Editorial

Adaptation to vitamin D deficiency: Age specific clinical presentations

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Vitamin D (VD) seems to have taken center stage in not only endocrine, but all medical, literature, in recent years. An enhanced understanding of the extra-skeletal actions of VD, elucidation of its autocrine and paracrine effects, and the heliophobic life-style followed by many cultures, such as in the Middle East and South Asia, have contributed to this. At the same time; however, the classic antirachitic effects of VD so important for growth in children, seem to have been neglected. This editorial highlights the age specific clinical presentations, including subtle symptoms and signs, noted in different pediatric age groups, and correlates this with the adaptive response to VD deficiency.

VD is critical for calcium (Ca) homeostasis and for mineralization of the skeleton, especially during periods of rapid growth, namely infantile and pubertal growth periods. Vitamin D deficiency (VDD) leads to rickets (a mineralization defect at the epiphyseal growth plates and bone tissue) and osteomalacia (a mineralization defect of bone tissue).[1]

The development of clinical manifestations of VDD rickets is dependent on many factors apart from the severity and duration of the VDD (circulating concentrations of 25-hydroxy vitamin D [25-OH-D]) [Table 1]. A potent adaptation process, mediated by parathormone (PTH) and insulin-like growth factor-I (IGF-I),[2-9][1] modifies the clinical and radiological manifestations of VDD. Therefore, overt cases of rickets and osteomalcia represent only the tip of the iceberg of patients with severe VDD and malfunction of adaptation.[2,10,11] It is noteworthy that when clinical rickets develops, the entire process occurs rapidly, within a few months.[12]

Table 1: Factors influencing clinical presentation of VDD

Severity of VDD (circulating concentrations of 25-hydroxy vitamin D)
Duration of VDD
Calcium demand (speed of growth)
Calcium intake and absorption
Balance between osteoblastic and osteoclastic activities
Balance between kidneys, gut, bone, parathormone and insulin-like growth factor-I

VDD: Vitamin D deficiency

Physiologic Adaptation

Without VD, only 10-15% of dietary Ca and about 60% of phosphorus is absorbed. The active form, 1,25-dihydroxy vitamin D (1,25-(OH) 2D3) markedly increases the efficiency of intestinal Ca and phosphorus absorption.[2-6] Serum levels below 30 ng/ml are associated with a significant decrease in intestinal Ca absorption. In children, adolescents, and adults; this is associated with increased PTH and deceased IGF-I secretion. Serum levels of 25-OH-D are directly related to bone mineral density with a maximum density achieved when the 25-OH-D level reached 40 ng/ml or more.[2-8]

PTH enhances the tubular reabsorption of Ca and stimulates the kidneys to produce 1,25-(OH) 2D3.[3-6] It also activates osteoblasts, which stimulate the transformation of preosteoclasts into mature osteoclasts.[3-6] Osteoclasts dissolve the mineralized collagen matrix in bone, causing osteopenia and osteoporosis[12-15] and provide enough Ca to prevent hypocalcemia.

There is a bidirectional link between IGF-I and VD, which is played out in different forms at the systemic (circulating)

[1]It is well appreciated that overt cases of rickets represent only the tip of the iceberg of infants and children with VDD.[30,31]

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and the local (growth plate) level. Systemically, IGF-I stimulates the production of 1,25-(OH) 2D3 by kidney cells independently of growth hormone (GH).[16-19] IGF-I stimulates bone formation, even in absence of GH, through an intrinsic action on osteoblasts. It supports proliferation, differentiation and matrix synthesis in cultures of osteoblast-like cells and bone organ cultures. It potently stimulates the production of type I collagen (the main structural protein of bone) and increases pro-collagenα1 (I) mRNA expression both in osteoblasts *in vitro* and in bone *in vivo*.[20-22] Lack of IGF-I, therefore, may impact skeletal health adversely.

Locally in the growth plate, 1,25-(OH) 2D3 potentiates local IGF-I synthesis in chondrocytes and stimulates cell proliferation and differentiation as judged by increased alkaline phosphatase (ALP) activity, collagen X mRNA, and matrix calcification in long-term experiments. 1,25-(OH) 2D3 stimulates chondrocytes proliferation and cell differentiation.[23] In rats 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.[24]

Pathophysiologic Adaptation in VDD

Consequently, during VDD decreased circulating and locally produced IGF-I in children appears to be a gradual adaptive process to inhibit linear growth (in growth plate) and bone mineral accretion (diaphysis). 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 consuming them in forming new bones. In addition, decreased circulating and locally produced IGF-I concentrations can 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 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). In addition, low IGF-I may also allow the catabolic effect of PTH necessary for effective release of Ca and explains the osteoporotic appearance of the diaphysis in rachitic children.[2,22-25]

Clinical Rickets in Children

Only a small number of infants, toddlers, adolescents, and adults with VDD develop clinical manifestations of rickets or osteomalacia, depending on the severity, duration, and adaptive responses of VDD.[2,10,11,26]

The typical clinical picture of rickets in children 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.[2-6,9] 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.[2-5,12]

Hierarchy of Abnormalities

In infants and toddlers, three sequential clinical (biochemical-hormonal-radiological) stages have been described [Table 2].[2]

The influence of adaptive mechanisms, mediated by PTH and IGF-I, can easily be noticed in the various stages of VDD. Radiological and biochemical abnormalities correspond well to hormonal changes noticed with VDD.

An analysis of growth with biochemical and radiological data of rachitic patients presenting with hypocalcemia (dysadapted) versus those with normocalcemia (adapted) supported this concept of adaptation [Table 2].

Growth Impairment in Rickets

Rickets is associated with growth impairment in infants and young children. Many factors contribute to impaired linear growth in these children with VDD [Table 3]. Marked improvement of linear growth with complete catch-up growth has been shown with proper treatment with VD.[5,10,13,22-29]

Clinical Rickets in Adolescents

In adolescents, presentation of severe and/or prolonged VDD markedly differs from young children. They present with vague manifestations including pain in weight bearing joints, back, thighs and/or calves, difficulty in walking and/or climbing stairs and/or running, muscle cramps, facial twitches and carpo-pedal spasms. Compared to children with VDD, adolescents have higher serum Ca, PO_4 and IGF-I concentration and lower PTH and ALP concentrations. Radiological changes are less frequent and less significant compared to children with rickets. These data denote better adaptation to VDD in adolescents compared with young children. This better adaptation in adolescents can be explained by their relatively larger bone

Table 2: Hierarchy of abnormalities in rickets

Stage	Biochemistry	Radiology	Adaptive response: IGF-1	Adaptive response: PTH
I (adapted)	Serum Ca and PO_4 concentration are normal, with mildly elevated PTH and ALP concentration	Near-normal epiphyseal and metaphyseal calcification without cupping or fraying with mild broadening of the joint space and normal diaphyseal thickness	Mild-moderate decrease in IGF-I production slows down linear growth at epiphyseal plate through slowing down chondrocyte maturation to the hypertrophic stage, slowing down calcification, and economizing use of Ca	Moderate and/or intermittent increase of PTH stimulates renal 1α (OH) 2D3 production, increases Ca absorption from gut, and maintains normal serum Ca concentration
II (less adapted)	Normal serum Ca, low serum PO_4 concentrations, high PTH and ALP (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 decreased metaphyseal and diaphyseal calcification leading to decreased linear growth	IGF-I decreases further with more slowing of bone growth	Persistently high PTH mediates significant osteoclastic activity on the bones to maintain normal serum Ca concentration. Hypophosphatemia occurs because of the phosphaturic effect of continuously elevated PTH, which further compromises mineralization of the growth plate and bones
III (dysadapted)	Serum Ca and PO_4 concentrations are low with considerably high PTH and ALP	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 sub-periosteal erosion of shafts and complete arrest of linear growth	Significantly low IGF-I, associated with very slow or arrested bone growth)	Failure of adaptive mechanism (high PTH) and significant exhaustion of bone hydroxyapatite lead to hypocalcemia

PTH: Parathormone, ALP: Alkaline phosphatase, IGF-I: Insulin-like growth factor-I

Table 3: Factors contributing to growth retardation in rickets

Defective mineralization and increased size of the hypertrophic layer of the growth plate with the deposition of excessive osteoid (in 100% of patients)
Deformities of the long bones of the lower limbs with bowing of both femur and tibia due to weakening of the shafts
Hypotonia (of the back muscles and ligaments) with tendency to postural kyphosis or kyphoscoliosis
Possible effect of vitamin D deficiency on growth hormone/insulin-like growth factor-I axis
Repeated infections probably due to the lack of vitamin D effect on immune system with subsequent effect on the nutritional status of the infant

mass (Ca and PO_4 stores) and lower requirement for Ca and PO_4/kg, due to relatively slower growth rate compared with infants and young children.[30,31]

Two different radiological patterns of severe VDD in adolescents have been detected. Pattern (I), with localized metaphyseal multilocular cystic lesions, occur in overweight adolescents with good intake of milk/milk products. Adolescents with pattern (I) appear to have better adaptation to VDD because of maintaining near-normal bone architecture of the cortex of long bones (better bone mass) and having higher serum PO_4 concentrations and absence of hypocalcemia episodes. Whereas pattern (II), with generalized diminished bone density, occurs in adolescents with relatively lower body mass index (BMI) (<18), with no or poor intake of milk and lower IGF-I versus those with pattern (I). The higher fat mass (BMI >25), IGF-I concentrations and consumption of milk (better Ca and phosphate intake) support better adaptation in adolescents with pattern (I). All these three factors have been shown to maintain bone density in children and adolescents.[30-36]

Clinical Rickets in Newborns

In newborns, the clinical and radiological manifestations of severe VDD newborns are scantily described. Deficient maternal VD status has been shown to be associated with lower birth weight, higher small for gestational age (SGA) risk and altered neonatal growth, both in weight and in length. Severe VDD in newborns usually present with hypocalcemia and hypocalcemic symptoms (dysadaption) including seizures; without significant rachitic changes apart from craniotabes. Radiologically minimal or no changes have been describes despite decreased mineralization detected by bone density scan. The poor adaptation of newborns to VDD, compared to older infants and toddlers, can be explained by their lower PTH secretion in response to hypocalcemia, decreased skeletal response to PTH, and decreased bone mass.[37-42]

Conclusion

In summary, clinical presentation of severe VDD markedly differs during the different stages of growth. Newborns appear to be less adapted whereas adolescents are better adapted to VDD. Pediatricians and physicians have to be aware about the variability of these different clinical presentations for proper diagnosis and management. While the concern of physicians about VDD in adults is mainly focused on the extra-skeletal manifestations, endocrinologists must not neglect the core biological skeletal effects of VDD, in the pediatric age group, the ones who need it the most.

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