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Metabolic Bone Disease in Pediatric Intestinal Failure Patients: Prevalence and Risk Factors

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Abstract

Purpose—Patients with intestinal failure (IF) are known to have impaired absorption of nutrients required for maintenance of skeletal mass. Rates and risk factors of low bone mineral density (BMD) are unknown in pediatric IF patients.

Methods—Following IRB approval, patients with IF having undergone DXA scans were identified, laboratory, clinical and nutritional intake variables were recorded. Low BMD was defined by a z-score of ≤ -2.0 . Univariate followed by multivariable regression analysis was performed.

Results—65 patients underwent a total of 99 routine DXA scans. 27 (41%) had Vitamin D deficiency, 22 (34%) had low BMD and 19 (29%) had a history of fractures. Variables noted to be associated with low BMD ($p < 0.1$) on univariate analysis were considered for multivariable regression. Multivariable regression identified WAZ and serum calcium levels ($p < 0.05$) as independent predictors of low BMD z-score. None of the other evaluated factors were associated with the risk of low BMD. Low BMD was not associated with risk of fractures.

Conclusion—There is a significant incidence of low BMD in children with IF. WAZ and lower serum calcium levels are associated with risk of low BMD. Additional long term prospective studies are needed to further characterize the risk factors associated with low BMD.

Keywords

Pediatric; metabolic bone disease; intestinal failure; bone mineral density; 25-OH D deficiency; fractures; DEXA

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Introduction

Intestinal failure (IF) is a condition characterized by inadequate functional bowel resulting in a malabsorptive state and inability to maintain hydration and nutrition needed to sustain growth and development. [1] The resulting limited gastrointestinal absorptive area, steatorrhea, and decreased entero-hepatic circulation of bile acids places children with IF at high risk for micronutrient deficiencies, [2] many of which are essential for growth and maintenance of skeletal mass. [3,4] Vitamin D deficiency for example is seen in as many as 68%. [5] Furthermore, neonates on parenteral nutrition (PN) for more than two weeks are at increased risk of calcium and phosphorus deficiency because of their limited solubility in solution. [6] The resulting hypocalcemia drives an increased level of parathyroid hormone, which in turn results in significant bone reabsorption over time. [7] Thus children with IF are at a substantial risk of acquiring low bone mineral density (BMD). The resultant loss of BMD is significantly more detrimental in this cohort as the insult coincides with time of maximal bone mass accrual in a child's development. [8]

While adult IF patients both during and after weaning from long-term parenteral nutrition (PN) are known to be at risk for metabolic bone disease with reported prevalence ranging from 32-67%, [9,10] the long term effects of IF and prolonged PN on the skeletal health of children are not well quantified. Additionally, despite understanding of the mechanisms that drive poor accrual of bone mass, specific risk factors for low BMD have not been identified in this population.

Therefore, this study aimed to: 1) quantify the rate of low BMD in children with IF 2) identify risk factors for reduced BMD, and 3) define the prevalence of fractures among children with IF and their relationship with low BMD.

Methods

Following IRB approval, records of 378 children with IF managed by the Centre for Advanced Intestinal Rehabilitation (CAIR), a multidisciplinary intestinal rehabilitation program at the Boston Children's Hospital, were reviewed. Dual-energy X-ray absorptiometry (DXA) scans are performed routinely once children in this program reach 5 years of age. Patients who underwent one or more DXA scans over a 10 year period between 2004 and 2013 were identified and in cases where multiple scans were performed the lowest bone mineral density z-scores were recorded for each patient.

Whole body DXA was performed in the anterior posterior position by a certified densitometry technologist using the Hologic Discovery A® (Hologic, Inc.) scanner, which generates X-rays at 2 energy levels (100 and 70 kV). A whole body phantom and weekly whole body phantom scans were performed locally as part of routine quality control. A series of transverse scans were made from the head to toe at 2 mm intervals. Area, body weight, fat mass, bone mineral content and lean tissue mass were recorded in grams for each region. Areal bone mineral density was calculated and reported in g/cm². Data were analyzed and interpreted at Boston Children's Hospital using the Hologic Pediatric Upgrade for children and adolescents up to age 20 years. [11] Bone mineral density (BMD) z-scores

were determined using normative data. [12] Laboratory, clinical, and nutritional intake variables deemed to be potential factors associated with risk of low BMD were recorded: estimated gestational age (EGA), gender, birth weight, residual small bowel length, presence of terminal ileum, percentage of calories from enteral nutrition (EN), history of intestinal failure associated liver disease (IFALD), empiric or culture proven diagnosis of small bowel bacterial overgrowth, use of anti-secretory medications, as well as serum levels of 25 hydroxyvitamin D (25-OH-D), calcium, parathyroid hormone, phosphorus, and citrulline.

Statistical analysis was performed using SPSS Version 21.0 (IBM, Armonk, NY). Patients with low BMD z-scores (≤ -2.0) were compared against those with relatively preserved BMD z-scores (> -2.0). Continuous variables were analyzed using Student's t- test and categorical variables were compared using Fisher's exact test. Significant factors identified via univariate analysis were subsequently tested by multivariable logistic regression analysis using backward selection to determine independent predictors of a low BMD using z-score cutoff of ≤ -2 and the likelihood ratio test statistic to assess statistical significance of the covariates. [13] Significant multivariate predictors are presented with odds ratios (OR) and 95% confidence intervals (CI). Continuous variables are presented as mean ($\pm$ S.D).

Results

65 pediatric patients with IF (34 males, 31 females) underwent a total of 99 DEXA scans between June 2004 and September 2013. The incidence of low BMD (z-score ≤ -2.0) was 34%. Baseline characteristics are shown in Table 1. Necrotizing enterocolitis was the leading underlying IF diagnosis. The mean residual small bowel length was 81.5 ($\pm$ 72.8) cm and mean duration of PN was 44.2 ($\pm$ 43.2) days.

Patients with BMD z scores ≤ -2.0 [n=22 (34%)] were compared to those with z scores > -2.0 [n=43 (66%)]. On univariate analysis (Table 2), the z-score ≤ -2.0 group had lower WAZ (p=0.01), lower serum calcium level (p=0.04), and higher serum PTH levels (p=0.006). No other variables were significantly different. Of note, residual small bowel length, presence of terminal ileum, small bowel bacterial overgrowth, duration of PN, and percent enteral nutrition did not appear to affect the risk of having low BMD. Overall, 27 (42%) patients had vitamin D deficiency (25-OH-D <30 mg/dl), however there was no statistical difference in the occurrence of vitamin D deficiency between the two BMD groups. Multivariable logistic regression analysis using backward selection identified WAZ and serum calcium level as independent predictors of a low BMD z-score (Table 3). [12] 5 out of the 9 patients with poor growth as depicted by a WAZ score of ≤ -2 had relatively preserved bone mineral density (BMD z-score > -2). 19 (29%) patients experienced at least one fracture. However there was no relationship with low BMD (p=1.00, Table 4).

Discussion

Children with intestinal failure (IF) overall, are at a uniquely high risk for poor bone mineralization. Factors such as malabsorption of essential micronutrients and minerals, [17] renal calcium wasting [14] and chronic metabolic acidosis due to high stool output and small

bacterial overgrowth [15] contribute to the risk of metabolic bone disease. Failure to accrue bone mass in this critical period during childhood results in long-term osteopenia (and its attendant morbidity) in adulthood that may be difficult to reverse.[7,9] Thus, ensuring optimal bone mineral density (BMD) in this population is essential; however, data regarding the incidence of and risk factors for low BMD among children with IF remains sparse.

In this retrospective review of 65 pediatric patients with IF managed by a multidisciplinary intestinal rehabilitation program, over a third had very low BMD (z-score -2.0). Low weight-for-age z-score (WAZ) and low serum calcium level were associated with lower BMD. Though vitamin D deficiency was highly prevalent in the entire cohort, it did not appear to affect the risk of low BMD. Interestingly enough low BMD did not predict rate of fractures over the study period.

Prevalence of biochemical and imaging evidence of metabolic bone disease has been reported in up to 61% adult patients with IF requiring PN support. [6,8,16] Data pertaining to prevalence of low BMD among pediatric IF patients are limited and interpretation is further obfuscated by lack of a uniform definition. Nonetheless, prevalence estimates ranging from 12-70% have been reported. [13,16] This study used dual energy x-ray absorptiometry (DXA), which is now considered the preferred technique due to its low radiation exposure, ease of performance and excellent reliability, [17] and utilized the International Society for Clinical Densitometry (ISCD) criteria for classifying low BMD. [18] Using this robust methodology, this investigation found that a substantial portion of children with IF (34%) meet the criteria for low BMD (z-score less than or equal to -2.0). Given that this period is essential for bone mass accrual, a large portion of these patients are at substantial risk for osteopenia in adulthood. [7]

Of the risk factors evaluated for low BMD, a low WAZ score was an independent predictor. While overall poor nutritional status as determined by low WAZ score is associated with low BMD z-scores, not all patients with growth failure as determined by WAZ <-2 had evidence of impaired bone mineralization (BMD z-score <-2). We know that appropriate development of skeletal tissue is contingent upon availability of appropriate quantities of several micro and macronutrients. These are more likely to be present in a well nourished patient. This implies overall nutritional well being is associated with improved skeletal health corroborating results from previous studies. [19] A particular subgroup of interest perhaps is children who are all enterally fed but experience growth failure and thus are on the brink of receiving parenteral nutrition. These patients if not properly monitored are at risk of developing micronutrient deficiencies leading to impaired bone mineralization. It is therefore advisable to weigh the risk of re-initiating PN against the possibility of impaired bone mineralization and therapy should be started expeditiously if deemed appropriate. Another critical prerequisite of appropriate bone homeostasis is the availability of adequate calcium reserves for optimal bone mineralization. Previous investigators have demonstrated calcium supplementation to be associated with decreased likelihood of metabolic bone disease. [16] Findings reported herein further support results of previous studies where by low serum calcium levels are noted to be independently predictive of low BMD. [16] However, given a wide distribution of serum calcium values, an individual threshold cutoff value associated with the risk of low BMD is difficult to determine statistically from our

cohort. Further, much larger studies will be required to ascertain such a cutoff. In the interim a reasonable clinical option would be to aim for the higher end of the normal spectrum of values in pediatric IF patients.

The impact of residual small bowel length and duration of PN therapy on bone mineral density has been debated with conflicting findings previously reported. [20] Both duration of PN and residual bowel length, which are inverse correlates of each other did not independently predict low BMD in this study, implying skeletal integrity can be maintained as long as delivery of appropriate quantity of necessary nutrients is ensured irrespective of the route. The higher prevalence of vitamin D deficiency (41%) in this cohort is also comparable to other reports in both pediatric and adult IF patients. [6,13] This is likely multifactorial culminating from a combination of disease related decrease in absorption and quite possibly compliance as a vast majority of these patients were prescribed supplemental vitamin D. [21] Of note vitamin D deficiency in and of itself did not translate into low BMD, a finding which has been noted in multiple previous studies evaluating both adult and pediatric PN dependent patients. [16]

Although mean serum PTH levels were significantly higher in the group with low BMD however multivariable models did not identify this as an independent association, with one possible explanation being that it is a covariate with serum calcium levels. Additionally in several instances serum PTH levels were not obtained co-temporally with DEXA scans. However since PTH and 25-OH-D work in tandem to maintain serum calcium levels it would be appropriate to optimize serum calcium and vitamin D to avoid the deleterious effect of secondary hyperparathyroidism.

A significant proportion of patients (29%) experienced fractures however no association with low BMD was seen. The majority of these fractures occurred during the initial critical illness in infancy. The lack of relationship is therefore not surprising given that most of the DXA scans were performed after 5 years of age. Further, the true sequelae of low BMD in childhood are likely to be seen in later adulthood.

Since not all intestinal failure patients with impaired growth had decreased bone mineral density it would be advisable to follow these children with an initial baseline and serial DXA scans for an initial risk stratification and subsequently to follow skeletal health.

One limitation of this study is its retrospective design and in some cases lack of simultaneous DXA studies and laboratory values. Additionally the complications of low BMD are more likely to occur in adulthood.

Conclusion

Metabolic bone disease associated with pediatric intestinal failure places a significant number of these patients at a lifetime risk of osteoporosis, as well as fractures. Appropriate skeletal health is contingent upon an adequate overall nutritional status of the patients. Additionally, appropriate supplementation of calcium with an aim to keep serum calcium levels in the upper limits of normal, may further reduce the incidence of metabolic bone disease in this patient cohort. Longer-term, prospective studies are needed to further

characterize both the risk factors associated with low bone mineral density and its clinical sequelae such as fractures.

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Table 1**Patient Characteristics**

Characteristic	Mean	Standard Deviation
Gestational Age (Weeks)	33.7	4.6
Birth Weight (Kilograms)	2.3	1.0
Residual bowel Length (cm)	81.5	72.8
Duration of PN (Months)	44.2	43.2
<u>Patient Characteristics</u>		
Characteristic	Number	Percentage (%)
PN at DXA scan	26	40
BMD z-score <-2.0	22	34
Fractures	19	29
Vitamin D def. (<30 ng/ml)	27	42

Table 2
Univariate Predictors of Low BMD (Z-score < -2.0)

Variable	<i>n</i>	DEXA < -2 (Mean ± S.D)	DEXA > -2 (Mean ± S.D)	p-value
Gestational Age (weeks)	62	34.7 ± 4.2	33.2 ± 4.8	0.23
Birth Weight (kgs)	47	2.8 ± 0.8	2.1 ± 1.1	0.05
Residual Bowel Length (cm)	41	95.5 ± 85.2	76.4 ± 68.6	0.47
Citrulline (μmol/L)	55	23.6 ± 13.9	27.2 ± 12.2	0.33
Duration PN (days)	55	1772.9 ± 1453.7	1126.1 ± 1194.3	0.09
Time since weaning of PN (days)	32	2127.9 ± 1921.9	2187.2 ± 1300.0	0.92
Percent Enteral Calories	65	59.7 ± 45.2	76.4 ± 38.2	0.12
WAZ	63	-1.6 ± 1.3	-0.9 ± 1.0	0.01*
Calcium (mg/dL)	55	9.2 ± 0.6	9.5 ± 0.5	0.04*
Phosphorus (mg/dL)	52	4.3 ± 0.7	4.4 ± 0.8	0.51
PTH (pg/mL)	43	42.5 ± 17.1	26.4 ± 18.5	0.006*
Vitamin D (pg/mL)	62	34.9 ± 14.7	33.2 ± 10.8	0.65

* Statistically significant.

Table 3
Multivariate Predictors of Low BMD (Z-score < -2.0)

Variable	Odds Ratio	95% CI	p value
WAZ	1.8	1.1-3.1	0.03 *
Calcium (mg/dL)	3.8	1.2-9.0	0.02 *
PTH (pg/mL)	1.07	0.99-1.15	0.73
PN duration (months)	0.99	0.97-1.02	0.34

* Statistically significant.