Rachitic Changes, Demineralization, and Fracture Risk in Healthy Infants and Toddlers with Vitamin D Deficiency[1]

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Purpose: To examine radiographic findings in children with vitamin D deficiency in comparison with biochemical marker levels and prevalence of fractures.

Materials and Methods: The parents or guardians of all participants provided written informed consent at the time of enrollment. The institutional review board approved the protocol, and HIPAA guidelines were followed. From a prospective sample of children seen for routine clinical care, 40 children with vitamin D deficiency (25-hydroxyvitamin D [25-OHD] level, ≤20 ng/mL) were identified, and high-detail computed radiographs of the wrists and knees were obtained. The children ranged in age from 8 to 24 months. Radiographs were scored by three readers with use of the 10-point Thacher score for rachitic changes and a five-point scale for demineralization. Serum calcium, phosphorus, alkaline phosphatase, and parathyroid hormone levels were determined. Fracture history was obtained for 35 of the 40 patients (88%).

Results: All readers identified rachitic changes at both readings in two patients (5%) and demineralization in two patients (5%). Interrater agreement was 65% for rachitic changes ($\kappa = 0.33$) and 70% for demineralization ($\kappa = 0.37$). When the majority of the raters determined that rachitic changes were absent at both readings, alkaline phosphatase levels were lower than those with other assessments (median, 267 vs 515 U/L [4.4589 vs 8.6005 μkat/L]; $P = .01$). When most raters determined that demineralization was present at both readings, serum 25-OHD levels were lower than those at other assessments (median, 9.0 vs 17.5 ng/mL [22.464 vs 43.68 nmol/L]; $P = .02$). No fractures were reported or identified radiographically.

Conclusion: In infants and toddlers with vitamin D deficiency, rachitic changes and definite demineralization are uncommon and fracture risk is low.

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During the past decade, there has been a resurgence of vitamin D deficiency worldwide (1–4). In the United States, the prevalence of vitamin D deficiency in children (25-hydroxyvitamin D [25-OHD] level ≤20 ng/mL) is estimated to be 16% (5). Investigators in studies of healthy infants (>6 months) and toddlers reported a prevalence ranging from 1.7% (6) to 12%–22% (7–10). In older infants and toddlers, the primary causes of vitamin D deficiency are nutritional deficiency and lack of sun exposure. Risk factors for vitamin D deficiency in infants and toddlers are breast-feeding without supplementation; drinking juice rather than milk; decreased intake of fortified foods; dark skin pigmentation; and little sun exposure because of geography, climate, or sunscreen use (10,11).

Severe vitamin D deficiency leads to a cascade of biochemical changes that alter bone metabolism and eventually can result in demineralization, rickets, and fractures (11). A low vitamin D level results in decreased intestinal absorption of calcium, which in turn causes increased levels of parathyroid hormone (PTH). PTH increases renal calcium resorption and phosphorus excretion, increases the production of endogenous vitamin D in the liver, and releases calcium from bone by means of increased osteoclastic activity. The result is an altered phosphorus-calcium product and decreased mineralization of collagen, with the development of osteomalacia or rickets in the immature skeleton (12,13).

The early radiographic changes of rickets are most evident in the physes of rapidly growing bones (eg, costochondral junctions, knees, and wrists) (14). With increased osteoclastic activity, the mineralization of bones is reduced; this is characterized by thinning of the cortical bone, coarse trabeculation, and diffuse radiolucency. The decrease in collagen mineralization at the zone of provisional calcification results in widening of the physis. The metaphysis has a widened, irregular, frayed appearance and may develop a cupped contour (15). Delayed growth, fractures, and bowing of the bones can occur (14,16).

The clinical presentation and biochemical changes owing to vitamin D deficiency vary according to patient age and the severity and chronicity of the deficiency. Infants younger than 6 months can present with hypocalcemic seizures, whereas older infants and toddlers more typically present with clinically and radiologically evident rachitic changes accompanied by elevations of PTH and alkaline phosphatase levels (17–19). The rachitic changes seen at radiography are proportional to the severity of the deficiency, and progressive biochemical changes are related to an altered calcium and phosphorus product (20).

The clinical significance of low 25-OHD levels in young children is unclear (21,22). There are limited data defining the 25-OHD concentration at which demineralization and rickets are evident radiographically. The relationship between the radiographic appearance of rickets and biochemical markers of bone metabolism (eg, PTH and alkaline phosphatase levels) in young children is also not well understood. In addition, there are no data regarding a child's fracture risk in the case of mild vitamin D deficiency versus that in florid clinical and radiographically evident rickets. These questions have become especially important in the examination of infants and children with multiple fractures suspected of being caused by abuse. In a commentary, Keller and Barnes (23) asserted that confusion in the diagnosis of rickets versus the diagnosis of abuse constitutes a national and international epidemic; however, that article has come under considerable criticism (16,24–28).

In 2008, Gordon et al (10) reported vitamin D deficiency in 44 (12.1%) of 365 healthy infants and toddlers and detailed the clinical and laboratory findings. We hypothesized that radiographically evident rickets and demineralization would correlate with biochemical abnormalities but that fracture risk would be low. The purpose of the current study was to examine radiographic findings in children with vitamin D deficiency in comparison with biochemical marker levels and prevalence of fractures.

Advance in Knowledge

- In otherwise healthy infants and toddlers with vitamin D deficiency, rachitic changes are uncommon and generally mild, definite demineralization is infrequent, considerable inter- and intraobserver variability occurs for both radiographic rachitic changes and demineralization, and fracture risk is low.

Implication for Patient Care

- In the setting of low vitamin D and normal alkaline phosphatase levels, radiographic rachitic changes are unlikely; therefore, evaluation with radiography may not be indicated, avoiding unnecessary radiation exposure.

Materials and Methods

Patients

Patients were identified from a parent study evaluating the prevalence of vitamin D deficiency (10). The parent study

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Abbreviations:
PTH = parathyroid hormone
25-OHD = 25-hydroxyvitamin D

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included 380 primary care patients (age range, 8–24 months; 192 girls with a mean age of 11.4 months ± 3.5 [standard deviation]; 188 boys with a mean age of 12 months ± 3.8) who were seen for routine well-child physical examinations between 2005 and 2007 (10). Vitamin D deficiency was defined as a serum 25-OHD level of 20 ng/mL or less (1,29,30). Children were excluded if they had a chronic disease or if they had received oral glucocorticoids, anticonvulsants, or other medications known to affect vitamin D metabolism 3 months before enrollment. Patients who were not being seen for a well-child check and those who did not have blood drawn that day were also excluded from participation. Within this group, routine blood biochemical markers were tested in 365 patients. Forty-four patients had vitamin D deficiency, and 40 of those 44 patients (91%; age range, 8–24 months; 22 girls with a mean age of 11.8 months ± 4.2; 18 boys with a mean age of 12.1 years ± 4.3) returned for bilateral wrist and knee computed radiography. Written informed consent was obtained from the parents or guardians. The Committee on Clinical Investigation (institutional review board) of Children's Hospital Boston approved the study, and Health Insurance Portability and Accountability Act guidelines were followed.

Laboratory Studies

Vitamin D level was measured at the time of a routine blood draw (ie, screening lead level and complete blood cell count). Serum 25-OHD levels were measured at ARUP Laboratories (Salt Lake City, Utah) by using chemiluminescence assay (Liaison; DiaSorin, Stillwater, Minn). Serum calcium, phosphorus, magnesium, and alkaline phosphatase levels were measured by using end-point assay with a multichannel analyzer (Cobas C501; Roche Diagnostics, Indianapolis, Ind). Intact PTH was measured at Nichols Institute Diagnostics (San Clemente, Calif) with use of a two-site chemiluminescence immunoassay. Samples were analyzed in multiple assays. Interassay coefficients of variation were 5.4%–7% for PTH, 8.6%–10% for 25-OHD, 0.7%–1.6% for alkaline phosphatase, and 1.5%–2.2% for the cations.

Radiographic Evaluation

Bilateral wrist and knee computed radiographs were obtained in the 40 patients. Using the routine departmental protocol for the assessment of metabolic bone disease, we acquired images with 50-μm resolution by using a dual side–read computed radiographic pediatric (0–3 years) hand-processing menu (Fuji Photo Film, Tokyo, Japan). The images were viewed in a darkened room by using a picture archiving and communication system (Synapse; Fujifilm, Stamford, Conn) and a single high-resolution (2560 × 2048) calibrated monitor (Dome C5i; Planar Systems, Waltham, Mass). Images were viewed with standard window level settings, and radiologists were allowed to adjust window and/or level and magnify the images.

Three Certificate of Added Qualification–certified pediatric radiologists (J.M.P.R., P.K.K., and S.A.C., with 7, 33, and 16 years of experience, respectively) examined images from each case at two separate sessions in a blinded fashion. A different random reading order for each reader and each session was prescribed by the study statistician (H.A.F.). Image identification data were deleted from the view before rater review.

The radiographs were evaluated for the presence of rachitic changes and demineralization. The radiologists documented the severity of rickets on bilateral wrist and knee radiographs by using an established 10-point scoring system (31), with the radius, ulna, femur, and tibia scored independently. The Thacher score progresses in half-point increments from 0 (normal) to 10 (severe). A score of more than 0 was considered abnormal.

Demineralization was assessed in each case by using a five-point Likert scale, with 0 being normal; 1, questionable; 2, mild; 3, moderate; and 4, severe. A score of more than 0 was considered abnormal.

Fracture Risk Questionnaire

A fracture questionnaire was administered only in the patients with vitamin D deficiency in whom radiographs were obtained. A follow-up interview was conducted by phone 2–3 years after the initial clinical encounter. The questionnaire included a history of fractures before and after study entry. If the patient had sustained a fracture, there were further questions about the child's age at occurrence, the bone involved, and the treatment. Responses were obtained from families of 35 of the 40 patients (88%).

Statistical Analysis

The radiographic findings were summarized separately for rachitic changes and demineralization. Rachitic changes were considered to be present if the reader assigned a Thacher score of more than 0 at both readings, absent if the score was 0 at both readings, and uncertain for all other scores. Demineralization was assessed similarly and was considered present with a demineralization score of more than 0 (questionable, mild, moderate, or severe) at both readings, absent with a score of 0 (normal) at both readings, and uncertain with other scores. We also examined a more stringent alternative, with demineralization considered to be present with a score of more than 1 (mild, moderate, or severe) at both readings, absent with a score of 1 or less (normal or questionable) at both readings, and uncertain with other scores.

For patient-based analysis, we combined the three readers' ratings and scored the condition as follows: present by unanimous decision; present by two-thirds majority; absent by unanimous decision; absent by two-thirds majority; or all other cases. For comparison of 25-OHD levels and other serum chemistry results, we simplified this scheme by combining the unanimous rating with the corresponding two-thirds majority rating.

We used the multicategory, multirater κ coefficient to measure interrater agreement (32). To quantify the relative variability of the Thacher and

demineralization scores among readers and within readers (measurement error) in comparison with variability among patients (true variation), we used the minimum variance quadratic unbiased estimation, or MIVQUE0, technique (33) to estimate the intraclass correlation coefficient for each measure as well as the standard deviation and percentage of total variance for the two components of measurement error.

We compared serum levels across the three categories by using the Kruskal-Wallis procedure to allow for skewed distribution (26). The prevalence of fracture history was calculated as a percentage with the exact 95% confidence interval.

In statistical testing, $P < .05$ was considered indicative of a significant difference. Software (SAS, version 9.2; SAS Institute, Cary, NC) was used for all computations.

Table 1

Agreement among Three Raters on the Presence of Rachitic Changes and Demineralization

Parameter	Rachitic Changes (Thacher Score >0)	Demineralization*	
		Lower Threshold	Higher Threshold
All assessments†			
Present, unanimous agreement	2 (5)	5 (12)	2 (5)
Present, majority agreement	0 (0)	1 (2)	0 (0)
Absent, unanimous agreement	24 (60)	5 (12)	26 (65)
Absent, majority agreement	10 (25)	13 (32)	10 (25)
All other cases	4 (10)	16 (40)	2 (5)
Unanimous agreement	26 (65)	10 (25)	28 (70)
κ Value‡	0.33 (0.19, 0.47)	0.25 (0.13, 0.38)	0.37 (0.22, 0.51)

Note.—Data are from a set of images in 40 patients presented in random order on two separate occasions. Except where indicated, data are numbers of patients, with percentages in parentheses.

* With the lower threshold, questionable, mild, moderate, and severe ratings were considered positive. With the higher threshold, only mild, moderate, and severe ratings were considered positive.

† A finding was considered present if a reader observed the condition at both readings of a given patient's image and absent if a reader did not observe the condition at either reading.

‡ Data are chance-corrected coefficients of agreement, with 95% confidence intervals in parentheses. A value of 1 indicates perfect agreement, and 0 indicates no more than chance agreement.

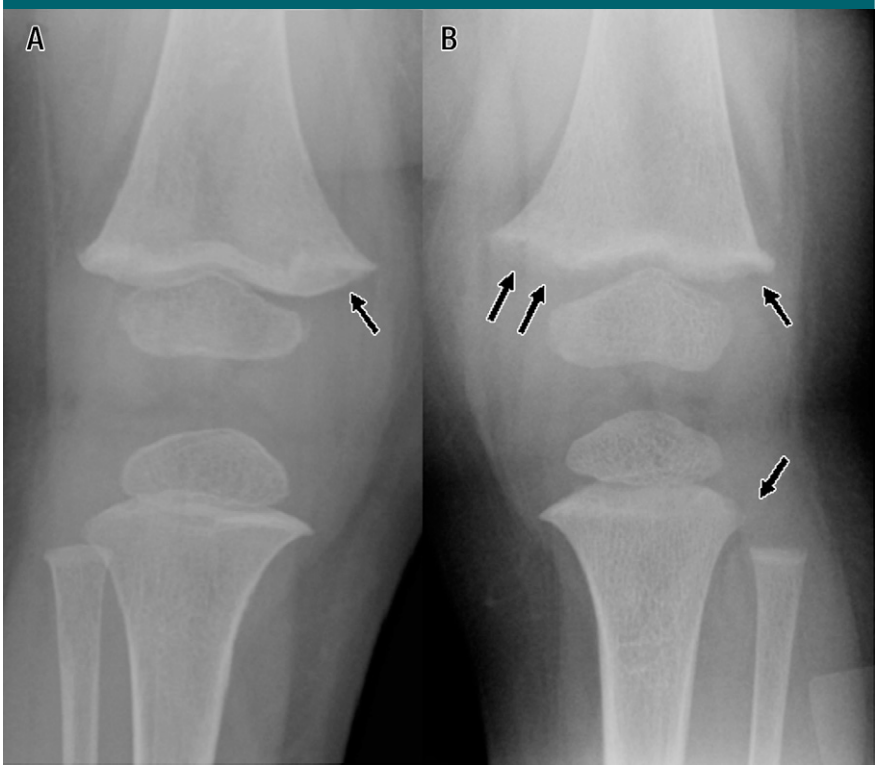
Results

All readers agreed at both readings that rachitic changes were absent in 24 of the 40 patients (60%) and present in two (5%) (Table 1). In only one of the latter two patients did the Thacher score reach 7, with loss of the zone of provisional calcification seen on the radiographs (Figure). In both cases, the demineralization score at every reading was 1 (mild) or 2 (questionable). Additional observations of rachitic changes were seen in 21 readings in 14 patients (35%), with all but one reading having a Thacher score of less than 3. No metaphyseal fragmentation or fractures were identified. Interobserver agreement for rachitic changes was 65%. The κ coefficient was 0.33 (95% confidence interval: 0.19, 0.47), which is conventionally termed a mild degree of chance-corrected agreement (Table 1). Variance of the Thacher score was largely attributable to true variation among patients, with intraclass correlation accounting for 70% of variance (Table 2). Measurement error (within-reader variation for a given image) accounted for most of the remainder (28%), whereas interrater variance was small (2%) (Table 2).

The biochemical marker most strongly related to the presence or absence of rachitic changes was alkaline phosphatase. In the two cases in which the readers agreed that rachitic changes were present, the alkaline phosphatase level was elevated (median, 495 U/L [8.3 μkat/L]) in comparison with the normal level when the majority agreed that rachitic changes were absent (median, 267 U/L [4.5 μkat/L]) ($P = .01$). A similar pattern for PTH, with a median level of 177 versus 34 pg/mL (18.6381 vs 3.5802 ng/L) in cases of agreement on the presence or absence of rachitic changes, respectively, was not statistically significant (Table 3).

Demineralization was analyzed with two thresholds. When questionable demineralization ratings were considered positive, all readers agreed in both readings that demineralization was present in five of the 40 patients (12%) and absent in five (12%). When the threshold was stricter and the questionable category was considered negative, all readers agreed that demineralization was present in only two cases (5%) and absent in 26 (65%) (Table 1). In the two positive cases, demineralization was classified as moderate in one patient and mild in the other. The interobserver agreement for demineralization with the low threshold was 25%, with a κ coefficient of 0.25 (95% confidence interval: 0.13, 0.38); this is conventionally termed mild chance-corrected agreement. When questionable cases were considered negative and the stricter threshold was used, the agreement increased to 70%, with a κ coefficient of 0.37 (95% confidence interval: 0.22, 0.51) (Table 1). Less than half the variance of the demineralization score (44%) was attributable to true variance among patients, and 55% of variance arose from within-rater variability between measurements. Differences among readers accounted for only 2% of variance in demineralization scores (Table 2).

With a lower threshold, rater agreement on demineralization was associated with lower 25-OHD levels (median, 7.0 ng/mL [17.472 nmol/L]; $P = .001$), elevated PTH levels (median, 52 pg/mL [5.4756 ng/L]; $P = .03$), and low phosphorus levels (median, 5.1 mg/dL [1.6473 mmol/L]; $P = .02$) (Table 3). With a higher threshold, the number of patients in the demineralization category was small, only two patients; however, demineralization was associated



Anteroposterior computed radiographs of the knee in the two patients with rachitic changes seen by all readers. *A*, Image of right knee in a 10-month-old child shows partial lucency of the zone of provisional calcification (arrow). The metaphyseal margin in the medial distal femoral metaphysis is intact. The average Thacher score was 1.6 (range, 0.5–2.0), there was mild demineralization, and the 25-OHD level was 11 ng/mL (27.456 nmol/L). *B*, Image of left knee in an 11-month-old child shows partial lucency of the zone of provisional calcification (arrows) and loss of the metaphyseal margin in the medial and lateral distal femoral metaphysis and the lateral proximal tibia metaphysis. No metaphyseal fragmentation is evident. The average Thacher score was 5.1 (range, 2–7), there was questionable demineralization, and the 25-OHD level was 7 ng/mL (17.472 nmol/L).

Table 2

Components of Variance for Thacher and Demineralization Scores

	Thacher Score*		Demineralization Score†	
Source of Variance	Variance	SD	Variance	SD
Among subjects‡	0.68 (70)	0.82	0.24 (44)	0.49
Among readers	0.02 (2)	0.14	0.01 (2)	0.09
Measurement error (residual)	0.27 (28)	0.52	0.30 (55)	0.54
All	0.97 (100)	0.98	0.54 (100)	0.74

Note.—SD = standard deviation (square root of variance). Numbers in parentheses are percentages.

* Scale ranged from 0 to 10; mean score was 0.27 (range, 0–7).

† Scale ranged from 0 to 5; mean score was 0.54 (range, 0–3).

‡ Among-subject percentage of variance is also known as intraclass correlation.

with lower 25-OHD levels (median, 9.0 ng/mL [22.464 nmol/L]; $P = .02$) (Table 3).

A fracture questionnaire was completed for 35 of the 40 patients (88%). None of these children had a history of fracture before or after treatment for vitamin D deficiency (fracture prevalence estimated as 0%; 95% confidence interval: 0%, 10%).

Discussion

The prevalence of vitamin D deficiency in the parent study was 12% (10). In these children, rachitic changes were rare and, when present, findings were subtle, as reflected by low Thacher scores. In our study, patients with rachitic changes had partial lucency of the zone of provisional calcification, with or without loss of the smooth metaphyseal margin. There were no cases exhibiting complete lucency of the zone of provisional calcification, fraying, or widening of the physis. Investigators in two studies—one in Seattle and one in Louisiana—examined hand and knee radiographs in predominantly breast-fed infants and children; none of these subjects received vitamin D supplementation. In the Seattle study (6), which included 246 children aged 6–15 months, rachitic changes were seen in only four children. In three children, these changes were limited to loss of the zone of provisional calcification, with or without metaphyseal cupping and fraying; only one patient had "frank rachitic changes" (6). In the Louisiana study (34), none of the infants (age, 0–6 month) with low vitamin D levels had rachitic changes visible on hand radiographs. Results from these studies suggest that although biochemical changes consistent with vitamin D deficiency are common in the general population, radiographic findings are rare and subtle.

Vitamin D deficiency can affect bone turnover, resulting in demineralization and the observation of osteopenia (osteomalacia) radiographically. In our study, there was wide variability in the assessment of demineralization within and among readers. Although demineralization was seen frequently when equivocal cases were viewed as positive, there was only one case that was rated as moderate. In that case, all readers agreed that demineralization was present. The patient had severe vitamin D

Table 3

Correlation of Serum Chemistry Findings with Rater Agreement on the Presence of Rachitic Changes and Demineralization

Parameter*	No. of Patients	Median Serum Level					
		25-OHD (ng/mL)	PTH (pg/mL)	Alkaline Phosphatase (U/L)	Calcium (mg/dL)	Phosphorus (mg/dL)	Magnesium (mEq/L)
All assessments	40	17.0	34	283	10.4	5.8	2.4
Rachitic changes							
Present, unanimous or majority agreement	2	9.0	177	495	10.3	3.9	2.3
Absent, unanimous or majority agreement	34	17.0	34	267	10.4	5.8	2.4
All other cases	4	16.5	54	515	10.4	5.4	2.3
P value†		.21	.43	.01	.90	.16	.40
Demineralization (with low threshold)							
Present, unanimous or majority agreement	6	7.0	52	431	10.0	5.1	2.4
Absent, unanimous or majority agreement	18	18.0	35	265	10.4	5.5	2.3
All other cases	16	17.0	20	284	10.4	6.0	2.4
P value†		.001	.03	.17	.10	.02	.64
Demineralization (with high threshold)							
Present, unanimous or majority agreement	2	9.0	28	304	10.4	5.5	2.3
Absent, unanimous or majority agreement	36	17.5	34	267	10.4	5.8	2.4
All other cases	2	7.0	421	687	8.4	3.4	2.3
P value†		.02	.06	.06	.07	.07	.64

Note.—To convert 25-OHD to SI units (nmol/L), multiply by 2.496. To convert PTH to SI units (ng/L), multiply by 0.1053. To convert alkaline phosphatase to SI units (μkat/L), multiply by 0.0167. To convert calcium to SI units (mmol/L), multiply by 0.25. To convert phosphorus to SI units (mmol/L), multiply by 0.323. To convert magnesium to SI units (mmol/L), multiply by 0.50.

* A finding was considered present if a reader observed the condition at both readings of a given subject's image and absent if a reader did not observe the condition at either reading.

† Test for equal distribution of serum level in the three agreement categories by using the Kruskal-Wallis procedure.

deficiency, including an undetectable 25-OHD level and no rachitic changes. In all other cases in which demineralization was observed, it was questionable or mild. When a more stringent criterion for demineralization was used, in which equivocal cases were considered negative, there were only two cases in which the readers agreed that demineralization was definitely present. The small number of cases with definite demineralization limits the correlation with biochemical markers, although our data suggest an association between demineralization and elevated PTH and low phosphorus levels.

Significant bone loss, as much as 30%–50%, is required before demineralization is apparent radiographically (35–37). The wide variability in the assessment of demineralization in our study is in agreement with that in the evaluation of osteoporosis on radiographs of adults. In adults, despite reader variability, the detection of osteopenia on conventional radiographs increases when there is significant demineralization measured by means of bone density studies, including dual-energy x-ray absorptiometry (38–42). The variability in our study points to the difficulty in assessing demineralization with digital radiography in the clinical setting. Future studies are needed in which demineralization and bone architecture are assessed optimally with quantitative techniques such as computed tomographic densitometry and thin-section magnetic resonance imaging (43,44).

The fracture prevalence in our sample was 0. Few study investigators have documented fractures in the setting of vitamin D deficiency or rickets in the infant and toddler population. Chapman et al (16) reviewed radiographs obtained in 40 children aged 2–24 months with nutritional, congenital, or secondary rickets and found fractures in seven patients (17.5%). The fractures were seen in mobile infants and in the setting of obvious rachitic changes, including metaphyseal fraying and cupping. Agarwal et al (45) reviewed wrist, knee, and pelvis radiographs in 25 toddlers (age range, 1–2.9 years) with nutritional rickets who presented with delayed walking and found fractures in two children (8%), each of whom had florid rachitic changes. Investigators in other studies reported fractures in young children with vitamin D deficiency but with no detailed description of the fractures or underlying appearance of the skeleton (19,46,47).

Our study has implications for the examination of infants and toddlers with multiple fractures. Fractures in this age group are rare. The yearly incidence of fractures ranges from 0.14% to 1% from birth to 11 months and from 0.06% to 3% from 1 to 2 years (48–50). In the study by Leventhal et al (49), fractures in children younger than 36 months were attributed to abuse in 12% and to metabolic abnormalities such as rickets in 0.12%—a 100-fold difference. In addition, results from that study showed that the likelihood of abuse as the cause of fractures in infants increased from 18.5% for single fractures to 85.4% for multiple fractures (49). Conversely, investigators in a study of infants and children with radiographic evidence of rickets found that 5% had single fractures and 13% had two to four fractures (16).

In our study, the prevalence of fractures in infants and toddlers with vitamin D deficiency or insufficiency was 0, and rachitic changes were rare and subtle; therefore, our findings do not support the assertion that vitamin D deficiency or insufficiency commonly results in multiple fractures that mimic child abuse. Child abuse remains the main diagnostic consideration in otherwise healthy infants and toddlers with multiple skeletal injuries. Our study provides an evidence base for estimating fracture risk in infants and toddlers who are vitamin D deficient that may lend support to medical opinions offered in medicolegal proceedings in which child abuse is alleged.

There is controversy regarding the effects of vitamin D deficiency on other biochemical markers of bone health. In our parent study sample, there was an inverse correlation between 25-OHD and PTH levels (10). Although not statistically significant, when rachitic changes were observed, PTH was elevated. This finding is similar to that in a study of infants and children with radiographically evident rickets that manifested with elevations of PTH and alkaline phosphatase levels (51,52). Alkaline phosphatase has been widely used for the evaluation of bone health in children. In our study, when most readers agreed that there were no rachitic changes, the alkaline phosphatase level was normal, and when all readers agreed that rickets was present (two cases), the alkaline phosphatase level was elevated. These data are similar to those in studies in infants and children in which nearly all patients with radiographs showing rachitic changes had elevated alkaline phosphatase levels (16,45,51). In a recent study, Taylor et al (6) suggested that measurement of alkaline phosphatase level was a good screening test for rickets in infants and toddlers. They proposed a threshold of 552 U/L (9.2184 μkat/L), above which the specificity of an elevated alkaline phosphatase level as a test for rickets was 97.4% and the positive predictive value was 40%.

One of the main limitations of our study is the relatively small number of older infants and children with vitamin D deficiency identified during screening in a well-child clinic population. However, our results showed the rarity of rachitic changes, demineralization, and fracture risk in this cohort. Because this was a cross-sectional sample, causality cannot be established. Another limitation is the subjective nature of scoring systems, which is reflected by the considerable inter- and intraobserver variability among observations of both rachitic changes and demineralization. We chose to consider any Thacher score greater than 0 as abnormal, so the prevalence of rachitic changes as judged by the readers likely was overestimated. The methodology of our study also did not ensure independence between the readings of rickets and demineralization. For example, a reader encountering rachitic changes could have been biased to rate the bones as demineralized as well.

In otherwise healthy infants and toddlers with vitamin D deficiency, rachitic changes and definite demineralization are uncommon and fracture risk is low. Infants and toddlers with vitamin D deficiency and normal alkaline phosphatase levels likely will have normal radiographs, a factor that should guide radiographic screening. When an otherwise healthy infant or toddler presents with unexplained fractures and vitamin D deficiency and radiographic and biochemical markers are absent, rickets is an unlikely explanation for the osseous injuries and a systematic evaluation by a multidisciplinary team should be considered.

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References

1. Holick MF. Resurrection of vitamin D deficiency and rickets. J Clin Invest 2006; 116(8):2062–2072.
2. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. J Nutr 2005;135(2):310–316.
3. Bowden SA, Robinson RF, Carr R, Mahan JD. Prevalence of vitamin D deficiency and insufficiency in children with osteopenia or osteoporosis referred to a pediatric metabolic bone clinic. Pediatrics 2008;121(6): e1585–e1590.
4. Zadshir A, Tareen N, Pan D, Norris K, Martins D. The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis 2005;15(4 Suppl 5): S5-97–S5-101.
5. Mansbach JM, Ginde AA, Camargo CA Jr. Serum 25-hydroxyvitamin D levels among US children aged 1 to 11 years: do children need more vitamin D? Pediatrics 2009; 124(5):1404–1410.
6. Taylor JA, Richter M, Done S, Feldman KW. The utility of alkaline phosphatase measurement as a screening test for rickets in breastfed infants and toddlers: a study from the Puget Sound pediatric research network. Clin Pediatr (Phila) 2010;49(12):1103–1110.
7. Cole CR, Grant FK, Tangpricha V, et al. 25-hydroxyvitamin D status of healthy, low-income, minority children in Atlanta, Georgia. Pediatrics 2010;125(4):633–639.
8. Ziegler EE, Hollis BW, Nelson SE, Jeter JM. Vitamin D deficiency in breastfed infants in Iowa. Pediatrics 2006;118(2):603–610.
9. Rovner AJ, O'Brien KO. Hypovitaminosis D among healthy children in the United States: a review of the current evidence. Arch Pediatr Adolesc Med 2008;162(6):513–519.
10. Gordon CM, Feldman HA, Sinclair L, et al. Prevalence of vitamin D deficiency among healthy infants and toddlers. Arch Pediatr Adolesc Med 2008;162(6):505–512.
11. Misra M, Pacaud D, Petryk A, Collett-Solberg PF, Kappy M; Drug and Therapeutics Committee of the Lawson Wilkins Pediatric Endocrine Society. Vitamin D deficiency in children and its management: review of current knowledge and recommendations. Pediatrics 2008;122(2):398–417.
12. Holick MF. Vitamin D deficiency. N Engl J Med 2007;357(3):266–281.
13. Griscom NT, Jaramillo D. "Osteoporosis," "osteomalacia," and "osteopenia:" proper terminology in childhood. AJR Am J Roentgenol 2000;175(1):268–269.
14. Daldrup-Link E. Essentials of pediatric radiology: a multimodality approach. San Francisco, Calif: Cambridge University Press, 2010; 252–258.

15. Greenspan A. Orthopedic imaging: a practical approach. 4th ed. Philadelphia, Pa: Lippincott Williams & Wilkins, 2004; 829–832.
16. Chapman T, Sugar N, Done S, Marasigan J, Wambold N, Feldman K. Fractures in infants and toddlers with rickets. Pediatr Radiol 2010;40(7):1184–1189.
17. Pettifor JM. Rickets and vitamin D deficiency in children and adolescents. Endocrinol Metab Clin North Am 2005;34(3):537–553, vii.
18. Ladhani S, Srinivasan L, Buchanan C, Allgrove J. Presentation of vitamin D deficiency. Arch Dis Child 2004;89(8):781–784.
19. Ward LM, Gaboury I, Ladhani M, Zlotkin S. Vitamin D-deficiency rickets among children in Canada. CMAJ 2007;177(2):161–166.
20. Soliman AT, El-Dabbagh M, Adel A, Al Ali M, Aziz Bedair EM, Elalaily RK. Clinical responses to a mega-dose of vitamin D3 in infants and toddlers with vitamin D deficiency rickets. J Trop Pediatr 2010;56(1):19–26.
21. Greer FR. Defining vitamin D deficiency in children: beyond 25-OH vitamin D serum concentrations. Pediatrics 2009;124(5): 1471–1473.
22. Wagner CL, Greer FR; American Academy of Pediatrics Section on Breastfeeding; American Academy of Pediatrics Committee on Nutrition. Prevention of rickets and vitamin D deficiency in infants, children, and adolescents. Pediatrics 2008;122(5):1142–1152.
23. Keller KA, Barnes PD. Rickets vs. abuse: a national and international epidemic. Pediatr Radiol 2008;38(11):1210–1216.
24. Jenny C. Rickets or abuse? Pediatr Radiol 2008;38(11):1219–1220.
25. Feldman K. Commentary on "congenital rickets" article [letter]. Pediatr Radiol 2009; 39(10):1127–1129; author reply 1130–1132.
26. Slovis TL, Chapman S. Evaluating the data concerning vitamin D insufficiency/deficiency and child abuse. Pediatr Radiol 2008; 38(11):1221–1224.
27. Schilling S, Wood JN, Levine MA, Langdon D, Christian CW. Vitamin D status in abused and nonabused children younger than 2 years old with fractures. Pediatrics 2011;127(5):835–841.
28. Slovis TL, Chapman S. Vitamin D insufficiency/deficiency: a conundrum. Pediatr Radiol 2008;38(11):1153.
29. Malabanan A, Veronikis IE, Holick MF. Redefining vitamin D insufficiency. Lancet 1998;351(9105):805–806.
30. Thomas MK, Lloyd-Jones DM, Thadhani RI, et al. Hypovitaminosis D in medical inpatients. N Engl J Med 1998;338(12):777–783.
31. Thacher TD, Fischer PR, Pettifor JM, Lawson JO, Manaster BJ, Reading JC. Radiographic scoring method for the assessment of the severity of nutritional rickets. J Trop Pediatr 2000;46(3):132–139.
32. Chmura Kraemer H, Periyakoil VS, Noda A. Kappa coefficients in medical research. Stat Med 2002;21(14):2109–2129.
33. Hartley HO, Rao JN, Lamotte LR. A simple 'synthesis'-based method of variance component estimation. Biometrics 1978;34(2): 233–242.
34. Ponnapakkam T, Bradford E, Gensure R. A treatment trial of vitamin D supplementation in breast-fed infants: universal supplementation is not necessary for rickets prevention in Southern Louisiana. Clin Pediatr (Phila) 2010;49(11):1053–1060.
35. Lachman E. Osteoporosis: the potentialities and limitations of its roentgenologic diagnosis. Am J Roentgenol Radium Ther Nucl Med 1955;74:712–715.
36. Stoker DJ. Interpreting the skeletal x-ray. Br J Hosp Med 1988;39(2):143–152.
37. Michel BA, Lane NE, Jones HH, Fries JF, Bloch DA. Plain radiographs can be useful in estimating lumbar bone density. J Rheumatol 1990;17(4):528–531.
38. Jergas M, Uffmann M, Escher H, et al. Interobserver variation in the detection of osteopenia by radiography and comparison with dual x-ray absorptiometry of the lumbar spine. Skeletal Radiol 1994;23(3): 195–199.
39. Ahmed AI, Ilic D, Blake GM, Rymer JM, Fogelman I. Review of 3,530 referrals for bone density measurements of spine and femur: evidence that radiographic osteopenia predicts low bone mass. Radiology 1998; 207(3):619–624.
40. Williamson MR, Boyd CM, Williamson SL. Osteoporosis: diagnosis by plain chest film versus dual photon bone densitometry. Skeletal Radiol 1990;19(1):27–30.
41. Wagner S, Stäbler A, Sittek H, et al. Diagnosis of osteoporosis: visual assessment on conventional versus digital radiographs. Osteoporos Int 2005;16(12):1815–1822.
42. Garton MJ, Robertson EM, Gilbert FJ, Gomersall L, Reid DM. Can radiologists detect osteopenia on plain radiographs? Clin Radiol 1994;49(2):118–122.
43. Griffith JF, Engelke K, Genant HK. Looking beyond bone mineral density: imaging assessment of bone quality. Ann N Y Acad Sci 2010;1192:45–56.
44. Habashy AH, Yan X, Brown JK, Xiong X, Kaste SC. Estimation of bone mineral density in children from diagnostic CT images: a comparison of methods with and without an internal calibration standard. Bone 2011; 48(5):1087–1094.
45. Agarwal A, Gulati D, Rath S, Walia M. Rickets: a cause of delayed walking in toddlers. Indian J Pediatr 2009;76(3):269–272.
46. Mylott BM, Kump T, Bolton ML, Greenbaum LA. Rickets in the dairy state. WMJ 2004;103(5):84–87.
47. Bener A, Al-Ali M, Hoffmann GF. Vitamin D deficiency in healthy children in a sunny country: associated factors. Int J Food Sci Nutr 2009;60(Suppl 5):60–70.
48. Hallal PC, Siqueira FV, Menezes AM, Araújo CL, Norris SA, Victora CG. The role of early life variables on the risk of fractures from birth to early adolescence: a prospective birth cohort study. Osteoporos Int 2009; 20(11):1873–1879.
49. Leventhal JM, Martin KD, Asnes AG. Incidence of fractures attributable to abuse in young hospitalized children: results from analysis of a United States database. Pediatrics 2008;122(3):599–604.
50. Thandrayen K, Norris SA, Pettifor JM. Fracture rates in urban South African children of different ethnic origins: the birth to twenty cohort. Osteoporos Int 2009; 20(1):47–52.
51. Weisberg P, Scanlon KS, Li R, Cogswell ME. Nutritional rickets among children in the United States: review of cases reported between 1986 and 2003. Am J Clin Nutr 2004; 80(6 Suppl):1697S–1705S.
52. DeLucia MC, Mitnick ME, Carpenter TO. Nutritional rickets with normal circulating 25-hydroxyvitamin D: a call for reexamining the role of dietary calcium intake in North American infants. J Clin Endocrinol Metab 2003;88(8):3539–3545.