Body composition using air-displacement plethysmography in children with intestinal failure receiving long-term home parenteral nutrition

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CLINICAL RELEVANCY STATEMENT

Children with intestinal failure (IF) are susceptible to poor growth in terms of body weight and height, but few previous studies have reported on their body composition. Despite close monitoring of weight and height and follow-up by a multidisciplinary team, we found that abnormalities of growth and body composition are common, with low weight-for-age, height-for-age and fat free fat mass, and high fat mass. Patients with IF may benefit from a patient-tailored approach based on their body composition, in order to maximize growth and prevent body composition-related complications later in life.

ABSTRACT

Background

Children with intestinal failure (IF) are at risk of growth failure, but little information about body composition is available. Our aim was to assess body composition using air-displacement plethysmography (ADP) and to relate it to clinical and growth parameters.

Methods

In this prospective descriptive observational two-center cohort study, children aged 2-18 years on home parenteral nutrition (PN) for ≥6 months underwent ADP measurement. Fat mass index (FMI) and fat-free mass index (FFMI) standard deviation scores (SDS) were calculated to normalize for small body size.

Results

Twenty-one out of 22 children, median age 7.4 years, underwent successful ADP measurement after a median PN duration of 5.5 years. They were significantly lighter (median weight-for-age-SDS -0.71, $p=0.004$) and shorter (median height-for-age-SDS -1.55, $p<0.001$) than the normal population mean; 52% were growing below target height range. They had low FFMI (median SDS -1.53, $p<0.001$) and high FMI (median SDS 0.80, $p=0.002$). Weight-for-height and BMI were significantly associated with FFMI and BMI with FMI, but children with the same weight and height showed different body composition. In 13 patients with 1-year follow-up, growth and body composition did not change significantly.

Conclusion

Children with IF receiving long-term PN show lower FFM and higher FM than healthy children. Additionally, children with similar routine growth parameters showed different body composition. Further studies should evaluate the effect of a patient-tailored approach including physical activity and nutrition advice based on body composition.

INTRODUCTION

In patients with intestinal failure (IF) the small bowel is too short or dysfunctional and therefore not able to absorb enough nutrients.[1] Consequently, children with IF depend on parenteral nutrition (PN) to maintain growth and development. Current growth monitoring is mainly based on measurements of weight and height and their course over time, and nutrition intake is adjusted accordingly. However, these measurements do not provide information about the quality of growth i.e. body composition, divided into fat mass (FM) and fat-free mass (FFM). In clinical practice, it is often necessary to increase the amount of PN to improve or maintain linear growth. However, this may result in excessive weight gain rather than improved height, suggesting that FM may be increased rather than FFM.

Previous studies reported that children with IF are significantly lighter and shorter than healthy chidren.[2-5] One study assessing body composition showed that they have a lower FFM.[3] In addition fully PN-dependent patients had increased FM.[3] The assessment of body composition is important since abnormal body composition can be associated with several determinants of cardiovascular disease, type 2 diabetes mellitus and metabolic syndrome.[6-8] In addition, FFM is one of the strongest predictors of bone mass, which is important because these children are already at risk of poor bone health.[9-13]

Most of the methods available to measure body composition have a number of methodological and practical limitations such as a lack of reference values for young children. Nowadays, body composition can be assessed by air-displacement plethysmography (ADP), which is well tolerated by children and does not involve radiation.[14] Our aims were to assess body composition in children with IF receiving long-term PN using ADP and to evaluate the relationship between growth measurements and body composition. Our hypothesis was that children with IF have abnormal body composition, which cannot be detected by standard measurements – ie, weight and height.

METHODS

Study population

All children on home PN attending the IF teams of the Erasmus Medical Center – Sophia Children's Hospital (Rotterdam, the Netherlands) and the Amsterdam UMC, Emma Children's Hospital, location AMC (Amsterdam, the Netherlands) were asked to participate in a descriptive prospective observational study from March 2015 onwards, which included the measurement of body composition. The minimum PN duration was 6 months and the minimum age of the patients was 2 years. We included patients who underwent a body composition measurement before May 2018. The study was approved by the local research ethical committees (MEC 2015-002, Dutch Trial Register NTR6080) and informed consent was obtained.

Data collection

Demographic and clinical data obtained from the medical records were age, gender and underlying disease. Patients were divided into surgical IF and functional IF (including both motility disorders and enteropathies). PN and enteral nutrition were prescribed according to the European Society of Paediatric Gastroenterology, Hepatology and Nutrition and European Society for Clinical Nutrition and Metabolism guideline.[15] Total caloric needs were based on calculated total energy expenditure and adjusted over time based on age and routine growth parameters by the IF team dietitians. The dietitians were not aware of the body composition results. The type of parental lipid used was mostly a mixed soybean/medium-chain triglycerides/olive/fish oil lipid emulsion or a mix of olive and soybean oil in case of all-in-one formulations for older children. PN characteristics collected included duration, calories per kg/day, and grams of carbohydrates, lipids and amino acid infusion per kg/day. In addition, the parenteral glucose infusion rate (milligram glucose/kilogram/minute) and parenteral non-protein energy:nitrogen ratio (non-protein calories divided by grams of nitrogen) were calculated. Total (parenteral, oral and enteral) calories were also expressed as total calories divided by resting energy expenditure as calculated by the Schofield formula.[16] Percentage PN was used as a measure of PN dependency and was defined as *% of energy provided by PN = (daily energy in kcal provided by PN / total daily energy intake in kcal) * 100*. Full PN dependency was defined as more than 80% of the intake provided by PN, and partial PN dependency as 1-80% of intake provided by PN.[3]

Anthropometrics

Weight and height were routinely measured using standard equipment including a clinical calibrated electronic scale and a stadiometer. Mid-upper arm circumference (MUAC) was measured with a measuring tape at the mid-point between the olecranon and the acromion of the nondominant arm, or of the left arm if the nondominant was not known. Sex-specific standard deviation scores (SDSs) were calculated for weight-for-age (WFA), height-for-age (HFA), weight-for-height (WFH), body mass index (BMI) and MUAC using the latest available Dutch national reference standards (TNO 2010 growth references, for MUAC TNO 2001) and the Growth Analyser Research Calculation Tool, which is a statistical and data analysis software program.[17,18] Target height (TH) in centimeters was calculated as follows for boys: 44.5+0.376×height of the father (cm)+ 0.411×height of the mother (cm). TH was calculated as follows for girls: 47.1+0.334×height of the father (cm)+ 0.364×height of the mother (cm). In addition, TH SDS and 95% TH range (±1.6 SDS) were calculated as described previously.[19,20] HFA/TH SDS, representing a parameter of current height compared with expected height based on parental heights, was calculated by subtracting TH SDS from HFA SDS.[21]

Body composition

Whole-body composition was assessed by ADP based on whole-body densitometry using the BOD POD (BOD POD body composition system including the pediatric option suitable for children above 2 years of age and at least 12 kg, COSMED, Ltd, Concord, CA, USA, **Figure 1**). This method is based on the assumption that the body can be separated into 2 compartments: FM and FFM, the latter including muscle, water, bone, and internal organs. Several studies have shown that ADP is comparable to multi compartment models[14,22-24] and the BOD POD has been validated for the measurement of body composition in children.[22,24,25]

Body composition was measured as soon as possible after obtaining informed consent and 1 year thereafter. All measurements were performed by experienced personnel using a standardized protocol. A detailed description of the BOD POD measurement is provided elsewhere.[22] Patients were assessed wearing tight swimwear, with their hair covered with a bathing cap. Body mass was measured on the integrated electronic scale and body volume was assessed in the test chamber by applying gas laws that relate pressure changes to volumes of air in the enclosed chamber. The body volume measurement required 2 or 3 tests that lasted 50 seconds each. The 2 body volume measurements that were closest in agreement were used by the system software to calculate the average body volume. Body-density was then computed from body mass and body volume and converted to percentage and absolute FM and FFM using sex-specific equations by Fomon and Lohman et al.[26,27] If applicable, the central venous catheter, feeding tube, enterostomy bag, or other additional devices were calibrated in the BOD POD before the measurement. For children up to 6 years of age, a customized seat with adjustable seat tray was used according to protocol.

As suggested by previous studies[28,29] for accurate assessment of body composition in populations with small body size such as the included group, FM index (FMI) and FFM index (FFMI) were calculated by dividing the

FM and FFM in kg by linear height^2 to normalize the body composition variables for body size. The BOD POD itself does not provide SDS, so we calculated age and sex-specific SDS using UK reference values for FFMI and FMI SDS,[30] which were created *de novo* for this study using the lambda-mu-sigma method,([31] which generates centiles by age for outputs taking into account any skew in the data, so that individual SDS can be assigned. We utilized the raw body-density data that were from 533 healthy individuals and used previously to calculate FFM and FM by the 4-component model,[30] along with matching published data on the density of fat-free tissue.[32] These reference data match very closely with our FFMI and FMI reference data published previously, which were calculated using the criterion 4-component model [30]. For children <4 years of age (4 patients at the first BOD POD measurement, none at the second measurement), for whom BOD POD reference data were not available, reference values were obtained from equivalent body composition reference data obtained from deuterium dilution (Wells, Fewtrell, and Cole, unpublished data).

Statistical analysis

Statistical analyses were performed using SPSS Version 21.0 (IBM, Armonk, NY, US). Categorical data are summarized as frequency counts and percentages. Continuous data are shown as median and interquartile range (IQR) or range. To determine whether growth and body composition differed significantly from that in the reference population, the Wilcoxon one-sample test (compared with zero) was used. Growth and body composition of children on full PN vs partial PN, those with functional vs surgical IF, and boys vs girls were compared with Fisher's exact test and Mann Whitney-U test. The Wilcoxon signed rank test was used to compare growth and body composition at baseline and at 1-year follow-up. Spearman's correlation coefficient was used to correlate growth SDS (WFA, HFA, WFH, BMI and MUAC) with body composition SDS (FMI and FFMI) and PN (duration and macronutrient intake) with growth and body composition SDS. A p-value <0.05 was considered significant.

RESULTS

Patient characteristics

Of 34 children included in the prospective observational study, 22 underwent body composition measurement. Three patients could not be measured because of a body weight <12 kg. In 3 patients, the parents did not agree to the body composition measurement because of general anxiety; in 3 other cases parents did not agree to the measurement because the BOD POD was situated in another hospital (in case of patients treated in Amsterdam). In 3 patients, the body composition measurement was not performed for logistic reasons or because of loss to follow-up. Of these patients, 1 measurement was stopped because the child was distressed. The remaining 21 measurements were considered to be reliable by subjective assessment and were included in the analysis.

Patient characteristics are presented in **Table 1.** The median age at the first body composition measurement was 7.4 years (3.7-17.3). More than half of the patients had functional IF (57%). Chronic intestinal pseudo-obstruction syndrome was the most common underlying disorder (n=6, 29%). At the time of the first body composition measurement, 9/21 patients (43%) were fully PN-dependent. All but 1 of the fully PN-dependent patients had functional IF. The median PN duration at the first BOD POD measurement was 5.5 years. Eighty-six percent of patients received PN every day. Two patients received PN for 6 days a week and 1 patient received PN for 5 days a week.

Anthropometry

Patients with IF were significantly lighter and shorter compared with reference values with a median WFA SDS of -0.71 (p=0.004) and median HFA SDS of -1.55 (p<0.001) (**Table 2, Figure 2).** One patient had a WFA <-2 (5%), 4 patients had a MUAC SDS <-2 (19%), and 7 patients had a HFA SDS <-2 (33%), indicating chronic malnutrition. None of the patients had WFH <-2 SDS. Eleven patients (52%) were growing below their TH range. Median distance between actual HFA SDS and TH SDS was -1.60 (IQR -2.36 to -0.26). Children with surgical IF had a significantly higher WFH-SDS (p=0.049) and BMI SDS (p=0.041). No significant differences in growth characteristics were found between boys and girls or those receiving full vs partial PN. One patient was in puberty, and 1 post-pubertal; the remaining patients were prepuberty at time of the body composition measurements.

Body composition

Median FMI SDS was 0.80 and median FFMI SDS was -1.53 (**Table 2**). FMI SDS was significantly higher than the reference population (p=0.002) whereas FFMI SDS was significantly lower (p <0.001). Thirty-three percent of the patients had a FFMI SDS <-2.

FFMI SDS and FMI SDS were not different between children with functional IF or surgical IF and children fully or partially PN-dependent. Boys had a significantly higher FMI SDS (p=0.006) than girls had. Age at time of the body composition measurement was negatively associated with FMI SDS (-0.47, p=0.033). Duration of PN and actual parenteral energy or macronutrient intake were not significantly associated with body composition SDS.

Anthropometry and body composition

At the first BOD POD measurement, a significant correlation was found between WFH-SDS and FFMI SDS (0.62, p=0.003) and between BMI SDS and FFMI SDS (0.60, p=0.004). BMI SDS was significantly associated with FMI SDS (0.51, p=0.017).

Classification of height measurements and body composition

When looking at the body composition measurements in more detail, several combinations of height parameters and body composition outcomes were possible (**Table 3**). The most commonly found combinations were impaired height with normal FMI and decreased FFMI (n=5) and normal growth with increased FMI and decreased FFMI (n=5).

Longitudinal measurements

A total of 13 patients had repeated body composition measurement after 1 year (**Table 4**). Their baseline growth and body composition SDS were not different from those in patients with only 1 measurement. The median difference in PN dependency between the first and second measurement was 0% (IQR 0 to 4%). Growth and body composition SDS did not change significantly between the first and second measurement.

DISCUSSION

This study shows that children with IF have significant body composition abnormalities, with lower FFM and higher FM after correction for their smaller body size. In contrast to their lower weight and height compared with the reference population, their WFH and BMI were not significantly different. To our knowledge, this is the first study to use ADP for the analysis of body composition in children with IF, and it was shown to be feasible. Moreover, this study also prospectively assessed longitudinal body composition changes, showing no significant changes in growth and body composition after 1 year.

Regardless of type of IF and PN dependency, all patients in our study had significantly low FFMI. Low FFM has also been described in previous studies in which most or all children were already weaned off PN.[2,33] In another study using dual-energy X-ray absorptiometry (DEXA) scans, patients had significantly low limb lean mass, especially patients with short bowel syndrome.[3] In addition to low FFM, patients had significantly high FMI. We found that boys had higher FMI than girls; it is uncertain if this is a real difference or if it reflects the relatively small sample size. No differences in body composition were found between groups classified by type of IF (surgical vs functional) or PN dependency, in contrast to the previous study.[3]

Patients were not only shorter compared with healthy reference children, but half of them were growing below their TH range. This in agreement with a previous study[2], although in most other studies investigating growth in pediatric IF patients this information is lacking.

In current clinical practice, WFH and BMI are frequently used as a proxy for FM. Strikingly, WFH and BMI of patients with IF were not significantly different from healthy references. This suggests that these frequently used routine parameters are not valid for estimating FM in these children. Indices based on weight and height alone are not sufficient, and body composition should be measured to evaluate FM and FFM. A variety of techniques are available for measuring body composition. This study was the first to use ADP in children with IF and found it to be a feasible method for measuring body composition in this population. **Table 5** summarizes the advantages and disadvantages of ADP compared with DEXA. Compared with other techniques, important advantages of ADP are that it can be used to measure body composition in infants, and it is possible to perform the measurement when the patient has equipment such as a central venous catheter and enterostomy bag in place. However, if not available, other techniques could also be used taking into account their limitations.

This study was the first to prospectively assess longitudinal body composition changes in children with IF. In contrast to the normal population,[34] we found that age at the first body composition measurement was negatively associated with FMI, which means that older children tend to have lower FMI than younger children. However, when looking at growth and body composition at baseline and 1 year, we did not find any significant differences.

Abnormal body composition has been observed previously in other chronic diseases such as cystic fibrosis [35], renal failure[36], cerebral palsy[37] and inflammatory bowel disease[38], but the pathophysiology remains poorly understood. Moreover, comparison with previous studies is difficult because of different ages, methodology and use of different body composition parameters. The abnormal body composition in patients with IF might be a consequence of excessive energy intake and potential overfeeding when adjustment of PN prescription is based on individual needs taking into account age, activity and routine growth parameters, but not including body composition. In addition, high protein intake has been associated with higher FM in healthy children [39], but on the other hand studies have shown that increased protein intake is important for accretion and maintenance of FFM.[40] We did not find any associations between parenteral protein intake and body composition parameters, although the median parenteral amino acid intake (2.0 g/kg/day) was quite high in comparison with the recommended daily parenteral intake of 1.0-2.0 g/kg/day.[15,41] Another factor that might play an important role is decreased physical activity. Although no formal assessment of physical activity was performed and most patients received PN only overnight and were able to participate in usual daily activities including school, clinical experience shows that the group of children with IF may be less active than healthy children. On the other hand, 1 previous study reporting normal FFM showed similar levels of physical activity compared with healthy controls using accelerometry.[42] A study in adults with IF showed that 73% had sarcopenia, which includes not only loss of skeletal muscle but also muscle function.[43] Other factors that might influence body composition include prematurity, although results are conflicting,[44-46] and chronic inflammation.[47]

The question of what constitutes optimal growth and how nutrition recommendations should be customized remains. Our results show that body composition abnormalities also occur in children with normal linear growth and children with normal routine weight parameters, so focusing on these standard parameters during follow-up, may lead to not recognizing deficiencies in FFM and/or excess in FM. Ideally, in our opinion, nutrition advice should be patient-tailored based on nutrition assessment, taking into account routine growth parameters but also incorporating results from body composition measurement and level of activity. Future intervention studies are needed to create these more customized nutrition recommendations. Currently, patients are advised to participate in normal daily activities as much as possible. However, it might be better to refer them to a physical therapist for a patient-tailored exercise program, for example, including muscle strength improving exercises. The effect of abnormal growth and body composition on long-term outcomes, including neurodevelopment, cardiovascular and metabolic risks, and bone mass development is not well known, and these topics also need to be addressed in future studies.

Our study had some limitations. First, we did not assess physical activity. Ideally, future studies should include assessment of physical activity as well as functional outcome measures, although some of these measures such as hand grip strength are of limited use in young children. Second, we compared body composition values with UK references for BOD POD, since no Dutch reference values are available for ADP. Thirdly, we did not assess the relationship between mucosal inflammation and growth or body composition, although a previous study showed that patients with mucosal inflammation had a higher BMI.[3] Since our patients do not regularly undergo endoscopic evaluation and do not routinely receive corticosteroids, we were not able to investigate this. Fourthly, we were unable to investigate specific associations between body composition and detailed aspects of PN, such as lipid emulsions and micronutrient intake. Future multicenter studies with a larger sample size are needed to give a more tailored advice about the 'best' PN in relation to body composition. Lastly, we did not assess visceral fat or regional fat distribution, although it is thought that visceral fat has more negative effects than subcutaneous fat has.[48]

In conclusion, despite close monitoring of growth and follow-up by a multidisciplinary team, significant abnormalities of body composition were found with significantly lower FFM and higher FM compared with normal values. This study shows that monitoring of body composition is essential in the treatment of children on long-term PN, especially since children with the same routine growth parameters showed different body composition. Children with IF may benefit from a patient-tailored approach with adjustment of nutrition intake and an advice regarding physical activity based on their body composition to maximize growth and prevent body composition-related problems later in life.

Table 1. Patient and PN characteristics

Characteristic	**n = 21** **n (%)**
Gender: male/female	11/10 (52/48)
Age at start of PN, months – median (range)	1.5 (0 months - 9 years)
Age at first BC measurement, years – median (range)	7.4 (3.7 - 17.3)
Prematurity	8 (38)
Duration of PN at first BC measurement, years – median (IQR)	5.5 years (1.1 - 9.4)
Type of IF	
Surgical IF	9 (43)
Functional IF	12 (57)
Motility disorder	8 (38)
Enteropathy	4 (19)
PN dependency at first BC measurement	
Full PN	9 (43)
Partial PN	12 (57)
% PN – median (IQR)	80 (56 - 100)
PN characteristics at first BC measurement – median (IQR)	
Energy (kcal/kg/day)	53.5 (37.3 - 69.8)
Energy/resting energy expenditure (%)	116 (103 - 158)
Carbohydrate (g/kg/day)	8.4 (4.9 - 11.7)
Glucose infusion rate (mg/kg/min)	5.8 (3.4 - 8.1)
Lipid (g/kg/day)	1.1 (0.8 - 1.6)
Amino acids (g/kg/day)	2.0 (0.8 - 1.6)
Nonprotein calories/nitrogen ratio	129:1 (103:1 - 150:1)
Total calories/resting energy expenditure (%)	167 (145 - 187)

Abbreviations: BC, body composition; IF, intestinal failure; IQR, interquartile range; PN, parenteral nutrition.

Legend: Full PN dependency was defined as > 80% of the intake provided by PN, and partial PN dependency as 1-80% of intake provided by PN.[3]

Table 2. Growth and body composition characteristics

At first body composition measurement	**n = 21** **n (%)**
Weight-for-age SDS	
Median (IQR)	-0.71 (-1.45 to -0.08)*
SDS < -2	1 (5)
Height-for-age SDS	
Median (IQR)	-1.55 (-2.15 to -0.89)[b]
SDS < -2	7 (33)
Below TH range	11 (52)
Weight-for-height SDS	
Median (IQR)	0.28 (-0.32 to 1.08)
SDS < -2	0 (0)
SDS > +2	1 (5)
Body mass index SDS	
Median (IQR)	0.37 (-0.50 to 0.75)
SDS < -2	0 (0)
SDS > +2	1 (5)
MUAC SDS	
Median (IQR)	-0.60 (-1.55 to -0.06)[b]
SDS < -2[a]	4 (19)
Fat mass index SDS (kg/m^2)	
Median (IQR)	0.80 (0.28 to 1.16)[b]
SDS > +2	1 (5)
Fat-free mass index SDS (kg/m^2)	
Median (IQR)	-1.53 (-2.26 to -0.84)[b]
SDS < -2	7 (33)

Abbreviations: IQR, interquartile range; MUAC, mid-upper arm circumference; SDS, standard deviation score; TH, target height.

Legend: [a] MUAC was measured in 20 patients. [b] significantly different from zero.

Table 3. Possible combinations of growth and body composition at first body composition measurement

n* (n=21)	Growth	Fat mass index	Fat-free mass index
5	Impaired	Normal	Decreased
5	Normal	Increased	Decreased
3	Normal	Normal	Decreased
2	Normal	Normal	Normal
2	Impaired	Normal	Normal
2	Impaired	Increased	Increased
1	Impaired	Increased	Normal
1	Impaired	Decreased	Normal

Legend: Impaired growth: growing outside target height range or having a height-for-age <-2 SD. Increased fat mass index or fat-free mass index: >+1 SD, decreased fat mass index or fat-free mass index: <-1 SD.

Table 4. Results of growth and body composition in children with 2 body composition measurements with 1-year interval.

Variable	**n = 13** **n (%) or median (IQR)**
Gender: male/female	6/7 (46/54)
Type of IF	
Surgical/functional	6/7 (46/54)
Time between measurements, years	1.00 (0.96 - 1.07)
Δ Weight-for-age SDS	-0.10 (-0.69 - 0.23)
Δ Height-for-age SDS	-0.14 (-0.33 - 0.13)
Δ Weight-for-height SDS	-0.09 (-0.68 - 0.47)
Δ Body mass index SDS	-0.29 (-0.58 - 0.16)
Δ Mid-upper arm circumference SDS	-0.49 (-1.25 - 0.82)
Δ Fat mass index SDS	0.16 (-0.48 - 0.31)
Δ Fat-free mass index SDS	-0.39 (-0.98 - 0.15)

Abbreviations: IF, intestinal failure; QR, interquartile range; SDS, standard deviation score.

Legend: Δ, change in growth or body composition SDS between baseline and at 1-year follow-up.

Table 5. Overview of commonly used methods for measuring body composition in children with IF.

	ADP	DEXA
Outcome measures	Fat mass Fat-free mass	Fat mas Fat-free mass Bone mineral content
Advantages	No radiation exposure High level of accuracy Fast Possible to calibrate devices/central venous line/additional material Reference values available for infants Possible to measure from birth onwards	Whole-body and regional data Body composition data can be generated together with bone health
Disadvantages	Expensive device Only whole-body data	Radiation exposure Differences between different scanners Very sensitive to subject motion Influence of central venous catheter/enterostomy

Abbreviations: ADP, air displacement plethysmography; DEXA, dual-energy X-ray absorptiometry; IF, intestinal failure.

Figure legends

Figure 1. BOD POD device with customized seat for young children (with permission of COSMED)

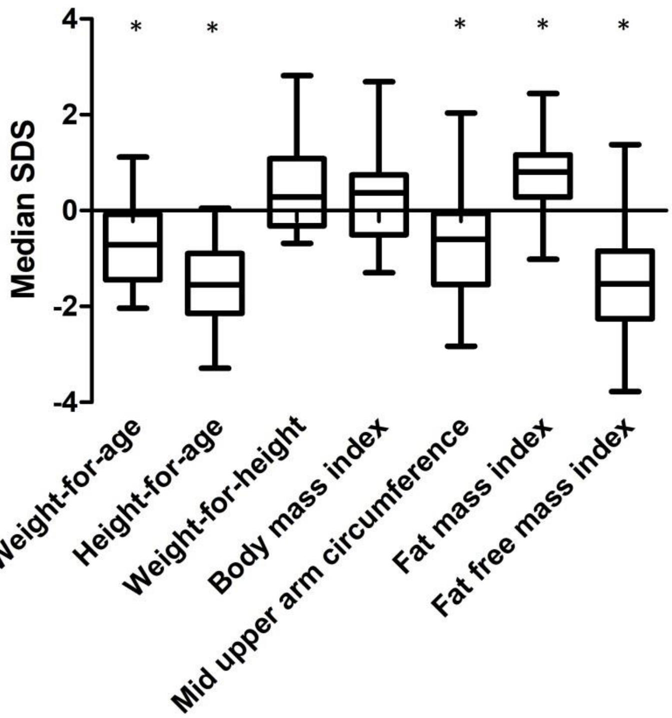

Figure 2. Anthropometric and body composition parameters at baseline, represented as median and ranges (n=21).

Legend: * significantly different from zero. **Abbreviations:** MUAC, mid-upper arm circumference; SDS, standard deviation scores.

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