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Original article

Bone mineral density and vitamin D in paediatric intestinal failure patients receiving home parenteral nutrition

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SUMMARY

Background & aims: Patients with intestinal failure (IF) are dependent on long-term home parenteral nutrition (HPN) to ensure growth and development. The primary aim of the present study was to assess bone mineral density (BMD) and vitamin D status in paediatric IF patients on HPN and a group of healthy children aged 2–18 years. Secondary aims were to assess growth, body composition, nutrient provision and physical activity.

Methods: An observational cross-sectional study was performed at Oslo University Hospital and at the Department of Nutrition, University of Oslo, from January to September 2017. Dual energy x-ray absorptiometry (DXA; Lunar Prodigy in IF patients and Lunar iDXA in healthy subjects) was performed to assess BMD and body composition. BMD z-score (BMDz) was calculated for total body and lumbar spine L2-L4 based on the integrated reference population in the software. Weight and height were measured for growth assessment. Nutrient provision was assessed by a 4-day food record. Blood samples were analysed for 25-hydroxy-vitamin D (25(OH)D) and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Physical activity was reported by a questionnaire.

Results: Nineteen IF patients and 50 healthy children were included. The mean age of participants was 10.0 years. The aetiology of IF patients was paediatric intestinal pseudo-obstruction (58%), short bowel syndrome (26%), and intestinal enteropathy (16%). Lower median BMDz for total body (−0.4 vs 1.1, $P < 0.001$) and lumbar spine L2-L4 (−0.9 vs 0.2, $P = 0.01$) were found in the IF group compared with the healthy children. Vitamin D provision was significantly higher in IF patients (17 μg/d vs 5.3 μg/d, $P < 0.001$). Both groups were sufficient in 25(OH)D (IF patients 71 nmol/L vs healthy 81 nmol/L). Nevertheless, IF patients had significantly lower $1,25(OH)_2D$ than healthy children (71 pmol/L vs 138 pmol/L, $P < 0.001$). The IF group was significantly shorter (height for age z-score −1,5 vs 0,1, $P = 0.001$) and lighter (weight for age z-score −1,0 vs 0,1, $P = 0.009$) compared with the healthy subjects. BMIz did not differ; however, body fat percentage was significantly higher in IF patients compared with

Abbreviations: BMD, Bone mineral density; BMDz, Bone mineral density z-score; BMI, Body mass index; BMIz, Body mass index for age z-score; ESPGHAN, European Society of Paediatric Gastroenterology, Hepatology and Nutrition; Htz, Height for age z-score; HPN, Home parenteral nutrition; IF, Intestinal failure; NNR, Nordic Nutrition Recommendations 2012; OUH, Oslo University Hospital; PN, Parenteral nutrition; RI, Recommended intake; TPN, Total parenteral nutrition; UiO, University of Oslo; Wtz, Weight for age z-score.

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healthy children (34% vs 25%, $P = 0.02$). A lower frequency of physical activity was found in the IF group compared with the healthy group ($P = 0.001$).
Conclusions: Paediatric IF patients on HPN had lower BMD, impaired growth, and higher body fat percentage in comparison with the healthy children. Despite a higher total supply of vitamin D in the IF group, the levels of 25(OH)D did not differ. Nevertheless, a significantly lower level of $1,25(OH)_2D$ was found in IF patients. The results raise questions regarding differences between oral and parenteral vitamin D provision and whether intestinal function is important for the metabolism of vitamin D.
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1. Introduction

Intestinal failure (IF) is a consequence of a reduced mass or function of the gut. Long-term home parenteral nutrition (HPN) is required to supply enough fluid, energy, macronutrients, and micronutrients. The most common diagnosis related to IF is short bowel syndrome, congenital absorptive defects, and motility disorders [1]. The reported prevalence varies across studies, ranging from 9.6 children per million in the Netherlands to 13.7 per million in the United Kingdom [2,3].

Metabolic bone disease in association with long-term parenteral nutrition (PN) was first described in paediatric patients in 2010 [4]. Peak bone mass refer to the maximum amount of bone accrued in an individual during young adulthood. It can be defined as the amount of bony tissue present at the end of the skeletal maturation [5] and occurs by the end of the second or early in the third decade of life [6]. Lifestyle factors influence 20–40% of adult peak bone mass. Therefore, optimization of modifiable lifestyle factors in childhood and adolescence is important for the prevention of osteoporosis, fractures, and bone pain. Evidence has been found for a positive contribution from calcium, vitamin D, and physical activity on bone health [7]. Due to the risk of precipitations in parenteral nutrition solutions, ensuring adequate amounts of calcium and phosphorus may be difficult. Poor nutritional status, including vitamin D deficiency, growth failure, and high fat mass, have been found in IF patients [4,8–13]. This can be related to suboptimal PN, malabsorption, and faecal loss of energy, proteins, fluids, and electrolytes. Inflammation, medical treatments (e.g. steroids), inactivity, and genetic factors may also contribute to poor bone health [7,14].

Few studies have analysed bone mineral density (BMD) and vitamin D status in children with IF on HPN. In particular, studies including data on nutrient supply from both parenteral and enteral nutrition routes are lacking. The primary aim of this study was to assess BMD and vitamin D status in a group of paediatric IF patients on HPN in comparison with a group of healthy children. The secondary aims were to assess growth, body composition, nutrient provision, and physical activity between the two groups.

2. Materials and methods

2.1. Subjects

An observational cross-sectional study was conducted on paediatric patients with IF treated with long-term HPN and a group of healthy children from March to September 2017. Inclusion criteria were patients aged 2–18 years and dependent on HPN for more than 6 months at routine follow-up examination at the Paediatric Intestinal Failure Team at Oslo University Hospital (OUH). A reference group of healthy children in the same age group was recruited using advertisement via social media. The inclusion criteria were residence in the Oslo area and eating a diet without any restrictions. Clinical and demographic data were obtained from medical records and questionnaires. Patients were examined at the hospital and the healthy participants at the Clinical Nutrition Research Centre at the University of Oslo (UiO). A subgroup of age- and sex-matched healthy participants was used to explore the vitamin D results.

2.2. Anthropometry

Patients' weight (kg) was measured by Seca weight (model 7701321004, seca gmbh & co. kg, Germany) and height (cm) by a stadiometer (Holtain Limited, Britain). Healthy participants were measured using a combined digital measuring station (Seca 284, seca gmbh & co. kg, Germany). Z-scores for weight for age (Wtz), height for age (Htz), and BMI for age (BMIz) were calculated based on the Norwegian reference population [15]. Underweight was defined BMIz <-2 and overweight as BMIz >2. Stunting was defined as Htz <-2.

2.3. Dual-energy x-ray absorptiometry

Dual-energy x-ray absorptiometry (DXA) is the preferred method for assessing bone and body composition as it is rapid and precise with robust paediatric reference data. DXA is considered safe with low effective x-ray dose (range, 0.03–15.2 μSV) [16]. Children aged 5 years and older were measured for BMD (g/cm^2) and bone mineral content (BMC, g) total body and anterior-posterior lumbar spine L2-L4, fat percentage, and lean mass. BMD z-score (BMDz) were calculated according to available reference materials in the software [17]. IF patients underwent DXA using Lunar Prodigy, software enCORE, version 16 (GE Healthcare, Lunar Corp., Madison, WI, USA) at the Department of Endocrinology, OUH. Healthy participants were measured at UiO by Lunar iDXA, software enCORE, version 16 (GE Healthcare). The scanners were calibrated daily by a phantom, and the same person evaluated all data. DXA is an area measurement and does not capture the depth of bone. Hence, volumetric BMD for children with poor growth will be underestimated. Adjusting for this is recommended [18], and results were adjusted for skeletal age measured by hand radiograph in three IF patients with Htz <-2. Suboptimal BMDz was defined as ≤-1 to -1.99, and low BMDz defined as ≤-2 [18].

2.4. Nutrient provision

All participants completed a 4-day food record [19], using household measures and a booklet of portion sizes [20]. All foods, drinks, and dietary supplements were recorded. IF patients were also instructed how to record tube-feeding and PN. Enteral

nutrition was defined as all oral intake and enteral nutrition support. DietistPro, a software for dietary analysis based on the Norwegian Food Composition Table [21], was used by trained dietitians to calculate nutrient intake. PN prescriptions were provided by the Hospital Pharmacies, and mean supply during 7 days was calculated and used in the analysis of total nutrient provision. Enteral nutrition was compared with recommended intake (RI) from the Nordic Nutrition Recommendations [22]. PN was compared with European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/European Society for Clinical Nutrition and Metabolism/European Society of Paediatric Research/Colorado Society for Parenteral and Enteral Nutrition recommendations [23–28]. Estimated energy requirement was calculated using sex, age, and weight and compared with Nordic Nutrition Recommendations for low activity level [22]. Parents and medical records provided data on the initiation and duration of PN.

2.5. Blood analyses

Blood samples were performed according to routine procedures at the study visit. The analyses were done at the Hormone Laboratory, OUH. Vitamin 25(OH)D was quantified by liquid chromatography–tandem mass spectrometry with determination of 25-hydroxyvitamin D2 (25(OH)D2) and 25-hydroxyvitamin D3 (25(OH)D3) levels. The sum of 25(OH)D2 and 25(OH)D3 levels is referred to as 25(OH)D. The coefficients of variation were 10–17% [29]. The method was standardised according to the Vitamin D Standardization Program. Vitamin D sufficiency was defined as total 25(OH)D > 50 nmol/L [30–32].

Enzyme immunoassay (IDS Nordic) was used to measure $1,25(OH)_2D$. The reference range for $1,25(OH)_2D$ was 75–250 pmol/L for children aged 3–18 years according to the manufacturer. The coefficients of variation were 9–11% [29].

Plasma parathyroid hormone (PTH), alkaline phosphatase (ALP), ionised calcium, phosphate, creatinine, urea, albumin, bilirubin, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma glutamyltransferase (GT) and C-reactive protein were analysed at the Department of Medical Biochemistry, OUH.

2.6. Physical activity

To assess usual physical activity level, the participants filled out a questionnaire on frequency per week of sessions lasting more than 30 min ("never or less than once," "1–3 sessions," "4 sessions or more"). Participation in different sports and the intensity of physical activity were also asked for in the questionnaire.

2.7. Statistical considerations

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25 (Armonk, New York). Shapiro–Wilk test was used for normality testing. Normally distributed data were presented as means and standard deviations, and an independent-samples *t*-test was used for analysis between pairs of groups. Non normally distributed data were presented as medians with 25th to 75th percentiles, and analysis between pairs of groups was performed by Mann–Whitney *U* test. Categorical data were presented as frequencies, and Chi-square or Fisher's exact test were used to test differences between groups. Missing variables were excluded pairwise. The level of significance was two-sided and set to $P < 0.05$. Subgroup analyses for vitamin D status were performed using age- and sex-matched healthy participants in comparison with the IF patients.

2.8. Ethical statement

Informed consent was collected from parents and participants aged 16–18 years. Approval for the study was obtained from the Regional Committee for Medical and Health Research Ethics in Norway (REC nr. 2016/391) and the Head of the Department and the Research committee, OUH. The study was registered in Clinical Trials (AEV2017/1), and the ethical standards of the Declaration of Helsinki were followed.

3. Results

3.1. Characteristics of participants

The study included all 19 available IF patients at OUH and a group of 50 healthy children. Characteristics of the participants are presented in Table 1. There were no differences in age between the groups (mean, 10.1 and 10.0 years, respectively). Pubertal stage was not assessed, but 32% of patients in the IF group and 30% of the healthy children were older than 12 years. There were significantly more boys in the IF group. The aetiology of IF patients was paediatric intestinal pseudo-obstruction (58%), short bowel syndrome (26%), and intestinal enteropathy (16%). Most subjects were Caucasian; one IF patient and one healthy child were Asian, and one patient was African. The IF patients had been on HPN for a median of 4.4 years at inclusion.

The IF group was significantly shorter (Htz) and lighter (Wtz) compared with the healthy group. BMIz did not differ between groups; however, body fat percentage was significantly higher in the IF group (Table 2). Overweight (BMIz >2) was found in 11% of IF patients and none of the healthy patients ($P = 0.07$), whereas none of the IF patients and 4% of the healthy children were underweight (BMIz <−2). Among the IF patients, 33% were classified as stunted compared with 4% of the healthy participants ($P = 0.003$).

3.2. Bone mineral density

Twelve of the IF patients and 46 of the healthy children were measured by DXA. Five IF patients and one healthy child could not manage the procedure, and two IF patients and three healthy patients were younger than 5 years. Two healthy children did not measure lumbar spine. In three of the DXA-measured IF patients, BMDz were adjusted for delayed growth according to skeletal age. Significantly lower median BMDz for total body (−0.4 vs 1.1, $P < 0.001$) and lumbar spine L2-L4 (−0.9 vs 0.2, $P = 0.01$) were found in the IF group compared with the healthy group (Fig. 1). A suboptimal BMDz for total body was found in 25% of the IF patients.

Table 1
Characteristics of participants.

	Intestinal failure (n = 19)	Healthy (n = 50)	*P*-value
Age, years (mean, SD)	10.1 (3.5)	10.0 (3.6)	0.93[a]
Gender (boys, n (%))	13 (68)	18 (36)	0.03[b]
Diagnosis, n (%)			
Motility disorder	11 (58)		
Short bowel syndrome	5 (26)		
Intestinal enteropathy	3 (16)		
Anthropometry, mean (SD)			
Height, cm	130.3 (19.2)	139.9 (18.4)	0.07[a]
Weight, kg	31.1 (11.2)	36.7 (14.4)	0.13[a]
BMI, kg/m^2	17.9 (2.4)	17.9 (3.2)	0.98[a]

SD: standard deviation.
[a] Independent-samples *t*-test.
[b] Chi-square, Continuity Correction.

Table 2
Growth, body fat percentage, and blood results in intestinal failure patients and in healthy children.

	Intestinal failure (n = 19)	Healthy (n = 50)	*P*-value
Growth, mean (SD)			
Htz	−1.5 (1.7)	0.1 (1.2)	0.001[b]
Wtz	−1.0 (1.6)	0.1 (0.9)	0.009[b]
BMIz	0.2 (1.0)	0.0 (1.1)	0.51[b]
Body composition, median (25–75 percentile)[a]			
Body-fat, %	33.6 (24.6–38.9)	24.9 (20.9–27.9)	0.02[c]
Plasma, median (25–75 percentile)			
PTH, pmol/L	4.6 (3.0–5.0)	4.1 (3.3–5.3)	0.97[c]
ALP, U/L	218 (200–301)	220 (174–257)	0.25[c]
Ionized calcium, mmol/L	1.27 (1.23–1.30)	1.26 (1.23–1.28)	0.68[c]
Phosphate, mmol/L	1.58 (1.30–1.60)	1.40 (1.30–1.50)	0.35[c]
Creatinine, μmol/L	37 (31–44)		
C-reactive protein	0.5 (0.5–46.5)	0.5 (0.5–34)	0.35[c]

SD: standard deviation, Htz: Height for age z-score, Wtz: Weight for age z-score, BMIz: Body mass index for age z-score, PTH: parathyroid hormone; ALP: alkaline phosphatase.
[a] n = 12/46, dual energy x-ray absorptiometry.
[b] Independent-samples *t*-test.
[c] Mann–Whitney *U* test.

Lumbar spine L2-L4 was low in 25% and suboptimal in 17% of IF patients, and suboptimal in 5% of healthy participants.

3.3. Nutrient provision

Parenteral, enteral, and total dietary provisions of macronutrients, vitamin D, calcium, and phosphorus are presented in Table 3. PN was used by all and enteral nutrition (oral diet and/or enteral nutrition support) by 79% of IF patients. Four patients were on total parenteral nutrition (TPN). Total energy intake was median 105% of RI in IF patients and 85% of RI in healthy children ($P = 0.08$). IF patients received a median of 76% of their estimated energy requirement from PN. Total energy, protein, and fat provision per kilogram (kg) were not significantly different, but carbohydrates were higher in IF patients compared with healthy children (9.3 g/kg vs 5.9 g/kg, $P = 0.005$; Table 3). The carbohydrate provision was higher than recommended by the parenteral guideline [26]. Amino acids [25] and lipids [27] were within recommendations.

Total vitamin D provision was significantly higher in IF patients compared with healthy children (17 μg/d vs 5.3 μg/d, $P < 0.001$; Table 3). Parenteral vitamin D_2 (median 10 μg/d) was used by 95%, and 1 patient was on fat-free PN. Oral vitamin D supplements were used by 32% of IF patients and 28% of healthy children.

All IF patients had parenteral calcium ($CaCl_2$) supply below recommendation. For parenteral phosphorus, 47% had an intake below the recommendation [28]. Sodium glycerophosphate ($C_3H_7Na_2O_6P$) was used by all IF patients, except one patient using monopotassium phosphate (KH_2PO_4). One IF patient used an oral calcium supplement (1000 mg/day). Enteral calcium intake was less than RI in 84% of IF patients and in 42% of healthy children [22]. Enteral phosphorus was less than RI in 74% of IF patients, but none of the healthy subjects. Enteral calcium and phosphorus intake were significantly lower in IF patients compared with healthy children (Table 3).

3.4. Vitamin D status

Both groups were sufficient in 25-hydroxy-vitamin D (25(OH)D) (IF patients 71 nmol/L vs healthy 81 nmol/L, $P = 0.29$; Fig. 2a). Analyses for age- and sex-matched groups did not change results (IF patients 71 nmol/L vs healthy 81 nmol/L, $P = 0.36$). No significant difference in 25(OH)D was found for healthy participants included during March–June (n = 34) compared with August–September (80 nmol/L vs 86 nmol/L, $P = 0.24$), or for matched groups (85 nmol/L vs 81 nmol/L, $P = 0.81$). Seasonal analyses of IF patients could not be done as all were included during March–June. Vitamin 25(OH)D < 50 nmol/L was found in two IF patients (10%), and one of these had severe deficiency (14 nmol/L). One healthy participant had 25(OH)D at 45 nmol/L. Vitamin 25(OH)D ≥ 75 nmol/L was found in 47% of the IF group and 66% of the healthy children.

The IF group had significantly lower 1,25-dihydroxyvitamin D levels compared with the healthy group (71 pmol/L vs 138 pmol/L, $P < 0.001$; Fig. 2b). Subgroup analyses for age- and sex-matched groups were performed, and a significant difference between the IF group and healthy children was still present (71 pmol/L vs 140 pmol/L, $P = 0.001$).

3.5. Other blood biomarkers

No significant differences were found between the IF patients and the healthy group for blood levels of PTH, ALP, ionized calcium, or phosphate (Table 2). Creatinine and urea were normal in all except two IF patients with elevated levels. Apart from elevated levels of; ASAT in three, ALAT in five and GT in two, all IF patients had normal liver function tests, including normal values for bilirubin and albumin. One IF patient had elevated ASAT, ALAT and GT, and was the only participant detected with severe vitamin D deficiency; 25 (OH)D 14 nmol/L.

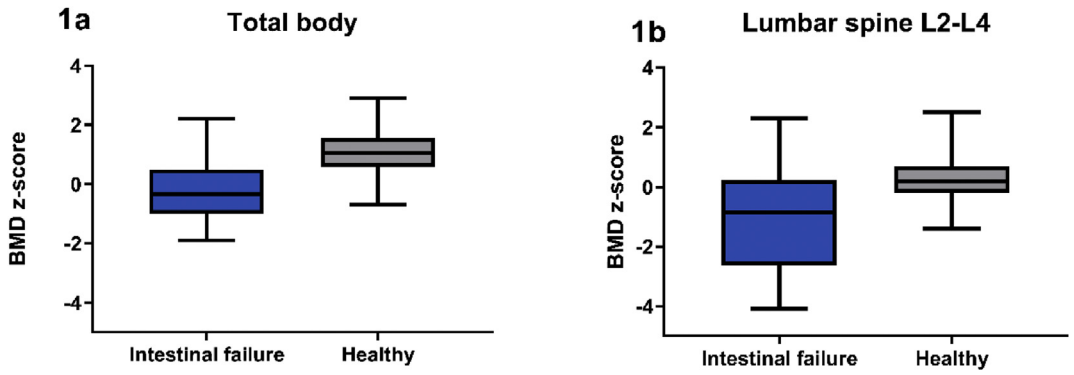

Fig. 1. BMD z-scores in paediatric intestinal failure patients (n = 12) and healthy children (total body n = 46, L2-L4 n = 44) in (a) total body ($P < 0.001$) and (b) lumbar spine L2-L4 ($P = 0.01$; Mann Whitney *U* test). Results were adjusted for delayed height (Htz <−2) in three intestinal failure patients.

Table 3
Daily nutrient provision in paediatric intestinal failure patients and healthy children and guidelines for enteral and parenteral nutrition.

Median (25–75 percentile)	Intestinal failure (n = 19)	Healthy (n = 50)	*P*-value[a]	Guideline enteral[b]	Guideline parenteral[c]
Parenteral nutrition					
Energy, kcal	1414 (687–1804)				
Energy, kcal/kg	37 (32–53)				75–25
Amino acids, g	45.4 (21.7–58)				
Amino acids, g/kg	1.3 (1.1–1.8)				2.5–1.0
Glucose, g	210.4 (95.5–265.3)				
Glucose, g/kg	5.5 (4.4–8.1)				8.6–1.4
Lipids, g	32.7 (17.0–55.0)				
Lipids, g/kg	1.1 (0.9–1.5)				≤3
Vitamin D, μg	10.0 (7.5–15.0)				10–15
Calcium, mmol/kg	0.15 (0.13–0.18)				0.25–0.4
Phosphorus, mmol/kg	0.20 (0.16–0.23)				0.2–0.7
Enteral nutrition					
Energy, kcal	705 (73–1100)	1913 (1499–2052)	<0.001		
Energy, kcal/kg	24 (2–35)	51 (39–69)	<0.001		
Protein, g	22.8 (2.0–38.3)	72.5 (57.3–90.5)	<0.001		
Protein, g/kg	1.0 (0.1–1.3)	2.3 (1.8–2.7)	<0.001	≥0.9	
Carbohydrates, g	94.6 (15.6–138.9)	216.1 (174.7–249.8)	<0.001		
Carbohydrates, g/kg	3.0 (0.3–4.7)	5.9 (4.4–8.3)	<0.001		
Lipids, g	20.8 (0.0–43.8)	67.0 (53.9–78.5)	<0.001		
Lipids, g/kg	0.7 (0.0–1.5)	2.0 (1.5–2.5)	<0.001		
Vitamin D, μg	3.0 (0.9–10.1)	5.3 (2.7–9.9)	0.42	10	
Calcium, mg	187 (20–574)	801 (652–985)	<0.001	600–900	
Phosphate, mg	368 (21–658)	1349 (1061–1746)	<0.001	470–700	
Total nutrient provision					
Energy, kcal	1834 (1278–2399)	1913 (1499–2052)	0.74		
Energy, kcal/kg	67 (42–74)	51 (39–69)	0.12		75–25
Protein, g	63.0 (48.3–77.0)	72.5 (57.3–90.5)	0.05		
Protein, g/kg	2.2 (1.4–2.6)	2.3 (1.8–2.7)	0.48	≥0.9	2.5–1.0
Carbohydrates, g	281.6 (181.9–368.0)	216.1 (174.7–249.8)	0.03		
Carbohydrates, g/kg	9.3 (6.2–11.2)	5.9 (4.4–8.3)	0.005		8.6–1.4
Lipids, g	55.0 (37.1–73.6)	67.0 (53.9–78.5)	0.13		
Lipids, g/kg	2.0 (1.4–2.3)	2.0 (1.5–2.5)	0.79		≤3
Vitamin D, μg	17.0 (10.5–26.2)	5.3 (2.7–9.9)	<0.001	10	10–15

PN: parenteral nutrition, EN: oral diet and/or enteral nutrition support.
[a] Mann–Whitney *U* test.
[b] Enteral recommendations for low activity level (The Nordic Nutrition Recommendations) [21].
[c] Parenteral recommendations for stable/recovery phase in children 1–18 years or weight >11 kg (European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)/European Society for Clinical Nutrition and Metabolism/European Society of Paediatric Research/Colorado Society for Parenteral and Enteral Nutrition recommendations) [22–27].

3.6. Physical activity

An overall lower level of physical activity participation was found in IF patients compared with healthy subjects (Table 4). A significant difference in sports participation was detected (26 vs 2%, $P = 0.01$), and the intensity of physical activity participation was lower in IF patients than in healthy participants ($P < 0.001$; data not shown).

4. Discussion

This cross-sectional study of paediatric IF patients on long-term HPN revealed lower BMD, impaired growth, and higher body fat percentage in comparison with healthy children. Vitamin D provision was higher in the IF patients compared with the healthy children, and total intake was in line with recommendations. The level of 25(OH)D was sufficient, and not different between the two

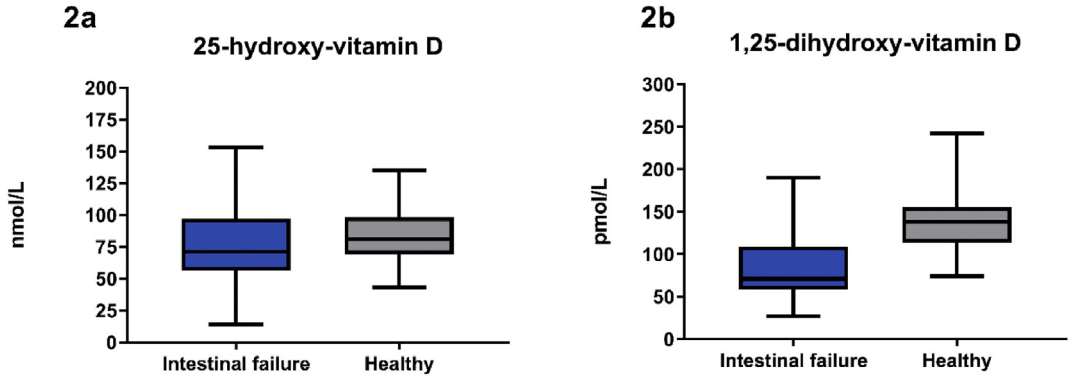

Fig. 2. Vitamin D status in paediatric intestinal failure patients (n = 19) and healthy children (n = 48) measured by (a) 25-hydroxy-vitamin D ($P = 0.29$) and (b) 1,25-dihydroxy-vitamin D ($P < 0.001$; Mann Whitney *U* test).

Table 4
Sessions of physical activity per week in the intestinal failure patients and in the healthy children.

	Intestinal failure	Healthy	*P*-value[a]
	n (%)	n (%)	
Sessions per week			
<1	5 (26.3)	1 (2)	0.001
1–3	12 (63.2)	28 (56)	
≥4	2 (10.5)	21 (42)	

[a] Fisher's exact test, effect size by Cramer's V = 0.444, $P = 0.001$.

groups. Nevertheless, a significantly lower 1,25$(OH)_2$D level was found in IF patients.

Significantly lower BMDz for total body and lumbar spine L2-L4 were found in IF patients compared with healthy children (Fig. 1). Total body BMDz was suboptimal in 25% of IF patients. In L2-L4 25% of IF patients had low, and 17% had suboptimal BMDz. Other studies support this finding [4,9,12,13,33–36], with prevalence values from 12.5 to 88%. Differences between studies are related to selected cut-off points, small study populations, heterogeneous aetiology, different skeletal sites reported, and differences in the correction methods for growth delay. In addition, most studies reported results for a combination of patients who were receiving and weaned off PN.

Stunting was found in 1/3 of IF patients, a significantly higher proportion than in healthy children. Other studies have confirmed the risk of growth delay in this patient group [4,8–12,34–37]. Growth delay can be multifactorial, e.g. related to the disease itself, genetics, inflammation, medications used, and/or related to malnutrition. In this study, a low provision of calcium and phosphate was found simultaneously to a low serum 1,25$(OH)_2$D. This combination increase the risk of growth delay and bone mineral deficits [7,38].

Lower physical activity was found in IF patients in comparison with healthy children (Table 4). This may be an important factor contributing to the reduced BMDz (Fig. 1) and higher body fat percentage detected in the IF patients (Table 2). Reliance on PN might reduce the possibility of participating in physical activities. Lean mass is a strong predictor for bone mass, as muscle force stimulates bone mineral accrual in children and adolescence [7]. Therefore, it is important to include individual advice on physical activity as part of the follow-up routine of patients on HPN.

High glucose supply could contribute to an increase in fat mass in IF patients. The proportion of overweight was not different between the two groups, but carbohydrate provision was higher in IF patients.. Compared with parenteral guidelines, total carbohydrate provision was above the recommendation [26]. This recommendation may also be discussed in terms of the importance of meeting energy requirements to ensure growth, and the alternatives of increasing lipids and/or amino acids. The recommendation for carbohydrates states that both enteral and parenteral supply should be evaluated together [26]. This is different from the recommendations for parenteral amino acids [25] and lipids [27] where enteral supply is not mentioned.

Differences in vitamin D, calcium, and phosphate provision were present between the groups (Table 3). Parenteral vitamin D supply (10 μg/d) was in accordance with the guideline of 10–15 μg/day [23]. The total vitamin D provision of IF patients was significantly higher than in the healthy children (17 vs 5.3 μg/day). Enteral intake was not different (3.0 vs 5.2 μg/day), both lower than RI of 10 μg/day [22]. Total provision of available calcium and phosphate in the IF group compared to the healthy is difficult to assess because of a combined supply from enteral and parenteral routes, and that absorption may be affected in the IF patients. However, results indicates low supply of both minerals, which is negative for optimization of bone health [7]. The combination with low vitamin 1,25$(OH)_2$D may be even more negative as the active form plays an important role in the control of calcium absorption in the intestine, hence; in securing sufficient calcium available for bone mineralization [7,38].

Vitamin 25(OH)D is regarded to be the best biomarker for vitamin D status [30–32]. This study found sufficient levels of 25(OH)D in both groups. Vitamin 25(OH)D status was close to optimal (Fig. 2a) [30–32]. Sun exposure might be higher in the healthy group, and could explain adequate status even if dietary provision was lower than in IF patients, and lower than recommended for healthy children. Seasonal differences in vitamin D status could be expected due to participants living in southern Norway at latitude 58–61°N [39,40]. However, no difference was found for healthy participants included during March–June compared to August–September. Other studies have reported vitamin D insufficiency in 20–68% of paediatric IF patients [12,13,33,34,36,37,41,42], which is more than the 5% found by Appleman et al. [43], and the 10% found in the present study. An explanation could be that these studies also included patients weaned off PN, and hence their absorption could be compromised. The close follow-up by the IF team may contribute to adequate status in our study group.

Both D_2 (vegetable/supplements) and D_3 (skin/animal/supplements) are transported to the liver and hydroxylated to 25(OH)D. With sufficient and no difference in 25(OH)D between the groups, the detection of a lower 1,25$(OH)_2$D in the IF patients compared with the healthy group is interesting (Fig. 2). This is different from another study of paediatric IF patients on PN where a normal value of 1,25(OH)2D was found [43]. Lower 1,25$(OH)_2$D level raises questions regarding the mechanism. Hypotheses may be a loss of 1,25$(OH)_2$D, an inadequate activation of 25(OH)D, or increased degradation of 1,25$(OH)_2$D in the IF group. Low 1,25$(OH)_2$D has usually been explained by chronic renal failure, but creatinine levels were normal in all except two IF patients (Table 2). PTH was not different between the two groups (Table 2). Another possibility could be that parenteral provision itself affects 1,25$(OH)_2$D. All IF patients received cyclical supply, median 12 h/day, and there is little knowledge on how this affects metabolic biorhythms. Low levels of 1,25$(OH)_2$D have also been found in for example, pneumonia [44] and after bone marrow transplantation [45]. Disease related factors, e.g. inflammation, could impact hydroxylation. A hypothesis may be that IF patients have an increased level of fibroblast growth factor 23 (FGF23). FGF23 down-regulate cytochrome p450 27B1 (CYP27B1) expression, resulting in reduced synthesis of 1,25$(OH)_2$D. It is known that the activation from 25(OH)D to 1,25$(OH)_2$D is dependent on hydroxylation by this specific enzyme. CYP27B1 has been detected in different cells and tissues, including the intestine [46]. Results may suggest that the intestine is more important for the metabolism of vitamin D than earlier recognized, and raises questions regarding differences in the effect of oral and parenteral provision of vitamin D for the metabolism into 1,25$(OH)_2$D.

Strengths of this study are the inclusion of all available IF patients on HPN at our center, and the comparison with a group of healthy children. An important strength was the detailed information on total diet, including both enteral and parenteral provision. A cross-sectional design and small sample size are limitations, and the results from this study must be interpreted with caution. Another possible limitation is the gender difference between the patients and the healthy children, even though the sub-analyses indicated that this was of minor impact for the vitamin D results. The healthy group was recruited by social advertisement, and could therefore be healthier than the general population which is also a

limitation. However, their dietary intake was comparable with results from the last national dietary investigation of 9-year-old Norwegians [47]. DXA was not performed in 5 IF patients due to issues of managing the examination. This might have contributed to an underestimation of bone deficit, as most of these patients were immobile. Pubertal stage, seasonal variations of vitamin D, or calcium and phosphate in the urine, were not assessed, which also are limitations of the study. The risk of type I errors due to multiple analysis is crucial to be aware of, and is related to the explorative study design.

Further studies are needed to confirm our results and improve knowledge. A multicenter RCT with adequate power could compare different modes of vitamin D, calcium and physical activity on bone mass, body composition and vitamin D biomarkers. This design could better answer questions regarding nutrition and lifestyle interventions. We also suggest that future studies investigates calciuria, phosphaturia, serum FGF23 and insulin resistance in IF patients. Better understanding of advanced nutritional treatment and its consequences on health is important as use of HPN is on the increase due to better treatment and nutritional care of children with IF.

Conclusion

Paediatric IF patients on HPN had lower BMD, impaired growth, and higher body fat percentage in comparison with healthy children. Provision of glucose was high, calcium and phosphorus low compared with recommendations for PN, and compared with healthy children. Vitamin D provision was higher in IF patients compared with the healthy children, and total intake as recommended for PN. The levels of 25(OH)D were sufficient for both groups. Nevertheless, a significantly lower $1,25(OH)_2D$ level was found in IF patients compared with healthy children. The results raise questions regarding differences between oral and parenteral vitamin D provision and whether intestinal function is important for the metabolism of vitamin D.

Statement of authorship

All persons who meet authorship criteria are listed as authors in the Title page.

JAK participated in conception and design of the study, collected the data, carried out the final analyses and drafted the manuscript. CNK and CS collected the data and contributed to the initial analyses of data. RAT contributed to conception and design, data collection and cooperated in the final analyses of dietary provision. KG and JB were responsible for DXA scanning, PMT was responsible for vitamin D analysis and PJ was responsible for the growth data analysis. BSB participated in the conception and design of the study, data collection and supervised the study. CH participated in conception, design, data analyses and supervised the study. All authors participated in interpretation of results, reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Declaration of Competing Interest

The authors report no conflicts of interests to declare.

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