Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print

DOI : 10.1097/MPG.0000000000002090

Growth, body composition and micronutrient abnormalities during and after weaning off home parenteral nutrition

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Conflicts of interest and source of funding: none declared

Acknowledgements: We would like to thank Noortje Rijnen, Simone Aarten and Lieke van Essen for helping with the data collection.

Abstract

Objectives

To assess growth, body composition and micronutrient abnormalities in children with intestinal failure (IF) over time, both during and after weaning off parenteral nutrition (PN).

Methods

Retrospective study in children on home PN between 2001 and 2015. Weight-for-age (WFA) and height-for-age (HFA) SD scores (SDS) were calculated, as well as fat mass (FM) and fat free mass (FFM) SDS obtained by DEXA. The course of growth parameters and body composition was analyzed with linear mixed models. All micronutrient measurements during the study period were obtained.

Results

Fifty-two patients were included with a median follow-up of 3.4 years. Seventy-one % weaned off after a median PN duration of 0.9 years. One year after the start of PN, 28 patients were still PN-dependent with median WFA-SDS of -0.66 and median HFA-SDS of -0.96, both significantly lower than zero. Catch-up growth was achieved during PN, but HFA-SDS decreased after weaning (p=0.0001). At a median age of 6.2 years, median %FM SDS was 0.30 and FFM SDS was -1.21, the latter significantly lower than zero. Frequent micronutrient abnormalities during PN were vitamin A (90%), zinc (87%) and iron (76%) and after weaning vitamin A (94%), E (61%) and 25-OH vitamin D (59%).

Conclusion

Children with IF demonstrate abnormal growth and body composition and frequent micronutrient abnormalities. Longitudinal evaluation showed that catch-up growth occurs during

PN, but height SDS decreases after weaning. This underlines the need for close monitoring, also after reaching enteral autonomy.

Keywords: intestinal failure; growth; body composition; micronutrient abnormalities; parenteral nutrition.

What is known

- Children with intestinal failure (IF) are at risk of growth failure and micronutrient abnormalities
- The course of growth during and after weaning parenteral nutrition (PN), as well as information about body composition is not well known

What is new

- During the period of PN catch-up growth can be achieved, but height-for-age decreases after weaning
- Children with intestinal failure have altered body composition with low fat free mass, also after weaning off PN
- Micronutrient abnormalities are common not only during PN, but also after weaning

Introduction

Intestinal failure (IF) is defined as a critical reduction of the gut mass or function, below the minimum needed to absorb nutrients and fluids.(1) In order to grow and develop, children with IF are dependent on parenteral nutrition (PN). Despite the treatment with PN, growth failure is an important problem in these children. Previous studies have shown that almost 50% of the children receiving long-term PN have a height below the normal range for age and that they are significantly lighter and shorter than healthy children.(2, 3) In current clinical practice, growth monitoring of children with IF is mainly based on the quantity of growth by measuring weight and height, whereas body composition e.g. the amount of fat mass (FM) and fat free mass (FFM) is not routinely measured. A previous study showed that children with IF had a significant deficit in limb lean mass, with high FM in children totally PN-dependent.(4) Abnormal body composition can be associated with cardiovascular and metabolic risks(5), but also with muscle weakness and reduced bone accretion.(6)

Next to growth failure, children with IF are at risk of micronutrient abnormalities.(7, 8) Factors that may contribute are malabsorption, resection of specific parts of the bowel and inflammation.(9, 10)

While previous studies focused on growth and body composition in a cross-sectional way, our aims were to assess the course of growth parameters and body composition over time and to quantify the prevalence of micronutrient abnormalities in children with IF, both during and after weaning off PN.

Methods

Study population

This was a single-center retrospective study evaluating all children receiving home PN (HPN) between January 2001 and January 2015. Patients were divided into functional (enteropathies and motility disorders) and surgical IF. The category surgical IF consisted of children with short bowel syndrome (SBS) and children after small bowel resection with a remaining small bowel length not as short as covered by the SBS definition. SBS was defined according to the Dutch National Working group Pediatric SBS(11) as a resection of ≥70% of the small bowel and/or a remaining small bowel length distal of Treitz <50 cm, <75 cm and <100 cm in preterm infants, term infants and children >1 year, respectively.

Approval of the local research ethics committee was obtained (MEC-2014-341). Since the retrospective data were analyzed anonymously, written informed consent was not necessary.

Data collection

We collected data from start of IF until January, 2015 by reviewing the hospital records, including patient and bowel characteristics, nutritional data, growth and body composition data. Start of IF was defined as the date of bowel resection for surgical IF and start date of PN for functional IF.

Nutritional data

Children on HPN were frequently seen at our outpatient clinic, but also after weaning off PN they visited the outpatient clinic at least yearly for growth monitoring, evaluation of nutritional intake and laboratory evaluation of micronutrients.

Weaning off PN was started when sufficient amounts of enteral/oral nutrition were tolerated. Patients were considered partially PN-dependent when receiving <80% of their

calories via PN, and weaned off PN when they received full enteral/oral nutrition and did not restart PN before the end of the study. Weaning off PN was only performed when growth was acceptable (height within target height range and weight and height between -2 and +2 standard deviation score (SDS)) and SDS of weight and height did not deviate from the individual's previous growth curves while on PN. PN was prescribed according to the ESPGHAN/ESPEN guideline(12) and nutritional intake was adjusted according to growth. For the patients included, the micronutrient supplementation parenterally received was Vitintra Infant®, Soluvit®, Peditrace® (<10 kg) and Addamel® (10-30 kg), customized as needed by the pharmacy. Micronutrients were supplemented either parenterally or enterally/orally according to the ESPGHAN/ESPEN guideline(12) and individually adjusted according to the measured levels, also after weaning.

Growth and body composition

Weight and height were measured using standard equipment. Sex- and age-adjusted SDS were calculated for weight (weight-for-age (WFA)/weight-for-height (WFH)) and height (height-for-age (HFA)) by using the up to date Dutch national reference standards(13) using the Growth Analyzer Research Calculation Tool.(14) The Fenton preterm growth charts were used until the gestational age of 40 weeks.(15) Afterwards, a corrected age was used until 2 years of age. Height and weight data were collected at 3, 6, 9, 12, 18 and 24 months after start of PN and afterwards on annual basis. When measurements were not available on the assigned day, the measurement closest to that day was chosen or noted as a missing value when there was no measurement available within 1 month. Additional measurements were collected if no measurements were available at the designed time points for the linear mixed model analysis (see

statistical analysis). Target height (TH), TH SDS and 95% TH range (± 1.6 SD range) were calculated with use of parenteral heights.(16)

Body composition data were obtained via dual energy X-ray absorptiometry (DEXA) scans, performed as routine care starting from around age 5, in order to monitor bone health. SDS for percentage fat (%FM) and absolute FFM were calculated using Dutch reference data, available for children ≥4 years of age.(17) Growth and body composition SDS <-2 were defined as abnormal.

Micronutrients

The micronutrients examined were vitamin A, B1, B6, total vitamin B12, 25-OH vitamin D, vitamin E, aluminum, chromium, copper, selenium, zinc, iron and ferritin. All measurements during the study period were collected and interpreted as normal or abnormal. If during the study period >1 micronutrient level was obtained in 1 patient, the most abnormal level (high or low depending on the micronutrient) on PN and the most abnormal level weaned off was identified as indicative of abnormality status. Children were clinically stable during micronutrient assessment, without signs of line sepsis or increased CRP.

Statistical analysis

Statistical analyses were performed using SPSS Version 21.0. Categorical data are summarized as frequencies and percentages and continuous data as median and interquartile range (IQR) or range. Differences in anthropometrics between patients on PN and patients weaned off were assessed using the Mann-Whitney *U* test and Fisher's exact test. To determine whether growth and body composition SDS differed significantly from healthy children, the Wilcoxon one-sample test was used. Spearman's correlation analysis was used to examine relationships between growth and body composition. The Fisher's exact test was used to compare the

prevalence of micronutrient abnormalities between children totally versus partially PN-dependent as well as functional versus surgical IF.

To evaluate the course of growth and body composition during and after weaning off PN we used linear mixed effect models. Mixed models appropriately account for the correlations in the repeated measurements of each subject. In addition, they provide valid inferences under the missing at random missing data mechanism. Moreover, they allow for measurements to be taken at different time points per patient, and appropriately model the longitudinal evolutions of each outcome. A linear mixed effects model was built for each of the three growth parameters, only including the patients that were able to wean. In the specification of these models we allowed the longitudinal evolutions to change after PN was stopped for each child. Moreover, we also allowed for potential nonlinear evolutions per parameter. To accommodate these features we used natural cubic splines of time, which explicitly allowed for a change in the evolutions after PN stopped. These terms were included both in the fixed and random-effects part of the models. To select the optimal random-effects structure and test whether the longitudinal evolutions were nonlinear we used likelihood ratio tests. To test whether there was a change in the longitudinal evolutions after PN we used an F-test. In addition, residuals analysis was performed to evaluate the models' assumptions. In the 12 patients with various subsequent HPN periods, a stop period of ≥6 months was seen as a definite stop for this analysis. The weight and height measurements of patients with a stop period <6 months were included in the analysis of growth on PN. For body composition, the fixed-effects part included the covariates PN duration, time intervals between start of PN and the measurements, and WFH-SDS. For the random-effects part random intercepts were included.

The optimal random-effects structure was chosen using the Akaike information criterion, while for the fixed-effects p-values were based on t- and F-tests.

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

Between 2000 and 2015, 62 children received HPN. Three patients deceased and 7 had their follow-up at another hospital, leading to 52 included patients with available follow-up data. Patient characteristics are shown in **Table 1**. Twenty patients (38%) had SBS. Thirty-seven patients (71%) weaned off PN after a median PN duration of 0.92 years. The median follow-up duration until January 1, 2015 was 3.35 years (IQR 1.53 – 6.61).

Growth

In total, 597 weight (median per patient 8) and 504 height measurements (median per patient 8) were obtained. For the cross-sectional analysis at one year after start of PN (with a range of 1 month before and after) growth data were available for 41 patients **(Supplemental Figure 1, Supplemental Digital Content, http://links.lww.com/MPG/B450)**. Twenty-eight patients (68%) were still dependent on PN and had a median WFA-SDS of -0.66, median HFA-SDS of -0.96, and median WFH-SDS of 0.06 (**Table 2**); both WFA-SDS and HFA-SDS were significantly lower than zero. For children weaned off PN, WFA-SDS was significantly lower than zero. There were no significant differences between growth parameters of children on PN

and children weaned off at 1 year after start of PN. In addition, no significant differences between children with surgical and functional IF were found.

Differences between actual height and TH could be calculated in 23 of 52 patients, at a median age of 2.1 years, 2 years after start of PN. Missing values were due to absence of the child's height or height of one of the parents. Median distance between actual HFA-SDS and TH SDS was -0.26 (IQR -0.87 to 0.85), whereas 2/23 patients were growing below their TH range.

Linear mixed models showed that the course of HFA-SDS was significantly different during and after weaning off PN (p=0.0001). **Figure 1** illustrates the course of HFA-SDS during and after weaning off PN according to the model, with different PN durations of 1 and 2 years. Visual inspection of this graph shows that median HFA-SDS was low at start of IF, but that catch-up growth occurred during PN, with a decrease in HFA after weaning off PN. For WFA-SDS (**Supplemental Figure 2, Supplemental Digital Content, http://links.lww.com/MPG/B450)** and WFH-SDS the course of growth was not different during and after weaning off PN, with catch-up growth during PN, but stable values after weaning (data not shown).

Body composition

Nineteen children (37%) underwent a DEXA scan as standard follow-up to monitor bone health (52% of the children were too young i.e. <4 years of age). For children with multiple DEXA scans, the results of the first DEXA scan were analyzed. The first DEXA scan was made at a median age of 6.2 years (IQR 5.4 – 9.3). At that time 13 patients (68%) were already weaned off PN, whereas 6 were still partially dependent on PN. Median HFA-SDS was -0.66, WFA-SDS -0.74 and WFH-SDS -0.68 (**Supplemental Figure 3, Supplemental Digital Content, http://links.lww.com/MPG/B450**). Median FFM SDS was -1.21 (IQR -1.93 to -0.87), which

was significantly lower than zero (p<0.001). Median %FM SDS was 0.30 (IQR -0.26 to 1.26), which was not significantly different from zero (p=0.08). FFM SDS was significantly positively associated to WFA-SDS (Spearman's rho 0.613, p=0.009) and HFA-SDS (0.744, p<0.001). For %FM SDS, only WFH-SDS was significantly associated (0.515, p=0.034).

Nine patients had multiple DEXA scans with a maximum of 8 scans. Using linear mixed models, course of WFH-SDS was positively associated with the course of %FM SDS over time with an increase of 0.7 SD in %FM for each 1 SD increase of WFH (p<0.001). For FFM SDS, no significant associations were found.

Micronutrient abnormalities

Table 3 shows the frequency of micronutrient monitoring during and after weaning off PN and the prevalence of abnormalities. There were no differences in the prevalence of abnormalities between children totally versus partially PN-dependent or surgical versus functional IF.

Discussion

This study aimed at evaluating the course of growth parameters and body composition and the prevalence of micronutrient abnormalities, during and after weaning off PN. Our study shows that 1 year after the start of PN, children with IF had a significantly lower weight than healthy children. When still on PN, children were also significantly shorter. In addition, children had lower FFM than healthy controls at their first DEXA. Moreover, this study is the first to evaluate the longitudinal course of growth during and after weaning off PN using linear mixed models, showing catch-up growth during PN, but a significant decrease of HFA-SDS after weaning.

We found that children with IF were significantly shorter and lighter 1 year after the start of PN, and still lighter after weaning off PN compared to the healthy Dutch growth reference population. Our results are comparable with a previous study by Raphael et al.(18) However, another study(19) reported normal growth measurements in weaned children, which may be explained by their small sample size and the fact that weaning took place for >2 years at time of assessment.

Of the growth parameters measured, height was impaired the most. This has been reported previously(2-4). Seventeen percent of the children had a height below the normal range for age 1 year after the start of PN. This is lower than the 50% reported by Pichler et al.(2), which may be explained by the fact that in that study almost all children were still (partially) dependent on PN (median time of 5 years) implying more severe IF, whereas in our study already one third was weaned off PN within 1 year. However, our children were not growing as expected based on their TH SDS, shown as negative median distance between actual HFA-SDS and TH SDS. Longitudinal evaluation showed catch-up growth during PN for all growth parameters, but a significant decrease of HFA-SDS after weaning, especially after a PN duration of 2 years. The fact that the course of WFA and WFH was not significantly altered after weaning suggests that patients weaned off PN receive enough oral/enteral nutrition to maintain their weight, but may suffer from persistent chronic malabsorption, and should maybe receive more nutrition (enteral or even parenteral) in order to maintain their linear growth course. Most important, this emphasizes the need for continuing follow-up after achieving enteral autonomy including a possible individualized nutritional intervention at a later stage after weaning especially in times of increased growth velocity such as puberty.

When monitoring growth, it is also important to evaluate body composition. As a result of low HFA in children with IF, WFH was not significantly different from healthy children. This could imply a good body composition, but when looking at the actual body composition results, patients had significant lower FFM, even when most of the children were already weaned off PN at the first measurement. This is in agreement with the previous study covering this topic.(4) Possibly due to the small sample size, FM was not significantly higher than in healthy references. Monitoring body composition is valuable since abnormal body composition is associated with several determinants of cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome.(5, 20, 21) In addition, FFM is one of the strongest predictors of bone mass.(6, 22, 23) Studies assessing body composition from diagnosis onwards are therefore necessary to determine what optimal growth in children with IF is.

Micronutrient abnormalities were commonly present during treatment with PN, but also after weaning. Reasons for these abnormalities will vary depending on the level of PN dependency and the existing degree of malabsorption of EN and enteral micronutrient supplements after weaning of PN. Especially fat-soluble vitamins were frequently deficient, which might be caused by fat malabsorption due to ileal resection, cholestasis or use of cholestyramine. Our results are generally in agreement with previous studies, although we found higher prevalence of abnormalities of most micronutrients.(7, 8, 24-27) In general, it is assumed that the micronutrient preparations in PN meet the nutritional requirements for totally PN-dependent children. As abnormalities were also found in children totally PN-dependent, we suggest reevaluation of micronutrient content in PN, especially for use in children on long-term PN.

Strikingly, not all micronutrients were monitored regularly, as no strict protocol was followed during the study period. It is therefore possible that monitoring was mainly performed in selected patients considered at high risk of abnormalities. Guidelines on micronutrient monitoring in children with IF vary widely and are not specific for weaned patients(12), but usually regular monitoring is recommended since most patients will not have clinical symptoms. In a recent paper, it is suggested that copper, selenium, zinc, vitamin A, E, D, B12, methylmalonic acid, prothrombin time, iron, total iron-binding capacity, RBC, folate, and carnitine (the latter if <1 year) should be monitored every 6 months in children on HPN.(28)

Overall it is remarkable that despite frequent involvement of a multidisciplinary team caring for children with IF both during PN and after weaning, abnormalities in growth and micronutrients were found. This may partly be explained by the underlying diseases or comorbidity rather than nutritional intake alone. The lack of protocolised care during the start-up years of the team was probably a contributing reason. Strict monitoring will, however, ensure timely diagnosis and adequate treatment, including micronutrient supplementation, or (re)start of enteral/PN if necessary.

The strengths of our study were the longitudinal design and the high number of growth measurements obtained which allowed for the linear mixed modeling analyses that give insight into the evaluation of growth over time during PN and after weaning. The main limitation of this study is its retrospective design. Detailed information on important factors that may influence growth, body composition and micronutrient levels, such as quality of PN and enteral/oral micronutrient supplementation could not be systematically collected and therefore not be taken into account. The fact that we did not find any differences in growth or micronutrient abnormalities between children totally and partially PN-dependent or with a different type of IF

could also be due to the relative small sample size. Large prospective studies according to a strict protocol are necessary to give more insight into these problems, in order to be able to relate growth, as well as bone age, body composition and micronutrient abnormalities.

In conclusion, this retrospective study showed that despite frequent monitoring, abnormalities in growth, body composition and micronutrients were common both during PN and after weaning. This may have large health implications later in life. With continuing improvement of prognosis, maintaining normal growth and body composition and adequate micronutrient levels become increasingly important in these children and necessitate monitoring by healthcare professionals, also after weaning. Future prospective studies should focus on what growth target should be aimed for in relation to achieving an optimal body composition and optimal development.

Acknowledgements: We would like to thank Noortje Rijnen, Simone Aarten and Lieke van Essen for helping with the data collection.

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Figure legends

Figure 1. Course of HFA-SDS during and after weaning off PN. Figure 1a illustrates the linear mixed effect model of the course of HFA-SDS in children with IF during and after weaning off PN with a PN duration of 1 year. Figure 1b illustrates the linear mixed effect model of the course of HFA-SDS during and after weaning off PN with a PN duration of 2 years. Red line represents median, dotted lines represent 95% confidence interval.

HFA, height-for-age; IF, intestinal failure; PN, parenteral nutrition.

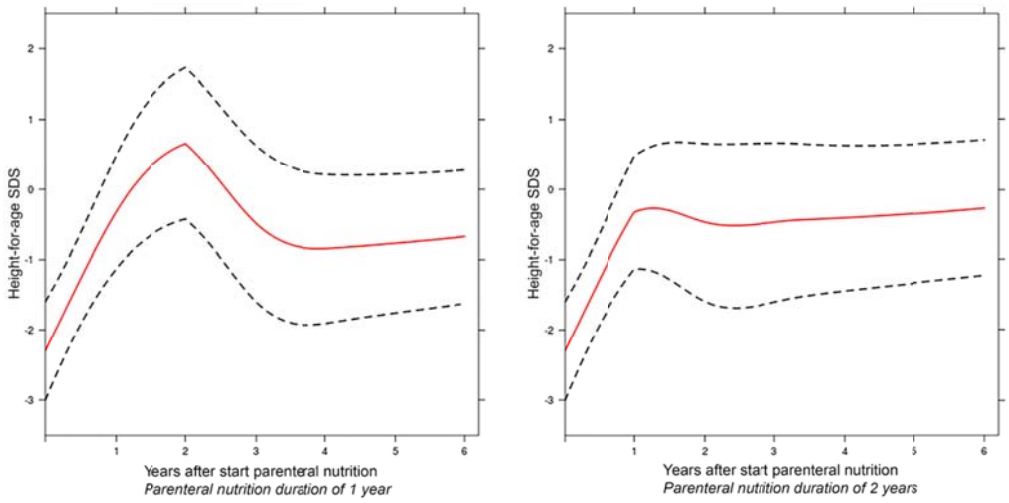

Table 1. Patient characteristics of children with intestinal failure receiving home parenteral nutrition

	n = 52 **n (%) or median (IQR)**	**Able to wean off PN** **n = 37**	**Not able to wean off PN** **n = 15**	**p-value**
Sex: female	29 (56)	22 (60)	7 (47)	NS
Prematurity (gestational age < 37 weeks) – n (%)	32 (62)	23 (62)	9 (60)	NS
Age at start of IF (days) – median (IQR)	6 (0 – 42 days, range 0 – 16 years)	3 (0-31)	18 (3-47)	NS
Category of IF – n (%)				NS
Surgical	41 (79)	32 (87)	9 (60)	
SBS, remaining small bowel length – median cm (IQR)	20 (49), 40 (22 – 49)	14 (38), 60 (45-80)	6 (40), 28 (16-70)	
Functional	11 (21)	5 (14)	6 (40)	
Enteropathy	8 (72)	4 (80)	4 (67)	
Motility disorder	3 (27)	1 (20)	2 (33)	

Underlying diseases – n (%)		NA	NA	NA
Intestinal atresia	11 (21)			
Necrotizing enterocolitis	10 (19)			
Volvulus	5 (10)			
Gastroschisis	5 (10)			
Gastroschisis with atresia	2 (4)			
Ileus	4 (8)			
Intestinal lymphangiectasia	2 (4)			
Other	13 (29)			
Ileocecal valve in situ – n (%)	34 (65)	25 (68)	9 (60)	NS
Colon in situ – n (%)	43 (83)	30 (81)	13 (87)	NS
PN duration until weaning off PN or until end of study if not able to wean, years – median (IQR)		0.92 (0.52 – 1.87)	2.36 (0.78 – 5.09)	NA
Age at weaning or end of study if not able to wean, years – median (IQR)		1.41 (0.61 – 2.81)	2.74 (1.23 – 7.96)	NA

IF, intestinal failure; NA, not applicable, NS, not significant, PN, parenteral nutrition; SBS, short bowel syndrome.

Table 2. Growth outcomes according to Dutch reference standards at 1 year after start of parenteral nutrition

	Children on PN (n = 28)		**Children weaned off PN (n = 13)**	
	n		**n**	
WFA-SDS **median (IQR)** **< -2 (n (%))**	28	-0.66 (-1.07 to -0.07)* 4 (14)	13	-0.89 (-1.76 to 0.21)* 2 (15)
HFA-SDS **median (IQR)** **< -2 (n (%))**	27	-0.96 (-1.68 to -0.07)* 6 (21)	13	-0.33 (-1.56 to 0.25) 1 (8)
WFH-SDS **median (IQR)** **< -2 (n (%))** **> +2 (n (%))**	27	0.06 (-0.79 to 0.88) 2 (7) 1 (4)	13	-0.37 (-1.29 to 0.37) 0 (0)

				0 (0)

HFA, height-for-age; PN, parenteral nutrition; WFA, weight-for-age; WFH, weight-for-height.

* significantly lower than zero.

Table 3. Micronutrient monitoring and prevalence of micronutrient abnormalities during and after weaning off PN.

Micronutrient (reference range)	**Patients assessed during PN** n	**Deficiency during PN** n (%) Median level of patients with deficiency (range, IQR)	**Patients assessed after weaning** n	**Deficiency after weaning** n (%) Median level of patients with deficiency (range, IQR)
25-OH vitamin D (50 - 120 nmol/L)	24	10 (42) 40.5 (20.0 – 48.0, IQR 34.5 - 44.3)	18	10 (56) 30.5 (5.0 – 46.0, IQR 13.3 - 42.8)
Total vitamin B12 (145 - 637 pmol/L)	29	2 (7) 71 (22 - 120, IQR NA)	18	4 (22) 87 (42 - 127, IQR 52 - 119)
Vitamin B1 (70 - 140 nmol/)	22	0 (0)	15	1 (7) 61 (range and IQR NA)
Vitamin B6 (35 - 100 nmol/L)	20	0 (0)	15	0 (0)
Vitamin A (1.25 - 3.00 µmol/L)	31	28 (90) 0.67 (0.22 - 1.16, IQR 0.47 - 0.89)	18	17 (94) 0.83 (0.33 - 1.21, IQR 0.62 - 0.97)
Vitamin E	31	12 (39)	19	12 (63)

(16.5 - 41.6 μmol/L)				
		11.4 (5.4 - 15.4, IQR 7.4 - 13.4)		10. (5.1 - 13.8, IQR 9.2 - 12.6)
Aluminum (< 0.36 μmol/L or < 21 μg/L)	18	0 (0)	6	0 (0)
Chromium (< 40.4 nmol/L)	12	0 (0)	3	0 (0)
Copper (9.6 - 20.1 μmol/L)	23	2 (9)	13	0 (0)
		8.3 (8.0 - 8.6, IQR NA)		
Selenium (63 - 142 μg/L)	19	3 (16)	13	3 (23)
		45 (30 - 48, IQR NA)		44 (25 - 58, IQR NA)
Zinc (64.3 - 124 μmol/L)	23	20 (87)	16	11 (69)
		13.9 (6.0 - 56.0, IQR 11.0 - 37.4)		13.0 (6.0 - 56.0, IQR 7.0 - 49.5)
Iron (5 - 3 μmol/L (< 1 year), 10 - 30 μmol/L (> 1 year))	45	34 (76)	20	13 (65)
		4.1 (1.5 - 14.3, IQR 3.2 - 4.6)		4.4 (2.0 - 8.3, IQR 3.2 - 7.2)
Ferritin (30 - 240 μg/L)	48	22 (46)	21	6 (29)

	8.5 (4.0 - 24.0, IQR 5.8 - 15.0)	7.5 (4.0 - 26.0, IQR 4.8 - 16.3)

NA, not applicable, PN, parenteral nutrition. Total patients in follow-up: 52 during PN, 37 after weaning of PN.