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Pediatric intestinal failure: Predictors of metabolic bone disease ☆

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ABSTRACT

Purpose: The purpose of this study was to identify risk factors for the development of metabolic bone disease (MBD) in pediatric intestinal failure (IF).
Methods: A retrospective single-center study of 36 pediatric IF patients who were screened for MBD was performed. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA). Simple regression analysis was initially performed to screen predictors, followed by multivariate step-wise linear regression analysis to identify risk factors of MBD.
Results: Mean lumbar spine BMD Z-score was -1.16 ± 1.32, and 50.0% of patients had a BMD Z-score less than −1.0. Deficiency of 25-hydroxyvitamin-D (25-OHD <30 ng/ml) was present in the 63.8% of patients, while 25.0% had hyperparathyroidism (intact parathyroid hormone (PTH) >55 pg/ml). Seven patients (19.4%) had bone pain, of which 4 (11.1%) suffered a pathologic fracture. Using multivariate analysis, parenteral nutrition (PN) duration predicted decreased BMD ($B = -0.132$, $p = 0.006$). Serum 25-OHD nonsignificantly correlated with BMD Z-score ($B = 0.024$, $p = 0.092$). Interestingly, repeat DXA after increasing vitamin D supplementation showed no improvement in BMD Z-score (-1.18 ± 1.49 vs -1.36 ± 1.47, $p = 0.199$).
Conclusions: Pediatric IF is associated with a significant risk of MBD, which is predicted by the duration of PN-dependence. These findings underscore the importance of BMD monitoring. Better therapies for treating IF-associated MBD are needed.

1. Background

Pediatric intestinal failure (IF) occurs when the gastrointestinal tract is unable to sustain life without supplemental parenteral nutrition (PN) [1,2]. The most common cause of IF in children is short bowel syndrome (SBS), followed by congenital absorptive defects, and motility disorders [3], all of which diminish the functional surface area of the gut, preventing adequate absorption of nutrients for growth and development [4]. Among other complications such as sepsis and cholestasis [3,5], patients on PN are at significantly increased risk of developing metabolic bone disease (MBD) [6,7]. This complication, which may manifest as bone pain or pathologic fractures [8], has been shown to disproportionally affect children with IF relative to matched controls [9–11].

The malabsorption that defines IF is a result of decreased intestinal surface area, sometimes compounded by the loss of key, nutrient-specific absorptive regions of the intestinal tract, such as the terminal ileum [12]. Inadequate absorption of calcium, magnesium, and phosphorous engenders prolonged abnormal mineral homeostasis [13], contributing to decreased bone mineralization. In addition, vitamin D deficiency, which is common in children with IF [14,15], may compound calcium and phosphorus dysregulation; leading to worsening abnormalities in bone mineralization.

While the risk of MBD in children with IF has been well established, little prognostic data are available to predict which PN-dependent children will develop MBD. Children on PN have significant limitations on the amount of calcium and phosphorus that can be safely added to the PN solution without the risk of precipitation. While vitamin D supplementation is commonly used in the management of children with IF, the effect of this strategy on MBD development has not been established [16]. Owing to improved medical and surgical management of IF patients, survival is far longer, though associated with prolonged PN-dependence [17–19]. Because of this, understanding the risk factors for MBD becomes increasingly important.

This study was designed to determine the covariates which predicted MBD in a cohort of patients treated at a multidisciplinary IF program. We first examined the bone mineral density (BMD) of IF patients who had undergone dual-energy X-ray absorptiometry (DXA) — a validated tool for tracking bone health in children [20]. We

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then evaluated predictors of developing MBD. Finally, we evaluated BMD changes over time for the subgroup of patients who had undergone an interval DXA.

2. Methods

2.1. Study design

This is a single-center retrospective study of pediatric patients with IF who underwent MBD screening with DXA. The study was approved by the University of Michigan Institutional Review Board (IRB no. HUM00053955). This cohort of patients represented those treated at our multidisciplinary IF-management program between 2006 and 2012. Data collected included gestational age, small bowel length, etiology of IF, presence of the ileocecal valve, duration of PN use, history of cholestasis (highest serum conjugated bilirubin ≥2.5 mg/dL), years since weaning from PN, 25-OH-vitamin D level, serum total calcium, and intact parathyroid hormone (PTH) level. Prematurity was defined as gestational age <37 weeks. Variables such as small bowel length, ileocecal valve presence, and cholestasis have previously been indicated as prognostic factors in pediatric SBS outcomes [21–23]. History of bone pain or pathologic fracture was obtained from the IF clinic note most proximate to the date of the DXA.

2.2. Inclusion criteria

Between the years 2006 and 2012, our IF program routinely began screening patients for MBD once they reached the age of 6 years. Those who underwent DXA at our center during this time were eligible for inclusion. IF was defined as a history of at least 60 days of PN dependence. Only patients diagnosed before 18 years of age were included.

Patients with IF were excluded if an incomplete assessment of MBD was performed. These patients either failed to undergo DXA or did not have laboratory evaluation within four weeks of DXA. In addition, patients with congenital bony abnormalities (n = 2) which could confound BMD measurement were excluded.

2.3. Small bowel length

Small bowel length was defined per the operative report from the surgical procedure at which the diagnosis of SBS was made. A standard method of antimesenteric measurement of unstretched intestine was used. Remaining small bowel was not routinely subdivided into ileal vs jejunal length. Rather than using absolute bowel length as a covariate, we calculated the percent of expected bowel length, corrected for a patient's gestational age at SBS diagnosis [22]. This allowed fair comparison of patients whose bowel was measured at different ages, adjusting for the significant increase in bowel length during the neonatal period [24,25].

2.4. BMD measurement

BMD (g/cm^2) of the lumbar spine (L1–L4) was measured via DXA, using a Hologic Discovery A scanner, and results were analyzed with auto low-density software version 12.6.1 (Hologic Inc., Bedford, MA, USA). BMD measurements were expressed as Z-scores, derived from comparisons to age- and gender-matched, equipment- and protocol-specific reference values [26]. BMD Z-score has been used by prior investigators as a measure of bone mineralization in children [20,27]. MBD was defined as a BMD Z-score of less than −1.0 [9].

2.5. Serum marker measurement

Serum 25-OH-vitamin D, calcium, phosphorus, and PTH levels were all measured within four weeks of the DXA scan. Serum 25-OH-vitamin D <30 ng/ml was defined as vitamin D deficiency [28]. Serum PTH was defined as elevated when >55 pg/ml [27].

2.6. Statistical analysis

Univariate linear regression analysis was first performed to screen all analyzed variables as possible predictors of MBD, using BMD Z-score as the dependent, continuous variable. All nonsignificant variables were eliminated, using a cutoff of $p < 0.1$ for inclusion in multivariate analysis. Multivariate step-wise linear regression analysis was then performed using remaining variables to identify significant predictors of decreased BMD Z-score. $P < 0.05$ was considered significant in the final model. This analysis was conducted for all patients who met inclusion criteria for the primary analysis and for patients who underwent repeat DXA for secondary analysis. Paired t-test was used to compare sequential DXA results. Statistical analysis was performed using SPSS Statistics 19.0 (IBM Corp, Armonk, NY). Data are expressed as mean ± standard deviation (SD), with B = unstandardized coefficient of linear regression models.

3. Results

3.1. Patient characteristics

A total of 38 patients with IF were identified who underwent DXA, with onset of IF treatment at our institution ranging from January 1988 to November 2009. All DXA scans were conducted between October 2006 and December 2012. Data were available for 36 patients who met inclusion criteria (21 male, 15 female; Table 1). Gestational age was 34.2 ± 4.5 weeks (mean ± SD; range 23–40 weeks), and 20 patients (55.6%) had a history of prematurity. Etiologies of IF included necrotizing enterocolitis, intestinal atresia, gastroschisis, volvulus, and non-SBS causes consisting of congenital mucosal and motility abnormalities. Mean follow-up was 9.0 ± 6.6 years (range 66 days–24.3 years). Duration of PN-dependence in this cohort was 5.1 ± 5.4 years, and 25 patients had weaned off PN by the time of their first DXA (69.4%). Thirteen patients (36.1%) remained on PN at the time of DXA.

Table 1
Demographics of IF patients.

	Number*	Percentage
Sex		
Male	21	41.7
Female	15	58.3
Etiology of IF†		
Necrotizing enterocolitis	8	22.2
Gastroschisis	7	19.4
Intestinal atresia	9	25.0
Midgut volvulus	10	27.8
Miscellaneous‡	5	13.9
Outcomes		
Follow-up	9.0 ± 6.6 years	
Gestational age	34.2 ± 4.5 weeks	
Premature (<37 weeks)	20	55.6
Duration of PN	5.1 ± 5.4 years	
Residual small bowel	22.9 ± 22.5% of expected	
Lack of ICV	22	61.1
History of cholestasis	18	50.0
Lumbar BMD Z-score	−1.16 ± 1.32	
25-OH-vitamin D deficiency	23	63.8
Hyperparathyroidism	9	25.0
Pathologic fracture	4	11.1
History of bone pain	6	16.7

* 36 patients met inclusion criteria.
† Etiologies are not mutually exclusive.
‡ Miscellaneous etiologies include microvillus inclusion disease, autoimmune enteropathy, and chronic intestinal pseudo-obstruction. IF = intestinal failure, PN = parenteral nutrition, ICV = ileocecal valve, BMD = bone mineral density.