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Vitamin D Deficiency and Low Bone Mineral Density in Pediatric and Young Adult Intestinal Failure

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Abstract

Objectives—To determine the prevalence and predisposing factors for vitamin D deficiency and low bone mineral density (BMD) in patients with intestinal failure (IF).

Methods—A retrospective review of patients with IF managed at the Cincinnati Children's Hospital Medical Center. IF was defined as history of parenteral nutrition (PN) >30 days. Vitamin D deficiency was defined as serum 25-OH vitamin D [25(OH) D] < 20ng/dL. Reduced bone mineral density (BMD) was defined using dual x-ray absorptiometry (DXA) Z-score – 2. A binary logistic regression model was used to test for association of significant risk factors and the outcome variables after univariate analyses.

Results—One hundred and twenty three patients with median age of 4 years (range 3–22 years) were evaluated. Forty-nine (39.8%) patients had at least a documented serum 25 (OH) D deficiency during the study interval while 10 out of 80 patients (12.5%) with DXA scans done had a low BMD Z-score. Age at study entry was associated with both 25 (OH) D deficiency ($P=0.01$) and low BMD Z-score ($P=0.03$). Exclusive PN at study entry was associated with reduced bone mass ($P=0.03$). There was no significant association between vitamin D deficiency and low BMD Z-score ($P=0.31$).

Conclusion—The risk of 25 (OH) D deficiency and low BMD Z-score increases with age among patients with IF. Strategies for monitoring and preventing abnormal bone health in older children receiving exclusive PN need to be developed and evaluated.

Keywords

Vitamin D; Intestinal Failure; Bone mineralization

INTRODUCTION

Intestinal failure (IF) occurs when severe intestinal malabsorption due to short bowel syndrome (SBS), congenital transport defects or motility disturbances mandate artificial nutrition to be administered parenterally [1]. This is due to a critical reduction of the

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functional gut mass below the level necessary to maintain adequate digestion and absorption of nutrients and fluid for normal growth [2, 3, 4, 5]. In children, the predominant underlying cause of IF is SBS usually due to resection for congenital (intestinal atresia, malrotation with volvulus) or acquired (necrotizing enterocolitis, vascular thrombosis, or trauma) disorders. Regardless of the cause for IF, nutrient malabsorption is common [6].

Vitamin D as a hormone interacts with its receptor in the small intestine to increase the efficiency of intestinal calcium and phosphate absorption. In addition, the regulation of renal calcium and phosphorous handling is mediated by vitamin D. Vitamin D₃ is synthesized either in the skin under the influence of ultraviolet light of the sun, or it is obtained from food, especially fortified milk [7,8]. Once it is produced in the skin or ingested from the diet, it is converted sequentially in the liver to 25-hydroxyvitamin D [25-(OH) D] and by the kidneys to its biologically active form, 1, 25-dihydroxyvitamin D [9]. Ultimately, vitamin D sufficiency is necessary for muscle and bone health [7, 9, 10–12]. Malabsorption of vitamin D occurs in patients with small bowel resection (13, 14), cholestasis (15, 16) and fat malabsorption [17]. Yang and colleagues reported a high prevalence of vitamin D deficiency (68%) among children with intestinal failure even after transitioning to 100% enteral nutrition [18]. Prolonged home PN has been identified as a risk factor for both vitamin D deficiency and insufficiency [19]. There is also a seasonal variation on cutaneous synthesis of vitamin D associated with significant increase in cutaneous vitamin D synthesis during the summer compared to winter [8, 20, 21]. Deficiency of vitamin D leads to abnormal bone health, muscle weakness and fractures [7]. Bone health can be assessed using dual-energy x-ray absorptiometry (DXA) which is relatively inexpensive, fast, and delivers a low radiation dose [22]. The goal of this study was to evaluate serum 25-(OH) D and BMD Z-score in this group of patients over a five year period. Our hypothesis was that IF patients are at increased risk for vitamin D deficiency and reduced BMD.

MATERIALS AND METHODS

Study design

This was a retrospective study of patients seen between August 1st 2007 and July 31st 2012 at the Intestinal Care Center of Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA.

Participants

One hundred and twenty-three children (aged 3 years) seen during the period under review were included in the study as they met criteria for IF defined by the need for PN support for greater than 30 days. The study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center.

Data

Relevant data of eligible patients were retrieved from the electronic medical record and an existing database. Information obtained included date of birth, age, sex, ethnicity, anthropometric centiles (weight, height, body mass index, weight for length), serum 25 (OH) D levels, lumbar spine (LS) BMD and LS BMD Z-scores. Data were obtained longitudinally for every visit when available throughout the 5 year follow up period. The months of March through August was defined as Spring/Summer while September to February was defined as Fall/Winter. Customarily, patients underwent measurement of serum 25-(OH) D measurements every 6 to 12 months and a DXA scan every 12 months.

Diagnostic methods

Serum 25(OH) D was measured by radioimmunoassay using a direct competitive chemiluminescence immunoassay (Diasorin Liaison, Stillwater Minnesota) with intra-assay coefficients of variation (CV) of 6.3% and 8.6% for mean concentrations of 21 and 65 ng/mL, respectively. The inter-assay CVs were $9.4 \pm 1.6\%$ and $7.7 \pm 4.2\%$ respectively. Serum 25(OH) D < 20ng/ml was defined as vitamin D deficiency [23]. Lumbar spine (LS) DXA scans were measured using Hologic Discovery A, Serial # 81400 (Hologic, Inc., Waltham, MA) to determine the BMD [22, 24]. The poster-anterior spines (lumbar vertebrae L1–L4) were obtained using standardized positioning techniques in the supine position to generate measures of areal BMD (g/cm²). The analysis of the LS DXA was with auto low density software version 12.7.3.1 (1% reproducibility). A DXA scan Z-score of less than or equal to -2 was defined as reduced [25]. The reported final BMD-z scores were adjusted for age and sex; and height for patients who were short for age and had reduced bone mass. “Short for age” was defined as height for age less than the 5th percentile based on the CDC growth standards [26]. Concurrent DXA BMD and Z-score were defined as measures done within six months of serum 25 (OH) D measurements. In our practice, patients were started on vitamin D at a dose of 8000 IU daily or 50,000IU weekly if their serum 25 (OH) D levels were below 20ng/dl. Weight, height and body mass index (BMI) percentiles were based Center for Disease Control (CDC) growth charts.

Data Analysis

The data were analyzed using SPSS version 19 for Windows (SPSS Inc, Chicago, IL) and statistical software R (R core Team, Vienna Austria). The BMD Z-scores in short for age patients (<5th percentile for age) were adjusted to the 50th percentile of height age [26]. Serum 25 (OH) D deficiency and categorized BMD Z-score were the outcome variables. Chi-squared test was used to test association between categorical predictors and each of the outcome variables. Binary logistic regression model was used to test for association between risk factors and each of the outcome variables. The relevant odds ratios and confidence intervals were calculated. A *P*-value of < 0.05 was regarded as significant. All reported *P*-values are 2-sided and all confidence interval reported are 95%.

RESULTS

Participant Characteristics

One hundred and twenty three patients aged 3 years with at least one documented serum 25 (OH) D level were enrolled in this study. This represented 90.4% (123 out of 136) of the entire population of IF patients aged 3 years seen at the Cincinnati Children’s Hospital Medical Center Intestinal Care Center during the period under evaluation. Among them, eighty (65%) had a concurrent DXA scan done. The median age of entry into the study was 4 years (range 3–22 years); and 57.7% were males. Children between ages 3 and 5 years accounted for 58.5% of the study population. Most of the patients were Caucasians (86.2%) and necrotizing enterocolitis (NEC) was the most common primary gastrointestinal diagnosis (23.6%). The characteristics of the patients are shown in Table 1. There was no difference in the body mass index (BMI) of African Americans and non-African Americans (*P*=1). Eleven patients with reduced BMD Z-scores but were short for age (<5th percentile height) had Z-scores adjusted to their 50th percentile height age.

Vitamin D and bone health

Our patients had a total of four hundred and forty-nine serum 25 (OH) D and 157 BMD measurements during the study interval. One hundred and forty-three concurrent measurements of 25 (OH) D and BMD were done (within six months of each other). The

overall mean difference in time between vitamin D and DXA measures was 37.4 ± 3.7 days. Among patients with low BMD Z-score, the mean difference in time was 36.8 ± 4.3 compared to 42.1 ± 7.4 among those with normal BMD Z-score ($P=0.56$). There was no significant association between vitamin D and either short stature adjusted ($P=1$) or non-adjusted ($P=1$) concurrent BMD-z-score status. Two hundred and thirty two (64.3%) of 276 vitamin D measurements during the winter/fall season were in the deficient range compared to 29% (129/173) during the summer/spring season ($P=0.015$). Twenty two of 97 (22.7%) DXA measures done during winter/fall season were abnormal compared to 9 of 60 (15%) measured in summer/spring ($P=0.3$).

Prevalence of vitamin D deficiency and abnormal bone health

Vitamin D deficiency was identified in 40% (49/123) of the patients (95% CI: 32%–49%). Twenty-nine of the 49 deficient patients (42.9%) had intermittent or persistent deficiency even after appropriate therapeutic doses of vitamin D has been started. Sixteen patients received vitamin D supplementation. Eight of the 49 deficient patients (16.3%) had been vitamin D supplemented prior to the discovery of deficiency. Twelve of the 16 vitamin D supplemented patients received daily vitamin D dosing while four patients were on weekly dosing. Six of 12 patients (50%) on daily supplementation developed deficiency compared to 2 of 4 (50%) among those on weekly supplementation. Ten (12.5%) out of 80 patients that had concurrent DXA scan done had reduced LS Z-score (95% CI: 6.9% – 21.5%) after adjusting for height age; and 8 of them (80%) were on vitamin D supplementation. The mean age of the children who were serum 25 (OH) D deficient was 7 years compared to 5 years among the non-deficient group ($P=0.04$). Similarly, the mean age of the children that had abnormal BMD Z-score was 9.9 years compared to 5.2 years among those that had normal BMD Z-score ($P=0.03$). Univariate analysis using chi-square test showed that age > 10 years was significantly associated with serum 25 (OH) D deficiency ($P=0.01$). Thirteen (68.4%) of 19 children above the age of 10 years compared to 36 (34.6%) of 104 children 10 years had 25 (OH) D deficiency ($P=0.01$). The risk for developing vitamin D deficiency when the subject is less than 10 years old is lower compared to the risk if older than 10 years of age (OR=0.23, 95% CI: 0.08–0.66). Although race was not significantly associated with serum 25 (OH) D deficiency, a higher proportion of African American (AA) (52.9%) compared to non-African Americans (37.3%) were vitamin D deficient ($P=0.29$). There was also a higher proportion of the African Americans (42.9%) compared to the other racial groups (20.2%) with intermittent or persistent vitamin D deficiency and this difference showed a trend ($P=0.09$) that did not attain statistical significance.

Categorized Age ($\leq$ or >10) was significantly associated with BMD Z-score ($P=0.02$). Four of ten children (40%) $>$ age of 10 years had reduced BMD Z-score compared to 5 out of 70 children (7.1%) ≤ 10 years. The risk for having abnormal BMD versus normal BMD when the patient is 10 years or under is lower than when the patient is older than 10 years (OR=0.12, 95% CI: 0.03–0.51). All patients with persistent or intermittent vitamin D deficiency compared to 11 out of 28 (39.3%) of those with only one documented vitamin D deficiency had reduced BMD Z-score ($P=0.02$). The mean PN duration among vitamin D deficient patients was 28.3 months compared to 29.3 months among vitamin D sufficient patients ($P=0.88$). Three of ten patients (30%) that were exclusively dependent on PN had vitamin D deficiency compared to 40 of 105 (38.1%) on enteral nutrition ($P=0.74$). Conversely, three of seven patients (42.9%) that were PN dependent compared to six of 70 (8.6%) of those receiving enteral nutrition (8.6%) ($P=0.03$) had reduced BMD Z-score. The mean PN duration among patients with reduced BMD Z-score was 36.9 ± 26.6 months compared to 26.6 ± 3.8 months among those with normal BMD Z-scores ($P=0.52$). A binary logistic regression analysis showed that only age was significantly associated with both serum 25 (OH) D deficiency ($P=0.04$) and reduced BMD Z-score ($P=0.01$) (shown in

tables 2 and 3). The odds ratio of increasing age being associated with vitamin D deficiency was 0.91 (95% CI: 0.85–0.1.0) and 0.8 (95% CI: 0.67 – 0.94) for reduced bone mass (Figure 1). When the impact of age (above and below 10 years) as a dependent variable was examined for both vitamin D and bone health status using a logistic regression model, only abnormal bone health remained significantly associated with age >10 years ($P=0.02$). The odds ratio was 0.16 (95% CI: 0.03–0.77).

DISCUSSION

No large studies have evaluated serum 25 (OH) D levels and bone mineral density (BMD) in children with IF. In this population of IF patients, the prevalence of vitamin D deficiency (abnormal serum 25 (OH) D) and reduced bone mass by DXA (after height correction) were 39.8% (95% CI: 31.6% – 48.7%) and 12.5% (95% CI: 6.9% – 21.5 %) respectively. Patients with vitamin D deficiency and low BMD Z-scores were more likely to be older than 10 years and exclusively on parenteral nutrition at study entry.

The high prevalence of vitamin D deficiency in this study of patients with IF compares with previous smaller reports [27–30]. Vitamin D deficient rickets has been previously reported in 4 children after weaning them off prolonged PN following small bowel resection [27]. Forty to 87% of adult patients with intestinal resection have vitamin D deficiency. [28–30]. Vitamin D deficiency in patients with IF is likely caused, in part, by malabsorption due to intestinal resection or dysmotility (2, 29). Intestinal resection may lead to reduced surface area or impaired vitamin D solubilization because of interruption of enterohepatic circulation of bile acids with ileal resection [31]. The high prevalence of vitamin D deficiency in our IF patients may relate to poor compliance with vitamin D supplementation and inadequate intake of vitamin D. Our patients were significantly more likely to be vitamin D deficient during the winter/fall season than in summer/spring seasons ($P=0.02$). The vast majority of our patients lived in latitudes between 35 degrees North (Knoxville) and 42 degrees North (Toledo) (Cincinnati is located at 39 degrees North). In those latitudes, significant variability exists between vitamin D levels measured in the summer and winter [32].

In a previous study of 24 children, Diamanti *et al* reported 83% with reduced BMD Z-score [33]. Their reported high prevalence contrasts with the 12.5% prevalence in our series. There may be a number of explanations: 1) Diamanti *et al* defined reduced bone mass as a Z-score of <-1 while our study used the criteria of ≤ -2 . Our definition was based on recent recommendations of the International Society for Clinical Densitometry (ISCD) [25]; 2) Only patients on long term PN (defined by at least 3 months of PN) were included in their study; 3) The BMD was not corrected for height age. The association between long term PN and metabolic bone disease has been described [34, 35]. Our study, however, did find that those on exclusive PN at study entry had a significantly higher rate of reduced bone mass but not vitamin D deficiency.

A major strength of this study was the analysis of age with vitamin D and bone mass status. We found that older age (>10 years) was significantly associated with both serum 25 (OH) D deficiency and reduced bone mass. These findings are similar to those described in children with chronic medical illness [36].

There was no significant association between serum 25 (OH) D and BMD. However, our patients with intermittent or persistent vitamin D deficiency had significantly reduced bone mass. There are conflicting reports regarding the relationship between serum 25 (OH) D and BMD [28]. Adults reported by Harderslev *et al* [28] had low serum 25 (OH) D that correlated significantly with lower BMD z-scores, however, Stein *et al* [37] found no

significant association between serum 25 (OH) D and BMD after adjusting for season, race, age and BMI among healthy young girls. Others have failed to show a correlation between the serum 25 (OH) D levels and BMD [38, 39].

The retrospective design of the study is a weakness which limits the ability to generalize these findings. However, the data are longitudinal and hypothesis-generating. A total of 449 serum 25 (OH) D and 160 BMD longitudinal measurements were performed during the study period and included in the analysis ranking this among the largest series evaluating vitamin D and bone health in this population of children.

CONCLUSIONS

The risk of vitamin D deficiency and low BMD increases with age among patients with IF. Vitamin D deficiency was also significantly more common in spring/fall season as was reduced bone mass in patients exclusively on PN. Patients with repeatedly deficient serum 25 OHD had significantly reduced bone mass. We recommend that older patients with IF and those on chronic PN be monitored closely for risk of abnormal bone health and be considered for routine vitamin D supplementation.

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Figure 1. Logistic regression showing the probability of developing vitamin D deficiency and reduced BMD Z-score with increasing age.

Table 1

Characteristics of the subjects

Age group (years)	n (%)
3–5	72 (58.5)
6–10	33 (26.8)
11–15	11 (8.9)
16–20	4 (3.3)
21–25	3 (2.4)
Gender	
Male	71 (57.7)
Female	52 (42.3)
Race	
Caucasian	106 (86.2)
African American	17 (13.8)
Primary gastro-intestinal diagnosis	
Necrotizing enterocolitis	29 (23.6)
Malrotation/Volvulus	15 (12.2)
Hirschsprung disease	13 (10.6)
Atresia	13 (10.6)
Mitochondrial disorders	11 (8.9)
Dysmotility	8 (6.5)
Gastroschisis	6 (4.9)
Gastroschisis plus atresia	6 (4.9)
Others	22 (17.9)

Table 2

Logistic regression model showing risk factors associated with vitamin D deficiency

Predictor	B	SE	P	Odds ratio	95% CI
Age	−0.08	0.04	0.04	0.91	0.85 – 1.0
Gender	0.05	0.39	0.90	1.05	0.49 – 2.25
Vitamin D supplementation	0.20	0.58	0.73	1.22	0.40 – 3.77

Table 3

Logistic regression model for risk factors associated with reduced bone mineral density

Predictor	B	SE	P	Odds ratio	95% CI
Age	-0.23	0.09	0.01	0.80	0.67 – 0.94
Gender	0.85	0.83	0.31	2.34	0.46 – 11.99
Vitamin D deficiency	-0.53	0.76	0.49	0.59	0.13 – 2.65
Vitamin D supplementation	0.90	1.09	0.41	2.45	0.29 – 20.65