Growth and bone health in pediatric intestinal failure patients receiving long-term parenteral nutrition\(^1\textsuperscript{-3}\)

Judith Pichler, Sirinuch Chomtho, Mary Fewtrell, Sarah Macdonald, and Susan M Hill

ABSTRACT

Background: Children with chronic intestinal failure (IF) treated with long-term parenteral nutrition (PN) may present with low bone mineral density (BMD). The cause may reflect small body size or suboptimal bone mineralization.

Objective: We assessed growth and bone health in children with severe IF.

Design: Height, weight, and fracture history were recorded. The lumbar spine bone mass was measured in 45 consecutive patients (24 male subjects) aged 5–17 y receiving PN for a median of 5 y. BMD and bone mineral apparent density (BMAD) [ie, adjusted-for-height SD scores (SDSs)] were calculated.

Results: Diagnoses were short bowel syndrome in 12 patients (27%), intestinal enteropathy in 20 patients (44%), and motility disorder in 13 patients (29%). Mean (±SD) weight, height, and body mass index SDSs were \(-0.8 \pm 1.3, -1.80 \pm 1.5, \text{ and } 0.4 \pm 1.3, \text{ respectively. The height SDS was less than \(-2 \text{ in 23 children (50\%). Patients with enteropathy or intestinal mucosal inflammation (associated with dysmotility or short bowel) were significantly shorter than patients without enteropathy (P = 0.007). The BMD SDS was \(-1.7 \pm 1.6, \text{ and the BMAD SDS was } \pm 1.4 \pm 1.5, \text{ independent of primary diagnosis or mucosal inflammation. Nineteen patients (42\%) had low BMD (SDS less than \(-2), \text{ and 14 patients (31\%) had low BMAD. In 25 patients studied at 1–2-y intervals, the BMD SDS fell significantly with time, whereas BMAD declined less, which suggested that a poor bone mineral accretion reflected poor growth. A total of 11 of 37 patients (24\%) had nonpathologic fractures (P = 0.3 compared with the general population).} \}

Conclusions: Approximately 50\% of children were short, and one-third of children had low BMD and BMAD. Children with enteropathy or intestinal mucosal inflammation are at greatest risk of growth failure. Close nutritional monitoring and bespoke PN should maximize the potential for growth and bone mass. Am J Clin Nutr 2013;97:1260–9.

INTRODUCTION

Intestinal failure (IF)\(^4\) occurs when there is a reduction in gastrointestinal function that results in inadequate absorption of fluid and nutrients. Parenteral nutrition (PN) is an essential supportive treatment of patients with severe IF (1). Long-term PN has been defined as treatment >27 d (2). The management of children with IF is challenging because, as well as treating the underlying cause of gastrointestinal disease, there is the additional problem of providing optimal nutrition for normal growth and development. Children with chronic persistent IF who require long-term PN may experience abnormal physical development including poor linear growth, weight gain, and bone formation and delayed puberty (3–6). These problems can be secondary to the disease itself, side effects of treatment, or the effect of systemic or local proinflammatory cytokines (3, 7).

Literature on metabolic bone disease in children receiving long-term PN is scant. However, several studies have suggested that chronic diseases in childhood can result in permanent bone damage or reduced bone mineralization and increased fracture risk (3). Therefore, ensuring optimal bone mass accretion is an important aspect when the chronic disease processes is managed, including in patients who require PN (3, 8, 9).

The cause of metabolic bone disease in patients receiving long-term PN seems to be multifactorial, and several hypotheses have been put forward to explain the pathogenesis. For example, osteomalacia has previously been reported in association with toxicity from aluminum in PN fluids (6, 8, 10). Aluminum exposure from PN over a relatively brief postnatal period in preterm infants was associated with lower bone mass up to 15 y later (11, 12). A negative calcium balance, variable parathyroid hormone concentrations, and vitamin D toxicity have been reported in adults receiving long-term PN (6). Some diseases that lead to IF are, themselves, associated with metabolic bone disease, whereas chronic intestinal inflammation and side effects of medications such as steroids may also contribute to poor bone formation and increased bone resorption.

Our hypothesis was that >50\% of children with severe IF and dependent on receiving PN support would have growth failure.

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\(^4\)Abbreviations used: ALP, alkaline phosphatase; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; IF, intestinal failure; PN, parenteral nutrition; SDS, SD score; 25(OH)D, 25-hydroxyvitamin D.

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and low bone density. Our aims were to 1) assess growth and bone health in children receiving long-term PN, 2) identify which IF-related factors were associated with reduced bone density, and 3) assess longitudinal changes in growth and bone mass by using dual-energy X-ray absorptiometry (DXA).

SUBJECTS AND METHODS

Study population

All children aged ≥5 y who were attending a specialist IF clinic at a tertiary pediatric center from 2002 to 2010 and had been discharged home receiving PN treatment for a minimum of 6 mo were included. All children had undergone extensive intestinal investigations including upper and lower intestinal endoscopy with mucosal biopsies. The children started to receive PN because of a lack of ability to absorb sufficient fluid and nutrients to maintain body weight and growth. All possible methods of feeding by using artificial feeding devices and types of liquid enteral feed (hydrolyzed protein or amino acid–based feed with or without medium chain triglyceride) and modified diets had been tried with specialist dietetic advice.

PN was administered by parents who had undergone a formal 2-wk training program with a specialist nurse. PN was infused overnight, which left the child free during the day to participate in usual childhood activities including attending school, sports (other than contact sports), and swimming.

All children had a DXA scan on an annual basis. An intestinal endoscopy with histologic biopsies, anthropometric measure, and biochemical and hematologic blood tests were performed during the same week.

Patients were grouped into the following 3 categories according to the major underlying disease that caused IF: 1) short bowel syndrome, 2) small intestinal enteropathy, and 3) intestinal motility disorder.

Demographic and clinical variables obtained from medical records were the age at start of long-term PN, current age, sex, weight, height, and BMI. Factors that might have predisposed subjects to low bone mass were also documented at the time of the first (baseline) scan, including intestinal mucosal inflammation and treatment with steroids.

All doses of enteral and parenteral corticosteroids were noted and converted to prednisolone equivalents if necessary. Corticosteroid exposure was summarized as the cumulative cortisone dose ≥6 mo before DXA and dose at the time of the DXA scan.

We also reviewed all patients, including those with a primary diagnosis of a motility disorder or short bowel syndrome, for intestinal mucosal inflammation. The incidence of small intestinal (duodenum and ileum) or colonic mucosal inflammation was obtained from histologic examination of mucosal biopsies obtained at upper and lower endoscopies. All biopsy specimens were reviewed by ≥2 pediatric pathologists. The presence and severity (graded as mild, moderate, or severe) of intestinal mucosal inflammation were classified according to usual or standard histopathologic criteria.

PN and enteral nutrition

PN-related factors recorded were the total duration of PN, number of infusions per week, and contents of glucose, amino acid, lipids, calcium, phosphate, and vitamin D per infusion. Intravenous fat-soluble vitamins were included when intravenous lipid was infused.

Children were divided into 2 groups according to their dependence on receiving PN. Patients in group A were totally PN dependent in that they received >80% of the recommended daily allowance as PN.

Patients in group B were partially dependent on receiving PN in that they had some intestinal absorptive capacity and received 30–80% of the recommended daily allowance as PN. Patients were monitored at specialist clinic visits and given individualized enteral nutrition support that ranged from daily oral supplements of vitamins and minerals to commercially available liquid enteral feeds taken orally or infused into the stomach or proximal small intestine.

Energy and protein provisions were concordant with European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Clinical Nutrition and Metabolism guidelines (2005) and were prescribed according to weight, tolerance, and nutritional requirements within the limitations of PN stability (13).

Anthropometric measures

Weight, height, and BMI were converted to and analyzed as SD scores (SDSs) on the basis of UK Growth Foundation’s published reference data obtained from a British reference population (1990) (14–16). Standard equipment, including clinical electronic scales for weighing and a length board, mat, or stadiometer, was used for the measurement of length or height. Concentrations of serum insulin-like growth factor I and insulin-like growth factor binding protein 3 measured within 6 mo of each DXA scan were documented.

Assessment of bone health

Children underwent an X-ray for bone age within 1 wk of bone densitometry as part of the clinical monitoring protocol. Lumbar spine (L2–L4) bone mineral density (BMD) was measured by using DXA (GE Lunar Prodigy) at baseline and at annual follow-up visits. Scans provided measurements of lumbar spine bone mineral content (g), bone area (cm²), areal BMD (g/cm²), and the machine-derived age and sex-adjusted BMD SDS. However, to adjust for body size, which is well recognized to significantly influence areal bone mass measurements, the bone mineral apparent density (BMAD) as the bone mineral content per bone area (g/cm³) was also calculated (17), and BMAD SDSs for age, sex, and ethnic group were derived by using UK DXA reference data (18, 19). A BMD or BMAD SDS less than −2 was regarded as low as recommended by the International Society for Clinical Densitometry position papers (20). A fracture history was also taken.

Biochemical markers of bone metabolism were documented, including alkaline phosphatase (ALP) and 25-hydroxyvitamin D [25(OH)D] measured ≥6 mo of the DXA scan. A Serum 25 (OH)D concentration <25 ng/mL was considered to represent vitamin D insufficiency (21).

Study approval

Patients underwent a DXA scan as part of routine annual nutritional monitoring. This review was considered to be an audit by the chair of the ethics committee.
Statistics

Statistical analyses were performed with SPSS software (version 20.0 Mac; SPSS Inc). Continuous variables were presented as median, minimum, and maximum values, and categorical data were presented as absolute frequencies and proportions. The chi-square test, t test (compared with zero), and ANOVA were used to compare patients with different underlying causes of IF and to examine the effect of demographic factors, PN- and IF-related factors, and underlying diseases on bone health outcomes and also to examine the effect of illness and treatment-related factors on changes in bone mass after adjustment for changes in body size and age. Regression coefficients and 95% CIs were reported. P < 0.05 was considered significant.

RESULTS

Patient characteristics

Demographic and diagnostic patient data for the period analyzed are shown in Tables 1 and 2. A total of 226 DXA scans were obtained from 45 consecutive patients [21 female subjects (47%) and 24 male subjects (53%); median of 3 scans (range: 1–10 scans) per patient].

The median age at the start of PN was 3.2 y (range: 0.2–15 y). The median age at first DXA scan was 8 y (range: 5–17 y), and the median time receiving treatment with PN at the first scan was 5 y (range: 3–12 y).

The underlying cause of IF was short bowel syndrome in 12 patients (27%), small intestinal enteropathy in 20 patients (44%), and motility disorder in 13 patients (29%). The 12 children with short bowel syndrome were aged 5–14 y when scanned. Two patients had undergone an intestinal resection for gastrochisis with atresia, one patient had undergone an intestinal resection for necrotizing enterocolitis, and 9 patients had undergone an intestinal resection for necrotic volvulus. There were 20 children with an enteropathy aged from 5 to 18 y when scanned. Diagnoses were intestinal epithelial dysplasia or tufting enteropathy in 6 children, congenital enteropathy of unknown cause in 5 children, autoimmune enteropathy in 4 children, Crohn disease in 2 children, and immunodeficiency-associated enteropathy in 3 children. The 13 children with intestinal dysmotility were aged from 5 to 18 y when scanned. Diagnoses were hollow visceral myopathy in 5 children, intestinal neuropathy in 2 children, total colonic aganglionicis in 4 children, and dysmotility of unknown cause in 2 children.

PN

Details of the content of PN prescribed during the period analyzed are shown in Table 1.

Eighteen children (40%) were totally dependent on receiving PN with minimal or no ability to absorb intestinal nutrients, and 26 children (58%) were partially dependent with some intestinal function. One child (2%) had stopped receiving PN when the baseline scan was performed.

Formulation details of the PN were available for 39 of 45 patients. The median nonnitrogen calorie administration per infusion was 59 kcal/kg [mean (±SD): 56 ± 16 kcal/kg; range 24–94 kcal/kg], the median carbohydrate administration per infusion was 11 g/kg (mean: 11 ± 3.7 g/kg; range: 4–18 g/kg), and the median nitrogen administration per infusion was 0.3 g/kg (mean: 0.3 ± 3.7 g/kg; range: 0.1–0.5 g/kg). Lipids were included in the formulation in 33 cases (85%). Thirteen children (39%) received lipids 2 times/wk, and 20 children (61%) received lipids 3 times/wk, with a median lipid administration per infusion of 1.8 g/kg (mean: 1.8 ± 1.1 g/kg; range: 0–3 g/kg). Vitamin D supplementation was given with lipid infusions. The median ergocalciferol supplementation per infusion was 20 IU/kg (range: 0–120 IU/kg). The median phosphate supplementation per infusion was 0.5 mmol/kg (range: 0.1–1.3 mmol/kg), and the median calcium supplementation per infusion was 0.4 mmol/kg (range: 0.1–0.9 mmol/kg).

Mucosal inflammation and use of steroids

Results of intestinal mucosal biopsy histology were available in 43 of 45 patients. In 31 cases (72%), inflammation of the intestinal mucosa was detected, and in 12 cases (28%), histology was normal. The severity of inflammation was mild in 24 cases (77%) and moderate or severe in 7 cases (23%). Five cases with short bowel syndrome and 8 cases with dysmotility had evidence of intestinal inflammation (Table 1).

Fourteen (31%) of 45 cases were treated with an oral low-maintenance dose of prednisolone (range: 2.5–15 mg; median: 10 mg/d; range: 0.02–1.3 mg/kg; median: 0.2 mg/kg) at the time of DXA scan. The cumulative steroid dose up to 6 mo before each DXA scan was 420–2520 mg (2–14 mg/d) per patient treated, with a median of 1680 mg or 9 mg/d. Thirteen of 14 patients given prednisolone treatment had evidence of persistent (although mild) intestinal mucosal inflammation, whereas in one patient, the inflammation had fully resolved.

Patient anthropometric measures

Mean weight, height, and BMI SDSs are given in Table 2. The mean weight SDS was −0.8 ± 1.3 (range: −4.9 to 2.3), the mean height SDS was −1.8 ± 1.5 (range: −4.5 to 1.1), and the mean BMI SDS was 0.4 ± 1.3 (range: −3.4 to 3). All 3 means were significantly different from zero with P < 0.001 for weight and height, and P = 0.04 for BMI compared with reference data. In all, 23 (50%) of 45 children had height SDSs less than −2, which was defined as growth failure.

Results for weight, height, and BMI SDSs according to diagnostic groups are shown in Figure 1. The height SDS was less than −2 in 5 (42%) of 12 children with short bowel syndrome, 14 (70%) of 20 children with small intestinal enteropathy, and 3 (23%) of 13 children with dysmotility. Significantly more patients with small intestinal enteropathy had a height SDS less than −2 compared with that of patients without enteropathy (P = 0.002). The height SDS was significantly lower in children with small intestinal enteropathy than in children with motility disorders (mean: −2.5 ± 1.2 compared with −1 ± 1.5; P = 0.007).

Twenty-four (53%) of 42 children had bone age measured. The median chronological age of these children was 9.2 y (range: 5–18 y) with a median bone age of 7.6 y (range: 3–16 y). Bone age was delayed by more than −2 SDSs in 9 (37%) of the 24 children.

Nineteen (63%) of the 31 children with intestinal inflammation had a low height SDS with a significantly lower mean height SDS...
<table>
<thead>
<tr>
<th>Patient demographics</th>
<th>Values</th>
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<tbody>
<tr>
<td>Patients ($n$ [M (%)])</td>
<td>45 [24 (53)]</td>
</tr>
<tr>
<td>Age at start of PN at home (y)</td>
<td>3.2 (0.2–15.2)</td>
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<tr>
<td>Age at time of DXA (y)</td>
<td>7.7 (5–18)</td>
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<tr>
<td>Time receiving PN at home pre-DXA (y)</td>
<td>5 (3.2–12)</td>
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<tr>
<td>Premature infants [$n$ (%)]</td>
<td>4 (9)</td>
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<td>Gestational ages of the 4 patients (wk)</td>
<td>25, 26, 34, 35</td>
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### Diagnosis [$n$ (%)]

- **Short bowel syndrome**: 12 (27)
- **Volvulus**: 9
- **Gastrochisis**: 2
- **Necrotizing enterocolitis**: 1

#### Small intestinal enteropathy

- **Intestinal epithelial cell dysplasia**: 6
- **Autoimmune enteropathy**: 4
- **Congenital enteropathy of unknown cause**: 5
- **Crohn disease**: 2
- **Immunodeficiency**: 3

#### Motility disorder

- **Hollow visceral myopathy**: 5
- **Total colonic aganglionosis**: 4
- **Intestinal neuropathy**: 2
- **Dysmotility of unknown cause**: 2

#### Intestinal mucosal biopsies [$n$ (%)]

- 43 (96)

#### Inflammatory infiltrate of intestinal mucosa [$n$ (%)]

- 31 of 43 (72)
  - **Mild inflammation [$n$ (%)]**: 24 (77)
    - Short bowel syndrome: 3
    - Small intestinal enteropathy: 15
    - Motility disorder: 6
  - **Moderate or severe inflammation [$n$ (%)]**: 7 (23)
    - Short bowel syndrome: 2
    - Small intestinal enteropathy: 3
    - Motility disorder: 2

#### Steroids used at baseline DXA scan [$n$ (%)]

- 14 (31)
  - Short bowel syndrome: 2
  - Small intestinal enteropathy: 8
  - Motility disorder: 4

#### Steroid dose (mg/d)

- 10 (2.5–15)

#### Steroid dose (mg·kg⁻¹·d⁻¹)

- 0.2 (0.02–1.3)

#### Cumulative steroid dose (mg)

- 1680 (420–2520)

#### Bone age performed [$n$ (%)]

- 24 (53)

#### Bone age (y)

- 7.6 (3–16)

#### Delayed bone age (less than −2 SDS) [$n$ (%)]

- 9 (20)

#### Biochemical markers for growth and bone health

- **IGF-I (ng/mL) ($n=18$)**: $168 \pm 99$³
- **IGF-I SDS**: $-0.1 \pm 1.2$ (−3.5 to 1.6)³
- **IGFBP-3 (ng/mL) ($n=18$)**: 2 (11)
- **IGFBP-3 SDS**: $2.6 \pm 0.8$
- **IGFBP-3 SDS less than −2 [$n$ (%)]**: 6 (33)
- **25(OH)D (ng/mL) ($n=30$)**: 57.6 ± 44
- **25(OH)D <25 ng/mL [$n$ (%)]**: 3 (7)
- **ALP (U/L)**: 207 ± 83
- **Low ALP [$n$ (%)]**: 9 (21)
- **High ALP [$n$ (%)]**: 6 (14)

#### PN characteristics [$n$ (%)]

- **Total parenteral nutrition**: 18 (40)
- **Short bowel syndrome**: 2 (11)
- **Small intestinal enteropathy**: 12 (67)
- **Motility disorder**: 4 (22)
- **Partial PN**: 26 (58)
- **Short bowel syndrome**: 10 (37)

(Continued)
(−2.3 ± 1.5) than that of children without inflammation (−0.8 ± 1.1) \( (P = 0.030) \). There was no association between the degree of growth retardation and inflammation severity.

There were no significant differences in anthropometric values when children who received partial and total PN were compared with children with and without steroid treatment. There was also no association between short stature and biochemical markers for growth and bone health.

DXA results at baseline

Results for the mean (±SD) BMD and BMAD for all patients are shown in Table 3. The BMD SDS was \(-1.7 ± 1.6\) (range: \(-6.5\) to \(1.5\) \( P < 0.001 \)), and the BMAD SDS was \(-1.4 ± 1.5\); range: \(-5\) to \(2.3\) \( P < 0.001 \). Overall, 19 patients (42%) had a BMD SDS less than \(-2\), and 14 patients (31%) had a BMAD SDS less than \(-2\).

The mean BMD SDS was \(-1.3 ± 1\) \( (P = 0.001) \) for patients with short bowel syndrome \((n = 12)\), \(-2 ± 1.7\) \( (P < 0.001) \) for patient with small intestinal enteropathy \((n = 20)\), and \(-1.6 ± 1.9\) \( (P = 0.01) \) for patients with motility disorders \((n = 13)\), with mean BMAD SDSs of \(-1 ± 1.3\) \( (P = 0.02)\), \(-1.7 ± 1.8\) \( (P < 0.001)\), and \(-1.4 ± 1.3\) \( (P = 0.002)\), respectively. There were no significant differences in BMD or BMAD SDSs according to diagnosis, degree of dependence on receiving PN, number of PN infusions per week, steroid use, the presence or severity of

<table>
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<th>TABLE 1 (Continued)</th>
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<tr>
<td>Patient demographics</td>
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<td>Small intestinal enteropathy</td>
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<tr>
<td>Motility disorder</td>
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<tr>
<td>Weaned off PN</td>
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<tr>
<td>Small intestinal enteropathy</td>
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<tr>
<td>Nights per week</td>
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<td>Fat infusions per week</td>
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<tr>
<th>Constituents per infusion</th>
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<tr>
<td>Volume (mL/kg)</td>
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<td>Calories (kcal/kg)</td>
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<td>Carbohydrates (g/kg)</td>
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<td>Nitrogen (g/kg)</td>
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<td>Lipids (g/kg)</td>
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<tr>
<td>Ergocalciferol (U/kg)</td>
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<tr>
<td>Phosphate (mmol/kg)</td>
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<td>Calcium (mmol/kg)</td>
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\(^1\) ALP, alkaline phosphatase; DXA, dual-energy X-ray absorptiometry; IGFBP-3, insulin-like growth factor binding protein 3; IGF-I, insulin-like growth factor I; PN, parenteral nutrition; SDS, SD score; 25(OH)D, 25-hydroxyvitamin D.

\(^2\) Median; range in parentheses (all such values).

\(^3\) Mean ± SD (all such values).

\(^4\) Median; range in parentheses (all such values).

\(^5\) Mean ± SD; range in parentheses (all such values).

\(^6\) Median; mean ± SD, range in parentheses (all such values).

<table>
<thead>
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<th>TABLE 2</th>
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<td>Demographics of patients during the period analyzed according to underlying diagnoses (^1)</td>
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<table>
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<tr>
<th>Patient demographics</th>
<th>Short bowel syndrome</th>
<th>Small intestinal enteropathy</th>
<th>Motility disorder</th>
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<tbody>
<tr>
<td>Patients [n (% of total)]</td>
<td>12 (27)</td>
<td>20 (44)</td>
<td>13 (29)</td>
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<tr>
<td>M [n (%)]</td>
<td>7 (58)</td>
<td>10 (50)</td>
<td>7 (53)</td>
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<tr>
<td>Age at start of HPN (y)</td>
<td>3.2 (0.3–10)</td>
<td>3.6 (0.2–15.2)</td>
<td>3.3 (0.2–15.2)</td>
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<td>Age at time of DXA (y)</td>
<td>8.7 (5.6–14.2)</td>
<td>8.6 (5.2–17.8)</td>
<td>9.2 (5.2–17.8)</td>
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<tr>
<td>Time receiving PN at home pre-DXA (y)</td>
<td>4.5 (2–11.4)</td>
<td>4.4 (0–12.6)</td>
<td>5.1 (1.1–10.9)</td>
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<tr>
<td>Premature infants [n (%)]</td>
<td>4 (9)</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Intestinal mucosal biopsies [n (%)]</td>
<td>11 (92)</td>
<td>20 (100)</td>
<td>12 (92)</td>
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<tr>
<td>No inflammation detected [n (%)]</td>
<td>6 (54)</td>
<td>2 (10)</td>
<td>4 (33)</td>
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<tr>
<td>Inflammatory infiltrate of intestinal mucosa [n (%)]</td>
<td>5 (46)</td>
<td>18 (90)</td>
<td>8 (67)</td>
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<tr>
<td>Mild</td>
<td>3</td>
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<td>6</td>
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<td>Moderate or severe</td>
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<tr>
<td>Steroids used at DXA</td>
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<td>8</td>
<td>4</td>
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<tr>
<td>PN characteristics</td>
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<tr>
<td>Total PN [n (%)]</td>
<td>2 (11)</td>
<td>12 (67)</td>
<td>4 (22)</td>
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<tr>
<td>Partial PN [n (%)]</td>
<td>10 (37)</td>
<td>7 (30)</td>
<td>8 (33)</td>
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<tr>
<td>Weaned off PN [n (%)]</td>
<td>—</td>
<td>1 (2)</td>
<td>—</td>
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\(^1\) DXA, dual-energy X-ray absorptiometry; HPN, home parenteral nutrition; PN, parenteral nutrition.

\(^2\) Median; range in parentheses (all such values).
intestinal inflammation, or presence of 25(OH)D deficiency. Children with ALP concentrations above the age-specific normal range had a significantly lower BMD SDS of \(-3.7 \pm 2.2\) than that of children with normal \((-1.5 \pm 1.5; P = 0.008)\) or low age-specific ALP concentrations \((-1.1 \pm 0.3; P = 0.06)\).

In a multivariate model that included age, weight, and height SDSs, the diagnostic code, and either steroid use or inflammation, the only significant predictor of the BMD SDS was age at the time of scan (coefficient: \(-0.22; 95\% \text{ CI: } -0.34, -0.1\)), with a trend toward a positive association with the height SDS in the model by using steroid use (height SDS coefficient: 0.35; 95\% CI: \(-0.01, 0.71; P = 0.06\)). The addition of bone age to the model did not alter findings.

Longitudinal measurements of bone mass

A total of 35 of 42 children were studied longitudinally. Demographic data for the period analyzed are shown in Table 4. These children had a total of 174 BMD measurements, with a median of 5 scans (range: 2–10 scans) per patient. The general trend was for height and BMD SDSs to decrease with age, which reflected below-average growth. Results of BMAD SDSs were more stable.

DXA compared after 1- and 2-y intervals

Twenty-five children had scans repeated after 1 and 2 y. Over the 1-y period, the mean age difference was 1.1 ± 0.2 y (range: 0.8–1.5 y). The mean change in SDSs between scans was 0 ± 1 (range: \(-1.6\text{ to } 3.3\); NS) for weight, 0 ± 0.4 (range: \(-0.5\text{ to } 0.6\); NS) for height, and 0 ± 1 (range: \(-1.4\text{ to } 3.1\); NS) for BMI. The mean change in BMD SDS was \(-0.3\pm 0.6\) (range: \(-1.3\text{ to } 1.3\); \(P = 0.005\)), and the mean change in BMAD SDS was \(-0.3\pm 0.6\) (range: \(-1.8\text{ to } 0.7\); \(P = 0.005\)).

There was no significant difference in the change in anthropometric measures or bone mass according to the primary diagnosis. Changes in anthropometric measure and (size-adjusted) bone mass over the 1-y period were not significantly predicted by treatment

<table>
<thead>
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<th>TABLE 3</th>
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<tbody>
<tr>
<td>Patient anthropometric measures and results of DXA at baseline*</td>
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<tr>
<td>Patient anthropometric measures</td>
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<td>Weight SDS</td>
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<td>Weight-for-height SDS</td>
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<td>Weight-for-height percentile</td>
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<td>Height SDS</td>
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<td>BMI SDS</td>
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<td>BMD SDS</td>
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<td>BMAD SDS</td>
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*All values are means ± SDs; ranges in parentheses. BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry; SDS, SD score.

\(2\)Cohort compared with reference data (1-sample \(t\) test); \(P\) was significantly different from zero for the SDS.

FIGURE 1. Patient mean (95\% CI) anthropometric SDS and bone mineral density were compared according to diagnosis (n = 45). Children with small intestinal enteropathy were significantly shorter than children with intestinal motility disorder (\(P = 0.007\)). With the use of a 1-sample \(t\) test, children’s data were compared with UK reference data. *Significant differences compared with the UK reference. SDS, SD score.
with low-dose steroids, the presence of intestinal mucosal inflammation, or whether patients received total or partial PN.

Over a 2-y period (mean age difference between scans: 2.1 ± 0.4 y; range: 1.7–2.6 y), there were no significant changes in weight, height, or BMI SDSs. The mean change in BMD SDS was −0.3 ± 0.6 (range: −1.8–0.7; P = 0.04), and the mean change in BMAD SDS was 0 ± 0.6 (range: −0.9–2.3; NS). Changes in anthropometric measure and bone mass over the 2-y period were not significantly affected by the current use of steroids, presence of intestinal mucosal inflammation, whether the patient was treated with total or partial PN, or (in children receiving partial PN) the number of nights per week that PN was given.

In multivariate models including changes in age, weight, and height SDSs, diagnosis, inflammation, and steroids, the only significant predictor of a change in the BMD SDS was a change in the weight SDS.

### Fracture

Fracture data were available for 37 children (80%). Eleven (24%) of 37 children had a history of fractures with a median of 1.3 fractures (range: 1–3 fractures) and incidence of 270 fractures/10,000 person-years. All fractures reported were nonpathologic. There was no association between the occurrence of fractures and known risk factors such as the underlying diagnosis, use of steroids, height, BMD and BMAD less than −2 SDS, intestinal inflammation, 25(OH)D deficiency, and delayed bone age.

### DISCUSSION

In this article, we described the burden of growth failure in children receiving long-term PN, with height SDSs less than −2 at baseline in 50% of patients, and low bone mineralization.
A low weight-and-height-for-age particularly occurred with enteropathy and mucosal inflammation associated with dysmotility or short bowel syndrome. Although we analyzed our patients in these 3 major diagnostic groups (ie, primary short bowel, motility, and mucosal disease), we did not find any association between the underlying disease type and growth and bone density other than mucosal inflammation. The reason for this finding may have been that mucosal inflammation has a greater effect on growth and bone density than any other features of the underlying diseases. Because approximately one-half of children with short bowel syndrome and two-thirds of children with motility disorder also had intestinal inflammation, there were insufficient numbers of children with short bowel syndrome or a motility disorder without inflammation to make a significant comparison between these 2 diagnoses.

One-third of children also had low BMD and BMAD SDSs, although no significant differences were associated with the disease type. The trajectory of bone mass for age tended to decrease with age, which appeared to reflect suboptimal growth because the reduction in size-adjusted bone mass was less marked. Analyses of changes in bone mass over 1- and 2-y periods showed a small decline in the BMD SDS, which was predicted most strongly by changes in the weight SDS, which, again, emphasized the major effect of growth on bone mass accretion. Few studies have described the prevalence of growth failure in children receiving long-term PN. The recent literature concerning this topic has been scarce, which makes comparison difficult, because significant advances in management, including guidelines for the administration of PN, have been made over the past 20 y (13). Growth-failure prevalence is an important topic because poor nutrition at critical periods can result in reduced adult height (12). Colomb et al (22) described abnormal growth in 75% of children who received long-term PN with alternating periods of slower and normal growth velocity. A low height SDS (less than −2) was also reported in 23% of children before intestinal transplantation (4). In contrast, 2 other studies reported significantly improved growth on commencement of long-term PN (3, 5). In one study, weight and height SDSs were within −2 SDs before PN, whereas after the start of PN, the height SDS significantly increased, and the weight SDS was maintained. The second study reported a 2-fold increase in growth velocity in 3 children (5).

The cause of growth failure in IF appears to be multifactorial and involves the following 4 factors: genetic growth potential, chronic inflammation, nutritional intake, and glucocorticoid treatment.

First, certain IF-associated diseases, such as microvillus inclusion disease and intestinal epithelial dysplasia or tufting enteropathy appear to genetically predispose individuals to a short stature (23–25, 27). Growth retardation in these patients remains unexplained by other factors such as nutrient or endocrine deficiency (26). An analysis of the effect of PN in tufting and intestinal epithelial dysplasia on linear growth showed a partial catch-up growth in 58% of cases (>0.5 SDSs), whereas in 25% of cases, the growth rate was unchanged. After 2 y of PN, patients were significantly shorter than age-matched controls (27).

Second, our finding that enteropathy and intestinal mucosal inflammation were associated with growth failure suggested that intestinal inflammation interferes with growth. Inflammatory mechanisms that lead to poor growth are probably similar to those in children with inflammatory bowel disease in whom the inflammatory process, per se, leads to altered secretion and action of growth-promoting hormones. Proinflammatory cytokines (28) [eg, TNF-α, IL-1β, and IL-6 (29–33)] are associated with growth failure. Animal studies have shown that excess proinflammatory cytokines inhibit bone growth by downregulating osteoblast proliferation and enhancing bone resorption by increasing osteoclast numbers (37, 38).

Third, malnutrition inhibits growth. In patients taking total PN, an adequate supply of sufficient nutrients and calories for optimal growth was guaranteed, but our data did not show this growth. One possibility is that children who are totally dependent on receiving PN are the sickest and in whom complications that might inhibit growth are most likely. However, our patients were well established taking home PN and the majority did not have sepsis or other major complications. In contrast, poor growth appeared to be related to the underlying gastrointestinal disease cause (27) rather than PN intake. In a previous study, growth-retarded children gained excess weight (22), whereas in our patients, weight was more proportional to height, probably because we purposely limited energy intake because extra nutrients (including protein) made our patients fatter without improved growth. As a result, the energy supplies of our patients were similar to those of regular- and slow-growth groups as previously reported (22), whereas nitrogen intake was up to 22% higher than that in the slow-growth group. We showed no association between any anthropometric variables and the degree of PN dependency.

A recent study reported an 83% prevalence of metabolic bone disease in children who required long-term PN with fractures in 17% (3). However, the definition of low bone mass used was a BMD SDS less than −1. With the use of a cutoff of an SDS less than −2 as recommended by the International Society for Clinical Densitometry Position Papers (20), we showed 42% of patients had BMD SDSs less than −2, with a prevalence of only 31% for low size-adjusted bone mass (BMAD). Our reported incidence of 24% trauma-associated fractures was similar to that in a previous study (3) and in the general population (P = 0.3) (35). The significant predictors of bone mass in our cohort were age and, to a lesser extent, height SDS, which were consistent with previous findings (3). We did not find a significant association between low BMD and diagnoses, even in longitudinal analyses, although the highest bone mass occurred in patients with short bowel syndrome, and the lowest bone mass occurred in patients with enteropathies, in line with results of adult studies (5, 6, 36). In a similar study in 24 children, significantly milder metabolic bone disease was reported in short bowel compared with enteropathic and motility disorders (3). In both that study and our study, the statistical power was limited by the small sample size.

The fourth factor that might have inhibited growth was glucocorticoid treatment (11, 12, 34). Glucocorticoids affect calcium and bone metabolism by directly affecting osteoblasts and reducing bone formation, increasing bone resorption, reducing intestinal calcium absorption, and increasing renal tubular calcium excretion. In our cohort, low bone mass was not significantly associated with steroid use, probably because a low-maintenance rather than high-dose steroids were given. However, it is difficult to distinguish between the effect of the underlying disorder and the impact of glucocorticoids on bone loss (39).
One previous study reported longitudinal changes in bone mass and showed a significant increase in bone mineralization after 1 y in 9 children receiving PN (3). In contrast, our longitudinal analysis over 1- or 2-y periods showed a mean decrease in BMD SDSs with time, which suggested that bone mass accretion was less than usually expected. In addition, individual trajectories of BMD and BMAD SDSs decreased over longer periods, which suggested that, overall, bone mass for age (BMD SDS) tends to decrease with time, whereas a decline in size-adjusted bone mass (BMAD SDS) is less marked. Our interpretation of these data is that bone mass accretion declines with increasing age primarily because of poor growth. Consistent with this interpretation was that the main predictor of change in bone mass SDS in our analyses was an altered weight SDS. These findings emphasized the importance of optimizing growth to achieve good bone growth and mineral accretion.

Our data were measurements primarily performed for clinical monitoring and, as a result, had limitations. For example, certain biochemical growth markers, bone health, and aluminum exposure data were incomplete.

In conclusion, our data suggest that growth failure is common and affects 50% of children receiving long-term PN. Approximately one-third of patients have low bone mass even after adjustment for reduced height. Poor bone mineral accretion with increasing age was associated with growth failure. These findings may have implications for final adult height, peak bone mass, and the potential risk of osteoporosis and fractures later in life. The results suggest close monitoring is needed to optimize later health. Our current practice and recommendations are to maximize calcium, phosphate, and vitamin D in PN formulations and give additional oral and enteral (and, if necessary, parenteral vitamin D) supplements if required. Children with poor growth and low BMD are also reviewed by a pediatric endocrinologist, and biphosphonate treatment is considered. Surveillance DXA scans are now commenced within 12 mo of discharge home for patients receiving PN.

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