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Original article

Bone health of children with intestinal failure measured by dual energy X-ray absorptiometry and digital X-ray radiogrammetry

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SUMMARY

Background & aims: Children with intestinal failure (IF) receiving long-term parenteral nutrition (PN) are at risk of developing low bone mineral density (BMD). Next to the dual energy X-ray absorptiometry (DXA) method, digital X-ray radiogrammetry (DXR) using the BoneXpert software has become available to obtain the Bone Health Index (BHI) in hand radiographs. In this study we 1) evaluated the prevalence of low BMD in children with IF using DXA and DXR, 2) compared DXA and DXR results, and 3) aimed to identify factors associated with low BMD.
Methods: A retrospective study was performed including all children with IF between 2000 and 2015 who underwent a DXA measurement and/or a hand radiograph. Z-scores of BMD total body (BMD TB) and lumbar spine (BMD LS), bone mineral apparent density (BMAD) and bone health index (BHI) were collected. A low BMD and low BHI were defined as a Z-score ≤ -2. DXA and DXR results were compared for cases in which a DXA and hand radiograph were performed within a 6 months' interval.
Results: Forty-six children were included. Overall, 24.3% of the children had a low BMD at the first DXA at a median age of 6 years; correction for growth failure (n = 6)) reduced this to 16.2%. Fifty percent had a low BHI at the first hand radiograph. Median DXA and BHI Z-scores were significantly lower than reference scores. Age, duration of PN and surgical IF were related to lower Z-scores at the first DXA. Paired DXA and DXR results (n = 18) were compared, resulting in a Cohen's kappa of 0.746 ('substantial') for BMD TB. Spearman's correlation coefficient for BHI and BMD TB Z-scores was 0.856 ($p < 0.001$). Hand radiography had a sensitivity of 90% and specificity of 86% (BMD TB).
Conclusions: Up to 50% of the children had a low BMD. Children with IF have a significantly poorer bone health than the reference population, also after weaning off PN. Bone health assessment by DXA and DXR showed good agreement, especially for Z-scores ≤ -2. DXR assessment using BoneXpert software seems to be feasible for monitoring of bone health in children with IF.

1. Introduction

Intestinal failure (IF) in children is defined as a critical reduction of the gut mass or its function below the minimum needed to absorb nutrients required for adequate growth and development. Children with IF depend on parenteral nutrition (PN) for the intake of the required nutrients. In spite of advanced treatment of IF, complications such as bone disease still often occur [1,2]. The cause of bone disease in children with IF seems to be multifactorial. The

Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; DXR, digital X-ray radiogrammetry; IF, intestinal failure; LS, lumbar spine; PN, parenteral nutrition; SBS, short bowel syndrome; SD, standard deviation; SDS, standard deviation score; TB, total body.

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following factors are thought to contribute: malabsorption or excess loss of calcium and phosphate, vitamin D or K deficiency, chronic intestinal inflammation, medication use (i.e. steroids), PN components (for example aluminum) and the underlying disease itself [2–4]. It has not yet been well established which factors contribute most to IF-associated bone disease.

The prevalence of low bone mineral density (BMD) in children with IF varies between 12.5% and 83%, depending on the definition used and adjustment for delayed growth [1,2,5]. Since more than 90% of the adult bone mass is gained during the first 2 decades of life, low BMD and its consequences may have a great negative impact [6]. Bone health of children with IF is monitored from the age of 4–5 years onwards, the lowest age for which reference data are available for dual-energy X-ray absorptiometry (DXA), the golden standard to assess bone health. However, recently a technique for the evaluation of bone health was introduced for which normative data for Caucasian children above 2 years of age are available. This technique is based on digital X-ray radiogrammetry (DXR) coupled with BoneXpert software (BoneXpert, Version 2, Visiana, Holte, Denmark) in hand radiographs. With this technique, the Bone Health Index (BHI) can be obtained based on the cortical thickness of the three middle metacarpals and the metacarpal width and length of the left hand [7]. Apart from the normative data for younger children, an advantage of DXR is the automated adjustment for actual bone age.

Clinical studies on low BMD in children with IF are scarce, usually cross-sectional and none made use of DXR. In this study we therefore aimed to: 1) evaluate the prevalence of low BMD in children with IF over time; 2) compare DXR and DXA in the assessment of BMD in children with IF; and 3) identify factors associated with low BMD.

2. Material and methods

2.1. Study population and design

All children followed by our multidisciplinary IF-team between 2000 and 2015 were evaluated. All children who underwent at least one DXA or DXR were included. Children could be dependent on PN or already weaned off. PN was prescribed according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Clinical Nutrition and Metabolism guidelines (2005), which take into account weight, tolerance and nutritional requirements [8]. Whenever possible, PN was infused overnight, so that the child could participate in daily life activities including school attendance and sports. Micronutrients (i.e. vitamin D and calcium) were supplemented or individually adjusted on the guidance of the measured levels, also in children weaned off PN. Children weaned off PN also visited our multidisciplinary team at least yearly, depending on their age and clinical condition.

We created three groups by the type of IF:

1) SBS, as defined by the Dutch National Working group on SBS in children [9]:
   - Resection of ≥70% of the small bowel and/or
   - Remaining small bowel length measured distal to the ligament of Treitz:
     - Premature: <50 cm
     - Term neonate: <75 cm
     - Infant > 1 year: <100 cm and
   - PN needed for > 6 weeks after bowel resection
2) Surgical IF – no SBS:
   - Resection of small bowel with remaining small bowel length after resection not as short as covered by the SBS definition above and
   - PN needed for > 6 weeks after bowel resection
3) Functional IF:
   - Motility disorder/enteropathy with need for PN > 6 weeks. Patients who underwent a bowel resection because of functional IF were also classified in this group on the basis of the primary underlying disease.

In clinical practice, some children dependent on HPN do not fulfill the criteria of a real SBS in terms of cm (or %) of small bowel left. They had for example necrotizing enterocolitis, but only a few centimeters were resected. In these cases, the small bowel length is probably not the problem. We therefore chose to classify these patients as surgical IF – no SBS. Due to the small group sizes of children with motility disorders and enteropathies and the fact that both disorders lead to long-term PN dependency, we decided to describe them as one group i.e. functional IF.

2.2. Data collection

We collected data from birth until January 1, 2015 by reviewing the hospital records. Data included patient characteristics, bowel characteristics, growth characteristics and duration of PN. For the patients in groups 1 and 2, start date of IF was defined as the date of first bowel resection. For patients with functional IF (group 3), the start date of PN was defined as start of IF. Prematurity was defined as a gestational age less than 37 weeks. Z-scores of weight-for-age (WFA), height-for-age (HFA), target height (TH) and weight-for-height (WFH) were calculated using Dutch reference data (2010) [10,11]. Patients were considered totally PN dependent when they received 100% of their calories as PN, partially PN dependent when they received less than 100% of their calories as PN. In addition, they were considered weaned off PN when they did not receive PN at the first DXA and did not restart PN afterwards, in contrast to temporary stop when they started again with PN before January 1, 2015.

2.2.1. Assessment of bone health

DXA measurements (GE Lunar Prodigy) were routinely made from the age of 4–5 years, providing measurements of total body (TB) and lumbar spine (LS, L2–L4) BMD (g/cm^2). TB and LS BMD Z-scores were determined by comparing the absolute values to national standards, depending on age and sex [12].

The influence of bone size on measurements of BMD was adjusted using the bone mineral apparent density (BMAD) method. For children with a HFA Z-score < −2 or TH outside the 95% TH range, the BMAD of the lumbar spine was calculated with the following formula [12,13]: BMAD = BMD lumbar spine*[4/(π*mean width of the second to fourth lumbar vertebral body)]. If growth data were not available for the day of DXA, the data obtained closest to this day were used. Data were noted as a missing value when no measurement had been done within the preceding 6 months.

TH in cm, TH Z-scores and 95% TH range were calculated as follows [14]:

- TH boys = 44.5 + (0.376*father's height in cm) + (0.411*mother's height in cm)
- TH girls = 47.1 + (0.334*father's height in cm) + (0.364*mother's height in cm)
- TH Z-score boys = (TH in cm − 183.8)/7.1
- TH Z-score girls = (TH in cm − 170.7)/6.3
- 95% TH range = TH Z-score ± 1.6 SD

Another method we used to adjust for delayed growth was by calculating the BMD with the height age, defined as the age at which the child's actual height was on the 50th percentile (HFA Z-score = 0). According to the International Society for Clinical

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