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Original article

Micronutrients in paediatric Intestinal Failure Patients receiving home parenteral nutrition

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SUMMARY

Background & aims: Children with intestinal failure (IF) receive parental nutrition to ensure adequate growth and development. The aim of this study was to assess micronutrient status in paediatric IF patients receiving home parenteral nutrition (HPN) in comparison to a group of healthy children.

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. All children with IF, aged two to 18 years, were invited to participate. A reference group of healthy children was recruited through social media advertisement. Dietary intake was assessed by a four-day food record, and enteral and parenteral provision was recorded. Blood samples were analysed for vitamins, minerals and haematology to assess iron status. Two spot urine samples from each subject were analysed for iodine concentration (UIC) and creatinine.

Results: Nineteen children with IF and 50 healthy children were included. The mean age of the participants was 10.0 years. IF-patients received a median of 76% of their estimated energy requirements from parenteral nutrition (PN). Recommended intake (RI) for iodine from the diet was reached by 16% of IF patients and 28% of healthy children. In the IF group there was a significant positive correlation between UIC and the percentage of iodine intake from oral diet and enteral nutrition support ($r = 0.57$, $p = 0.03$). Although the IF patients had a median parenteral iodine supply of more than twice the ESPGHAN recommendation, the median UIC was 89 μg/L indicating insufficient iodine status. This may suggest that the ESPGHAN recommendation for iodine in paediatric parenteral nutrition is too low. The healthy children had sufficient iodine status according to the median UIC (133 μg/L). IF patients had significantly lower total provision of iron compared to the healthy children, 4,9 vs 8,4 mg/day ($p = 0.01$) with 21% of IF patients and 28% of healthy children reaching RI for iron. The prevalence of anaemia was higher in IF patients than in the healthy children (40 vs.10%, $p = 0.016$).

Conclusion: The study indicates an insufficient iodine and iron status among paediatric IF patients. Iodine status was associated with enteral provision and patients had insufficient status even if they received the ESPGHAN recommendation of iodine.

Trial identification number: Clinical Trials AEV2017/1. 2016/391/REK sør-øst B.

Abbreviations: EER, Estimated energy requirements; ESPGHAN, European Society of Paediatric Gastroenterology Hepatology and Nutrition; HPN, Home parenteral nutrition; IF, Intestinal failure; GI, Gastro-intestinal; PIPO, Paediatric intestinal pseudo obstruction; PN, Parenteral nutrition; RI, Recommended intake; TPN, Total parenteral nutrition; UIC, Urinary iodine concentration.

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1. Introduction

Intestinal failure (IF) is defined as a critical reduction of functional gut mass below the minimum needed for the absorption of nutrients and fluids necessary to maintain health and growth [1,2]. IF can result from anatomical resection of the gut length resulting in short bowel syndrome, neuromuscular diseases causing dysmotility of the gastro-intestinal (GI) tract, or diseases of the intestinal epithelium causing chronic malabsorption [3–5]. The insufficient digestion and absorption in these patients make parenteral nutrition (PN) vital [6,7]. Patients with IF may be eligible for treatment with home parenteral nutrition (HPN) [8], which enables the patient to receive this nutritional treatment at home when hospitalization is no longer required. HPN is widely recognized to improve the quality of life of both children and families involved [9].

Even so, growth failure and negative energy- and protein balances have previously been reported among paediatric HPN patients [10,11]. In addition, it is essential to prevent micronutrient imbalances in long-term HPN [12]. Children are especially vulnerable to micronutrient deficiencies due to growth and development. Therefore, monitoring vitamin and mineral status is recommended in these patients [13,14]. Neelis et al. found low blood values of vitamin A in 90%, zinc in 87%, and iron in 76% of IF children on HPN [15]. Other studies have indicated that supplying iodine and iron may be challenging [16–20]. Retrospective reports on the outcome of long term HPN have mostly aimed at describing survival, growth pattern, macronutrient status and time to weaning off HPN [9,10,14]. Several studies have focused on the micronutrient status during and after weaning of PN [7,15,21,22] Only a few studies have focused on the micronutrient status in children with chronic IF dependent on long-term PN, and data on micronutrient provision is often incomplete or lacking [22,23]. The aim of the present study was to assess micronutrient provision and status in a group of paediatric IF patients on home parenteral nutrition in comparison to a group of healthy children.

2. Methods

2.1. Subjects

An observational cross-sectional study was conducted on paediatric patients treated with HPN due to IF and a group of healthy children from March to September 2017. The IF patients were recruited at routine follow-up examination by the Paediatric Intestinal Failure Team at Oslo University Hospital. The inclusion criteria were age between two and 18 years and dependent on HPN for more than 6 months. A reference group of healthy children in the same age group was recruited by social media advertisement. The inclusion criteria were residence in the Oslo region, age 2–18 years, and a normal diet. Clinical data on primary diagnosis of IF, time of commencing and length of HPN treatment were obtained from medical records of the IF patients. Demographic data, data on parenteral education and living arrangements and gastrointestinal symptoms were obtained from a questionnaire, completed by patients and healthy children if over 16 years and by parents if under 16, in order to compare IF patients and healthy children.

2.2. Anthropometrics

Anthropometric measurements of weight and height were registered at routine follow-up examinations at the HPN-clinic at Oslo University Hospital for the IF children. For the healthy children, the same measurements were obtained at a visit to the Clinical Nutrition Research Centre at the University of Oslo. The anthropometric measurements were analysed by calculating standard deviation scores (SDS) for weight for age (weight SDS), height for age (height SDS) and BMI for age (BMI SDS), based on the Norwegian reference population [24].

2.3. Nutrient intake

A 4-day food record was kept for all the participants, using house hold measures and booklet of portion sizes [25]. Information on the amount and types of enteral and parenteral support was collected for the IF children. An internet based dietary analysis program (DietistPro) was used to calculated dietary intake of energy, protein, fat, carbohydrate, electrolytes, minerals, trace elements and vitamins based on the mean intake of the four days from diet and enteral support (EN), parenteral nutrition and total provision of nutrients for the IF patients and dietary intake for the healthy children. Prescriptions for the parenteral nutrition solutions were provided by Hospital Pharmacies and were calculated and added to the diet analysis by a dietitian. Data on the initiation and duration of parenteral nutrition were provided by parents and medical records. Parenteral nutrition was supplemented with multivitamin and trace element parenteral products. The Nordic Nutrition Recommendations [26] were used as reference values for recommended intake (RI) from diet and EN. The proportion (%) of participants that reached the RI for different nutrients was determined for both groups. Nutrient reference values for parenteral nutrition were taken from the ESPGHAN guidelines on paediatric parenteral nutrition [27,28] and the proportion of IF patients reaching the recommendations assessed. Minerals and trace element provision from parenteral nutrition were calculated per kg body weight in order to be able to compare the values to the ESPGHAN recommendations.

2.4. Blood samples

The blood samples of the IF patients were analysed for haematology (haemoglobin, ferritin, iron, total iron binding capacity (TIBC), MCV, MCH, transferrin receptor), C-reactive protein, albumin, vitamins A and E, folate, B12, zinc, selenium, copper, carnitine, liver status (ASAT, ALAT, gamma-GT, bilirubin), lipid status (cholesterol, HDL, LDL) and thyroid function (thyroid stimulating hormone (THS), free thyroxine (FT4)). Only a selection of these

Table 1
Classification of anaemia and cut-off values for iron deficiency according to WHO [29,30].

Age		Haemoglobin g/dl			Ferritin ug/L
		Mild Anaemia	Moderate Anaemia	Severe Anaemia	Iron deficiency
6 months–4 yrs		10,0–10,9	7,0–9,9	<7,0	<12
5–11 years		11,0–11,4	8,0–10,9	<8,0	<15
12–14 years		11,0–11,9	8,0–10,9	<8,0	<15
>15 years	Girls	11,0–11,9	8,0–10,9	<8,0	<15
	Boys	11,0–12,9	8,0–10,9	<8,0	<15

Table 2
Baseline characteristics, Gastrointestinal symptoms, Aetiology of Intestinal Failure and Nutritional Treatment.

	Intestinal failure (n = 19)	Healthy (n = 50)	p-value
General characteristics			
Gender, Boys %	68%	36%	0.02
Age in years, mean (SD)	10.1 (3.51)	10.0 (3.59)	0.93
Height SDS, mean (SD)	−1.52 (1.69)	0.65 (1.18)	0.001
Weight SDS, mean (SD)	−1.02 (1.57)	0. 60 (0,93)	0.009
BMI SDS, mean (SD)	0.20 (1.04)	0.02 (1.07)	0.51
Parents living together	79%	84%	0.62
Gastro intestinal symptoms Daily/weekly			
Gastro intestinal symptoms	95%	16%	<0.001
Loose stools	68%	2%	<0.001
Gastro Intestinal pain	63%	4%	<0.001
Constipation	26%	2%	0.005
Regurgitation	16%	4%	0.08
Vomiting	15%	0%	0.02
Gas	90%	4%	<0.001
Aetiology			
PIPO	58%		
Short Bowel Syndrome	26%		
Chronic Malabsorption	16%		
Nutritional treatment			
Median age at PN initiation, years (min–max)	3 (0–10)		
Median time on PN, years (min–max)	4.4 (0.8–16.4)		
Median PN days per week (min–max)	7 (4–7)		
Median volume PN, ml (min–max)	1268 (297–2030)		
Median time per PN infusion, hours (min–max)	12 (9–15)		
EER covered by PN	76%		
TPN	21%		
PN + Enteral nutrition support	16%		
PN + Diet	37%		
PN + Enteral nutrition support + Diet	26%		

SDS = Standard deviation Scores, PIPO = Paediatric Intestinal Pseudo Obstruction, PN = Parenteral nutrition, EER = Estimated energy requirements, TPN = total parenteral nutrition.
P-value = differences between Intestinal failure and Healthy children

parameters were analysed in the reference group (haematology, C-reactive protein, albumin, folate and B12). Anaemia was determined using the WHO's reference value for haemoglobin according to age and sex [29] and iron deficiency was determined using reference values for ferritin [30] (Table 1).

2.5. Urine samples

Two spot urine samples were collected during the 4-day diet recording for the analysis of iodine and creatinine. Iodine samples were analysed at the Norwegian University of Life Sciences. Sufficient iodine status according to urinary iodine content (UIC) was set as 100 ug/L in accordance with the WHO's cut off value [31]. Urine creatinine was analysed at the laboratory of Oslo University Hospital. The estimated 24-h urinary iodine content (Est24hrUIC) was calculated to adjust for hydration status using the equation suggested by Montenegro-Bethancourt et al. [32]. Est24hrUIE were then assessed in relation to the recommended daily iodine intake adjusted for 15% non-renal iodine loss.

2.6. Statistics

Statistical analyses were performed using IBM SPSS Statistics for Windows version 25. Categorical variables are presented as numbers (n) and frequencies (%). Continuous variables are tested for normality. Normally distributed data is presented as means with

Table 3a
Median vitamin provision from enteral and parenteral nutrition in intestinal failure patients and diet in healthy children (25th-75th percentile).

	Intestinal Failure (n = 19)						Healthy (n = 50)					
	Total		Enteral		PN		Dietary intake		Reference		P values[a]	
	Median	(25–75 p)	Median	(25–75 p)	Median	(25–75 p)	Median	(25–75 p)	RI	PN	Total	Enteral
B1 mg	2,6	(2,2–3,0)	0,6	(0,1-1)	2,5	(1,8–2,5)	1,3	(1,1-1,5)	0,6–1,4	1,2	<0.001	<0.001
B2 mg	3,8	(3,2–4,2)	0,8	(0,1-1)	3,5	(2,6–3,6)	1,4	(1,1-1,7)	0,7–1,7	1,4	<0.001	0.001
B6 mg	4,2	(3,6–4,5)	0,5	(0,1-1,4)	3,9	(2,9–4,0)	1,4	(1,1-1,8)	0,7–1,6	1	<0.001	0.001
B12 ug	5,6	(4,9–7,4)	1,9	(0,4–3,0)	4,9	(3,7–5,0)	4,5	(3,3–6,5)	0,8–2,0	1	0.014	<0.001
Folate ug	416	(393–528)	83	(16–182)	393	(300–400)	187	(153–228)	80–300	140	<0.001	<0.001
Niacin mg	42	(36–45)	5,7	(0–12,5)	39,3	(29,4–40)	14,4	(11,4–18,6)	9–19	17	<0.001	<0.001
Vit A ug	1078	(690–1800)	266	(72–600)	690	(525–1035)	485	(371–761)	350–900	150	<0.001	0.015
Vit C mg	109	(100–136)	15	(1–86)	98	(74–100)	65	(44–81)	30–75	80	<0.001	0.004
Vit E mg	13,3	(7,2–17,8)	4,5	(0,3–10)	6,4	(4,7–9,6)	10,5	(7,9–13,6)	5–10	11	0.1	0.003

IF = Intestinal Failure, PN = Parenteral Nutrition, Reference RI = Recommended daily intake (Diet and Enteral nutrition support, Nordic nutritional recommendations), Reference PN = ESPGHAN recommendations.
[a] P values Total: median Total (Enteral + PN) provision in the IF group compared to intake from diet in healthy children. P values Enteral: Median Enteral provision (diet and enteral nutrition support) in the IF group compared to dietary intake in the healthy children.

Table 3b
Median total mineral and trace element provision from enteral and parenteral nutrition in intestinal failure patients and diet in healthy children (25th-75th percentile).

	Intestianl Failure (n = 19)						Healthy (n = 50)					
	Total		Enteral		PN		Diet		Reference		P-value[a]	
	Median	(25–75 p)	Median	(25–75 p)	Median	(25–75 p)	Median	(25–75 p)	RI	PN	Total	Enteral
Cu mg	0,6	(0,3–1,3)	0,4	(0–1,1)	0,3	(0,2–0,3)	0,9	(0,8–1,1)	0,4–0,9		0.06	0.005
Cu ug/kg					8,8	(5,6–11,4)				20		
Iodine ug	116	(85–159)	40	(3,6–80,5)	94	(60–111)	88	(72–142)	90-150[b]		0.9	<0.001
Iodine ug/kg					2,7	(0,3-3,4)				1		
Iron mg	4,9	(1,7–10,1)	4,3	(0,6–9,3)	0,8	(0,5–0,9)	8,4	(7,0–10,3)	8-15[c]		0.01	0.003
Iron ug/kg					20	(0–300)				50–100		
K mg	2520	(1867–3600)	928	(27–1625)	1602	(1002–2200)	2520	(2073–3058)	1800–3500		0.9	<0.001
K mmol/kg					1,5	(0,7–1,8)				1–3		
Mg mg	173	(94–228)	103	(15–148)	65	(48–96)	263	(230–338)	120–350		<0.001	<0.001
Mg mmol/kg					0,1	(0,04–0,17)				0,1		
Na mg	2189	(1481–3105)	601	(47–1052)	1564	(927–2189)	2527	(1947–2999)			0.4	<0.001
Na mmol/kg					2,5	(1,0–2,7)				1–3		
Se ug	71	(58–108)	18,6	(2,6–48)	57,2	(36,5–65,5)	37	(30–50)	25–60		<0.001	0,007
Se ug/kg					1,7	(1,4–2,1)				2–3		
Zn mg	6,5	(4,5–11,2)	4	(0,6–7,5)	3,6	(2,3–4,3)	9,7	(7,3–11,9)	6–12		0.017	<0.001
Zn ug/kg					100	(90–130)				50		

IF=Intestinal Failure, Enteral = Diet and Enteral nutrition support, PN = Parenteral Nutrition, Reference RI = Recommended intake (Diet and Enteral nutrition support, Nordic nutritional recommendations), Reference PN = ESPGHAN recommendations Mg = magnesium, Na = sodium, K = potassium, Zn = zinc, Se = selenium, Cu = copper.
[a] P values Total: median Total (Enteral + PN) provision in the IF group compared to intake from diet for in healthy children. P values Enteral: Median Enteral provision (diet and enteral nutrition support) in the IF group compared to dietary intake in the healthy children.
[b] Lowest at 2–5 yrs, gradually increasing until age 17.
[c] highest value for girls 14–17 yrs.

standard deviation (SD). Non-normally distributed data is presented as medians with range (minimum–maximum). The two-sided significance level was set at five % for all statistical analysis. Data on general characteristic and gastrointestinal symptoms are expressed as frequencies and the IF patients and healthy children are compared using the Chi-square test. Anthropometric data are compared using Independent Sample T-test. Data on provision of nutrients are presented as median with 25th and 75th percentile. Differences in total provision and enteral provision of a micronutrient between the two groups are tested separately, using the Mann-Whitney U test. Micronutrient status and haematology are presented as medians with range and the two groups are compared using Mann-Whitney U test. Numbers of subjects with values above or below the normal range are presented as frequencies (%). Spearman's correlation coefficient is used to explore correlations between iodine status (UIC) and nutritional parameters, as well as anaemia and nutritional parameters. Differences in the prevalence of anaemia in the two groups is tested using Fisher's Exact test.

2.7. Ethics

Informed consent was collected from both parents for children under 16 years and 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), the Head of the Department and the Research committee, Oslo University Hospital. The study was registered in Clinical Trials (AEV2017/1), and the Ethical standards of the Declaration of Helsinki were followed.

3. Results

The study included all 19 children with IF between 2 and 18 years old who were treated with HPN and seen at Oslo University Hospital between January and September 2017. Another 50 healthy children were recruited as a reference group. The baseline characteristics and clinical data are presented in Table 2. The mean age was 10.1 years in the IF group and 10.0 years in the healthy group, and there were significantly more boys in the IF group. The primary diagnosis of IF included paediatric intestinal pseudo obstruction (PIPO) (58%), short bowel syndrome (26%) and chronic malabsorption (16%). The IF patients were significantly shorter (length SDS) and lighter (weight SDS) than the healthy group, but there was no difference in BMI SDS. Parenteral education level (results not shown) and living arrangement did not differ between the two groups. The IF patients had significantly more GI symptoms than the healthy children and gas production was the most frequently reported symptom (90% of the IF patients).

The median age of HPN initiation was three years, with 47% having commenced HPN during their first year of life. The median treatment duration was 4.4 years. The median number of days of infusion per week was seven with a median duration of 12 h per infusion. As presented in Table 2, four patients had 100% PN, three had PN in combination with enteral nutrition support (EN), seven were treated with PN together with oral diet and five with PN in combination with both EN and diet. PN was the main provider of nutrition with EN and/or diet covering a mean of 2-4% of estimated energy requirements.

We found no clear correlation between the underlying cause of IF and the type of nutritional support, except for TPN which was provided to PIPO patients only. There was no significant difference in median total energy intake (1834 vs 1913 kcal) between the IF patients and the healthy group.

PN was individually tailored for most patients, but two IF patients received standard all-in-one bags (Fresenius Standard 15–40 kg, Fresenius Kabi Norway). All patients were provided with a water-soluble multivitamin and a trace element parenteral product. All but one patient also received a fat-soluble multivitamin parenteral supplement.

3.1. Micronutrient intake

The data on micronutrient provision are shown in Table 3a and b. In the IF group, there was a significantly higher total provision of vitamin A, all the water-soluble vitamins (B1, B2, niacin, B6. B12,

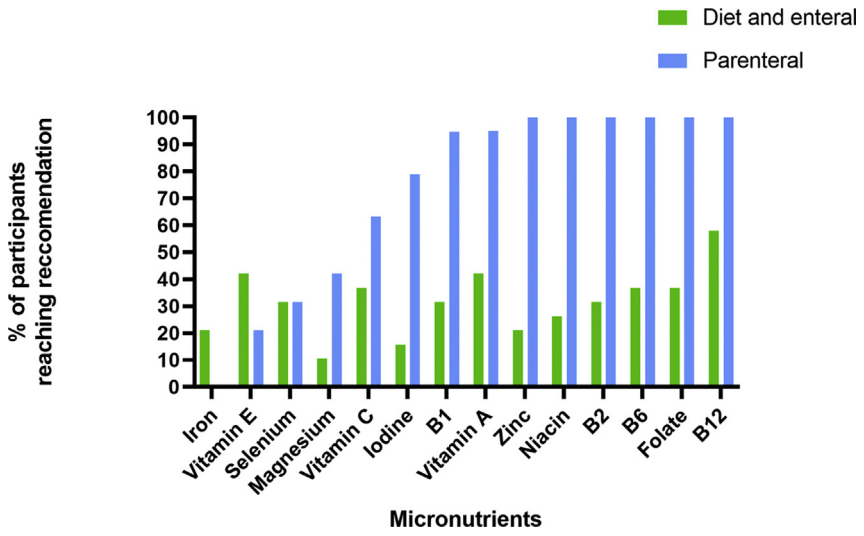

Fig. 1. Frequency of IF patients reaching the enteral (RI) and parenteral recommendation for individual micronutrients. Diet and Enteral = Recommended intake (RI) for Diet and enteral nutrition support.Parenteral = ESPGHAN guidelines = Recommended provision in Parenteral nutrition.

folate, C), and selenium than the healthy children. The IF group had a significantly lower provision of iron, magnesium, and zinc than the reference group. No difference was found in total provision of vitamin E, copper, iodine, potassium or sodium between the two groups.

As shown in Fig. 1, 58% of the IF group met the dietary recommendation (RI) for B12 through diet and enteral nutrition support, but the RI was reached by only 42% for vitamin A and E, 37% for vitamin C; 32% for B1, B2 and selenium, 26% for niacin,; and less than 22% for zinc and magnesium. The RI for iodine and iron was reached by 16 and 21%, respectively. IF patients were provided most of their iodine from PN (63% of total provision) and the main contributor of iron for the majority of IF children were diet and/or enteral nutrition support, however the provision was less than 50% of RI.

The ESPGHAN guidelines [27,28] for micronutrient provision in PN were met by 95% of the IF group in the case of B-vitamins, zinc and vitamin A, by 63% for vitamin C, 42% for magnesium, 32% for selenium, and 21% for vitamin E. Median provision of iodine was more than twice the recommended amount (2,7 ug Iodine/kg)

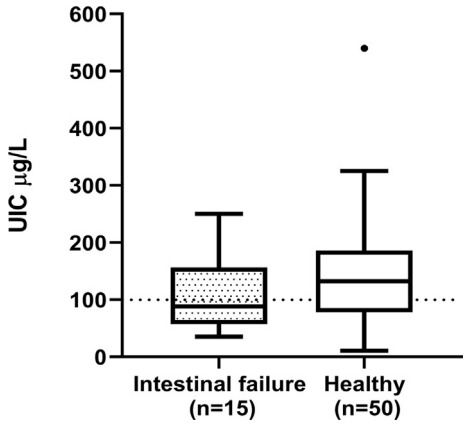

Fig. 2. Urinary Iodine Content (UIC) in intestinal failure and healthy children. The horizontal line indicates the median, the box indicates the interquartile range (25th percentile to 75th percentile), the whiskers represent observations within1.5-times the inter quartile range and the dot indicate outliers. The dotted line indicates the cut off value for sufficient status of 100 ug/L.

(Table 3b) and the PN recommendation for iodine was met by 79% of the IF patients. None met the PN recommendation for iron.

Over 70% of the healthy children reached the RI for B1, B2, B6, B12, vitamin E, vitamin C, copper, magnesium and zinc, and more than 50% the RI for niacin, vitamin A and selenium. Only 28% reached the RI for iodine and iron, however median dietary intake covered 73% of the iodine recommendation and more than 80% of the iron recommendation.

3.2. Micronutrient status

3.2.1. Iodine

The median urine iodine concentration was under the WHO cut-off value for deficiency in the IF group (89 umol/L) but not in the healthy children (133 umol/L) (Fig. 2).

Frequency of sufficiency iodine status, urinary iodine content (UIC), iodine intake and percentage of iodine recommendation reached according to sufficiency status in the two groups is described in Table 4. Iodine deficiency was frequent in all children, and not significantly different between the IF group and the healthy children (53 vs 40% respectively). When correcting for urine creatinine (Est24hrUIC), the frequency of iodine deficiency rose to 67% in both groups.

There were significant positive correlations between iodine status (UIC) and percentage of RI met for iodine in both groups (IF; $r = 0.62$, $p = 0.01$, Healthy; $r = 0.35$, $p = 0.01$). In the IF group there was a significant positive correlation between UIC and the percentage of iodine intake from oral diet and enteral nutrition support ($r = 0.57$, $p = 0.03$), as well as a significantly negative correlation between the percentage of total iodine provision covered by PN and UIC ($r = -0.52$, $p = 0.03$).

When looking at the iodine provision in PN, there was no correlation between meeting the ESPGHAN guidelines for iodine and UIC. As illustrated in Fig. 3 as many as 6 out of 12 of the patients who met the daily recommended iodine dose in PN, had insufficient iodine status.

3.2.2. Iron

The IF group had significantly lower iron intake (Table 3b) and significantly lower haemoglobin level (Table 5) than the healthy group. There were significant differences between the groups in

Table 4
Prevalence of iodine sufficient and insufficient status (WHO cut off), iodine status, provision of iodine and prevalence of reaching recommendations from diet/enteral nutrition (RI) and parenteral nutrition in Intestinal Failure patients and Healthy children.

	UIC	Intestinal failure n = 15			% reaching RI for iodine (diet and EN)	% reaching PN rec for Iodine	Healthy n = 50			% reaching RI for Iodine
		%	UIC ug/L	Total Iodine provision ug			%	UIC ug/L	Iodine provision ug	
Insufficient status	<100	53%	58 ug/L	96 ug	0%	75%	40%	69 ug/L	75 ug	15%
Normal	≥100	47%	157 ug/L	150 ug	14%	86%	60%	178 ug/L	121 ug	40%

UIC = urinary Iodine content, EN = enteral nutrition support, RI = recommended intake enterally (diet and EN), PN rec = recommended PN provision, ESPGHAN guidelines, Total Iodine provision = Iodine from diet/EN and parenteral nutrition, WHO cut-off values(31).

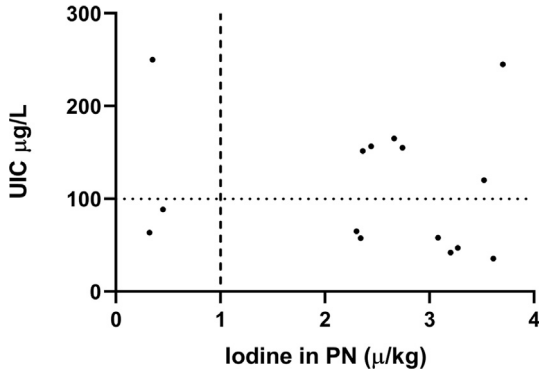

Fig. 3. Urinary Iodine Content (UIC) in relation to Iodine per kg in Parenteral Nutrition (PN) in the IF group (n = 15). The dotted line indicates the WHO cut-off for insufficient iodine status (UIC <100 ug/L). The stippled line indicates the ESPGHAN recommendation for iodine provision in PN (1 ug/kg).

iron nutrition biomarkers such as MCV, serum iron, transferrin saturation and transferrin receptor. Except for transferrin receptor and serum iron, all values were within the normal range.

A significantly higher prevalence of anaemia was found in the IF group, where 40% of the children were classified as mildly to moderately anaemic according to the WHO's classification (Fig. 4), in comparison to 10% among the healthy children. The IF group received 33% of their iron from PN, in which the median iron provision in PN was 26 ug/kg which is only half of the PN recommendation. Three patients did not receive any iron in their PN. There were no correlations between iron provision from diet, enteral nutrition support or parenteral nutrition and any of the iron parameters in blood.

Among the IF group, anaemia was significantly associated with the age of initiation of HPN. The median age of commencing HPN was one year among anaemic children compared to 5 years among those without anaemia (p = 0.04). In addition, there were significant association between anaemia and the duration of HPN treatment, 9.5 vs. 3.1 years in those with and without anaemia, respectively (p = 0.01).

3.2.3. Other micronutrients

The IF group had significantly higher B12 levels than the healthy group, and elevated levels were found in 78% of the patients (Table 6). Only one IF patient (6%) had lower vitamin A than the reference. We found no vitamin E deficiency, in terms of either tocopherol in the blood or for cholesterol and triglyceride corrected vitamin E. Elevated vitamin E was frequent (70%). Low magnesium was found in two patients and low zinc in one. None had selenium deficiency.

3.2.4. Other blood biomarkers

Around 30% of the IF group had one or more elevated liver function test (result not shown). None were found to have elevated lipids or triglycerides. As for thyroid status, low FT4 was found in two IF patients, and high FT4 in two, but none had elevated TSH. Albumin was normal in all IF patients. Low carnitine (free and total) was found in 19% of the IF patients.

4. Discussion

In this cross-sectional study, lower UIC and a significantly higher prevalence of anaemia was found in paediatric IF patients on HPN than healthy children. We found adequate serum levels of most other micronutrients despite of lower than recommended enteral intake and/or parenteral provision of some nutrients (Se, Vit E and Mg). Low serum levels of vitamin A was found in one, low magnesium in two and low zinc in one patients. IF patients received a median of 76% of their estimated energy requirements (EER) from PN. PN covered 63% of the total provision of iodine, whereas iron was mostly provided by oral diet and enteral nutrition support.

In contrast to other studies [7,15,21–23] on micronutrients in IF patients, we found adequate levels of vitamins and most trace

Table 5
Haematology in Intestinal Failure patients and healthy children, medians (min/max) and frequency of low and elevated levels.

Haematology	Value	Intestinal Failure (n = 19)	Healthy (n = 49)	Reference	p-value	Low/elevated levels (%)	
						IF	Healthy
Haemoglobin	g/dl	11,6 (9,9–13,5)	12,4 (10,8–14,1)	≥11.0–13[a]	0.01	42% low	12% low
MCV	fL	85 (79–88)	82 (74–93)	70/76/78–87/95/98[a]	0.02		2% low
MCH	Pg	28 (26–32)	28 (25–31)	23/25–31/33[a]	0.40		
TIBC	umol/L	65 (43–105)	68 (43–80)		0.90		
Iron	umol/L	9 (4–25)	14 (3–26)	5-20/25[a]	0.003	10% low, 6% elevated	2% low, 4% elevated
Ferritin	ug/L	59 (13–378)	37 (16–111)	<12/<15[a]	0.09	6% low	16% elevated
Transferrin	g/L	2,7 (1,7–4,2)	2,7 (1,7–3,2)	1,9–3,3	0.95		
Transferrin-saturation		0,12 (0,08–0,34)	0,21 (0,05–0,41)	0,05/0,06–0,39/0,58[a]	0.005		
Transferrin-receptor	mg/L	4,0 (2,3–7,0)	3,2 (2,3–5,4)	1,9/2,2–4,4/5,0[a]	0.007	20% elevated	4% elevated
C-reactive protein	mg/L	0,5 (0,5–46,5)	0,5 (0,5–34)	<4,0	0.35	11% elevated	4% elevated

IF=Intestinal Failure.
[a] Age dependent, MCV - mean corpuscular volume, MCH - mean corpuscular haemoglobin, TIBC – total iron binding capacity.

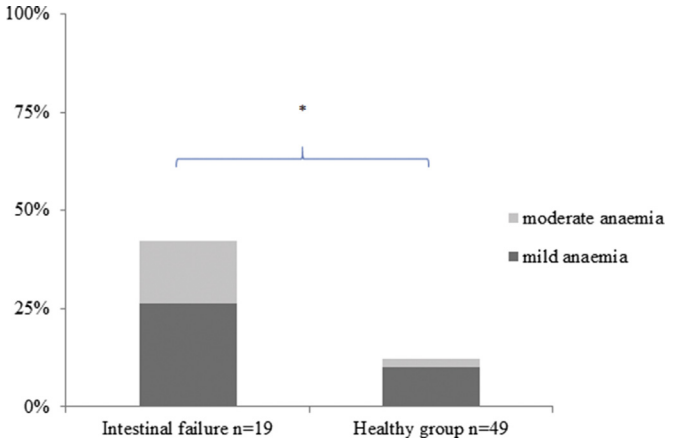

Fig. 4. Prevalence of anaemia (mild and moderate) in Intestinal Failure Patients and Healthy Children. *p = 0.016.

elements. Previous studies have been retrospective in design without information on enteral and/or parenteral nutrition. Many have focused on patients in transition between parenteral nutrition and full enteral nutrition, a period where the patients could be at risk due to malabsorption of enteral nutrition and insufficient enteral micronutrient supplementation [7,15,21]. In some cases PN was not supplemented with all vitamins or trace elements [17,22] The patients in our study were all on stable regimens of parenteral nutrition. In addition, they all received a parenteral water-soluble multivitamin solution, at a median of one standard dose which led to a significantly higher provision of these vitamins than in healthy children on normal diet. Moreover, the IF group was provided with a fat-soluble vitamin solution and a multi trace element solution. This could also explain the lack of nutritional deficiencies found in our study.

The IF group received a median of 2.7 ug of iodine per kg in their PN, which is more than twice the amount recommended by ESPGHAN [28]. Despite this there was a high prevalence of insufficient iodine status, defined as UIC <100 ug/L with more than half of the IF group below the cut-off value. This was true even when correcting for hydration status with urine creatinine (Est24hrUIC). In comparison 40% of the healthy children had UIC values < 100 ug/L and the prevalence rose to 67% when correcting for hydration status (Est24hrUIC). There are few studies on iodine status in patients treated with HPN. Iodine is difficult to study and there has previously been a widespread notion that the needs for iodine in patients receiving PN were covered by the use of iodine containing antiseptics [33]. However, these products are no longer used on a regular basis. In Europe PN is commonly supplemented with iodine by a multi trace element solution. In contrast, trace element supplementation of PN in the United States (US) is often done by individually adding the different trace elements and iodine is not routinely included in this supplementation [18]. There have been a few case reports of hypothyroidism due to iodine deficiency in children on HPN in the US [34–36] and a recent study found high prevalence of iodine deficiency in paediatric IF patients provided HPN without iodine, with 33% developing hypothyroidism [18]. However, these studies are on children who were not provided with intravenous iodine and cannot be used to evaluate the current ESPGHAN recommendation for iodine in PN.

There is a large discrepancy between the amount of iodine recommended in the diet (90–150 ug in children 2–18 years old) and in parenteral nutrition (1 ug/kg/day) [33]. The newly published ESPGHAN guidelines did not increase the recommendation even if the authors recognized that the risk of iodine deficiency is high. Instead, ESPGHAN suggests that patients on long-term PN should be regularly monitored for iodine status by measuring their thyroid hormone concentration (TSH) [28]. We found little sign of disturbances in thyroid function in our group of IF patients. All subjects had TSH within the normal range even if four IF patients had FT4 values that were slightly outside the reference range. However, even if TSH may be slightly raised by iodine deficiency, values often remain within the normal range and are therefore a rather insensitive indicator of iodine nutrition in children and adults. This is true for FT4 as well [33]. Moreover, thyroid dysfunction is a late consequence of iodine deficiency. Cognitive function and behaviour may be negatively affected much earlier compared to thyroid hormone production [37]. This was, however, not investigated in the present study.

Considering that 90% of iodine in the diet is absorbed in the intestine it is illogical for the parenteral guideline to be so much lower than enteral requirements. Especially for small children with low weights the discrepancy between enteral and parenteral recommendation is large as the PN guideline is based on weight. Premature low weight children were found to be at high risk of iodine deficiency in one study [38]. Even though our group of IF patients were provided more than twice the ESPGHAN iodine recommendation they still showed signs of insufficient iodine status. The same was found in an adult group of IF patients treated with HPN and there is a need for more studies to establish iodine requirements in HPN [12].

Table 6
Median blood values (min/max) of micronutrient status in Intestinal Failure patients and healthy children and frequency of low and elevated levels.

(value)	Intestinal failure n = 19	Healthy n = 49	Reference	p-value	Frequency of low/elevated levels (%)	
					IF	Healthy
Vitamins						
B12 (pmol/L)	717 (432–1912)	436 (162–955)	>150	<0.001	78% elevated	2% deficiency 8% elevated
Folate (mmol/L)	38 (15–46)	20 (5–46)	>7	<0.001		2% deficiency
Vitamin A (umol/L) 6% elevated	1,7 (1,1–4,7)		1,2–3,6		6% deficiency	
Vitamin E (umol/L)	28 (14–40)		12–43			
Corr Vit E[a] (umol/mmol)	7,5 (4,5–9,8)		3,5–6,4		70% elevated	
Minerals/Trace elements						
Magnesium (mmol/L)	0,81 (0,66–1,05)		0,7–0,94		6% deficiency	
Zinc (umol/L)	17,5 (9–30)		10,1–16,6		6% deficiency 50% elevated	
Selenium (umol/l)	1,3 (0,9–1,5)		0,8–1,6			

[a] Corrected vitamin E: Vitamin E/(triglycerides + Cholesterol). IF - Intestinal Failure.

The prevalence of low UIC was higher in the IF group than among the reference group. IF patients were provided most of their iodine from PN (63% of total provision). Nevertheless, UIC had a significantly positive correlation with the amount of iodine from the diet, and enteral provision of iodine seems important in ensuring sufficient iodine in children treated with HPN.

It seems warranted to recommend that clinicians evaluate the iodine provision from diet and enteral nutrition support in their IF patients on HPN and look more to the recommendations of enteral nutrition to avoid iodine deficiency in this group. In cases of low enteral tolerance iodine can be added to PN as an individual supplement [33].

Diet and/or enteral nutritional support were the main contributor of iron for the majority of IF patients in this study. Nevertheless, they met less than 50% of the recommended intake of iron, while the healthy group met more than 80%. Iron is difficult to provide in parenteral nutrition due to concerns about compatibilities [20]. Moreover, enteral supplementation may not be effective in IF patients due to malabsorption, the use of antacid drugs and the risk of GI complications. In this study the IF group had a significantly higher prevalence of mild and moderate anaemia than the healthy children. IF patients with anaemia tended to have been treated with HPN for significantly longer and commenced HPN at a younger age than those without. However, most iron parameters were within the normal range and none of the participants were diagnosed with iron deficiency. Other studies have found high rates of both anaemia and iron deficiency anaemia in children and adult IF patients on HPN [19,20,23]. Diagnosing iron deficiency and iron deficiency anaemia can be challenging because depletion occurs in stages and may be asymptomatic. Defining iron deficiency in IF patients is particularly difficult as many have low-grade inflammation even if C-reactive protein levels are normal [39]. Therefore, it is important to consider the complete medical picture. Haemoglobin, ferritin, total iron binding capacity and transferrin saturation should be monitored regularly to track changes. Some authors have recommended measuring transferrin receptor to establish iron deficiency because this parameter is not affected as much by inflammation [13]. However, we found no associations between transferrin receptor, anaemia, haemoglobin or ferritin in our study. Iron deficiency anaemia has detrimental effects on a child's development and can affect immune function, physical work capacity, and mental, motor, and emotional development [40–42]. Therefore, monitoring iron status is important, and regular iron intravenous supplementation should be considered in individuals who are at risk, such as those with minimal enteral diet, patients with chronic inflammation and young girls after menarche.

A strength of this study is that all IF patients on HPN at our center at the time of investigation were included. In addition, detailed data on provision of nutrients from diet, enteral nutrition support and parenteral nutrition was obtained at the same time as measurements of micronutrient status in blood and urine.

However, some limitations should be noted. The sample size of IF patients on HPN was small, allowing for type 2 errors. The reference group was recruited by advertisement in social media and participants could therefore be healthier than the general population. However, the dietary intake of the reference group was comparable to the intake of Norwegian 9 year olds in the last national dietary investigation study in Norway [43]. Another possible limitation is the validity of urine iodine as a marker of iodine deficiency among children on parenteral nutrition. This study raises questions regarding iron and iodine status of IF patients on home-parenteral nutrition and further studies are needed on measurements to avoid deficiencies of these nutrients.

5. Conclusion

In this cross-sectional study of paediatric IF patients an adequate nutritional status and nutrient provision were found for most micronutrients. The exceptions were iodine and iron. Compared to healthy children, IF patients had poorer iodine and iron status. Anaemia was prevalent, and iron provision was low. Iodine status was associated with enteral provision and when providing twice the ESPGHAN recommendation, insufficient iodine status still occurred in the IF population.

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Conflict of Interest

The authors report no conflicts of interests to declare.

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