The influence of vitamin D and osteoporosis on fracture healing

Gorter, E.A.

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Vitamin D deficiency in pediatric fracture patients: prevalence, risk factors, and vitamin D supplementation

Gorter EA
Oostdijk W
Felius A
Krijnen P
Schipper IB

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ABSTRACT

Objective

Although vitamin D levels are not routinely monitored in pediatric fracture patients, identification of children with a vitamin D deficiency may be clinically relevant because of the potential role of vitamin D in fracture healing**.** This study aimed to determine the prevalence of vitamin D deficiency in a pediatric fracture population and to identify risk factors for deficiency.

Patients and Methods

In this cross-sectional study all pediatric patients (<18 years), who were treated for a fracture of the upper or lower extremity from September 2012 to October 2013 in the outpatient setting of a level one trauma center, were included. Vitamin D deficiency was defined as a serum calcidiol <50 nmol/L. Potential risk factors for vitamin D deficiency were analysed using multivariable logistic regression analysis.

Results

A total of 108 boys (58%) and 79 girls, mean age 11.1 years (SD 3.9), with 189 fractures were included. Sixty-four children (34%) were vitamin D deficient. Of those with follow-up measurements, 74% were no longer deficient after supplementation. Vitamin D status did not influence the occurrence of complications during fracture treatment. Independent risk factors for vitamin D deficiency were higher age, season (spring) and a non-Caucasian skin type.

Conclusion

Clinicians who treat children with a fracture should inform patients and parents on vitamin D supplementation. Vitamin D measurement and supplementation may be needed for children with a non-Caucasian skin type or for those who present with a fracture during spring months.

INTRODUCTION

Up to 60% of boys and 40% of girls sustain a fracture during childhood.[1-5] Increased participation in competitive sports and the relative under-mineralization of the skeleton during the early phase of the pubertal growth spurt may contribute to the high fracture rate.[6] Vitamin D deficiency is considered a global health problem.[7] The prevalence in healthy European children varies between 8% and 95% depending on risk factors such as geographical location, sun exposure, skin type, vitamin D supplementation or the presence of obesity.[7,8] Vitamin D is essential for bone mineralization and maintenance of bone quality through its vital role in the regulation of calcium and skeletal homeostasis.[9] Although vitamin D plays a role in the complex cellular processes of fracture healing, studies that address risk factors for vitamin D deficiency, the clinical effects of vitamin D deficiency or supplementation on fracture healing are scarce and inconclusive.[9,10]

Low bone mineral density is a risk factor for fractures.[11] Infants with severe vitamin D deficiency, such as is present in rickets, have a tendency towards increased fracture rates.[12,13] The possible relation between vitamin D deficiency and the occurrence of pediatric fractures has not yet been established.[14-17] A recent study showed that a lower vitamin D status is associated with fractures requiring surgery, but not with the occurrence of fractures [18]. Although the prevalence of vitamin D deficiency in children in the general population has been well described[7,8], the prevalence of vitamin D deficiency in the pediatric fracture population is less often reported with a wide variation ranging from 8% to 47% (Table 1).[14,15,17-21]

The primary aim of the present study was to determine the prevalence of vitamin D deficiency in a general pediatric trauma population, who sustained a fracture in the upper or lower extremity. The second aim was to identify the risk factors for vitamin D deficiency in this patient group.

Table 1. Prevalence of vitamin D deficiency (calcidiol < 50mol/L) in pediatric fracture patients

Study	Year	Included fracture population	Prevalence of vitamin D deficiency
Schilling *et al*.[15]	2011	118 children younger than 2 years old	8%
Ceroni *et al*. [20]	2012	100 children with a fracture of the upper- or lower extremity	12%
Minkowitz *et al*.[18]	2015	369 children	18%
Contreras *et al*.[17]	2014	100 children with a fracture	20%
Olney *et al.*[21]	2008	68 children with two or more fractures in the past	21%
James *et al.*[19]	2013	213 children with a fracture of the upper extremity	24%
Rayn *et al*.[14]	2012	76 African American children with a forearm fracture	47%

PATIENTS AND METHODS

Approval for this cross-sectional study was obtained from the institutional Medical Ethics Review Committee. The study included all consecutive pediatric patients (age < 18 years), who were treated for a fracture of the upper or lower extremity between 1 September 2012 and 1 October 2013 in the outpatient clinic of our level 1 trauma center. According to Dutch law, children from 16 are considered able to give informed consent themselves for study participation. For children of 12 to 16 years consent from both the child and the parents is needed before inclusion. In children younger than 12 years only consent of the parents is necessary. In this study, conservatively treated children and/or their parents received study information and were asked to provide written informed consent in the plaster room approximately one week after fracture. In case of operative treatment children and/or their parents were asked to provide written informed consent before surgery. After consent was obtained, blood was taken, questionnaires were filled out and patient demographics and fracture type were documented.

Table 2. Schedule for supplementation of children with vitamin D deficiency (25-hydroxyvitamin D <50nmol/L).

Children younger than 1 year		Children older than 1 year	
Clinical, biochemical or radiological signs of rickets?		Clinical, biochemical or radiological signs of rickets?	
No	Yes	No	Yes
• 1,000 IU vitamin D per day during 4 weeks followed by • 400 IU (10 µg) vitamin D per day during 3 months	• 50,0000 IU vitamin D per day during 4 weeks followed by • 400 IU (10 µg) vitamin D per day during 3 months	• 2,000 IU vitamin D per day during 4 weeks followed by • 400 IU (10 µg) vitamin D per day during 3 months	• 50,000 IU vitamin D per day during 8 weeks followed by • 400 IU (10 µg) vitamin D per day during 3 months

A blood sample was taken during the first follow-up visit after fracture. The serum concentration 25-hydroxyvitamin D was measured using an Electro Chemo Luminescence Immuno Assay from Roche Diagnostics (Modular E170). In the literature there is no consensus on the appropriate vitamin D levels, which may explain the inconsistent data found on the effect of vitamin D deficiency on the occurrence of hyperparathyroidism, metabolic bone disease and hypocalcaemia. The American Academy of Pediatrics[22], the Pediatric Endocrine Society[23] and the Institute of Medicine[24] consider a serum concentration vitamin D > 50nmol as sufficient/normal. Also, according to their recommendations a minimum serum concentration of 50nmol/L should also be maintained or should be the target value in case of supplementation. Serum concentrations below this 50nmol/L were defined as deficient by the Endocrine Society Clinical Practice Guideline.[25] Based on these definitions and target values we defined a vitamin D deficiency as serum 25-hydroxyvitamin D level < 50nmol/L (20 ng/ml) in our study. In case of a

vitamin D deficiency, children were referred to a pediatrician for further assessment, supplementation according to the schedule presented in Table 2. and follow-up. BMI was determined according to gender and age. Classification of being underweight, having a normal weight, or being overweight or obese was based on the BMI distribution for Dutch boys and girls in 2009.[26] Month of fracture was categorized into autumn (September, October, November), winter (December, January, February), spring (March, April , May) and summer (June, July, August).

The children and/or their parents, completed a questionnaire on potential risk factors for vitamin D deficiency including medical history, medication, sun exposure and vitamin D usage prior to the fracture.[27] In the questionnaire, daily UV-radiation exposure was defined as the average number of hours spent outdoors between 10:00 am and 03:00 pm.[27-29] Skin type was determined using the Fitzpatrick scale[30] (*Type I*: pale white skin, always burns, never tans; *Type II*: white skin, burns easily, tans minimally; *Type III*: white skin, burns moderately, tans uniformly; *Type IV*: light brown / moderate brown skin, burns minimally, always tans well; *Type V:* Brown, rarely burns, tans profusely; *Type VI:* dark brown to black skin, never burns).

Complications concerning fracture healing including refracture, epiphysiodesis, malunion, delayed union and non-union, that occurred within 6 months after the fracture, were documented.

Patient characteristics are presented as mean with standard deviation (SD) or as number (percentage). Patient groups were compared using the Student's t-test for continuous variables and the Chi-squared test or Fisher's exact test for categorical data, as appropriate. Patients characteristics with a univariable association ($p \leq 0.10$) with vitamin D deficiency were combined in a multivariable logistic regression analysis to identify independent risk factors for these conditions. The strength of selected risk factors was expressed as the adjusted odds ratio (OR) with its corresponding 95% confidence interval (CI). Statistical analysis was performed with SPSS software version 20 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.). P values <0.05 were considered statistically significant.

RESULTS

A total of 587 children with fractures (40% located in the distal forearm), including 352 boys (60%) and 235 girls, with a mean age of 10.2 years (SD 4.1) were eligible. Of these children 187 (31.9%) participated after providing written informed consent, 108 were boys (58%) and 79 girls, with a mean age of 11.1 years (SD 3.9)(Table 3). Together they sustained 189 fractures, of which the most frequent (43%) were distal forearm fractures (Figure 1). Most of the fractures were treated nonoperatively (n=161; 85%). The majority

of the operated fractures were treated with K-wires (14/28) or Elastic Stable Intramedullary Nailing (6/28). Of the 187 children 73 (39%) had previously sustained a fracture (Table 3).

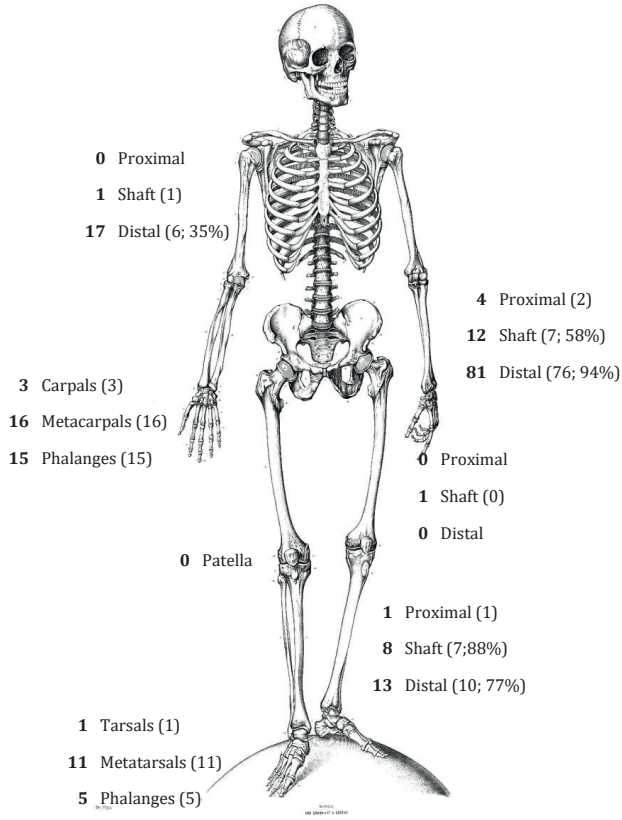

Figure 1. Fracture location and treatment of 189 fractures. The bold numbers indicate the number of fractures. The number (%) of conservatively treated fractures are indicated between parentheses.

Medication was used by 23 (18%) patients, predominantly against (allergic) asthma (salbutamol and/or salmeterol /fluticasone), attention deficit hyperactivity (methylphenidate), or diabetes (insulin). Most patients, 163 (88%), had a Caucasian skin type (Fitzpatrick skin type I, II or III). Vitamin D supplements were used by 24 (13%) patients (although no previous vitamin D deficiency was reported), mostly as a component in a multivitamin. Four of the five children younger than four years received vitamin D supplements (although recommended in the Netherlands), and only one of the 22 children with a dark skin type (IV or V) aged 4 years and older received vitamin D supplementation.

Table 3. Univariable association and Multivariable logistic regression analyses of patient characteristics / risk factors for vitamin D deficiency. Results are presented as number (%) unless indicated otherwise.

Characteristic			Vitamin D deficiency				Risk factor	
			Total n = 187	Yes n = 64	No n = 123	p	OR	Adjusted OR (95% CI)
Gender	Boy		108 (58)	41 (38)	67 (62)	0.21		
	Girl		79 (42)	23 (29)	56 (71)			
Age, years*			11.1 (3.9)	12.3 (3.4)	10.4 (4.1)	0.002	1.15	(1.04 - 1.26)
BMI	Underweight		33 (19)	9 (27)	24 (73)	0.67		
	Normal weight		118 (68)	42 (36)	76 (64)			
	Overweight / Obese		23 (13)	8 (35)	15 (65)			
Skin-type	Caucasian (type I, II, III)		163 (88)	49 (30)	114 (70)	0.001		Reference
	Non-Caucasian (type IV, V, VI)		23 (12)	15 (65)	8 (35)		4.71	(1.68 - 13.2)
Fracture history	Fracture	Yes	73 (39)	25 (34)	48 (66)	1.00		
		No	114 (61)	39 (34)	75 (66)			
Use of medication	Any	Yes	23 (12)	5 (22)	18 (78)	0.18		
		No	164 (88)	59 (36)	105(64)			
Use of vitamin D	Vitamin D supplements	Yes	24 (13)	6 (25)	18 (75)	0.31		
		No	163 (87)	58 (36)	105 (64)			
Sun exposure	Number of hours /day*		1.80 (0.9)	1.65 (0.9)	1.83 (0.9)	0.20		
	Sun vacation in previous month	Yes	20 (11)	1 (5)	19 (95)	0.004	0.11	(0.01 - 0.88)
		No	166 (89)	62 (37)	104 (63)			Reference
Season of fracture	Summer		53 (28)	11 (21)	42 (79)	0.02		Reference
	Autumn		44 (24)	12 (27)	32 (73)		1.70	(0.59 - 4.90)
	Winter		37 (20)	16 (43)	21 (57)		2.64	(0.95 - 7.39)
	Spring		53 (28)	25 (47)	28 (53)		3.15	(1.23 - 8.11)

*Mean (standard deviation)
OR: odds ratio, CI: confidence interval, BMI: body mass index

The blood sample for determination of serum 25-hydroxyvitamin D levels was taken at a median of 8 days after fracture (range 0 - 69 days). With a mean of 64.9 (SD 27) a total of 123 children (66%) had a 25-hydroxyvitamin D level ≥ 50 nmol/L and 64 children (34%) were vitamin D deficient (25-hydroxyvitamin D < 50nmol/L).

Potential risk factors (univariable p≤ 0.10) for vitamin D deficiency were higher age, non-Caucasian skin type and season (winter and spring) (Table 3). A potentially protective factor against vitamin D deficiency was a holiday with high sun exposure within the previous month. Combined in the multivariable logistic regression model, all these factors were shown to be independent risk/protective factors for vitamin D deficiency.

The 64 children with a vitamin D deficiency were referred to the pediatrician (Figure 2) of whom 51 actually visited the pediatrician. No clinical, biochemical or radiological signs of rickets were found in any of these children. Osteopenia was diagnosed with a DEXA scan in one of two children with celiac disease. All 51 children were treated according to the protocol shown in Table 1. In 39 of them the serum 25-hydroxyvitamin D measurement was repeated after 4 months; 29 (74%) were no longer vitamin D deficient (Figure 2). No vitamin D intoxication occurred in any of the supplemented children.

The mean follow-up in the 160 conservatively treated patients was 6.1 weeks (range 1-59 weeks). During the cast immobilization, which lasted on average 3.7 weeks, no complications occurred. In 3 of the 160 children a refracture occurred respectively within one month, after 6 weeks and after 5 months after removal of the cast respectively. In 3 of the 160 children a refracture occurred respectively within one month, after 6 weeks and after 5 months after removal of the cast. In these 3 children the initial 25-hydroxyvitamin D levels were 119, 39 and 23 nmol/L respectively. Only in the last patient the vitamin D level was determined at the second presentation, which showed to be sufficient. The occurrence of complications after cast immobilization was not related to the initial vitamin D status in this cohort. The 28 children with an operatively treated fracture had an average follow-up of 15.4 weeks (range 1-42 weeks). In 21 children, the fixation material was removed according to the treatment protocol. In the operatively treated group all fractures healed without complications within 6 months after inclusion.

DISCUSSION

The results of this study show that 34% of the pediatric fracture patients had a vitamin D deficiency, all patients were without signs of rickets. Higher age, a non-Caucasian skin type and spring season were independent risk factors for vitamin D deficiency. After four months of treatment with vitamin D, 74% of the children with an initial vitamin D deficiency were no longer vitamin D deficient.

In literature, a prevalence of 8% to 47% vitamin D deficiency is described in the pediatric fracture population (Table 1). Inclusion into our study was not limited to certain age groups, type of treatment, skin type or fracture location. The observed prevalence of 34% vitamin D deficiency, therefore probably also reflects the prevalence in the general pediatric fracture population. Schilling *et al*.[15] found a far lower incidence of 8% vitamin D deficiency in 118 children younger than 2 years with a fracture. This low prevalence may be age and country dependent due to the recommendation of the American Academy of Pediatrics to supplement vitamin D in the very young children[31]. As no children younger than 2 years were present, we could not compare these data to our results. On the other hand, Ryan *et al*.[14] examined 76 African American children with a forearm fracture and found 47% to be vitamin D deficient. The inclusion of only children with a dark skin type, a risk factor for having a vitamin D deficiency, probably explains why they found so many more vitamin D deficient children in their population compared to our pediatric population. This obvious variation in vitamin D deficiency prevalence clearly reflects the presence or absence of certain risk factors. The five children with a dark skin type (type V or VI) that were included in our study were indeed all vitamin D deficient. Olney *et al*.[21] retrospectively identified children with a history of two or more fractures and found a vitamin D deficiency prevalence of 21% in this group. The results of James *et al*.[19] were limited to children with an upper extremity fracture, and showed a vitamin D deficiency in 24%. Ceroni *et al*.[20] included 100 adolescent (between 10 and 16 years) patients with upper- or lower limb fractures and found in 12 (12%) a vitamin D deficiency. We documented prevalence of 46% vitamin D deficiency in 98 children between 10 and 16 years.. Ceroni *et al*.[20] only included operatively treated children and measured the vitamin D concentration at once after storage, which may help to explain the difference in prevalence. Similar to our study, Contreras *et al*.[17] did not limit their inclusion to age or fracture location, although they did not report the patients' skin type, whereas Minkowitz *et al*.[18] included all fracture locations in a population between 2 - 18 years. They found a vitamin D deficiency in 20% and 18% respectively. The seeming differences in prevalence between our and other studies may have resulted from seasonal differences and differences in geographical distribution or latitude,[27,32] but also from differences in characteristics of the study populations. It should be noted that in our study only 12% of the children had a non-Caucasian skin type and our study population tended to be more towards adolescence with a mean age of 11.1 years.

To our knowledge, only James *et al*.[19] and Minkowitz *et al*.[18] described risk factors for vitamin D deficiency in a pediatric fracture population. Although not tested in a multivariable analysis, they also described a significant effect of skin type on the serum concentration of vitamin D. In contrast to our results, age and season did not seem to affect the serum calcidiol level in study of James *et al*.[19] Contreras *et al*.[17] merged the fracture group with the non-fracture group and described risk factors for an insufficient vitamin

D concentration (< 75nmol/l). They also found more insufficiency in non-Caucasian children, as well as in children presenting in the winter and spring. Some established risk factors for vitamin D deficiency in a nonfracture population have been reported in the literature. One of these is obesity.[22] Because vitamin D is a fat-soluble vitamin, a higher dose of vitamin D supplementation in obese children is recommended.[22] Although some studies have identified obesity as a risk factor for vitamin D deficiency, we did not find this relation in our pediatric fracture population.

Results of studies in many countries and also national data on Dutch children indicate that prevalence of vitamin D deficiency is not expected to differ in children with or without a fracture [14,17,18,20,21,33,34]. Thus, routine vitamin D measurement in children with a fracture should be avoided. The prevailing advices of the National Health Councils render routine vitamin D measurement in children with a non-Caucasion skin type unnecessary. The Dutch Health Council advises daily vitamin D supplementation of 400IU (International Units) in children up to four years in order to prevent rickets.[35] In children of four years and older the Health Council advises standard daily vitamin D supplementation with 400IU in children with a light skin type (Fitzpatrick skin type I, II or III) who have insufficient daily sun exposure (<15 min between 11:00 AM and 03:00 PM) and in all children with a dark skin type (Fitzpatrick skin type IV, V or VI).[35] This amount of 400IU is consistent with estimated average requirement described by the Institute of Medicine[24] and the Endocrine Society Clinical Practice Guideline even a describes higher (600-1000IU) daily recommendation for children at risk for vitamin D deficiency. Our results also indicate that these recommendations are poorly implemented; only 1/22 children with a dark skin type aged ≥ 4 years had received vitamin D supplementation prior to the study. And we identified a non-Caucasian skin type as a independent risk factor for vitamin D deficiency. A result also described by James *et al*.[19], Contreras *et al*.[17] and Minkowitz *et al*.[18]. The overall awareness of the importance of an adequate vitamin D status in these children and knowledge of the advice of the Health Council (supplementation with 400IU per day in the risk population) should become part of the fracture treatment protocol.

A limitation of our study was the low participation rate. The most commonly reasons provided by children and their parents for non-participation were fear for blood collection and the increased time spent in the hospital. The low participation rate may have introduced a selection bias, but the included group of children seemed representative based on the available information of all eligible children regarding age, gender, fracture location and seasonal distribution. Although blood samples were obtained as soon as possible after the fracture had occurred, this took place up to two months after initial trauma. The delay in some patients resulted in a less accurate determination of the vitamin D status at the time of injury. Another limitation was that data concerning fracture

healing was obtained retrospectively, with all well known short comings of retrospective data acquisition.

In conclusion, this study has shown that one in three children with a fracture can be vitamin D deficient. Nevertheless, routine vitamin D measurement in children with fractures is not recommended. The results of our study also show that higher age, a non-Caucasian skin type and spring season are risk factors for vitamin D deficiency in pediatric fracture patients. Clinicians who treat children with a fracture should inform the patient and their parents about the prevailing advice regarding vitamin D supplementation and also note the presence of potential risk factors. Vitamin D measurement and supplementation can be considered in children with a non- Caucasian skin type and in those who present with a fracture during spring months.

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