



# Evaluation of body composition as a potential biomarker in spinal muscular atrophy

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## Abstract

**Introduction:** We aimed to investigate the correlation between body composition (BC) and spinal muscular atrophy (SMA)-specific motor function assessments.

**Methods:** Patients with SMA types I or II, aged 1 to 10 years, were recruited in this cross-sectional study. The protocol included anthropometric measurements, and dual-energy X-ray absorptiometry to assess fat mass (FM), lean mass (LM), fat-free mass (FFM), FM and FFM indexes (FMI, FFMI), and motor function assessments (Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders scale for SMAI, and Hammersmith Functional Motor ScaleExpanded for SMAII).

**Results:** Eighty-eight children were included. All had a higher FM percentage than reference values. Motor function was moderately correlated with body mass index (BMI), FFMI, and LMI in SMAI, and weakly correlated with FFMI, LMI, and LM:FM ratio in SMAII.

**Discussion:** BC shows promise as a potential biomarker for SMA, but further studies are needed.

## KEYWORDS

body composition, fat-free mass, Hammersmith Functional Motor ScaleExpanded, spinal muscular atrophy, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders

## 1 | INTRODUCTION

The approval and implementation of nusinersen as a treatment for spinal muscular atrophy (SMA) in several countries has changed the natural history of the disease by prolonging survival and improving motor function.<sup>1,2</sup> Other therapies are being developed, widening the landscape of potential treatments for the near future. However, the wide variability in the natural clinical course and that after treatment

prompts the need to validate new biomarkers for future clinical trials, and in the planning of patient-specific therapeutic programs.<sup>3</sup>

Dual-energy X-ray absorptiometry (DEXA) is the "gold standard" to study body composition (BC)<sup>4</sup> and is being used increasingly to detect disease severity and monitor disease progression in neuromuscular disorders.<sup>5</sup> The aim of the present study was to investigate the correlation between BC and disease-specific motor function assessments in SMA. Our hypothesis was that higher levels of residual

**Abbreviations:** BC, body composition; BMC, bone mineral content; BMI, body mass index; BW, body weight; CHOP INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; DEXA, dual-energy X-ray absorptiometry; EMA, European Medicines Agency; FDA, US Food and Drug Administration; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; HFMSE, Hammersmith Functional Motor ScaleExpanded; LM, lean mass; SL, supine length; SMA, spinal muscular atrophy; SMAI, type I spinal muscular atrophy; SMAII, type II spinal muscular atrophy.

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muscle bulk, as indicated by fat-free mass (FFM), are correlated with higher motor function scores.

## 2 | METHODS

### 2.1 | Subjects and study design

Patients were recruited between April 2015 and May 2018 as part of a large, ongoing, longitudinal, multicenter study on nutritional status in SMA, according to the following inclusion criteria:

- Genetically confirmed diagnosis of 5q SMA types I or II.
- Age 1 to 10 years.
- Ability to perform DEXA scan and motor assessment.
- Absence of previous treatment with nusinersen or enrollment in a clinical trial.

This study was approved by the ethics committees of the University of Milan and Carlo Besta Neurological Institute Foundation. All parents signed informed consent before patient enrollment.

### 2.2 | Anthropometric measurements

Body weight (BW) and supine length (SL) were collected by the same trained dietitians (R.D.A. and A.F.) according to a previously published standardized protocol,<sup>6,7</sup> and body mass index (BMI; kg/m<sup>2</sup>) was calculated.

Growth assessment was made using the 2000 US Centers for Disease Control and Prevention growth charts.<sup>8</sup> BW and SL z-score values below −1.645, corresponding to the <5th percentile, were considered underweight and stunted, respectively. BMI z-score values below −1.645 and above +1.645, corresponding to the <5th and >95th percentiles, were considered wasted and obese, respectively.

### 2.3 | BC measurements

DEXA scans (iDXA; General Electric, formerly Lunar Corp, Madison, Wisconsin) equipped with a pediatrics software application were used. The FFM was calculated by adding bone mineral content (BMC) to lean mass (LM). The FM percentage (FM%) was obtained as  $100\% \times [\text{total body fat mass (g)}] / [\text{total body mass (fat mass + lean mass + bone mass of total body)} (g)]$ . Because total FM, FFM, and LM are related to body surface, we also calculated FM (FMI; kg/m<sup>2</sup>), FFM (FFMI; kg/m<sup>2</sup>), and LM (LMI) indexes by dividing total FM, FFM, and LM by height squared. The FFM/FM ratio was also calculated. The total FM percentage of BW was interpreted according to the BC of reference children<sup>9</sup> calculating the percentage of agreement between measured FM percentage with the respective reference values for sex and age.

### 2.4 | Motor function assessment

Motor function was assessed by the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) scale in SMAI<sup>10</sup> and the Hammersmith Functional Motor ScaleExpanded (HFMSE) in SMAII children,<sup>11</sup> performed by trained physiotherapists (M.T.A. and R.Z.) who were blinded to anthropometric measurements.

### 2.5 | Statistical analysis

Discrete variables are reported as percentages. Continuous variables were checked for normality. As most continuous variables had non-Gaussian distributions, nondiscrete variables are reported as 25th, 50th, and 75th percentiles. For the same reason, the Spearman correlation was used to investigate the association of motor scales scores with the BC. We considered a correlation to be weak, moderate, or strong when the coefficient was below 0.3, near 0.5, or approaching +1.0, respectively.<sup>12</sup>  $P < .05$  was considered statistically significant. Statistical analysis was performed using STATA version 12.0 (StataCorp, College Station, Texas).

## 3 | RESULTS

### 3.1 | Sample

Eighty-eight children (49 females, 39 males) were included in the analysis, 43 with SMAI and 45 with SMAII (see Figure S1 online). Table S1 shows their characteristics. At the time of enrollment, the children were receiving supportive care according to the recommendations of the Consensus Statement for Standard of Care in SMA.<sup>13</sup> Anthropometric measurements, BC, and motor function scores are reported in Table 1.

### 3.2 | Nutritional status

SMAI and SMAII children showed median weight and height z scores, respectively, lower and equal to the median values of standard of growth charts. BMI z scores showed the children to be underweight, especially those with SMAI.

### 3.3 | Body composition

All the children had a higher FM percentage compared with the respective reference values for sex and age (median percentage of body fat above normal range: 16.7%; minimum 2.1%, maximum 45.0%).

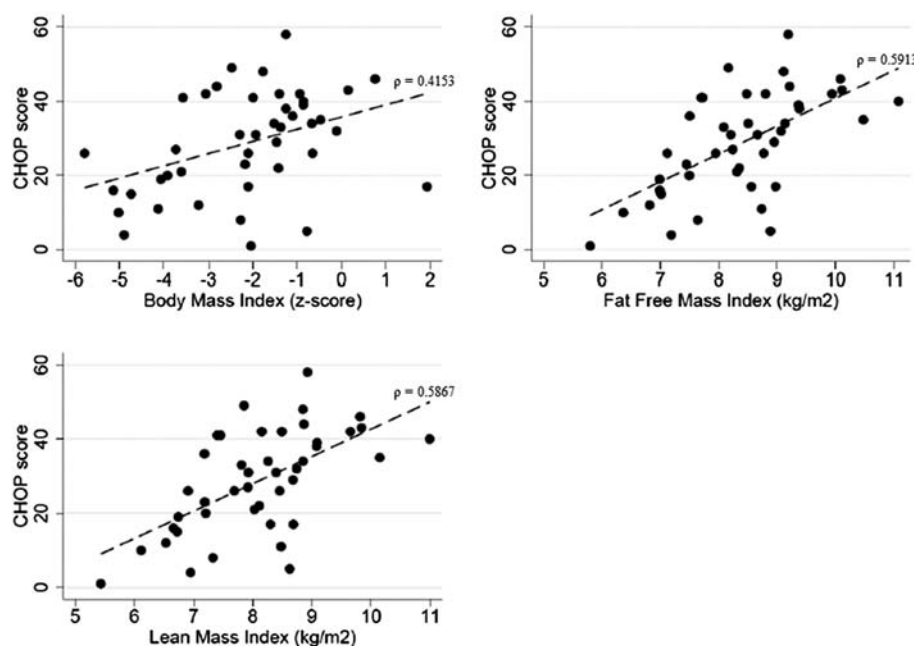
### 3.4 | Motor function

Results for the SMAI and SMAII patients are presented in Table 1.

**TABLE 1** Anthropometric measurements, body composition, and motor function scores of study subjects

	SMAI			SMAII			Total		
	P25	P50	P75	P25	P50	P75	P25	P50	P75
Age (months)	5	8	14	33	47	66	8	27	50
Anthropometric measurements									
Weight (kg)	6.4	7.5	8.5	11.6	14.0	18.6	7.5	10.1	14.3
Weight (z score)	−1.96	−1.21	−0.24	−2.11	−0.90	−0.22	−1.98	−1.04	−0.23
Length (cm)	66.5	72.0	79.0	91.0	100.0	117.5	72.3	89.5	102.0
Length (z score)	−0.120	0.76	1.57	−1.410	−0.130	1.04	−0.840	0.34	1.50
BMI (kg/m <sup>2</sup> )	12.3	14.1	15.4	12.7	14.1	14.7	12.6	14.1	15.2
BMI (z score)	−0.57	−1.99	−0.86	−2.52	−1.72	−0.52	−2.81	−1.76	−0.73
Body composition									
Fat mass (kg)	2.4	2.6	3.4	3.7	4.7	7.6	2.6	3.6	5.0
Fat-mass index (kg/m <sup>2</sup> )	4.0	5.3	6.0	4.0	5.2	6.1	4.0	5.3	6.0
Fat-free mass (kg)	4.0	4.4	5.3	7.3	9.1	10.8	4.4	6.5	9.3
Fat-free mass index (kg/m <sup>2</sup> )	7.5	8.5	9.1	7.8	8.6	9.5	7.6	8.5	9.2
Lean mass (kg)	3.8	4.3	5.1	7.0	8.7	10.3	4.3	6.2	8.9
Lean mass index (kg/m <sup>2</sup> )	7.2	8.2	8.9	7.4	8.2	9.0	7.3	8.2	8.9
Lean:fat mass ratio	1.3	1.6	2.0	1.3	1.5	2.0	1.3	1.6	2.0
Motor function									
CHOP INTEND score	17	29	42				17	29	42
HFMSE score				6	10	16	6	10	16

Abbreviations: BMI, body mass index; CHOP INTEND, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HFMSE, Hammersmith Functional Motor ScaleExpanded; P25, 25th percentile; P50, 50th percentile; P75, 75th percentile.

**FIGURE 1** Correlation between nutritional status, body composition, and CHOP scores  
CHOP, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders score

### 3.5 | Correlation between nutritional status, BC, and motor function

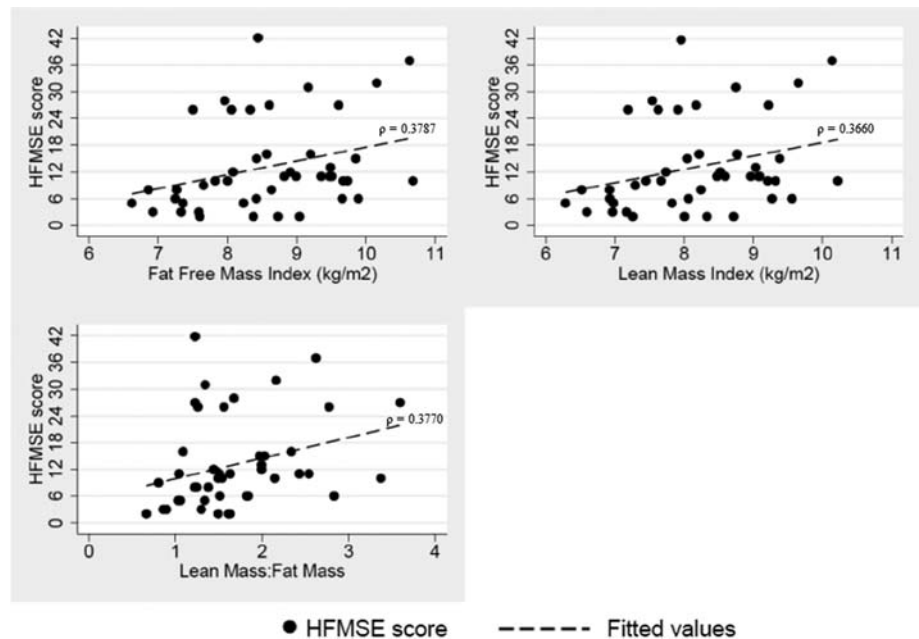
The CHOP INTEND score in SMAI correlated moderately with BMI, FFMI, and LMI (see Table S2 online, and Figure 1). Similarly, HFMSE score in SMAII correlated weakly with FFMI, LMI, and LM:FM ratio, but was not correlated with BMI (Figure 2).

## 4 | DISCUSSION

In this study we have shown that FFM, and more specifically FFMI and LMI, correlated with motor function in both SMAI and SMAII patients, thus representing a potential biomarker for disease severity.

Despite advances in clinical and pharmacological management of SMA patients, knowledge of their nutritional status and optimal

**FIGURE 2** Correlation between nutritional status, body composition and HFMSE scores  
HFMSE, Hammersmith Functional Motor ScaleExpanded



nutritional management remains limited. In our cohort, 44% of all patients (54% of SMAI) were underweight (BMI z score less than  $-2$ ), with only 1% (1 SMAII patient) overweight. FM was increased in both SMAI and SMAII, showing increasing values with age. Previous studies by our group and others have shown that FM is increased and FFM decreased in SMA patients compared with healthy peers,<sup>6,14,15</sup> and that FFM and lean body mass are significantly lower in SMAI than SMAII.<sup>6</sup> Some authors have also reported that adiposity is increased in nonambulatory, high-functioning SMAII compared with low-functioning, and ambulatory patients.<sup>16</sup> Due to this altered BC and the lack of SMA-specific growth charts, regular assessment of BC by DEXA has been included in the updated Standard of Care Recommendations to ensure proper nutritional management.<sup>17</sup>

Sproule et al<sup>16</sup> speculated that high FMI, as frequently observed in SMAII patients, could negatively impact motor function. We did not find any correlation between FMI and motor function in SMAII patients, but LM:FM ratio (and not BMI, unlike in SMAI) correlated with motor scores. This could be explained by the higher prevalence of severely underweight SMAI children, whereas those with SMAII had nutritional status that varied from under- to overnutrition, for which management of BC rather than of weight is of primary importance.

Our data show that motor abilities were weakly to moderately correlated with FFM and LMI in both SMAI and SMAII patients. This is not surprising given that the degree of muscle atrophy and residual muscle bulk, secondary to the underlying pathophysiology of the disease, likely play a major role in determining motor function in SMA patients.

Although the regular assessment of BC is widely acknowledged to be important in health maintenance and nutritional management of children with SMA, it is rarely included in the routine follow-up

assessments. The main reasons for this are that DEXA is not always available in clinical centers, and that other simpler techniques including skinfold-based measures and predictive formulas are currently not available for SMA. Another limitation to the implementation of the use of DEXA in pediatric clinical trials is related to the (relatively small) amount of radiation exposure.

The phase 3 studies of nusinersen have shown that some patients respond well to treatment with acquisition of unexpected motor milestones, whereas others have a more limited clinical response. The time between the first symptoms and the first dose in patients with SMAI and the age of those with SMAII have been reported to influence response to treatment.<sup>1,2</sup> However, these aspects cannot alone explain the wide interindividual variability in response to treatment. The high cost of orphan drugs may emerge as a limitation to guaranteeing the worldwide accessibility of treatments to all SMA patients,<sup>18</sup> and the need to predict individual response or to identify rules to stop or switch treatment to tailor therapy to patients will increase over time. There is a strong need to identify informative clinical and laboratory biomarkers that may allow monitoring of disease progression and may predict responders. The role of DEXA as a secondary outcome measure to provide this information will require further investigation.

In conclusion, this study has demonstrated that better BC is associated with higher motor abilities in SMA patients. Our findings further emphasize the importance of monitoring nutritional status in the management of SMA patients. BC shows some promise as a potential biomarker, but the strength of the correlations is not sufficiently uniform or consistent to yield immediate application. Further studies to validate the assessment of BC as a biomarker for SMA, investigating modifications in BC and motor function over time, and correlating BC with clinical response to treatment will be performed in the near future.

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## CONFLICT OF INTEREST

G.B. received speaker and consultancy honoraria from AveXis, Roche, PTC, and Sarepta Therapeutics. C.M. received a speaker's honorarium from Roche. The remaining authors declare no conflicts of interest.

## ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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