Kadhim et al., Pediatr Therapeut 2011, 1:2
DOI: 10.4172/2161-0665.1000103

Pediatrics & Therapeutics
ISSN: 2161-0665

Research Article Open Access

Vitamin D Status in Pediatric Patients with Osteogenesis Imperfecta

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Abstract

Osteogenesis Imperfecta (OI) is a heterogeneous genetic disorder causing skeletal fragility. Although there is increasing awareness about the important role of vitamin D in pediatric bone health, specific data regarding vitamin D status are limited and sometimes unavailable in children with musculoskeletal disorders, such as OI. In this study, we aimed to examine the prevalence of vitamin D deficiency, insufficiency and sufficiency in children with OI. We used a retrospective cohort (case-only) study of 61 children diagnosed with OI. The study variables were analyzed using descriptive statistics. 25-hydroxyvitamin D serum levels less than 20 ng/ml were considered deficient, levels between 20–32 ng/ml were considered insufficient, and levels more than 32 ng/ml were considered sufficient. Sixty one patients (31 boys, 30 girls) were classified according to Sillence type (type I, n = 31; type III, n = 14; and type IV, n = 16). Overall, vitamin D insufficiency and deficiency were identified in approximately half of the patients (50.9%). Vitamin D sufficiency was observed in the majority of infants and toddlers from birth to 3 years (n=13, 56.5%) and in children aged 4–10 years (n=12, 57.1%). A minority of children over the age of 10 were vitamin D sufficient (n=5, 29.4%). The majority of Caucasian patients (n=26, 54.2%) were vitamin D sufficient. Sufficient vitamin D levels were more prevalent among type I OI patients (n =19, 61.3%). Type III patients were found to have an equal prevalence of vitamin D insufficiency (n=6, 42.9%) and sufficiency (n=6, 42.9%). Vitamin D insufficiency was most prevalent in type IV (n=8, 50). Patients with an elevated BMI had a higher prevalence of vitamin D insufficiency (n=4, 57.1%). Further studies are recommended to clarify the relationship between vitamin D serum level and BMI in OI patients.

Keywords: Osteogenesis Imperfect; Vitamin D deficiency; Insufficiency; Sufficiency; Prevalence

Abbreviations: OI: Osteogenesis Imperfecta; [25(OH)D]: 25-hydroxy vitamin D; BMI: Body Mass Index

Introduction

Osteogenesis Imperfecta (OI) is a heterogeneous genetic disorder causing skeletal fragility ranging from in utero death due to multiple fractures, to an average lifespan with severe osteoporosis and other extra-skeletal manifestations [1,2]. Typically, OI is caused by mutations in the Collagen I α1 or α 2 genes [1,2]. Type I collagen is the major structural protein found in bone and mutations can lead to a decreased amount of normal protein or an abnormal protein in the matrix [3]. Sillence and Rimoin [4] classified OI into four distinct types based on both clinical and radiographic characteristics. Patients with type I OI have the mildest and most common form of the disease. Although some fractures may be present at birth, fractures in this group begin classically in the toddler period when ambulation begins [1,2]. Type II OI is lethal in the perinatal period as a result of multiple rib fractures and respiratory insufficiency [1,2]. Type III OI is a severe form of OI with fractures and skeletal deformity being present at birth. Repeated low energy fractures occur and are associated with progressive skeletal deformity [1,2]. Type IV OI is a moderate form of the condition with fractures often present at birth, but typically the number and severity of fractures are less than type III, although skeletal deformity resulting from the fractures is uniform [1,2]. Treatment of all patients with type III, IV and some patients with type I OI with pamidronate disodium has been recommended [5,6]. The incidence of OI is estimated to be approximately 1 in 10,000 live births with type I by far and away being the most common [2]. There are now other rare forms of OI which have been described using additional clinical, histomorphometric, and genetic criteria [2].

Over the last decade, there has been increasing awareness of the role of vitamin D in bone health. The role of vitamin D has been studied at all ages of the life cycle [7], with specific attention given to pediatric patients, ranging from fetuses in utero [8], to infants and toddlers [9], children [10-12] and adolescents [13]. Humans get vitamin D from skin exposed to sunlight, from their diet and from dietary supplements [14]. This vitamin D is metabolized in the liver to 25-hydroxyvitamin D [25(OH) D] which is used to determine a patient's vitamin D status [14]. Although there is no clear consensus on optimal levels of 25(OH) D as measured in serum, most experts agree that a level of 20 ng/ml or less is vitamin D deficiency [14]. The 25 (OH) D level which determines sufficiency is less clear and remains open for debate [7,15,16]. For our purposes, we will select a 25(OH) D level of more than 32 ng/ml as sufficient, as defined by Hollis [15]. Levels between 20 and 32 are then said to be insufficient. Specific data suggest that vitamin D insufficiency was observed in 80% of children with osteopenia or osteoporosis referred to a metabolic bone clinic [11]. There is, however, a paucity of published data assessing vitamin D status in pediatric OI patients. Two very recent publications by the same group exploring vitamin D status in an OI population seemed to demonstrate a positive association between 25(OH) D levels and lumbar spine areal bone mineral but no clear evidence of association between other markers of bone mineralization, bone metabolism or bone mass in children with OI. [17,18] The primary aim of this study was to determine the prevalence of vitamin D sufficiency, insufficiency and deficiency in pediatric patients with OI upon their entry into the OI clinic. Given the

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Received August 21, 2011; **Accepted** November 12, 2011; **Published** November 13, 2011

Citation: Kadhim M, Holmes L, Bober MB, Rogers KJ, Kallur A, et al. (2011) Vitamin D Status in Pediatric Patients with Osteogenesis Imperfecta. Pediatr Therapeut 1:103. doi:10.4172/2161-0665.1000103

rarity of OI, the small number of children available for study and our treatment of any deficiency or insufficiency with supplementation, our secondary goal was to examine the data for possible trends which could provide insight into this unique patient population.

Materials and Methods

Study design, sample size and population

After receiving approval from the Nemours Delaware Institutional Review Board, we conducted a retrospective study to assess the initial vitamin D status among our patients with OI. The diagnosis and type of OI was confirmed by a medical geneticist. Between 2003 and 2010, there were 61 pediatric patients evaluated and diagnosed with a form of OI. To be eligible for inclusion in this study, all participants needed to have at least one 25(OH) D level. To estimate the power of the study, we used sample size (n= 61), type 1 error = 0.05 (5%) and the effect size at 0.02 (20%). With these parameters, we obtained a power of 28%, which is insufficient to examine the difference between vitamin D categories (sufficient, insufficient, and deficient) and other variables such as sex, age, and Sillence type. As result of this power insufficiency, we used descriptive statistics to scribe our sample.

Clinical and laboratory data collected

Medical records were reviewed and data extracted included: Type of OI, sex, age, race, height/length, weight, fracture history and status of treatment with bisphosphonates. Laboratory data values collected included: serum calcium, phosphorus, and 25(OH) D levels. Individual laboratory reference norms and the dates of blood collection were also obtained.

Statistical analysis

All analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL). We checked for missing data before the analysis. Descriptive statistics (frequencies and percentages) were used to assess the study characteristics. To assist in analysis, we categorized our patient into three groups based upon their 25(OH) D levels: vitamin D sufficient (> 32 ng/ml), vitamin D insufficient (20–32 ng/ml), and vitamin D deficient (< 20 ng/ml). Furthermore, body mass index (BMI) was calculated and compared with Center for Disease Control and Prevention growth charts [19-21]. We categorized our patients into three BMI groups: appropriate (5% to 95%), underweight (< 5th percentile), and overweight (> 95th percentile). This same approach was used to examine the prevalence of vitamin D using study variables.

Results

The characteristics of our OI patient population are presented in Table 1. Of the 61 patients, there were 31 boys and 30 girls. The mean age of our patients was 7.2 ± 5.8 years. Sillence type I classification was the most prevalent subtype in our sample (50.8%) followed by type IV (26.2%) and type III (23%). Most patients (65.9%) were in the normal BMI range; however, BMI was not available in some, particularly those who were younger than 2 years. A review of the records demonstrates that when standing height measurement could not be obtained due to deformity or inability to stand, length was measured instead of height. Overall, vitamin D insufficiency and deficiency were identified in approximately half of the patients (50.9%). Although data were not available for calcium serum levels for some patients, a large proportion of our patients had a normal calcium serum level (n = 38, 97.4%). The phosphorus serum levels were also normal in our sample; however, this information was unavailable in 25 patients. In our sample, 62.8%

Variable		n (%)
Sex		
	Boys	31 (50.8)
	Girls	30 (49.2)
Age (years)		
	0–3 years	23 (37.7)
	4–10 years	21 (34.4)
	> 11 years	17 (27.9)
Race		
	Caucasian	48 (78.7)
	Asian	1 (1.6)
	Black	4 (6.6)
	Other	8 (13.1)
Sillence type		
	I	31 (50.8)
	III	14 (23.0)
	IV	16 (26.2)
BMI[ε]		
	Low (< 5%)	7 (17.1)
	Normal (5%–95%)	27 (65.9)
	High (> 95%)	7 (17.1)
Vitamin D level		
	Deficient (< 20 ng/ml)	9 (14.8)
	Insufficient (20–32 ng/ml)	22 (36.1)
	Sufficient (> 32 ng/ml)	30 (49.1)
Calcium serum level[†]		
	Normal	38 (97.4)
	High	1 (2.6)
Phosphorus serum level[‡]		
	Normal	33 (91.7)
	High	3 (8.3)
Pamidronate treatment		
	With treatment	38 (62.3)
	Without treatment	23 (37.7)
Fracture (during study period)		
	Less than 10	29 (47.5)
	More than 10	32 (52.5)

Notes and abbreviation: n = number of patients. [ε] Body mass index (BMI): 5 patients with missing height/length data and 15 patients were younger than two years. [†] Twenty-two patients with no calcium serum level evaluation done with vitamin D level evaluation. [‡] Twenty-five patients with no phosphorus serum level evaluation done with vitamin D level evaluation.

Table 1. OI Patient Population Characteristics.

were treated with pamidronate disodium. Our study was insufficiently powered to detect statistical significance between any of the above characteristics. Assessments of the initial vitamin D levels were performed in 2003 (n=2, 3.3%), 2005 (n=1, 1.6%), 2006 (n=13, 21.3%), 2007 (n=12, 19.7%), 2008 (n=18, 29.5%), 2009 (n=9, 14.8%) and 2010 (n=6, 9.8%).

Table 2 characterizes the patients vitamin D status by the study variables, including sex, age, race, Sillence type, BMI, fracture count, pamidronate treatment, and the season in which the 25(OH) D level was obtained. The total number of girls who were vitamin D deficient was 6, while 3 boys were deficient. Vitamin D sufficiency was observed in the majority of infants and toddlers from birth to 3 years (n=13, 56.5%) and in children aged 4–10 years (n=12, 57.1%). A minority of children over the age of 10 were vitamin D sufficient (n=5, 29.4%). The majority of Caucasian patients (n=26, 54.2%) were vitamin D sufficient. Results of the vitamin D status by Sillence type are displayed graphically in Figure 1. Sufficient vitamin D levels were more prevalent

among type I OI patients (n =19, 61.3%). Type III patients were found to have an equal prevalence of vitamin D insufficiency (n=6, 42.9%) and sufficiency (n=6, 42.9%). Vitamin D insufficiency was most prevalent in type IV (n=8, 50%). A normal BMI was observed at a higher prevalence in patients with a sufficient level of vitamin D (n =16, 59.3%; Figure 2) while patients with an elevated BMI had a higher prevalence of vitamin D insufficiency (n=4, 57.1%). Patients who had fewer than 10 fractures had a higher prevalence of sufficient vitamin D levels (n = 17, 58.6%); of these, 16 were type I.

Discussion

The primary aim of this study was to determine the prevalence of vitamin D sufficiency, insufficiency and deficiency in pediatric patients with OI upon their entry into the OI clinic. Given the rarity of OI, the small number of children available for study and our treatment of any deficiency or insufficiency with supplementation, our secondary goal was to examine the data for possible trends which could provide insight into this unique patient population. We recognized early on in our research that this study was insufficiently powered to detect statistical significance between any of the studied patient characteristics. Despite this, we believe that in this unique patient population, any information learned could prove helpful in patient care. Although there has been extensive study of vitamin D in bone health at many life stages, there is no clear consensus on optimal levels of 25(OH) D as measured in serum [7-14]. Most experts do agree however, that a level of 20 ng/ml or less is vitamin D deficiency [14]. The 25(OH) D level which determines sufficiency is less clear and remains open for debate [7,15,16]. For our purposes we selected a 25(OH) D level of more than 32 ng/ml as sufficient [15]. Levels between 20 and 32 are then said to be insufficient.

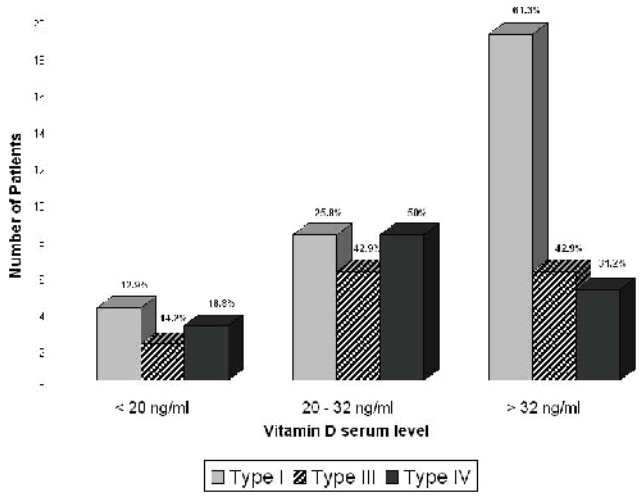

Figure 1: The distribution of vitamin D serum levels by Sillence classification among pediatric patients with osteogenesis Imperfecta (OI).

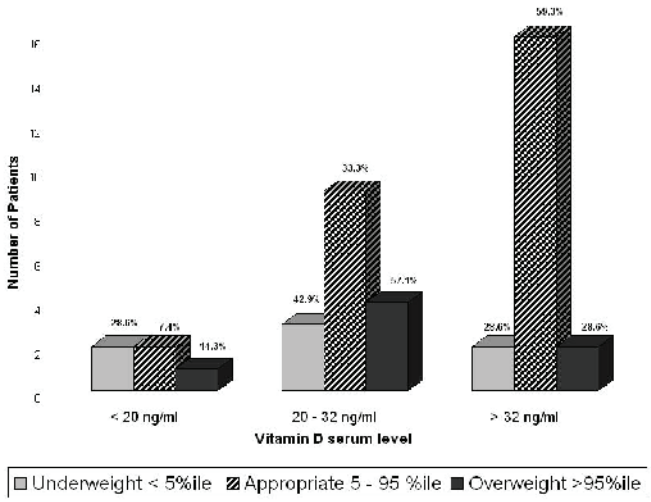

Figure 2: The distribution of vitamin D serum levels by body mass index (BMI) among pediatric patients with osteogenesis Imperfecta (OI).

In our cohort, there did not appear to be any difference in vitamin D sufficiency between boys (n=15, 48.4%) and girl (n=15, 50.0%). Children older than 11 years of age appeared less likely to be sufficient when compared to either children under 3 years or between 4 and 10 years. Patients with type I OI were more likely to have sufficient levels of vitamin D (See Table 2 and Figure 1). Type I patients, have the mildest form of OI and in general, would be more likely than patients with type III or IV OI to be outdoors and therefore more likely to have exposure to sunlight. The BMI value can be considered a reliable test for a direct measure of body fat in children and adolescents [22]. As vitamin D is a fat-soluble vitamin, high BMI has been linked to vitamin D insufficiency [23]. A similar study observed improvement in vitamin D serum levels with weight loss [24]. The BMI calculation in some of our patients was problematic due to skeletal deformity or the inability to bear weight. When possible, length was measured as used as a surrogate for height. In our cohort, vitamin D insufficiency or deficiency (n=5, 71.4%) was more likely than sufficiency (n=2, 28.6%) in children with a BMI more than 95th percentile (See Table 2 and Figure 2). These results seem to support previous research indicating an association between vitamin D deficiency and an increased BMI [23,24]. Given the limitations of BMI as a direct estimate for body fat and the limitations of its calculation in our population, this should be interpreted with caution. Fracture count stratified by vitamin D status is difficult to interpret, due to the differences in the age at presentation and type of OI. Larger numbers of patients need to be assessed before even a trend might emerge.

Treatment of all patients with type III, IV and some patients with type I OI with pamidronate has been recommended [5,6] and a significant number of our patients are on pamidronate therapy. There is no well described mechanism by which Pamidronate affects vitamin D metabolism. In addition to possible bisphosphonate therapy, all children with OI in our clinic have dietary calcium intake and 25(OH) D levels assessed at regular intervals. The practice in our clinic has been to treat vitamin D deficiency or insufficiency with a dietary vitamin D supplement to achieve levels in the 30-40 ng/ml range; this is a major reason why this study assessed initial levels. While we recognize the new recommendations for increased vitamin D intake [7], and do think it is likely to help the overall population to achieve vitamin D sufficiency, the effectiveness of these recommendations in this OI population remains to be seen. Patients with types III and IV OI are often diagnosed in utero or at birth and, as such, their initial vitamin D status is likely more reflective of their mother's status than their dietary intake. In our older, more severely affected patients, use of dietary supplements is very common, and in our experience, daily supplementation of 1000-2000 International Units is necessary to achieve sufficiency.

Variables	Vitamin D Range		
	< 20 ng/ml	20 to 32 ng/ml	> 32 ng/ml
	n (%)	n (%)	n (%)
Sex			
Boys	3 (9.7)	13 (41.9)	15 (48.4)
Girls	6 (20.0)	9 (30.0)	15 (50.0)
Age (years)			
0–3 years	5 (21.7)	5 (21.7)	13 (56.5)
4–10 years	2 (9.5)	7 (33.3)	12 (57.1)
> 11 years	2 (11.8)	10 (58.8)	5 (29.4)
Race			
Caucasian	5 (10.4)	17(35.4)	26 (54.2)
Asian	1 (100)	0 (0)	0 (0)
Black	2 (50)	0 (0)	2 (50)
Other	1 (12.5)	5 (62.5)	2 (25.0)
Sillence type			
Type I	4 (12.9)	8 (25.8)	19 (61.3)
Type III	2 (14.2)	6 (42.9)	6 (42.9)
Type IV	3 (18.8)	8 (50.0)	5 (31.2)
BMI			
Low (< 5%)	2 (28.6)	3 (42.9)	2 (28.6)
Normal (5%–95%)	2 (7.4)	9 (33.3)	16 (59.3)
High (> 95%)	1 (14.3)	4 (57.1)	2 (28.6)
Fracture count			
< 10	4 (13.8)	8 (27.6)	17 (58.6)
> 10	5 (15.6)	14 (43.8)	13 (40.6)
Pamidronate treatment			
Without treatment	4 (17.4)	5 (21.7)	14 (60.9)
With treatment	5 (13.2)	17 (44.7)	16 (42.1)
Season			
Winter	3 (15.8)	6 (31.6)	10 (52.6)
Spring	2 (20.0)	4 (40.0)	4 (40.0)
Summer	4 (20.0)	7 (35.0)	9 (45.0)
Autumn	0 (0)	5 (41.7)	7 (58.3)

Abbreviations and notes:
Descriptive statistics of vitamin D categories and its distribution among study variables.
BMI, body mass index

Table 2: OI Patient Population Characteristics and Vitamin D Status.

The major strength of this study is that it is the first published assessment of vitamin D status in children with OI in the United States. Overall, there is a paucity of published data assessing vitamin D status in pediatric OI patients, although there have been two very recent publications by the same researchers in Canada [17,18]. On the other hand, our study was limited due to a small sample size that did not allow for sufficient power and the application of inferential statistics in the comparisons between sex, BMI, Sillence types, and vitamin D status. Secondly, the design used in this study was a retrospective cohort (case-only) based on previously performed measurements and assessments which were performed in a clinical setting. 25 (OH) vitamin D levels were done in different send-out laboratories, based upon an individual patient's health insurance. It is clear that there is some inter-laboratory variability which may have affected the precise reliability of the measurements [25]. Future studies on this population need to include a much larger number of patients to be able to have sufficient power to test hypotheses and a prospective study, which could assess dietary intake of vitamin D and sunlight exposure in a longitudinal manner. All 25(OH) D levels should be tested at the same laboratory by the same methodology. This would likely require a multicenter approach.

Acknowledgements

Authors' role:

- Study conduct and design: Muayad Kadhim, Laurens Holmes Jr., and Richard Kruse.
- Data collection: Muayad Kadhim
- Data analysis: Muayad Kadhim, Laurens Holmes Jr.
- Data interpretation: Muayad Kadhim, Laurens Holmes Jr., Richard Kruse, and Michael B. Bober
- Drafting the manuscript: Muayad Kadhim, Laurens Holmes Jr., Michael B. Bober and Richard Kruse
- Reviewing the manuscript content: Muayad Kadhim, Laurens Holmes Jr., Richard Kruse, Kenneth J. Rogers, Lauren Davey, and Anthony Kallur.
- Approving the final manuscript: Muayad Kadhim, Laurens Holmes Jr., Michael B. Bober, Richard Kruse, Kenneth J. Rogers, Lauren Davey, and Anthony Kallur.

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