

## Brief Report

# Manifestations of Severe Vitamin D Deficiency in Adolescents: Effects of Intramuscular Injection of a Megadose of Cholecalciferol

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## Summary

We recorded the manifestations of severe vitamin D deficiency (VDD) in 40 adolescents before and 3 and 6 months after treatment with a mega dose of cholecalciferol (10 000 IU kg<sup>-1</sup>, max 600 000 IU). Significant improvement of symptoms related to VDD was reported in 34/40. Three months after the injection, serum calcium, phosphate, alkaline phosphatase and parathormone were normal in all adolescents with VDD with 25-hydroxyvitamin D (25OHD) level = or >20 ng ml<sup>-1</sup>. After 6 months, the majority had 25OHD level <20 ng ml<sup>-1</sup>. Two patterns of radiological changes have been recorded with complete healing achieved in all patients after a year of therapy. A mega dose of cholecalciferol is an effective therapy for treatment of VDD in adolescents for 3 months but not for 6 months. Radiographs of the ends of long bones are still valuable tool for diagnosis and follow-up of these patients.

**Key words:** Vitamin D Deficiency (VDD), adolescents, radiology.

## Introduction

High prevalence of vitamin D deficiency (VDD) is reported from all over the world even in sunny places especially during the winter [1, 2]. Vitamin D is important for musculoskeletal health, particularly in girls during pubertal growth. Optimal intestinal Ca absorption occurs at a serum 25-hydroxyvitamin D (25OHD) concentration of approximately 32 ng ml<sup>-1</sup>. VDD leads to secondary hyperparathyroidism and increased bone turnover. The clinical spectrum ranges from subclinical to frank deficiency with levels <20 ng dl<sup>-1</sup> [1–8]. In prolonged and/or severe cases, manifestations of rickets/osteomalacia evolve [9, 10]. Asymptomatic adolescents with VDD have high risk of developing hyperparathyroidism with failure to achieve peak bone mass, bone loss and increased risk of fractures [1, 4, 8, 11].

The aims of this study were to investigate the magnitude of VDD in a random sample of adolescents, describe the clinical picture in adolescents with severe VDD (25OHD <10 ng ml<sup>-1</sup>) and monitor the effects of treatment with a mega dose of intramuscular (IM)

cholecalciferol. Forty children with severe VDD were used as controls.

## Patients and Methods

In this prospective study, 100 adolescents attending the general practitioner (GP) clinic for checkup were randomly selected to assess the prevalence of VDD. Those with severe VDD (25OHD <10 ng ml<sup>-1</sup>) were referred to the Endocrine Clinic at Hamad Medical Centre, Doha, Qatar, between October 2005 and October 2006. Detailed history taking and full clinical examination were performed. Laboratory investigations included measuring serum creatinine, Ca, PO<sub>4</sub>, insulin-like growth factor-I (IGF-I) [radioimmunoassay (RIA)], 25OHD (RIA) and parathormone (PTH) (intact molecule) (RIA) concentrations. A routine radiological film of the wrist or knee was obtained. Patients with VDD were treated with an intramuscular injection of cholecalciferol [10 000 U kg<sup>-1</sup>, max 600 000 IU (15 mg)]. During each clinic visit, every 2–3 months, the anthropometric and radiological parameters were reassessed and recorded and the laboratory tests repeated.

## Results

In 100 randomly selected adolescents (60 females, 40 males), 62 had VDD (25OHD  $<20$  ng ml $^{-1}$ ) and 40 had severe VDD (25OHD  $<10$  ng ml $^{-1}$ ). They presented with pain in weight bearing joints, back, thighs and/or calves (32/40), difficulty in walking and/or climbing stairs and/or running (9/40), muscle cramps (12/40), facial twitches (4/40) and carpo-pedal spasms (2/40).

Serum PO4 concentration was significantly lower and PTH and alkaline phosphatase (ALP) concentrations higher in children vs. adolescents with VDD (Table 1). One mega dose injection maintained serum 25OHD levels at normal level ( $>20$  ng ml $^{-1}$ ) and achieved significant improvement of symptoms in 37/40 for 3 months. IGF-I concentrations increased significantly after treatment and were correlated significantly with 25OHD concentrations in all the patients ( $r=0.61$ ,  $P<0.001$ ). Significant inverse correlation was detected between serum 25OHD and PTH concentrations ( $r=0.447$ ,  $P<0.01$ ). Serum creatinine levels and 2 h urine calcium/creatinine excretion index remained normal in all patients throughout the study.

In 26/40 adolescents with severe VDD, two radiological patterns have been identified. In pattern (I) ( $n=8$ ), the lesions appear as metaphyseal multilocular cystic lesion with sclerotic margins, located subcortically without significant cortical erosions, periosteal reaction, osteoporosis or other metaphyseal manifestations. Whereas pattern (II) ( $n=18$ ) appears as generalized diminished bone density with prominent primary and secondary bone trabeculations, widening of the metaphyseal zone with relatively more lucency (loss of all bone trabeculations). No cupping or fraying of the metaphyses was identified (Fig. 1).

TABLE 1  
Laboratory data for adolescents with VDD before vs. after treatment

Adolescents with VDD	Before treatment, $n=40$	After treatment, $n=40$
	Mean $\pm$ SD	Mean $\pm$ SD
PO4 mmol l $^{-1}$	1.4 $\pm$ 0.5	1.7 $\pm$ 0.4*
Ca mmol l $^{-1}$	2.1 $\pm$ 0.3	2.3 $\pm$ 0.1*
ALP U l $^{-1}$	404 $\pm$ 212	212 $\pm$ 69*
25OHD ng ml $^{-1}$	9.3 $\pm$ 4.6	27.7 $\pm$ 9.2*
PTH pg ml $^{-1}$	122.9 $\pm$ 55.5	24.8 $\pm$ 9.58
IGF-I (ng ml $^{-1}$ )	166 $\pm$ 45	203 $\pm$ 55*

\* $p<0.05$  after vs. before treatment.

## Discussion

The prevalence of severe VDD (40%) appears to be high. Adolescents (26/40) with 25OHD level  $<10$  ng ml $^{-1}$  have radiological evidence of VDD with elevated serum PTH and ALP levels and reduced serum phosphate. Children with VDD showed significantly higher ALP and PTH levels and higher incidence of hypocalcemia compared with adolescents with VDD. In addition, the radiological signs of rickets were less prominent in adolescents vs. children with VDD. These data denoted better adaptation to VDD in adolescents compared with young children. Adaptation is mediated through increased PTH and reduced IGF-I. Increased PTH stimulates alpha hydroxylation of vitamin D with more calcium and PO4 absorption from the gut and induces osteoclastic activity to maintain normocalcemia. Low IGF-I decelerates linear growth and decreases calcium use in bones. In addition, low IGF-I level permits the catabolic action of PTH on the bone. Better adaptation in adolescents can be explained by their relatively larger bone mass (Ca and PO4 stores) and lower requirement for calcium and PO4 kg $^{-1}$  due to relatively slower growth rate compared with infants and young children [12].

Complete healing of the radiological signs of rickets was achieved in the majority (24/26) of adolescents within 6–12 months (Fig. 1). A study of bone histomorphometric changes in 28 patients with osteomalacia treated with vitamin D and calcium showed a significant reduction in osteoid volume and an increase in mineralized bone volume in cortical and trabecular bone after therapy [13]. A meta-analysis showed significant increases in lumbar spine bone mineral density after a year of therapy [14].

Two different radiological patterns of severe VDD in adolescents ( $n=26$ ) have been detected. Pattern (I), with localized metaphyseal multilocular cystic lesions, occurred in overweight adolescents with good intake of milk/milk products. Whereas pattern (II), with generalized diminished bone density, occurred in adolescents with relatively lower body mass index (BMI) ( $<18$ ), with no or poor intake of milk and lower IGF-I vs. those with pattern (I). 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 PO4 concentrations and absence of hypocalcemic episodes (two patients with pattern II had symptomatic hypocalcemia). This can be explained by their higher fat mass (BMI  $>25$ ), IGF-I concentrations and consumption of milk (better calcium and phosphate intake). All these factors have been shown to maintain bone density in children and adolescents [15–18] (Table 2).

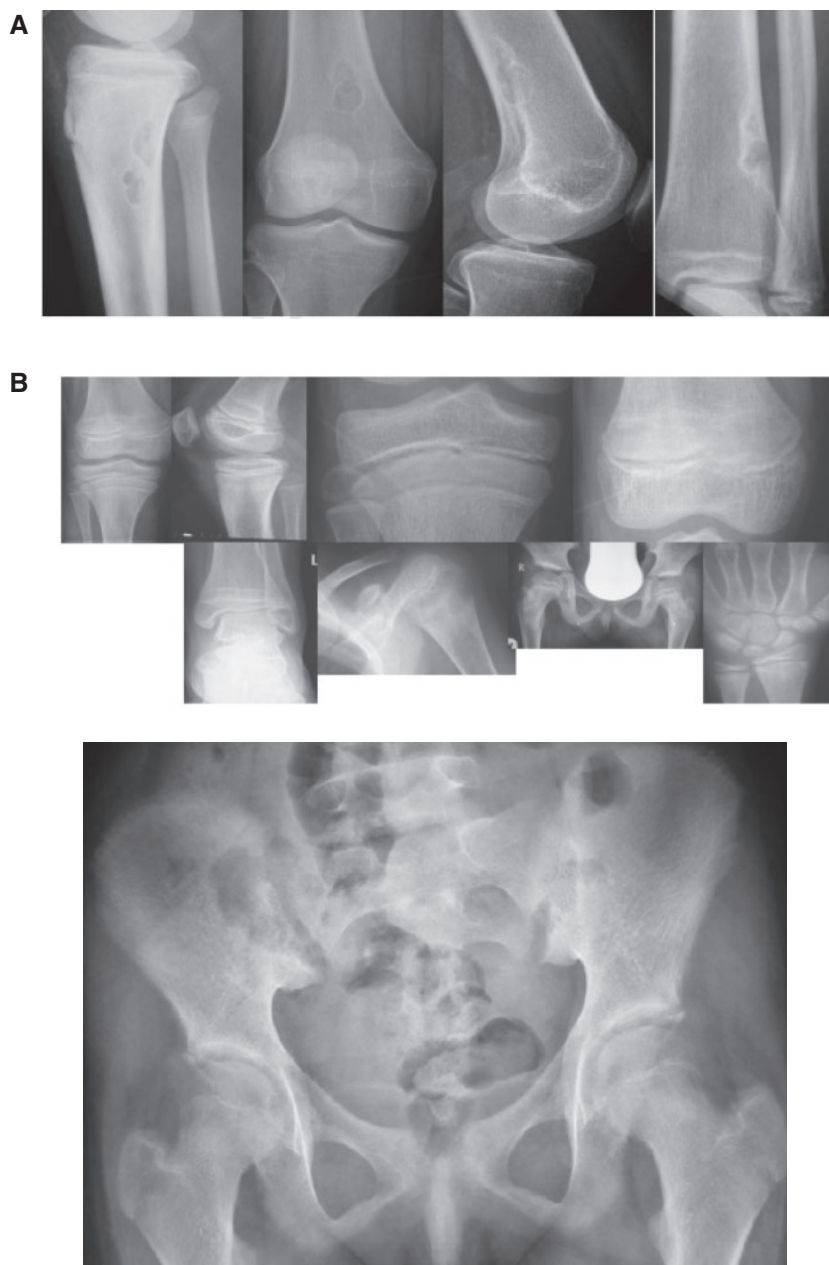


FIG. 1. (A–C) Radiological changes in adolescents with VDD. (A, pattern I) With metaphyseal multilocular cystic lesions which have sclerotic margins at subcortical location without significant cortical erosions, periosteal reaction, osteoporosis or other metaphyseal manifestations. (B, pattern II) With generalized diminished bone density with widening and significant lucency (zone of poor ossification) of the metaphyseal zone with rather loss of all bone trabeculation and osteoporosis of the diaphysis of long bones and the apophyses of ischial bone and iliac. (C) Radiological changes before vs. 6 months after treatment in an adolescent.

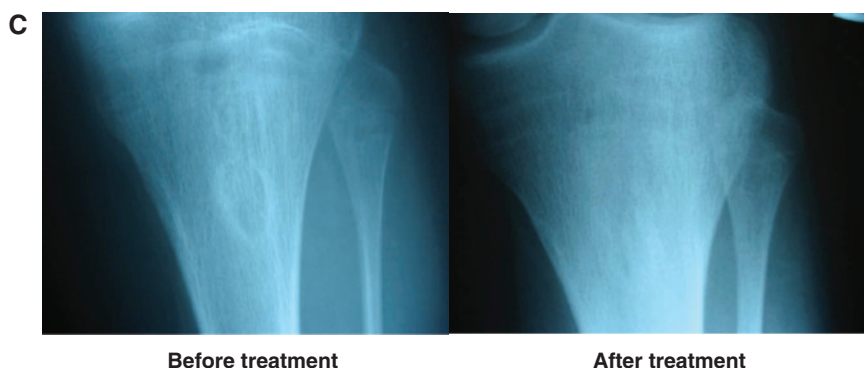


FIG. 1. Continued.

TABLE 2  
 Characteristics of adolescents with VDD with different  
 radiological patterns

Adolescents	With pattern (I), n = 8	With pattern (II), n = 18
Age (years)	14.2 ± 2.7	14.5 ± 3.1
BMI	27.3 ± 2*	16.8 ± 1.5
PO4	1.5 ± 0.15*	1.35 ± 0.18
Ca	2.2 ± 0.16	2.05 ± 0.38
ALP	456 ± 98*	375 ± 101
25OHD	8.9 ± 1.5	9.3 ± 1.2
PTH	119 ± 52	129 ± 46
IGF-I (ng ml <sup>-1</sup> )	199 ± 78*	142 ± 56

\* $p < 0.05$  pattern I vs. pattern II.

In conclusion, even in sunny climates, adolescents may be at risk of VDD. A mega dose of cholecalciferol is an effective therapy for the treatment of VDD in adolescents for 3 months.

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