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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 and laboratory, clinical, and nutritional intake variables were recorded. Low BMD was defined by a z-score of less than or equal to −2.0. Univariate followed by multivariable regression analysis was performed.

Results: Sixty-five patients underwent a total of 99 routine DXA scans. Twenty-seven (41%) had vitamin D deficiency, 22 (34%) had low BMD, and nineteen (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.

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 enterohepatic 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% to 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.

2. 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

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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). 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/cm^2. 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 antisecretory 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 (less than or equal to −2.0) were compared against those with relatively preserved BMD z-scores (greater than −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 low BMD using z-score cutoff of less than or equal to −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 (±SD).

3. 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 less than or equal to −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 (±72.8) cm and mean duration of PN was 44.2 (±43.2) days.

Patients with BMD z-scores less than or equal to −2.0 [n = 22 (34%)] were compared to those with z-scores greater than −2.0 [n = 43 (66%)]. On univariate analysis (Table 2), the z-score less than or equal to −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%) of patients had vitamin D deficiency (25-OH-D < 30 mg/dl), however there were no statistically significant differences 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 less than or equal to −2 had relatively preserved bone mineral density (BMD z-score greater than −2). 19 (29%) patients experienced at least one fracture. However there was no relationship with low BMD ($p = 1.00$).

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
Characteristic	**Number**	**Percentage (%)**
PN at DXA scan	26	40
BMD z-score of less than −2.0	22	34
Fractures	19	29
Vitamin D deficiency (<30 ng/ml)	27	42

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 owing 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 remain sparse.

In this retrospective review of 65 pediatric patients with IF managed by a multidisciplinary intestinal rehabilitation program, more than a third had very low BMD (z-score less than or equal to −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 during 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% to 70% have been reported [13,16]. This study used dual energy X-ray absorptiometry (DXA), which is now considered the preferred technique owing 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 less than −2 had evidence of impaired bone mineralization (BMD z-score of less than −2). We know that appropriate development of skeletal tissue is contingent upon availability of appropriate quantifies of several micro and macronutrients. These are more likely to be present in a well nourished patient. This implies that 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 reinitiating PN against the possibility of impaired bone mineralization and therapy should be started expeditiously if deemed appropriate.