Original Article

Association between serum copper concentration and body composition in children with spinal muscular atrophy: a cross-sectional study

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Background and Objectives: The role of serum copper in modulating body composition in patients with spinal muscular atrophy (SMA) remains uncertain. This study aimed to illustrate the correlation between serum copper concentration and body composition in children with SMA. **Methods and Study Design:** This study was conducted at a pediatric medical center in China from July 2019 to August 2022. The study included anthropometric measurements, serum analysis for copper, magnesium, zinc, and iron, as well as comprehensive body composition assessments. Multivariate analysis was utilized to assess the connection between serum copper concentration and body composition metrics. **Results:** This cross-sectional analysis included 87 patients [median (IQR) age: 7 years (5–10), 57.5% male] diagnosed with SMA receiving comprehensive multidisciplinary management. The results revealed a positive association between serum copper concentration and both fat mass percentage (β = 0.50, 95% confidence interval (CI): 0.07 to 0.92, p = 0.025) and fat-muscle ratio (β = 0.02, 95% CI: 0.01 to 0.03, p = 0.009). Conversely, a negative correlation was found between serum copper concentration and muscle mass percentage (β = -0.70, 95% CI: -1.11 to -0.29, p = 0.001). **Conclusions:** These findings suggest a correlation between copper concentration and body composition in SMA, offering valuable insights for addressing metabolic dysregulation in these patients.

Key Words: anthropometric variables, body composition, pediatric patients, serum copper, spinal muscular atrophy

INTRODUCTION

Spinal muscular atrophy (SMA) is characterized by motor neuron degeneration, leading to skeletal muscle atrophy and, if untreated, potential premature death.[1] Pediatric-onset SMA is classified into three main types (1 to 3) based on age of onset and maximum motor function in untreated patients: Type 1—no sitting or rolling, Type 2—sitting but not walking, and Type 3—walking with limitations.[1] In recent decades, multidisciplinary supportive care guidelines have been established as the standard of care for SMA.[2,3] Recent treatment strategies aimed at increasing functional survival motor neuron (SMN) protein levels have shown both safety and clinically significant improvements in achieving motor milestones.[4] However, it remains unclear whether these SMN-inducing therapies effectively address body composition abnormalities often seen in SMA patients, such as reduced muscle mass and increased fat mass.[5] The simultaneous presence of sarcopenia and obesity increases the risk of negative health outcomes, including insulin resistance, dyslipidemia, and hypertension, which can lead to type 2 diabetes mellitus and cardiovascular diseases.[6]

Physical activity and nutritional intervention have been documented as effective strategies for managing obesity and sarcopenia.[7] However, improving body composition through exercise in individuals with SMA is challenging. Although the specific mechanisms remain unclear, studies have confirmed the role of micronutrients in obesity and sarcopenia.[8-10] Copper, an essential trace element, acts as a crucial co-factor in enzymatic reactions and is vital for cellular metabolism.[11] It participates in mitochondrial function, inflammatory responses, antioxidative functions, and fat metabolism.[12] However, excess-

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ive copper concentration may lead to oxidative damage and inflammatory reactions, potentially contributing to the development of obesity.[10] High copper concentration have been linked to reactive oxygen species (ROS) caused by oxidative stress, which can activate proteolytic systems, causing muscle protein breakdown and subsequent muscle loss. Moreover, ROS may impair mitochondrial function and biogenesis, thereby contributing to muscle degradation.[13-14] Zinc, magnesium, and iron are essential trace elements involved in oxidative stress processes and may play significant roles in developing sarcopenia, a condition characterized by muscle loss and excessive fat mass.[15-17]

Multiple studies have demonstrated a correlation between serum copper concentration and body composition in the general population.[18-21] However, the relationship between serum copper concentration and body composition in patients with SMA remains unclear.

This study aimed to investigate the correlation between serum copper concentration and body composition, as assessed by dual-energy X-ray absorptiometry (DXA).

METHODS

Participants and study design

This cross-sectional study enrolled individuals with spinal muscular atrophy (SMA) who were treated at our hospital between July 2019 and August 2022. The criteria for inclusion were as follows: (1) genomic characterization of 5qSMA, (2) under 18 years old, and (3) provision of informed consent. Individuals meeting the following criteria were excluded: (1) the presence of a concomitant illness or a recent history of acute illness, (2) previous spinal fusion surgery or the existence of metallic surgical implants, (3) received disease-modifying treatment, and (4) absence of DXA test results. The research protocol was approved by the Ethics Committee of Children's Hospital, Zhejiang University School of Medicine (2019-IRB-171). Written informed consent was obtained from the participants' parent/legal guardians/next of kin to participate in the study. Figure 1 illustrates the process for patient selection.

Measurement of variables

Anthropometric measurements were conducted by an experienced dietitian using standard protocols. If a patient could not stand, height was measured using arm span instead. Blood samples were collected and centrifuged to separate the serum, which was subsequently analyzed using the MB5 multi-channel atomic absorption spectrophotometer (Beijing Persee General Instrument Company Limited, Beijing, China) to determine the copper, iron, magnesium, and zinc concentrations. Blood samples were obtained after a fasting period for lipid profiling. Serum concentrations of triglycerides and cholesterol were accurately measured using a Beckman Coulter automated biochemical analyzer. Disease classification was determined based on the highest level of athletic capacity attained. Data on the frequency, content, and intensity of rehabilitation therapy in patients were also recorded. Patients undergoing rehabilitation therapy at least three times a week for at least 1 hour per session were placed in the rehabilitation group, while those not meeting these criteria were classified as non-rehabilitation group.

Study outcomes (dependent variables)

Following a 12-h fasting period, body composition parameters—including fat mass, fat-free mass, and bone mass—were assessed using whole-body DXA scans (Hologic Horizon W model, Hologic Inc, Danbury, CT, USA). Muscle mass (MM) was calculated by subtracting the bone mass from the fat-free mass. Fat mass percentage (FM%) and muscle mass percentage (MM%) were

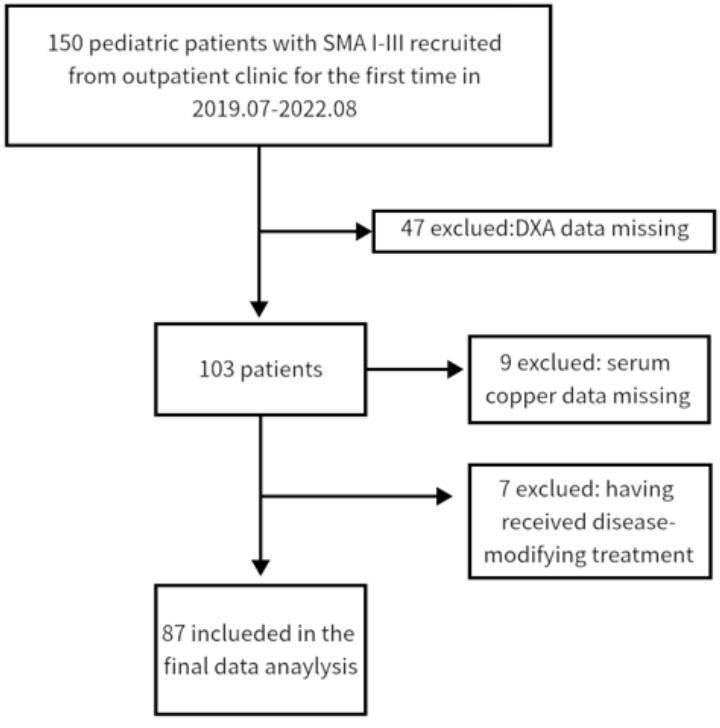

Figure 1. Flow diagram of patient selection during the study

ascertained by dividing each respective mass by the total body weight. The Fat-to-Muscle Ratio (FMR) was also derived as a quotient of fat mass to muscle mass.[22]

Statistical analysis

Continuous data are depicted using mean (standard deviation) in cases of normal (Gaussian) distribution or using medians along with interquartile ranges (IQR) for data exhibiting skewness. Categorical variables were expressed in terms of frequencies and proportions. For continuous data, analysis of variance in serum copper tertiles was conducted by Kruskal–Wallis H test for skewed data and the one-way ANOVA for data with a normal distribution. For categorical variables, chi-square test was implemented.

FM%, MM%, and FMR were included as outcome variables, and other variables were included as potential confounders, in generalized linear models (GLMs) to assess the associations. Furthermore, multivariate linear regression models were performed to evaluate the associations. Covariates were chosen according to their relevance to the outcomes of interest or if they led to modifications in the effect estimates exceeding 10%. After considering the clinical significance, we adjusted for age, sex, type, height, total cholesterol (TC), zinc, iron, and magnesium. Serum copper concentration was also categorized into categorical variables based on tertiles, and the *p* value for the trend was calculated to confirm the results. Results are presented as beta coefficients (β) with accompanying 95% confidence intervals (CIs).

Sensitivity analyses were conducted to confirm the findings' accuracy and reliability. To investigate the possible influence of unmeasured confounders on the association between serum copper concentration and body composition, E-values were computed. These values determine the smallest effect size an unaccounted confounder would need to nullify the observed relationship between the two variables.

Statistical significance was established at a two-tailed *p* value of <0.05. The R software package (http://www.R-project.org, The R Foundation) and Empowerstats (http://www.empowerstats.com, X&Y Solutions, Inc., Boston, MA, USA) were utilized for all statistical computations.

RESULTS

Baseline characteristics

In total, 150 patients were initially selected for screening. After excluding ineligible candidates, 87 patients were subsequently included in the analysis for this study. Table 1 provides a comprehensive overview of the participants' baseline characteristics categorized by serum copper tertiles. The median age was 7 years [interquartile range (IQR) of 5–10 years], and 57.5% of participants were male.

The data revealed notable variations in baseline characteristics across serum copper tertiles. Specifically, age and height differed significantly, with the first tertile having a median age of 9 years ($p = 0.027$) and the tallest average height compared to the other tertiles ($p = 0.015$). In contrast, there were no significant differences in the distribution of sex and SMA types among the tertiles, with *p*-values of 0.472 and 0.238, respectively. Biochemical assessments showed significant variation in zinc concentration across tertiles ($p = 0.009$), while triglyceride, cholesterol, and iron concentrations remained consistent. Significant differences were also observed in fat mass percentage and the fat-to-muscle ratio among the tertiles

Table 1. Baseline characteristics of children with spinal muscle atrophy according to the tertiles of serum copper[†]

Variable	Tertile 1[‡]	Tertile 2[‡]	Tertile 3[‡]	*p* value
N	26	32	29	
Age, years	9.00 (5.25–12.00)	6.00 (4.00–8.00)	7.00 (6.00–10.00)	0.027
Sex (n, %)				0.472
Male (%)	15 (57.7%)	16 (50.0%)	19 (65.5%)	
Female (%)	11 (42.3%)	16 (50.0%)	10 (34.5%)	
Type[§]				0.238
1 (%)	2 (7.69%)	4 (12.5%)	0 (0.00%)	
2 (%)	12 (46.2%)	19 (59.4%)	16 (55.2%)	
3 (%)	12 (46.2%)	9 (28.1%)	13 (44.8%)	
Rehabilitation				0.329
No (%)	12 (48.0%)	16 (50.0%)	9 (32.1%)	
Yes (%)	13 (52.0%)	16 (50.0%)	19 (67.9%)	
Height (cm)	131.1 (19.5)	117.0 (17.4)	126.3 (18.1)	0.015
Weight (kg)	28.4 (13.9)	23.7 (11.1)	26.9 (11.9)	0.341
TG (mmol/L)	0.88 (0.37)	0.76 (0.30)	0.96 (0.47)	0.138
TC (mmol/L)	4.30 (0.77)	4.39 (0.96)	4.29 (1.16)	0.912
Zinc (μmol/L)	84.9 (12.1)	78.7 (8.52)	87.7 (13.4)	0.009
Iron (mmol/L)	8.88 (0.97)	8.45 (0.77)	8.70 (0.92)	0.178
Magnesium (mmol/L)	1.59 (0.15)	1.63 (0.14)	1.69 (0.16)	0.048
Muscle mass percentage (%)	55.2 (10.6)	51.0 (10.4)	49.2 (6.56)	0.060
Fat mass percentage (%)	40.0 (9.55)	46.7 (9.61)	45.9 (6.98)	0.010
Fat-muscle-ratio	0.77 (0.29)	0.98 (0.36)	0.96 (0.25)	0.026

TG, triglycerides; TC, cholesterol

[†]Values were presented as n/N (%), median (IQR), or mean (standard deviation).

[‡]Serum copper level (μmol/L): Tertile 1, 16.6 (15.6–17.1); Tertile 2, 19.2 (18.5–20.3); Tertile 3, 25.1 (23.2–28.5).

[§]Type 1: no sitting or rolling, Type 2: sitting but not walking, and Type 3: walking with limitations

($p = 0.010$ and $p = 0.026$, respectively).

Association between variables and body composition parameters

Table 2 summarizes the associations between different variables and body composition parameters (MM%, FM%, and FMR) in children with SMA. Notably, serum copper concentration and MM% were found to have a significant negative association (β = -0.49, 95% CI: -0.89 to -0.08, $p = 0.020$), indicating that higher serum copper concentration correspond to a lower MM%. Additionally, height and weight were identified as influential factors with significant associations to body composition parameters, with weight being particularly prominent. In contrast, age, sex, and some biochemical parameters (zinc, iron, and magnesium) did not show significant associations with the body composition measurements in the studied cohort.

Independent relationship between serum copper concentration and body composition parameters

Table 3 presents the results of a comprehensive multivariate linear regression analysis investigating the association between serum copper concentration and crucial body composition metrics (FM%, MM%, and FMR) in individuals with SMA.

In the unadjusted model, serum copper exhibited a significant negative association with MM% (β = -0.49, 95% CI: -0.89 to -0.08, $p = 0.020$), a relationship that persisted even after adjusting for confounding variables, such as age, sex, cholesterol, iron, magnesium, type, height, and zinc in Model 2. The fully adjusted model revealed that an increase of one unit in serum copper was associated with increased FM% (β = 0.50, 95% CI: 0.07 to 0.92, $p = 0.025$) and elevated FMR (β = 0.02, 95% CI: 0.01 to 0.03, $p = 0.009$).

A stratified analysis categorizing serum copper into tertiles clarified the relationship dynamics. Participants in higher serum copper tertiles showed a significant reduction in MM%, along with an increase in FM% and FMR, compared to those with serum copper concentration below 17.73 μmol/L in Model 2 (fully adjusted) ($p < 0.01$ for trend). However, these trends were inconsistent in Crude and Model 1 analyses for FM% and FMR.

DISCUSSION

In our cross-sectional study in China, involving 87 individuals with SMA, we used univariate and multivariate linear regression analyses to explore the relationship between serum copper concentration and body composition. In both the unadjusted and slightly adjusted models, a significant correlation was found between serum copper concentration and MM%, while no substantial link was observed between serum copper concentration and FM%

Table 2. Association between variables and body composition

Variables	Statistics†	Muscle mass percentage (%)‡	Fat mass percentage (%)‡	Fat-muscle-ratio‡
Age	7.00 (5.00–10.0)	-0.08 (-0.56, 0.40) 0.749	0.14 (-0.33, 0.60) 0.563	0.00 (-0.01, 0.02) 0.600
Sex (n,%)				
Male (%)	50 (57.5%)	0	0	0
Female (%)	37 (42.5%)	-1.91 (-6.00, 2.17) 0.362	0.98 (-2.96, 4.91) 0.627	0.05 (-0.09, 0.18) 0.484
Type				
1	6 (6.90%)	0	0	0
2	47 (54.0%)	-1.78 (-9.85, 6.29) 0.667	-1.19 (-8.90, 6.51) 0.762	0.03 (-0.23, 0.30) 0.818
3	34 (39.1%)	2.12 (-6.12, 10.35) 0.616	-5.14 (-13.0, 2.72) 0.203	-0.12 (-0.39, 0.15) 0.380
Rehabilitation				
No	37 (43.5%)	0	0	0
Yes	48 (56.5%)	-0.31 (-4.43, 3.81) 0.883	-0.42 (-4.45, 3.61) 0.839	0.00 (-0.13, 0.14) 0.961
Height (cm)	124.4 ± 19.0	-0.10 (-0.20, 0.01) 0.070	0.07 (-0.03, 0.18) 0.159	0.00 (-0.00, 0.01) 0.067
Weight (kg)	26.2 ± 12.3	-0.32 (-0.47, -0.17) <0.0001	0.29 (0.15, 0.44) 0.0002	0.01 (0.01, 0.02) <0.0001
TG (mmol/L)	0.86 ± 0.39	-4.85 (-9.93, 0.23) 0.065	3.15 (-1.78, 8.08) 0.214	0.13 (-0.04, 0.30) 0.131
TC (mmol/L)	4.33 ± 0.97	-1.17 (-3.26, 0.92) 0.276	0.94 (-1.07, 2.94) 0.364	0.03 (-0.04, 0.10) 0.453
Zinc (μmol/L)	83.6 ± 11.9	0.02 (-0.15, 0.19) 0.846	-0.03 (-0.19, 0.13) 0.721	-0.00 (-0.01, 0.00) 0.733
Iron (μmol/L)	8.66 ± 0.89	0.55 (-1.73, 2.84) 0.635	-0.24 (-2.44, 1.95) 0.828	-0.01 (-0.08, 0.07) 0.816
Magnesium (μmol/L)	1.64 ± 0.15	-9.75 (-23.01, 3.50) 0.153	11.6 (-1.05, 24.22) 0.076	0.33 (-0.11, 0.76) 0.150
Copper (μmol/L)	20.8 ± 4.87	-0.49 (-0.89, -0.08) 0.020	0.40 (0.00, 0.79) 0.051	0.01 (-0.00, 0.03) 0.057

TG, triglycerides; TC, cholesterol

†Data were presented as n, n (%), mean ± SD, or median (IQR).

‡Data were represented as β (95% CI) and p value.

Table 3. Multivariable linear regression analysis on serum copper and body composition[†]

Exposure	Crude[‡]	Model 1[§]	Model 2[¶]
Muscle mass percentage (%)			
Copper	-0.49 (-0.89, -0.08) 0.020	-0.50 (-0.91, -0.09) 0.019	-0.70 (-1.11, -0.29) 0.001
Copper tertile			
Low	0	0	0
Middle	-4.17 (-9.04, 0.71) 0.098	-4.24 (-9.27, 0.78) 0.102	-4.70 (-9.49, 0.09) 0.058
High	-5.96 (-10.91, -1.01) 0.021	-6.11 (-11.10, -1.13) 0.019	-8.75 (-13.90, -3.61) 0.001
p for trend	0.021	0.018	0.001
Fat mass percentage (%)			
Copper	0.40 (0.00, 0.79) 0.051	0.40 (0.00, 0.80) 0.051	0.50 (0.07, 0.92) 0.025
Copper tertile			
Low	0	0	0
Middle	6.75 (2.17, 11.33) 0.005	7.23 (2.52, 11.95) 0.004	6.85 (2.08, 11.62) 0.006
High	5.97 (1.32, 10.62) 0.014	6.01 (1.33, 10.69) 0.014	7.45 (2.32, 12.58) 0.006
p for trend	0.018	0.017	0.006
Fat-muscle-ratio			
Copper	0.01 (-0.00, 0.03) 0.057	0.01 (-0.00, 0.03) 0.056	0.02 (0.01, 0.03) 0.009
Copper tertile			
Low	0	0	0
Middle	0.20 (0.05, 0.36) 0.014	0.22 (0.05, 0.38) 0.011	0.24 (0.08, 0.40) 0.005
High	0.19 (0.03, 0.35) 0.024	0.19 (0.03, 0.36) 0.023	0.28 (0.11, 0.45) 0.002
p for trend	0.029	0.027	0.003

[†]Data were presented as the β coefficient (95% CI) *p* value. The lowest tertile was the reference for serum. Outcome variables: Muscle mass percentage, fat mass percentage, and fat-muscle ratio. Exposure variable: Serum copper and copper tertile.
[‡]Crude: not adjusted.
[§]Model 1: adjusted for age and sex.
[¶]Model 2: adjusted for age, sex, cholesterol, iron, magnesium, type, height, and zinc concentrations

or FMR. In the comprehensively adjusted model, a negative association was observed between serum copper concentration and MM%, while a positive association with both FM% and FMR was noted. This pattern persisted when serum copper concentration was analyzed as a categorical variable.

Our study supports previous research, highlighting a strong correlation between elevated serum copper concentration and obesity prevalence in pediatric populations. Analyses from the 2011–2014 and 2011–2016 National Health and Nutrition Examination Surveys have also shown a significant positive association between serum copper concentration and obesity indices in individuals aged 6–19 years.[19, 23] Notably, these studies primarily used body mass index (BMI) and waist circumference to characterize obesity, despite their limitations in differentiating adipose tissue from muscle mass. A study by Wu et al. also found significant correlations between elevated serum copper concentration and increased body fat percentage in adults, which further expands our understanding.[21] Similarly, Liang et al. revealed intricate correlations, demonstrating that elevated plasma copper concentration was associated with increased fat deposition and an altered ratio of fat to lean mass in the pediatric cohort, evaluated using DXA.[18] Our findings are consistent with those of Lee et al., who reported elevated hair copper concentration in individuals with reduced muscle mass, despite our study using blood samples for copper quantification.[20] In contrast, Ngu et al. used bioelectrical impedance analysis and found a positive correlation between serum copper concentration and body fat mass, along with an inverse relationship with skeletal muscle mass in adults with metabolic syndrome characteristics.[24] Our study explores these relationships specifically in individuals with SMA, differing from broader population studies. Consistent with existing research, our findings highlight that individuals with SMA have higher fat mass and reduced fat-free mass compared to healthy individuals.[25,26] Central to our findings is the confirmation of a significant association between serum copper concentration and body composition dynamics, specifically in the context of the unique physiology of patients with SMA.

Although disease-modifying therapies have shown notable clinical benefits, particularly in muscle mass and strength, they do not offer a complete cure and their effects are not consistently substantial.[27,28] Our findings suggest a novel approach for treating SMA, indicating that lowering serum copper concentration might reduce fat mass and increase muscle mass, addressing metabolic dysregulation in SMA. Further research and clinical trials are essential to validate these results and develop effective treatment strategies for the SMA population.

A meta-analysis by Banach et al. established a clear link between decreased serum zinc and magnesium concentrations and increased fat mass. However, the relationship between serum iron concentration and fat mass remains inconclusive and requires further investigation.[15] Another meta-analysis by Van Dronkelaar et al., focusing on older adults, found no significant correlation between serum zinc, magnesium, and iron concentrations and muscle mass.[29] Due to the limited sample size, our study lacks sufficient statistical power to fully analyze the correlations between body composition and zinc, magnesium, and copper concentrations. Additionally, our focus on children with SMA differs significantly from the predominantly adult and older adult populations in the aforementioned meta-analyses.

To the best of our knowledge, this study is among the few examining the relationship between serum copper concentration and body composition in SMA patients.

While observational studies are inherently susceptible to confounding factors, we applied rigorous statistical adjustments to minimize these. Additional analyses, including categorizing serum copper into tertiles and examining trends, further strengthen the validity of our findings.

Our study has several limitations. First, the cross-sectional design prevents us from establishing causal relationships. Due to the rarity of SMA, our sample size was small. Despite this, we observed correlations between serum copper and muscle mass and fat mass, with statistical power of 0.73 for MM%, 0.72 for FM%, and 0.70 for FMR. Additionally, as our study focused solely on SMA patients, the results may not be applicable to non-SMA populations. Additionally, our participants were mostly over five years old, which may limit the applicability of our findings to those under five. Our study also lacked inter- and intra-coefficient analysis of serum trace elements. Despite potential measurement errors, we observed a relationship between serum copper and body composition. More precise measurements could have revealed a stronger effect size with narrower confidence intervals, though any errors likely biased results toward the null hypothesis.

In this study involving individuals with SMA, serum copper showed an inverse relationship with MM% and a positive relationship with FM% and FMR. Our research adds valuable evidence to the ongoing discussion about the role of lower serum copper concentration in improving body composition.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors have no conflicts of interest to declare.

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