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

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ABSTRACT

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.

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 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.

MATERIAL AND METHODS

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 home PN 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.

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.

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/cm2). 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

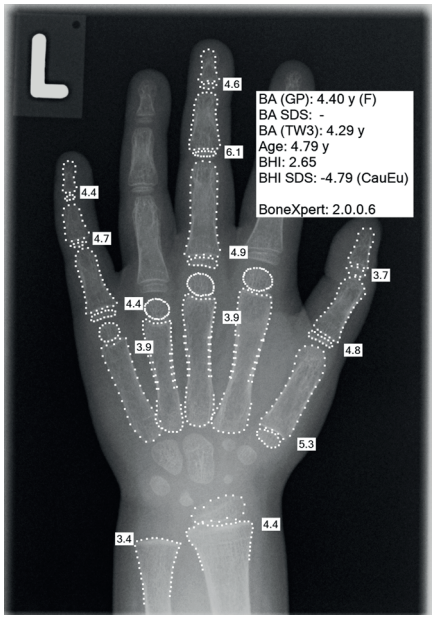
Another method we used to adjust for delayed growth was by calculating the BMD with the height age, defined as the age at which the child's actual height was on the 50th per-

centile (HFA Z-score=0). According to the International Society for Clinical Densitometry, a BMD or BMAD Z-score ≤ -2 was regarded as low.[15]

Next to the use of DXA, bone health was also examined with DXR (**Figure 1**). Standard hand radiographs were taken of the left hand. Bone age was determined based on Greulich-Pyle and the BHI was determined with the BoneXpert software.[7] The formula used is BHI = π x (1 – T/W) / $(LW)^{0.33}$. T is defined as the cortical thickness of the three middle metacarpals, W is the metacarpal width, and L is the bone length. The BoneXpert automatically compares the BHI to a Caucasian reference population with the same sex and converts it to a Z-score adjusted for bone age.[7] Images of hand radiographs made before December 2003 were not available to analyze. Reference values are available for boys above 2.5 years and girls above 2 years of age, and therefore only hand radiographs above this age were analyzed.

The 25-hydroxyvitamin D (25(OH)-vitamin D) concentration in serum was documented, and considered insufficient if < 50 nmol/l. Additionally, the history of fractures was collected.

Figure 1. Example of hand radiograph analyzed with the BoneXpert software



Abbreviations: BA (GP), bone age determined based on Greulich-Pyle; BA SDS, bone age based on Greulich Pyle Z- score; CauEU, Caucasian European patient, BA (TW3), bone age determined based on Tanner-Whitehouse; age, calendar age; BHI, bone health index; BHI SDS, bone health index Z-score.

This study was performed in accordance with the ethical principles of the Declaration of Helsinki. Approval of the local research ethics committee was obtained (MEC-2014-341). Since the retrospective data were analyzed anonymously, a written informed consent was not necessary.

Statistical analysis

Statistical analysis was performed using SPSS Version 21.0 (IBM, Armonk, New York). Categorical variables are summarized as frequency counts and percentages, and continuous variables as mean ± SD when normally distributed or as median and interquartile range (IQR) when not normally distributed. The median duration of PN before the DXA measurement or hand radiograph was calculated with the Kaplan Meier survival curve, since some of the patients were still receiving PN at time of the measurement/radiograph. Differences in continuous variables between the groups were tested using the Mann-Whitney U test for two-groups comparisons, and the Kruskal-Wallis tests for more than two groups. Differences in categorical variables between the groups were tested with the Fisher's exact test. Differences between patients on PN and patients weaned from PN were assessed using the Fisher's exact test and Mann-Whitney U test. To determine whether bone health in the study population differed significantly from that in the reference population, the Wilcoxon one-sample test (compared with zero) was used. To evaluate the change in BMD, the differences between paired measurements (DXA 1 and DXA 2) were calculated and expressed as change per year.

Variables tested for association in univariate regression analysis at the first DXA included sex, age, type of IF, 25(OH)-vitamin D, HFA Z-score (both continuous and dichotomous as Z-score < or ≥ -2), HFA Z-score below TH, WFA and WFH Z-score (both continuous and dichotomous as Z-score < or ≥ -2) and duration of PN. All these variables were included for the multivariate regression analysis with backward elimination (significance level for removal 15%).

To account for the correlations in the repeated measurements of each child we used linear mixed effects models. The fixed-effects part included the covariates duration of PN, presence of PN at measurement, type of IF, interactions between type of IF and duration of PN and the time intervals between the DXA measurements. For the random-effects part random intercepts were included. The optimal random-effects structure was chosen using the AIC criterion, while for the fixed effects p-values were based on t- and F-tests.

DXA and DXR results were compared for cases when the hand radiograph was made within 6 months before or after the DXA. To account for different methodologies, Z-scores were compared. Continuous Z-scores were compared with Cohen's kappa, Spearman correlation coefficient and linear regression.

Statistical significance was set at p-value of 0.05. In case of multiple comparisons, an adjusted significance level was used according to the Bonferroni correction (significance level = 0.05/number of comparisons).

RESULTS

Patient characteristics

Forty-six of the 107 patients followed by our multidisciplinary IF-team between 2000 and 2015 underwent at least one DXA or hand radiograph and were included. Patient characteristics are shown in **Table 1**. The median age at start of IF was 18 days (IQR 3 – 167 days). Twenty-one children (46%) had SBS, 15 children (33%) surgical IF – but no SBS, and 10 children (22%) functional IF. Volvulus was the most common underlying disease, i.e. in 22% of the patients.

DXA results – first DXA

In total, 71 DXA measurements were obtained from 37 patients, with a median of 1 measurement per patient (range 1 - 8 measurements) (**Table 2**). At the first DXA, 76% of the patients were already weaned off PN for a median of 60.1 months (IQR 41.2 – 75.2 months, range 1.3 – 119.1 months). At the first DXA at a median age of 6 years, 24.3% of the children had a low BMD (either BMD TB, LS or BMAD Z-score ≤ -2). Median BMD TB, BMD LS and BMAD Z-scores were significantly lower than the reference population ($p = 0.006$; $p < 0.001$ and $p = 0.004$ respectively). Compared to the reference population, also children weaned off PN at the first DXA had a significantly lower median BMD TB ($p = 0.021$), BMD LS ($p < 0.001$) and BMAD Z-score ($p = 0.012$) than the reference population.

There were no significant differences in BMD Z-scores or BMAD Z-score at the first DXA between the three different groups of IF. Children still receiving PN at the first DXA had a significantly lower median BMD TB Z-score (-1.81, IQR -3.00 to 0.47) than children weaned off PN (-0.34, IQR -1.26 to 0.04, $p = 0.048$). Furthermore, the proportion of patients with a BMD TB Z-score ≤ -2 was significantly higher in the group of patients on PN versus the group of patients weaned off PN ($p = 0.008$).

Factors associated with low BMD

Having an older age at the first DXA was related to lower BMD TB and LS Z-scores at the first DXA ($p = 0.026$ and $p = 0.045$ respectively, in univariate analysis). In addition, having a lower HFA Z-score, a HFA Z-score < -2, a higher WFH Z-score and a longer duration of PN before the first DXA were related to lower BMD LS Z-scores ($p = 0.001$, $p = 0.004$, $p = 0.043$ and $p = 0.044$ respectively).

In a multivariate model that included all variables having an older age at the first DXA and having surgical IF were related to both lower BMD TB and LS Z-scores at the first DXA (**Table 3**). Having a higher WFH Z-score and a longer duration of PN before the first DXA were related to lower BMD LS Z-scores.

At the first DXA or hand radiograph (acceptable time interval ± 6 months), 16 children (33%) had an insufficient 25(OH)-vitamin D. The number of children with an insufficient vitamin D was not significantly different between the group children still on PN and the group children already weaned off. Using univariate or multivariate analysis, this factor was not a significant predictor of BMD Z-scores.

Table 1. Patient characteristics

	N = 46
Gender: male – n (%)	20 (44)
Prematurity (Gestational age < 37 weeks) – n (%)	23 (50)
Age at start of IF (days) – median (IQR)	18 (3 – 167)
HPN – n (%)	29 (63)
Category of IF – n (%)	
SBS	21 (46)
Volvulus	8 (17)
NEC	4 (9)
Intestinal atresia	4 (9)
Gastroschisis	1 (2)
Gastroschisis with atresia	1 (2)
Gastroschisis with volvulus	1 (2)
Ileus	1 (2)
Other	1 (2)
Surgical IF – no SBS	15 (33)
NEC	3 (7)
Intestinal atresia	3 (7)
Volvulus	2 (4)
Ileus	2 (4)
NEC with volvulus	2 (4)
NEC with ileus	1 (2)
Gastroschisis with atresia	1 (2)
Other	1 (2)
Functional	10 (22)
Enteropathy	6 (13)
Motility disorder	4 (9)
Whole small bowel in situ – n (%)	7 (15)
Remaining length small bowel known – n (%)	33 (72)
Remaining length small bowel – median cm (IQR)	50 (31 – 76)
Ileocecal valve in situ – n (%)	27 (59)
Colon in situ – n (%)*	36 (78)
History of enterostomy – n (%)	34 (74)

Legend: *Of which 9 patients without their cecum due to an ileocecal resection.
Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; NEC, necrotizing enterocolitis; SBS, short bowel syndrome.

Table 2. Demographics and results of bone health assessment of patients analyzed divided into three categories

	Total	SBS	Surgical IF – but no SBS	Functional IF
	n = 46	n = 21 (46%)	n = 15 (33%)	n = 10 (22%)
Gender (male (%))	20 (44)	8 (38)	7 (47)	5 (50)
Age at start of IF – days (IQR)	18 (3 – 167)	7 (2 – 43)*	15 (1 – 49)#	395 (24 – 4419)*#
Patients with ≥ 1 DXA (n (%))	37 (80)	18 (86)	14 (93)	5 (50)
Age at first DXA – years (IQR)	6 (5.5 – 9.9)	6.3 (5.5 – 9.8)	5.7 (5.4 – 7.4)	7.5 (5.3 – 14.3)
PN characteristics at first DXA				
Total PN (n (%))	1 (3)	0 (0)	0 (0)	1 (20)
Partial PN (n (%))	8 (22)	4 (22)	1 (7)	3 (60)
Weaned off PN/temporary stop of PN (n (%))	28 (76)	14 (78)	13 (93)	1 (20)
Time receiving PN before first DXA in months – median (IQR)	9.4 (4.6 – 14.3)	10.2 (1.3 – 19.1)	4.5 (1.3 – 7.8)	67.6**
BMD Z-score total body at first DXA – median (IQR)	-0.53 (-1.38 – 0.03)	-0.45 (-1.29 – 0.02)	-0.56 (-1.56 – -0.05)	-1.26 (-3.00 – 2.67)
BMD Z-score total body ≤ -2 at first DXA (n (%))	5 (14)	1 (6)	2 (14)	2 (40)
BMD Z-score lumbar spine at first DXA – median (IQR)	-0.79 (-1.75 – -0.18)	-0.88 (-1.63 – -0.68)	-0.31 (-1.43 – 0.08)	-1.95 (-3.88 – 1.44)
BMD Z-score lumbar spine ≤ -2 at first DXA (n (%))	6 (16)	3 (17)	1 (7)	2 (40)
BMAD Z-score at first DXA – median (IQR)	-0.53 (-1.32 – 0.28)	-0.80 (-1.66 – 0.06)	-0.32 (-0.96 – 0.44)	-0.65 (-3.00 – 1.59)
BMAD Z-score ≤ -2 at first DXA (n (%))	5 (14)	2 (11)	1 (7)	2 (40)
Patients with ≥ 1 hand radiograph (n (%))	34 (74)	18 (86)	7 (47)	9 (90)
Age at first hand radiograph – years (IQR)	4.6 (3.0 – 7.2)	4.2 (3.0 – 6.4)	5.2 (3.5 – 7.3)	3.9 (2.8 – 12.1)
Difference between calendar age and bone age > 1 year (n (%))	9 (27)	3 (17)	1 (14)	5 (56)
BHI Z-score at first hand radiograph – median (IQR)	-2.24 (-3.60 – -0.66)	-1.48 (-3.50 – 0.06)	-2.66 (-3.17 – -0.85)	-3.13 (-4.29 – -1.31)
BHI Z-score at first hand radiograph ≤ -2 (n (%))	17 (50)	6 (33)	5 (71)	6 (67)

Legend: * Significant difference between SBS and functional IF (p = 0.008), # Significant difference between surgical IF but no SBS and functional IF (p = 0.007). ** Due to the low number of events, no 95% CI is given and differences between groups could not be analyzed.

Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; IF, intestinal failure; IQR, interquartile range; LS, lumbar spine; PN, parenteral nutrition; SBS, short bowel syndrome; TB, total body.

Table 3. Factors associated with BMD TB and LS Z-scores – results from multivariate analysis

	BMD TB Z-score B-coefficient	p-value	BMD LS Z-score B-coefficient	p-value
Age	-0.185	p = 0.047	-0.253	p < 0.001
Duration of PN	NA	NA	-0.027	p = 0.010
Group of IF (functional)	1.959	p = 0.019	1.534	p = 0.010
WFH Z-score	NS	NS	-0.366	p = 0.033
HFA Z-score	NS	NS	NA	NA
WFA Z-score	NS	NS	NA	NA

Abbreviations: BMD, bone mineral density; HFA, height-for-age; IF, intestinal failure; NA, not applicable, excluded from regression analysis; NS, not significant; LS, lumbar spine; PN, parenteral nutrition; TB, total body; WFA, weight-for-age; WFH, weight-for-height.

Patients with growth failure

At the first DXA, 6/36 children (17%) had growth failure (HFA Z-score < -2). The median BMAD Z-score of these patients was higher (-0.95 (-3.28 - -0.50)) than the BMD LS Z-score (-2.08 (-2.79 - -1.69)). Two out of these 6 children had a BMAD Z-score ≤ -2, in comparison with a BMD LS Z-score ≤ -2 in 3 of these children.

When using the BMAD for children with a height Z-score below their target height range (6/31, 19%), the median BMAD Z-score was -0.68 (-1.32 – 0.65) in comparison with a BMD LS Z-score of -1.89 (-2.03 – -0.29). While 1 of these 6 children had a BMD LS Z-score ≤ -2, none had a BMAD ≤ -2.

When using the height age method for recalculating BMD values, the median corrected BMD TB Z-score was -0.20 (-0.90 – 0.40) versus the uncorrected -0.53 (-1.38 – 0.03). The median corrected BMD LS Z-score was -0.5 (1.1 – 1.5) versus the uncorrected -0.79 (-1.75 – -0.18). The proportion of patients with a BMD Z-score ≤ -2 changed from 5 to 3 (BMD TB) and 6 to 2 (BMD LS) using this correction method. **Table 4** shows the BMD Z-scores at the first DXA, using corrected values for the children with growth failure. Using these values, 16.2% of the children had an abnormal BMD Z-score (either abnormal BMD TB or BMD LS).

Table 4. BMD Z-scores at the first DXA of all children, using corrected values for children with growth failure

	Total group n = 37
BMD Z-score TB, using height age corrected BMD values for children with GF, median (IQR)	-0.37 (-1.29 – 0.03)
BMD Z-score TB ≤ -2, using height age corrected BMD values for children with GF, (n (%))	3 (8)
BMD Z-score LS, using BMAD values for children with growth failure, median (IQR)	-0.71 (-1.43 – -0.18)
BMD Z-score LS ≤ -2, using BMAD values for children with growth failure, (n (%))	5 (14)

Abbreviations: BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; GF, growth failure; LS, lumbar spine.

Longitudinal bone health measurements

Thirteen children had multiple DXA measurements. The median age difference between the first and the second DXA measurement was 2.01 years (1.09 – 2.44 years). The median change in Z-scores per year was +0.16 SD (-0.07 – 0.51) for BMD TB and +0.09 (-0.05 – 0.54) for BMD LS. Using linear mixed models, we did not find any significant predictors of the course of BMD.

Hand radiograph results – first hand radiograph

In total, 66 hand radiographs were obtained from 34 children (Table 2), with a median of 1 hand radiograph per patient (range 1 – 6 hand radiographs). Five hand radiographs (7.6% of all) could not be analyzed due to technical reasons, 1 hand radiograph (1.5%) could not be analyzed because of the very low bone age of this patient. Median BHI Z-score was significantly lower than the reference population ($p < 0.001$). Seventeen children (50%) had a BHI Z-score ≤ -2.

Fractures

In total, 4 children developed multiple fractures, all after minimal trauma, including one child with vertebral compression fractures. The underlying diseases were congenital villous atrophy of unknown origin, jejunal atresia, filamin A mutation with intestinal pseudo-obstruction and microvillus inclusion disease. The age at the first fracture was 5.4 years, 7.7 years, 2.1 years and 1.9 years, respectively. All children were 100% PN dependent at the time of the first fracture. Three patients received bisphosphonates. Two of them had BMD Z-scores TB and/or LS ≤ -2. For the other patient Z-scores were not available because of his young age. The youngest patient did not receive bisphosphonates since her DXA Z-scores were good. None of the patients used enteral or parenteral corticosteroids.

Comparison of DXA and hand radiograph

Z-scores

At a median chronological age of 10.4 (DXA) and 10.1 years (hand radiograph), 24 measurements from 18 patients were paired. Hand radiography (BHI) had a sensitivity of 90% (BMD TB) and 60% (both BMD LS and BMAD) and a specificity of 86% (BMD TB), 79% (BMD LS) and 93% (BMAD) when taking DXA as the reference method (**Tables 5a, 5b and 5c**).

In 16.7% (BMD TB) and 20.8% (BMD LS and BMAD) of the pairs, DXA Z-scores and BHI Z-scores differed > 2 SDS (total of 7 analyzed pairs in 4 patients).

Table 5a. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMD total body) in 18 children

	Low BMD TB	Normal BMD TB	Total
Low BHI	9	1	10
Normal BHI	2	12	14
Total	11	13	24

Table 5b. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMD lumbar spine) in 18 children

	Low BMD LS	Normal BMD LS	Total
Low BHI	6	4	10
Normal BHI	3	11	14
Total	9	15	24

Table 5c. Comparison of classification of bone health according to X-radiograph (BHI) and DXA (BMAD) in 18 children

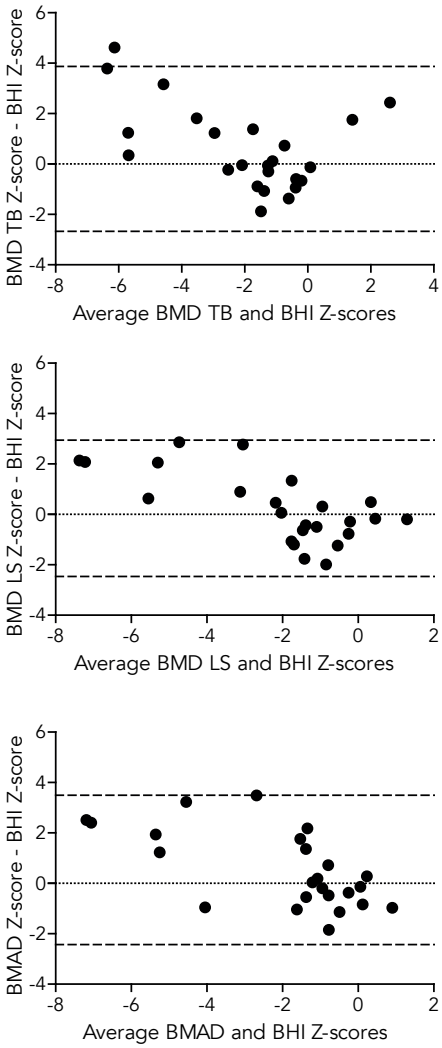
	Low BMAD	Normal BMAD	Total
Low BHI	6	4	10
Normal BHI	1	13	14
Total	7	17	24

Legend: Data are presented as n. Low = Z-score ≤ -2, Normal = Z-score > -2.
Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; LS, lumbar spine; TB, total body.

Continuous values

Comparison of continuous values of BMD methods yielded Cohen's kappa values of 0.746 (BMD TB, considered substantial), 0.393 (BMD LS, considered fair) and 0.573 (BMAD, considered moderate). There was a significant positive correlation between the BHI Z-score and DXA Z-scores (BMD TB Z-Score; 0.856, $p<0.001$; BMD LS Z-score; 0.799, $p<0.001$ and BMAD Z-score; 0.647, $p=0.001$). **Figure 2** shows the Bland-Altman plots.

Figure 2. Bland Altman plots indicating the differences between DXA (BMD TB, LS and BMAD) and hand radiograph measurements (BHI) for Z-scores



Legend: The horizontal axis shows the mean of the two methods (DXA and DXR) and the vertical axis indicates the difference. The dotted lines represent the 95% limits of agreement.
Abbreviations: BHI, bone health index; BMAD, bone mineral apparent density; BMD, bone mineral density; DXA, dual energy X-ray absorptiometry; LS, lumbar spine; TB, total body.

DISCUSSION

The aim of this study was to assess the prevalence of low BMD in children with IF and to compare two different methods to assess bone health in these children. We also aimed to identify factors influencing the bone health. Our results suggest, firstly, that hand radiography is a feasible alternative method for the assessment of bone health in children with IF. Secondly, we found that up to 50% of the children with IF have a low BMD and that children with IF have a significantly lower BMD than healthy controls. More important, our results show that low BMD is also common after weaning off PN. Thirdly, we found several factors influencing BMD Z-scores at the first DXA, although we could not find any significant predictors of the course of bone health in this retrospective cohort.

To our knowledge, this study is the first comparing DXA and DXR in children with IF. Since hand radiographs are part of the routine growth work-up in children with IF, DXR is an easy method to obtain information about bone health and does not need additional radiation. Other important advantages of DXR include the availability of reference values for young children, direct adjustment for bone age and low costs.[16,17] Correlation coefficients between DXR and DXA were comparable with coefficients found in previous studies in children with growth hormone deficiency and acute leukemia.[18] The Bland Altman plots show that the difference between DXR and DXA tends to be larger when the average of these methods is more negative. Additionally, the variability is not consistent, which is probably due to the relatively small number of measurements. Results for DXR and DXA differed greatly (> 2 Z-scores) in 7 analyzed pairs obtained from 4 patients. In all cases, the BHI Z-score was more negative than the BMD TB Z-score, likely because DXR is more sensitive to deviations than DXA. Additionally, in 5 of these 7 pairs, both the BMD TB Z-score and the BHI Z-score were ≤ -2. Most important for clinical practice, our results show that the agreement between DXR and DXA was good for low BMD (Z-scores ≤ -2), as defined by the International Society for Clinical Densitometry.

Unfortunately, 5 (7.6%) of the hand radiographs could not be analyzed by the BoneXpert software because they were too sharp. This percentage was higher than that in previous studies.[19,20] This could be explained by the fact that those images were not originally intended for BoneXpert analysis. The BoneXpert method is intended to be used on digital radiographs which have not been artificially sharpened by image postprocessing (so called edge enhancement). Since we were unable to recover the original 'raw' images, these images could not be analyzed. In future application of the BoneXpert, it should be ensured that the hand radiographs are not postprocessed excessively.

In this study, the prevalence of low BMD ranged between 14 and 50% depending on the method used (DXA or DXR). A previous study in children with IF reported a prevalence

of low BMD of 83% measured by DXA but used a cut-off BMD Z-score < -1 instead of Z-score ≤ -2.[2] Another study[1] reported a prevalence of low BMD (Z-score ≤ -2) of 42%. The discrepancy in the prevalence of low BMD obtained by DXA measurements may be explained by the different populations studied. The patients in this study by Pichler et al. received PN for a longer period before the first DXA was made (5 years versus 9 months), were older (8 versus 6 years) and commonly had mucosal inflammation and steroid use.[1] Furthermore, most of our patients were weaned off PN at the first DXA. The prevalence we found is comparable with that found by Mutanen et al.[4] This emphasizes the need for continued monitoring of bone health after weaning off PN.

In the present study, the prevalence of children with a low BHI measured by DXR was higher than the prevalence of low BMD measured by DXA. This is probably due to the fact that hand radiographs were performed in children too young for a DXA measurement considered having a high risk of low BMD. Regarding the consequences of low BMD, 4/46 children (8.7%) had multiple fractures, which is lower than previously reported.[1,2,21]

Median BMD and BMAD Z-scores were significantly lower than those in the reference population, not only for patients still receiving PN but also for children already weaned off PN. This is comparable with previous studies.[1,4] BMD Z-scores between the first and second DXA showed a small increase in BMD Z-scores. A previous longitudinal study showed a significant increase in BMD after 1 year in children on PN.[2] Another study, however, reported a mean decrease in BMD Z-scores over 1 and 2 years.[1] These studies are difficult to compare because of different study populations and definitions. In order to be able to compare study results, we propose to use the definition of the International Society for Clinical Densitometry.

Among all the PN and IF-related factors, age and duration of PN had a significant negative influence on the BMD Z-scores of the first DXA. Surgical IF was related to lower Z-scores at the first DXA, in contrast to other studies showing that children with enteropathies and motility disorders had the lowest bone mass.[1,2] Additionally, having a higher WFH Z-score was related to lower Z-scores. This might be explained by the fact that children with a higher WFH Z-score have lower HFA Z-scores (poorer growth), and therefore are inappropriately diagnosed with low BMD because correction for poor growth is not taken into account. In our population, the WFH Z-score was significantly higher in the group of children with a HFA Z-score < -2 ($p = 0.049$, results not shown). 25(OH)-vitamin D levels were not a significant predictor of BMD Z-scores. Using linear mixed models correcting for the correlations in the repeated measurements we did not find any significant predictors of the course of BMD. This may be explained by the relatively small number of repeated measurements in this study.

At the first DXA, around 20% of the children had growth failure or was growing below their TH range. Using the BMAD and height age for these patients reduced the number of children inappropriately diagnosed with low BMD, comparable with the study of Fewtrell et al.[22] Overall, 24.3% of the children had a low BMD at the first DXA without correction for growth failure. Correction reduced this to 16.2%, which might be more realistic. However, BMAD and corrected BMD Z-scores are mainly used for research purposes and not regularly in clinical practice. Additionally, around 25% of the patients had a delayed bone age (difference of > 1 year with calendar age). It would therefore be useful to correct the BMD for bone age in these patients. However, since only 2 of these patients with a delayed bone age had a DXA measurement within 6 months of the hand radiograph, this analysis was not possible.

Some limitations of this study should be addressed. First, as we only included children that underwent a DXA or hand radiograph, there could be a selection bias. Since no strict protocol was followed during the early years of the inclusion period, it is possible that the DXA measurements and hand radiographs were mainly made in children considered at high risk of poor bone health. When we compared these 46 patients to the other 60 patients treated between 2000 and 2015 by our IF team who did not underwent a DXA measurement or hand radiograph, the duration of PN was significantly longer for the described study population (10 months) than for the children that did not underwent a DXA or hand radiograph (6 months). However, the children that did not undergo a DXA measurement or hand radiograph were significantly younger that the children included in our study (median age at January 1, 2015 of 2.9 years versus 9.4 years) and 20 of them were still too young to undergo a DXA measurement or hand radiograph. Prospective studies with monitoring of bone health according to a strict follow-up protocol, will lead to more insights. Second, results of hand radiographs and DXA measurements could not be compared for the younger infants, while the use of the hand radiographs is especially important in this group. Third, because of the retrospective nature of our study, data on associated clinical factors important for bone health, such as vitamin/mineral intake, enteral intake and physical activity could not be systematically collected and therefore not be taken into account. It is, however, part of our practice to give supplements when necessary and nutritional advice at each outpatient visit. Fourth, as our data were collected retrospectively and bone health was measured as part of clinical monitoring, only relatively few repeated measurements were available, restricting longitudinal analysis. Fifth, it was difficult to compare subgroups because of their small sample sizes. Despite these limitations, this longitudinal study still provides novel findings in a representative population of children with IF.

In conclusion, up to 50% of the children with IF in this study were found to have low BMD, even after adjustment for growth failure. Low BMD may have great implications

for gaining peak bone mass and is a risk factor of bone fractures. Close monitoring, prevention and treatment of poor bone health is therefore essential. Since most of these children were already weaned off PN, bone health should be monitored also after weaning. Although further prospective studies need to confirm this, DXR using the BoneXpert software seems to be feasible for monitoring BMD in children with IF, which can be applied from the age of 2.5 years onwards.

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Addendum

Treatment of intestinal failure-associated bone fractures with bisphosphonates

ABSTRACT

Background/aims

Children with intestinal failure (IF) are at risk for developing low bone mineral density and osteoporosis. Bisphosphonates can be used for the treatment of osteoporosis. The aim of this study was to describe the effect of bisphosphonates on prevention of IF-associated bone fractures.

Methods

All children treated by the IF team in the Erasmus Medical Center – Sophia Children's Hospital from August 2003 to June 2016 with bone fractures who had received bisphosphonates were included retrospectively.

Results

Out of a total of 55 patients, 3 children with bone fractures who had received bisphosphonates were identified. Underlying diseases were congenital villous atrophy, jejunal atresia and intestinal pseudo-obstruction. Two children developed vertebral compression fractures. With a follow-up between 25 and 132 months after the start of bisphosphonates, new fractures were not seen in 2 of the 3 children. No serious side effects were found.

Conclusion

In our IF population of the last 13 years, 3 children developed bone fractures and received bisphosphonates. After the start of bisphosphonates, no new fractures were seen in 2 of the 3 patients. Future larger, controlled prospective studies are needed to confirm the effect of bisphosphonates on the prevention of IF-associated bone fractures.

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.[1] Children with IF depend on parenteral nutrition (PN). They are at risk for developing a low bone mineral density (BMD), which seems to be multifactorial.[2,3]

Current monitoring of bone health takes place from the age of 4-5 years onwards, when reference data are available for dualenergy X-ray absorptiometry (DEXA). The prevalence of low BMD in children with IF varies between 13% and 83%, depending on the definition and adjustment for delayed growth.[2,3] Studies have demonstrated that the risk of fractures increases with declining BMD.[4] How often children with IF experience fractures varies between 5% and 24%.[2,3,5] The diagnosis of osteoporosis is made when vertebral compression fractures are present or when the patient has a clinically significant fracture history (≥ 2 long bone fractures by age 10 years or ≥ 3 long bone fractures at any age up to age 19 years) and a BMD SD score (SDS) ≤ -2.0.[6]

Bisphosphonates are used for the treatment of osteoporosis. They inactivate osteoclasts and thereby inhibit bone resorption. One study showed that treatment with bisphosphonates was effective for improving BMD in six children with IF-associated bone disease.[7] None of these children experienced fractures, so it is not well known whether bisphosphonates also have an effect on prevention of IF-associated bone fractures.[7] In this report, we describe 3 children with IF-associated bone fractures and the consequent treatment with bisphosphonates.

MATERIALS AND METHODS

All children with IF who were attending the multidisciplinary IF outpatient clinic in the Erasmus Medical Center – Sophia Children's Hospital from August 2003 to June 2016 who had developed bone fractures were included retrospectively. Our population consisted of 61 children who received home PN (HPN), 6 of them were lost to follow up because of transfer to another IF outpatient clinic.

All fractures were confirmed with x-rays. We collected the BMD SDS obtained with DEXA, based on Dutch reference data.[8] When the height-for-age (HFA) SDS was < -2.0, we calculated the bone mineral apparent density (BMAD).[8] The protocol was to perform DEXA scans from the age of 4-5 years onwards in all children on HPN, and earlier in children with fractures. DEXA scans were repeated every two year when the SDS were normal and yearly when the SDS was < -1. For metatarsal and vertebral compression fractures, we considered the development of multiple fractures at the same moment as one fracture.

PN was described according the European Society for Paediatric Gastroenterology, Hepatology and Nutrition guidelines. We gave bisphosphonates intravenously. Patient 1 received pamidronate in an administration scheme of 3-day infusion every 3 months. This protocol was changed into single-day pamidronate (2 mg/kg) every 3 months for all consecutive patients. All patients received half dose the first time. We collected data from birth until January 10, 2017 by reviewing the medical records.

The local Institutional Review Board of the Erasmus MC in Rotterdam waived the need for consent.

RESULTS

Patient characteristics

Out of the total of 55 patients with IF receiving HPN and treated by our IF team (35 children with PN > 1 year), 3 children with bone fractures who were treated with bisphosphonates were identified. **Table 1** shows the characteristics of these 3 children, whereas **Table 2** displays the DEXA scan results and number of fractures in relation to treatment with bisphosphonates. All fractures were symptomatic.

Table 1. Characteristics of the 3 children with IF and bone fractures

Patient	Sex	Ethnicity	Underlying disease	Age at first fracture years	Duration of PN at first fracture years	Vertebral compression fractures	Other fractures	Age at January 10, 2017 years
1	F	Caucasian	Villous atrophy of unknown origin	5.4	5.0	1: L3 2: Th10-Th12, L1-L2	1: Spiral fracture tibia 2: Distal femur 3: Distal humerus 4: Distal radius (greenstick)	22.5
2	M	Indo-Mediterranean	Jejunal atresia	7.7	7.7	1: Almost all thoracic vertebrae and L1-L4	-	9.9
3	M	Caucasian	Filamin A mutation with intestinal pseudo-obstruction	2.1	1.9	-	1: Distal radius 2: Distal antebrachii 3: Distal femur 4: Proximal radius 5: 4th metatarsal bone 6: Distal fibula 7: 2nd – 5th metatarsal bone	4.7

Abbreviations: IF, intestinal failure; PN, parenteral nutrition.

Patient 1 was born with congenital villous atrophy of unknown origin, for which she started with PN soon after birth. She received PN until the age of 10 years. After that she did tolerate full enteral nutrition. During PN she developed 4 bone fractures and the diagnosis osteoporosis was made. Because of muscle weakness she was walking with a rolling walker. One year after weaning from PN, she developed vertebral compression fractures and started with pamidronate. Her last pamidronate infusion was 9 years ago, after which she did not develop any bone fractures.

Patient 2 is a boy with jejunal atresia and a remaining small bowel length of 65 cm. He was dependent on PN from birth onwards, mainly due to gastrointestinal motility problems. At the age of 7 years, he developed backache. A lateral spinal radiograph showed vertebral compression fractures. Besides the treatment with pamidronate, he wore a brace for a few months. He did not develop any bone fractures after the start of pamidronate.

Table 2. DEXA scans and bone fractures before and after treatment with bisphosphonates

Patient	Age at the start of pamidronate years	Duration of PN at the start of pamidronate years	Height for age at the start of pamidronate SDS	DEXA before pamidronate BMD SDS	DEXA after pamidronate BMD SDS (months after first pamidronate)	Number of pamidronate infusions n (years)	Fractures before pamidronate n (months)	Fractures after start pamidronate n (months)
1	11.55	9.80	-6.12	TB: - 1.7 BMAD LS: not possible	TB: - 4.0 (39) BMAD LS: -5.9 (39)*	4 (1.8)	5 (134)	0 (132)
2	7.93	7.93	-0.03	TB: - 2.7 LS: - 3.3	TB: -1.7 (25) LS: -2.1 (25)	6 (1.6)	1 (25)	0 (25)
3	2.38	2.09	0.05	Not available	TB: Not measured LS: -1.8 (23)	8 (2.1)	2 (95)	5 (29)

Legend: * 2 years after last dose of pamidronate.
Abbreviations: BMAD, bone mineral apparent density; BMD, bone mineral density; DEXA, dual energy X-ray absorptiometry; LS, lumbar spine; PN, parenteral nutrition; TB, total body.

Table 3. Serum concentrations of vitamin D, calcium, phosphate, PTH and ALP and intake of vitamin D, calcium and phosphate before treatment with bisphosphonates

Patient	25-OH vitamin D (mmol/L)	Calcium (mmol/L)	Phosphate (mmol/L)	PTH (pmol/L)	ALP (U/L)	Vitamin D intake (IE/day)	Calcium intake (mmol/kg/day)	Phosphate intake (mmol/kg/day)
1	72	2.11	1.42	11.5*	255	1000 cholecalciferol + 0.3 microgram alphacalcidol orally	Unknown, no PN	Unknown, no PN
2	81	2.40	1.51	5.6	539*	600 (PN) + 1600 cholecalciferol orally	0.2 (PN) + 1000 mg calcium carbonate orally	0.8 (PN)
3	34*	2.32	1.45	22.8*	325	400 (PN)	0.2 (PN)	0.2 (PN)

Legend: *abnormal values. Reference values: 25-OH vitamin D: 50-120 nmol/L, calcium: 2.10-2.60 mmol/L, phosphate: 1.10-1.95 mmol/L (1-3 years) and 1.00-1.80 mmol/L (3-12 years), PTH: 1.4 – 7.3 pmol/L, ALP: <410 U/L (infant), <424 U/L (child).
Abbreviations: ALP, alkaline phosphatase; PN, parenteral nutrition; PTH, parathyroid hormone.

In patient 3, osteoporosis was highly suspected because of the recurrent low impact bone fractures he developed. However, no reference values for BMD are available for his age. Unfortunately, the Bone Health Index could not be determined with the BoneXpert software because of poor image quality of the hand radiograph. As a side effect, hypocalcaemia was found, for which the calcium intake was increased 3-4 times the standard.

Risk factors

Patient 1 and 3 used prophylactic low-molecular weight heparin during treatment with PN to prevent catheter-related thrombosis. No steroids were used. We optimized the amounts

of vitamin D and calcium (both in the PN and enterally) in all children (**Table 3**), after which the serum concentrations normalized. Vitamin K levels were normal in all children. They did not have renal disease. All patients were 100% PN dependent when they developed their first fracture, as they did not tolerate any enteral nutrition except minimal enteral feeding. Aluminum toxicity was not likely because of the use of polyethylene bags. All patients had decreased physical activity when they developed their first fracture; they were less active during daily life and did not do sports. Therefore, we stimulated the performance of weight-bearing exercise. Patients 2 and 3 were still dependent on PN on January 10, 2017.

DISCUSSION

Poor bone health is a serious problem in children with IF.[2,3] Until now, studies mainly reported about the prevalence of low BMD [2,3], and it is not well known if bisphosphonates are effective in preventing future fractures. From the total group of 55 patients receiving HPN, 4 children (7.3%) developed bone fractures. In comparison with previous studies, the percentage of children that developed fractures is low.[2,3,5] The young age of these children illustrates the severity of IF-associated bone disease. Three patients were treated with bisphosphonates. The 4th patient did not receive pamidronate because of good DEXA values. After treatment with bisphosphonates no new fractures were seen in 2 of the 3 patients.

The cause of poor bone health seems to be multifactorial. Factors that may contribute are lack of physical activity, the underlying disease and vitamin D deficiency. All children did not tolerate any enteral nutrition at the time of their first fracture, which suggests that these children might lack some essential nutrients for bone accretion. Furthermore, it is striking that in the present report, all children had a lack of physical activity. The fact that patient 2 regained normal daily activities and therefore had a marked increased physical activity after starting bisphosphonates could have contributed to the fact that he did not develop any further fractures. Regarding the underlying disease, bone disease and fractures have not been described previously in patients with filamin A mutation.[9] Another study did not find an association between the occurrence of fractures and the underlying diagnosis.[10] When comparing the 3 children that received bisphosphonates with the other 33 children on HPN that also underwent DEXA scans, the median BMD SDS for this group at the first DEXA were higher (-0.45 for total body and -0.78 for lumbar spine). Furthermore, vitamin D deficiency was also frequently found in the population of 55 children on HPN.

Early detection and treatment of poor bone health is essential. When children are totally dependent on PN, we advise to make DEXA scans yearly, to be informed about the risk of osteoporosis. Our advice is to perform yearly hand radiographs starting from the age of 2 years to evaluate bone health with the BoneXpert software.[11] With this software it is possible to obtain a Bone Health Index (BHI) SDS. The main advantage of this software is the direct adjustment for bone age and the fact that reference values are available for young children i.e. ≥ 2.5 years of age. Attention should be paid when children with a low BMD present with back pain and a lateral spinal radiograph should be made at low threshold. When the diagnosis osteoporosis is made or highly suspected, children should be referred to a pediatric endocrinologist and bisphosphonates should be considered. A possible side effect of bisphosphonates might be inhibition of growth plate activity and therefore bisphosphonates should be given only when indicated. We give pamidronate

2 mg/kg/day every 3 months for 1 year. After that maintenance for two years may be considered. Moreover, prevention of poor bone health is very important and includes stimulating the performance of weight-bearing exercise, e.g. walking stairs. Calcium and vitamin D intake should be optimized both enterally (if possible) and parenterally.

To the best of our knowledge, we are not aware of any study reporting on children with IF-associated bone fractures who received bisphosphonates. In our IF population of the last 13 years, 4 children with IF developed IF-associated bone fractures, of whom 3 received bisphosphonates without serious side effects. No new fractures were seen in 2 of the 3 patients after the start of bisphosphonates; future larger, controlled prospective studies are needed to confirm a therapeutic effect.

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