-term insulin-like growth factor–I (IGF-I) or growth hormone (GH) treatment on bone metabolism and on production of 1,25-dihydroxycholecalciferol in GH-deficient adults. J Clin Endocrinol Metab 1998; 83:81-7.
[19] Condamine L, Vztovsnik F, Friedlander G, Menaa C, Garabedian M. Local action of phosphate depletion and insulin-like growth factor–I on in vitro production of 1,25-dihydroxyvitamin D3 by cultured mammalian kidney cells. J Clin Invest 1994;94:1673-9.
[20] Wright NM, Papadea N, Wentz B, Hollis B, Willi S, Bell NH. Increased serum 1,25 dihydroxyvitamin D after growth hormone administration is not parathyroid hormone–mediated. Calcif Tissue Int 1997;61:101-3.
[21] Hock JM, Centrelle M, Canalis E. Insulin-like growth factor–I has independent effects on bone matrix formation and cell replication. Endocrinology 1988;122:254-60.
[22] Schmid C, Ernst M, Binz K, Zapf J, Froesch ER. The endocrine/paracrine actions of IGFs on bone. In: Spencer EM, editor. Proceedings of the second international symposium of insulin-like growth factors. New York: Elsevier; 1991. p. 591-605.
[23] Tanaka H, Quarto R, Williams S, Barnes J, Liang CT. In vivo and in vitro effects of insulin-like growth factor–I on femoral mRNA expression in old rats. Bone 1994;15:647-53.
[24] Krohn K, Haffner D, Hugel U, Himmele R, Klaus G, Mehls O, et al. 1,25(OH)2D3 and dihydrotestosterone interact to regulate proliferation and differentiation of epiphyseal chondrocytes. Calcif Tissue Int 2003; 73:400-10.
[25] Robson H, Siebler T, Shalet SM, Williams G. Interactions between GH, IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. Pediatr Res 2002;52:137-47.
[26] Yonemura K, Fujimoto T, Fujigaki Y, Hishida A. Vitamin D deficiency is implicated in reduced serum albumin concentrations in patients with end-stage renal disease. Am J Kidney Dis 2000;36:337-44.
[27] Klaus G, Weber L, Rodriguez J, Fernandez P, Klein T, Grulich-Henn J, et al. Interaction of IGF-I and 1 alpha, 25(OH)2D3 on receptor expression and growth stimulation in rat growth plate chondrocytes. Kidney Int 1998;53:1152-61.
[28] Lund B, Charles P, Egsmose C, Lund B, Melsen F, Mosekilde L, et al. Changes in vitamin D metabolites and bone histology in rats during recovery from rickets. Calcif Tissue Int 1985;37:478-83.
[29] Rennie LM, Beattie TF, Wilkinson AG, Crofton P, Bath LE. Incidental radiological diagnosis of rickets. Emerg Med J 2005;22:534-7.
[30] Hatun2 S, Islam Ö, Cizmecioglu F, Kara B, Babaoglu K, Berk F, et al. Subclinical vitamin D deficiency is increased in adolescent girls who wear concealing clothing. J Nutr 2005;135:218-22.
[31] Zeghoud F, Vervel C, Guillozo H, Walrant-Debray O, Boutignon H, Garabedian M. Subclinical vitamin D deficiency in neonates: definition and response to vitamin D supplements. Am J Clin Nutr 1997;65:771-8.
[32] Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of the effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on estrogen with osteoporosis. Lancet 1997; 350:550-5.
[33] Reeve J, Bradbeer JN, Arlot M, et al. hPTH 1-34 treatment of osteoporosis with added hormone replacement therapy: biochemical, kinetic, and histological responses. Osteoporosis Int 1991;1:162-70.
[34] Siam A, Rahim M, Hammoudeh M, Albari B, Izzat KA, Sarakbi H, et al. Vitamin D deficiency in Qatar. APLAR J Rheumatol 2006;9 (Suppl 1):A32-3.
[35] Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of vitamin D deficiency. Arch Dis Child 2004;89:781-4.