

Association of physical activity and nutritional intake with muscle quantity and quality changes in acute stroke patients

Running title: Muscle quantity and quality in acute stroke

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Acknowledgments: We are extremely grateful to participants in the present study and collaborated nursing staff in the hospital.

Sources of funding

None.

Declaration of interest

The authors report no conflict of interest.

Keywords: Acute Stroke; Physical Activity; Nutritional intake; Fat free mass; Phase angle.

Tables: 3

Figures: 1

Word count: 250/250 words (abstract), 2902 words (manuscript)

Abstract

Objectives: To evaluate longitudinally the muscle properties of acute stroke patients and examine the association between physical activity and nutritional intake.

Materials and methods: This study enrolled 21 stroke patients (72.7 ± 10.4 years).

Muscle quantity (fat-free mass, appendicular skeletal muscle mass) and quality (extracellular water/intracellular water ratio, phase angle) were assessed using a bioelectrical impedance device at baseline (within three days) and two weeks after stroke onset. Physical activity and sedentary were calculated from the accelerometer data. Total energy and protein intake were calculated from the dietary surveys as nutritional intake. The association of physical activity, sedentary, and nutritional intake with the rate of changes in muscle properties was examined.

Results: The fat-free mass significantly decreased (from 43.4 ± 8.0 to 42.2 ± 7.6 kg), and the skeletal muscle was unchanged (from 17.8 ± 4.2 to 17.7 ± 4.0 kg) after two weeks. The extracellular water/intracellular water ratio significantly increased (from 0.63 ± 0.02 to 0.65 ± 0.03) and the phase angle significantly decreased (from 5.1 ± 0.6 to $4.9 \pm 0.8^\circ$), suggesting that the muscle quality have declined. Correlation analysis showed that the extracellular water/intracellular water ratio was significantly associated with physical activity [metabolic equivalents ($\rho = -0.61$)] and sedentary ($\rho = 0.67$) and that the phase

angle was significantly associated with physical activity [metabolic equivalents ($\rho=0.69$)], sedentary ($\rho=-0.68$), and nutritional intake [total energy ($r=0.45$), protein ($r=0.45$)].

Conclusions: The fat-free mass and muscle quality (extracellular water/intracellular water ratio and phase angle) declined two weeks after stroke. Physical activity and nutritional intake were lower in patients with decreased muscle quality, suggesting the importance of exercise and nutrition in the acute phase.

(250/250 words)

Keywords: Acute Stroke; Physical Activity; Nutritional intake; Fat free mass; Phase angle.

Introduction

Stroke leads to muscle wasting due to physical inactivity and malnutrition (1, 2). The loss of muscle mass carried over from the acute phase to the recovery phase during rehabilitation reduces the home discharge rate and activity of daily living (3). Therefore, to provide more suitable rehabilitation after stroke, it is necessary to initiate tactics to prevent muscle loss from the acute stroke phase. However, only few studies have examined the longitudinal changes in muscle properties and related factors in the acute phase.

The basic properties of muscle quantity, including cross-sectional area, volume, or mass, and muscle quality, such as intrinsic force-producing capacity, are key determinants of muscle strength (4, 5). Thus, it is important to evaluate muscle properties in terms of both muscle quantity and quality (6). Previous studies have shown longitudinal changes in muscle quantity after stroke (7, 8). However, few longitudinal studies have focused on the muscle quality in stroke.

During the acute post-stroke period, most patients experience physical inactivity and malnutrition due to bed rest, decreased motor function, lowered level of consciousness, and dysphagia (9). In terms of physical activity, it has been shown that longer bed rest and sedentary behavior in the acute post-stroke period are associated with

lower physical function at discharge or 3 months later (10, 11). Similarly, early mobilization and physical activity are associated with high functional outcomes (11, 12). Thus, physical activity during the acute phase may prevent the deterioration of muscle function. Furthermore, in terms of nutritional intake, adequate total energy and protein intake prevent muscle loss (13). These studies suggest that physical activity and nutrition prevent muscle wasting (10-13). However, to the best of our knowledge, no reports have examined the association of physical activity and nutritional status with changes in muscle properties, especially in the acute post-stroke period.

This study aimed to examine the longitudinal changes in muscle properties, including quantity and quality, in relation to physical activity and nutritional intake, in acute stroke patients. The hypothesis was that both muscle quantity and quality would decline during the acute phase and that higher physical activity and nutritional intake would be associated with less decline in muscle properties.

Materials and Methods

Study design and participants

This observational study included patients aged 20–90 years old, who were diagnosed with stroke (cerebral infarction or hemorrhage) by board-certified neurologists or

neurosurgeons at the Kyoto University Hospital from January to July 2021, and who provided consent within 3 days of onset. Patients who could not agree to the study concept and could not follow orders or sign the consent form due to their significant decline in consciousness level, cognitive function, or motor function; with physical limitation of movement before admission; and unable to participate due to their medical condition were excluded.

Twenty-eight patients met the inclusion criteria of the study. Four patients were excluded because they were discharged to their home from the hospital or transferred to another convalescent rehabilitation hospital within the first week. Another three were excluded because they could not be measured by muscle property analysis either at baseline or post-measurement due to their medical treatment schedule. Therefore, 21 patients were enrolled in the present study. We evaluated the following patient characteristics: age, body mass index, diagnosis of stroke, side of paresis, National Institutes of Health Stroke Scale (NIHSS; a 15-item impairment scale, score range of 0–42 with none to most severe neurological deficits) (14, 15), Brunnstrom Stage (BRS), Functional Independence Measure (FIM), Functional Ambulation Categories (FAC; score range 0–5) (16), Modified Water Swallowing Test (MWST; score range 1–5) (17), Mini Nutritional Assessment (MNA; score range of 0–30) (18), comorbidities, and laboratory

data (C-reactive protein, albumin, total protein). The participants' characteristics are presented in Table 1. All participants were fully informed of the procedures and purpose of the study, which conformed to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants. This study was approved by the ethics committee of the Kyoto University Graduate School and the Faculty of Medicine (approval number: R2748).

Muscle property

A bioelectrical impedance analyzer (InBody S10; InBody Japan Inc., Tokyo, Japan) with a segmental multi-frequency approach (1 kHz, 5 kHz, 50 kHz, 250 kHz, 500 kHz, and 1 MHz) was used for muscle property analysis. Measurements were taken at baseline (within 3 days from stroke onset) and two weeks after onset, at the same time of the day (from 4 p.m. to 6 p.m.), considering the effects of diurnal variation of body water. To integrate the physical characteristics (height and body weight) into Inbody software, we extracted the indicators, including fat-free mass (FFM), fat mass, skeletal muscle mass, skeletal muscle index (SMI), total body water (TBW), ratio of extracellular water (ECW) to intracellular water (ICW), and phase angle. FFM and appendicular skeletal muscle mass (ASM) were used as indices of muscle quantity, while the ECW/ICW ratio and

phase angle were used as indices of muscle quality (19, 20). The osmotic balance of ICW and ECW depends on the diffusion of water inside and outside of the cell. The ECW/ICW ratio indicates biomarkers for muscle quality, which means non-contractile tissue, including interstitial fluid in the extracellular space relative to skeletal muscle (19). Therefore, a high ECW/ICW ratio indicates loss of muscle quality. The phase angle at 50 kHz was calculated using the following equation: phase angle ($^{\circ}$) = $\arctan(\text{reactance/resistance}) \times (180/\pi)$. The phase angle is determined by the lean body mass, TBW, and the ratio of ECW to TBW (21). Therefore, phase angle has been proposed as an indicator of body cell mass and integrity (20), and a large phase angle indicates high muscle quality. The ECW/ICW ratio and phase angle calculated for the entire body were used in further analyses.

Physical activity and sedentary behavior

Physical activity and sedentary behavior were measured using a tri-axial accelerometer (ActiGraph wGT3X-BT, ActiGraph LLC, Pensacola, FL, USA) placed on the ankle of the non-paralyzed side. The accelerometer was worn for 24 h per day, except when bathing or during examinations, from the day of consent to the discharge from the hospital. The accelerometer data was analyzed using a specialized software (ActiLife Version

6.13.4; ActiGraph LLC, Pensacola, FL, USA). The total activity [metabolic equivalents (METs)], sedentary time, and moderate-to-vigorous physical activity (MVPA) time for two weeks from stroke onset were calculated from the acceleration data using the aforementioned software. The cut-off points for activity intensity were based on a validity study (22): sedentary, ≤ 99 counts; and MVPA, $\geq 1,952$ counts.

Nutritional intake

Nutritional intake surveys were conducted twice a week (once in the first half of the week and the other in the latter half) for two weeks. On the day of the survey, medical staff, such as nurses, physical therapists, or registered dietitians, collected information on all daily intakes, including food provided from the hospital, enteral nutrition, peripheral infusions, and additional food or beverages purchased by patients themselves. The percentage of food intake was assessed using a visual estimation method based on the amount remaining after intake on an 11-point scale from 0% to 100% (23). To increase the validity, the percentage of intake was measured for each dish, instead of only two categories of main and side dishes. The registered dietitian calculated the total daily energy and protein intake based on the intake information. The mean nutritional intake, presented as the average of two days per week, was used in the analysis.

Statistical analysis

Statistical analyses were performed using SPSS version 22.0. (IBM Japan Inc., Tokyo, Japan). The normality of the data was evaluated using the Shapiro–Wilk test. A paired *t*-test or Wilcoxon signed-rank test was used to compare the physical activity and nutritional status between the first and second weeks. In addition, a paired *t*-test or Wilcoxon signed-rank test was used to compare the FIM, FAC, the body composition, and muscle property changes between baseline and two weeks after stroke onset. The associations between muscle property changes (FFM, ASM, ECW/ICW ratio, or phase angle) and age, activity (METs/day, % in sedentary, or % in MVPA), and nutritional status (energy or protein intake) were examined using Pearson's or Spearman's correlation coefficients. Statistical significance was set at $p < 0.05$.

Results

Recovery Activities of Daily Living and walking ability in two weeks

FIM motor and cognitive score were significantly increased at two weeks (motor score, from 24.6 ± 15.0 to 60.5 ± 23.6 ; cognitive score, from 27.6 ± 7.8 to 31.8 ± 5.0 ; both $p <$

0.01). FAC was also significantly increased from 0 (0, 0) at baseline to 3 (1.5, 4) at two weeks ($p < 0.01$).

Physical activity and nutrition status

Physical activity and nutritional intake indices at the first and second weeks after stroke onset are shown in Table 2. There were significant increases in total energy ($p < 0.01$) and protein intake ($p < 0.01$) in the second week, but no significant change in the physical activity indices between the first and second weeks. The percentage of oral intake was significantly increased ($p < 0.01$), and the percentage of peripheral parenteral nutrition was significantly decreased ($p < 0.01$) in the second week. In terms of gastrointestinal symptoms, the percentage of constipation decreased significantly in the second week ($p < 0.01$).

Body composition and muscle property changes

Changes in body composition and muscle properties between baseline and two weeks after stroke onset are shown in Table 3. Body weight ($p < 0.05$) and FFM ($p < 0.05$) were significantly decreased after two weeks. In contrast, the ECW/ICW ratio was significantly increased in the whole body ($p < 0.01$), paralyzed side ($p < 0.01$), and non-paralyzed side

($p < 0.01$), indicating a decline in muscle quality. The phase angle was significantly decreased in the whole body ($p < 0.05$) and paralyzed side ($p < 0.01$), suggesting that muscle quality declined. The phase angle did not change significantly on the non-paralyzed side.

Relationships with muscle quantity and quality changes

The results of the correlation analysis between changes in muscle quantity or quality and age, physical activity, or nutritional intake are shown in Figure 1. Changes in FFM and ASM showed significant positive correlations with age ($r = 0.54$ and $r = 0.54$) and no significant correlations with physical activity or nutritional intake. The change in the ECW/ICW ratio was significantly correlated with age ($r = 0.57$), METs ($\rho = -0.61$), sedentary ($\rho = 0.67$), and MVPA ($\rho = -0.48$). Changes in phase angle were significantly correlated with age ($r = -0.65$), METs ($\rho = 0.69$), sedentary ($\rho = -0.68$), MVPA ($\rho = 0.54$), total energy ($r = 0.45$), and protein ($r = 0.45$).

Discussion

The present study investigated longitudinal changes in muscle quantity and quality in patients with acute stroke. The results showed that FFM decreased two weeks after stroke

onset, and both muscle quality indices (ECW/ICW ratio and phase angle) also declined. In contrast, ASM did not change for two weeks during the acute stroke phase. Physical activity indices were also significantly related to the ECW/ICW ratio, and physical activity and nutritional intake indices were significantly related to the phase angle. Therefore, higher physical activity, less sedentary time, or higher total energy and protein intake suppressed the decline in muscle quality. This study is the first report to evaluate changes in muscle properties, including both muscle quantity and quality in the acute phase after stroke, and to reveal associations of muscle quantity/quality with physical activity and nutritional intake. These results suggest that exercise and nutritional therapy could possibly suppress the decline in muscle quality, especially in the acute phase after stroke.

A previous study reported that 0.4%–0.6% of muscle mass was lost daily due to bed rest within 14 days (24). In addition, another study reported that quadriceps muscle thickness was significantly decreased in the acute phase after stroke onset (8). In contrast, the decrease in FFM in the present study was 0.2%–0.3% daily, and no decrease was observed in any of the indices of skeletal muscle mass, ASM, paralyzed/non-paralyzed side muscle mass, and SMI. Therefore, it is possible that the present study recruited participants who could prevent muscle wasting compared to previous studies (8, 24). The

fact that we observed a decrease in FFM including the trunk muscle and no change in ASM suggests that the atrophy of trunk muscles was greater than that of limb skeletal muscles. There are no reports on the differences in muscle atrophy after stroke between trunk and limb skeletal muscles, and future studies focusing on trunk muscles are necessary. Meanwhile, the significant increase in the ECW/ICW ratio and the significant decrease in the phase angle, that is, the decline in muscle quality, suggest that muscle quality may reflect changes in muscle properties more sensitively than muscle quantity and that muscle quality assessed by bioelectrical impedance device can be used as an index to capture subtle changes in muscle status. Muscle quality should be examined in more studies in the acute phase of stroke. In addition, it is necessary to examine how a decline in muscle quality affects outcomes such as muscle function, physical function, and mortality.

The results of this study indicate that physical activity is related to changes in muscle quality. Particularly, it is interesting to note that not only the magnitude of total activity (METs), an index of quantity, but also a decrease in sedentary behavior, an index of intensity, was associated with the maintenance of muscle quality. High-intensity physical activity is often difficult during the acute phase. Meanwhile, eating, dressing, transferring, and toileting are considered light physical activities of 1.5–2.5 METs (25).

Thus, it is important to approach patients to perform self-care activities by themselves. In terms of nutritional intake, both total energy and protein intake were associated with changes in muscle quality. A previous study reported that energy intake in the first week after stroke onset was associated with changes in muscle thickness of the quadriceps muscle after 4 weeks (26). Furthermore, it has been reported that intervention with high-energy and high-protein supplementation during the first week of stroke was able to suppress weight loss (27). Therefore, it is possible that acute nutritional intake suppresses muscle quality loss in the early stroke period and prevents future muscle quantity and weight loss.

Correlation analysis showed a significant positive correlation between age and muscle quantity (FFM and ASM) or ECW/ICW ratio, and a significant negative correlation between age and phase angle. In other words, muscle quantity was decreased in younger age and increased in older age, while muscle quality showed a greater decline in older age. The rate of change in FFM and ASM showing a positive correlation with age was unexpected. Older age is a risk factor for muscle wasting due to short-term bed rest (28); therefore, the present study contradicts the results of this previous study. There are two possible reasons for this inconsistency. First, younger patients had higher pre-hospital physical activity than older patients; consequently, hospitalization may have resulted in a

greater decrease in physical activity and thus a greater loss of muscle mass. Second, BIA estimates muscle quantity larger than the actual value in older patients because water content in the body affects the calculation of muscle quantity, and older patients had a larger increase in water content due to worsening of edema during hospitalization. Thus, we do not think positively that older people can maintain muscle quantity. On the contrary, we believe that the assessment of muscle quantity alone may mislead to actual muscle property changes. The correlation analysis showed that older participants had a greater decline in muscle quality, and it is necessary to interpret both muscle quantity and quality when assessing changes in muscle properties.

This study has several limitations. First, the severity of stroke evaluated by the NIHSS was 4.3 ± 4.2 and the recovery of physical function measured by FIM motor score and FAC were from 24.6 ± 15.0 to 60.5 ± 23.6 and from 0 (0, 0) to 3 (1.5, 4), suggesting that most of the participants had mild severity and made good recovery. We have not been able to recruit patients with severe symptoms who cannot leave the bed or take food orally at all due to severe motor function deficit, coma, or dysphagia. Second, because changes in muscle properties are expected to decline more in patients with severe symptoms, the results of this study may underestimate muscle wasting compared with other studies, including those with severe conditions. Third, baseline measurements were conducted

within 3 days, but not immediately after stroke onset; the mean day from the onset to the baseline measurement was 1.9 days, but the fact that intravenous therapy and other treatments had already been started may have affected the results of BIA assessment. In future studies, it would be necessary to incorporate the assessment of changes in muscle properties, physical activity, and nutritional intake into the general treatment routine and to measure them immediately after the onset of stroke in all patients, including severe cases.

Conclusion

FFM and muscle quality (ECW/ICW ratio and phase angle) declined in the early phase of stroke at two weeks after onset. Physical activity and nutritional intake were also significantly associated with changes in muscle quality, suggesting that higher physical activity, less sedentary time, and greater total energy and protein intake likely prevent muscle quality decline in the acute stroke phase.

Declarations of interest

Conflict of Interest

The authors report no conflict of interest.

Funding

None.

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Table 1. Characteristics of participants

Sex, men/women	16/5
Age, years	72.7 ± 10.4
BMI, kg/m ²	24.2 ± 5.1
Diagnosis, CI/ICH	18/3
Side of paresis, right/left	10/11
NIHSS	4.3 ± 4.2
BRS, median (IQR)	5 (4, 6)
- Category (I/II/III/IV/V/VI), n	1/4/0/2/5/9
FIM motor score	24.6 ± 15.0
FIM cognitive score	27.6 ± 7.8
FAC, median (IQR)	0 (0, 0)
- Category (0/1/2/3/4/5), n	17/0/4/0/0/0
MWST, median (IQR)	5 (4, 5)
- Category (1/2/3/4/5), n	1/0/0/8/12
MNA score before stroke	25.6 ± 2.9
- Category (malnourished/at risk/normal), n	0/7/14
Comorbidities, n (%)	
- Previous stroke	3 (14.3)
- Hypertension	16 (76.2)
- Atrial fibrillation	2 (9.5)
- Dyslipidemia	9 (42.9)
- Diabetes mellitus	9 (42.9)
- Chronic kidney disease	0 (0)
Smoking, n (%)	13 (61.9)
Laboratory data (n=20)	
- CRP, mg/L	0.15 ± 0.20
- Albumin, g/dL	3.96 ± 0.39
- Total protein, g/dL	7.15 ± 0.73

Abbreviations: CI, cerebral infarction; ICH, intracerebral hemorrhage; NIHSS, National Institutes of

Health Stroke Scale; BRS, Brunnstrom Stage; IQR, interquartile range; FIM, Functional Independence

Measure; FAC, Functional Ambulation Categories; MWST, Modified Water Swallowing Test; MNA,

Mini Nutritional Assessment; CRP, C-reactive protein.

Table 2. Activity and nutritional status in acute stroke period

	First week	Second week	Mean
Activity status			
- Total activity, METs/day	1.04 ± 0.07	1.05 ± 0.07	1.05 ± 0.07
- Sedentary, %	90.9 ± 7.8	90.5 ± 6.1	90.7 ± 6.8
- MVPA, %	1.08 ± 1.91	1.24 ± 1.58	1.16 ± 1.61
Nutrition intake			
- Energy, kcal/day	982.1 ± 463.5	1373.1 ± 353.9**	1177.6 ± 335.6
- Energy/weight, kcal/kg/day	15.7 ± 7.0	23.1 ± 7.1**	19.4 ± 5.5
- Protein, g/day	39.8 ± 21.1	56.2 ± 14.4**	48.0 ± 15.8
- Protein/weight, g/kg/day	0.64 ± 0.34	0.95 ± 0.29**	0.79 ± 0.27
Ingestion methods			
- Oral, % days	66.9 ± 31.1	93.9 ± 16.6**	80.4 ± 22.1
- Enteral, % days	0 ± 0	2.7 ± 12.5	1.4 ± 6.2
- Parenteral, % days	33.1 ± 31.1	3.4 ± 7.7**	18.3 ± 18.4
Complication for nutrition			
- Constipation, % days	61.7 ± 27.5	42.9 ± 31.6**	52.3 ± 26.4
- Diarrhea, % days	8.8 ± 13.2	11.4 ± 18.7	10.1 ± 13.8
- Vomiting, % days	0 ± 0	0 ± 0	0 ± 0

Asterisks indicate significant changes compared with the first week (**, $p < 0.01$).

Abbreviations: MET, metabolic equivalent; MVPA, moderate-to-vigorous physical activity

Table 3. Body composition and muscle property changes

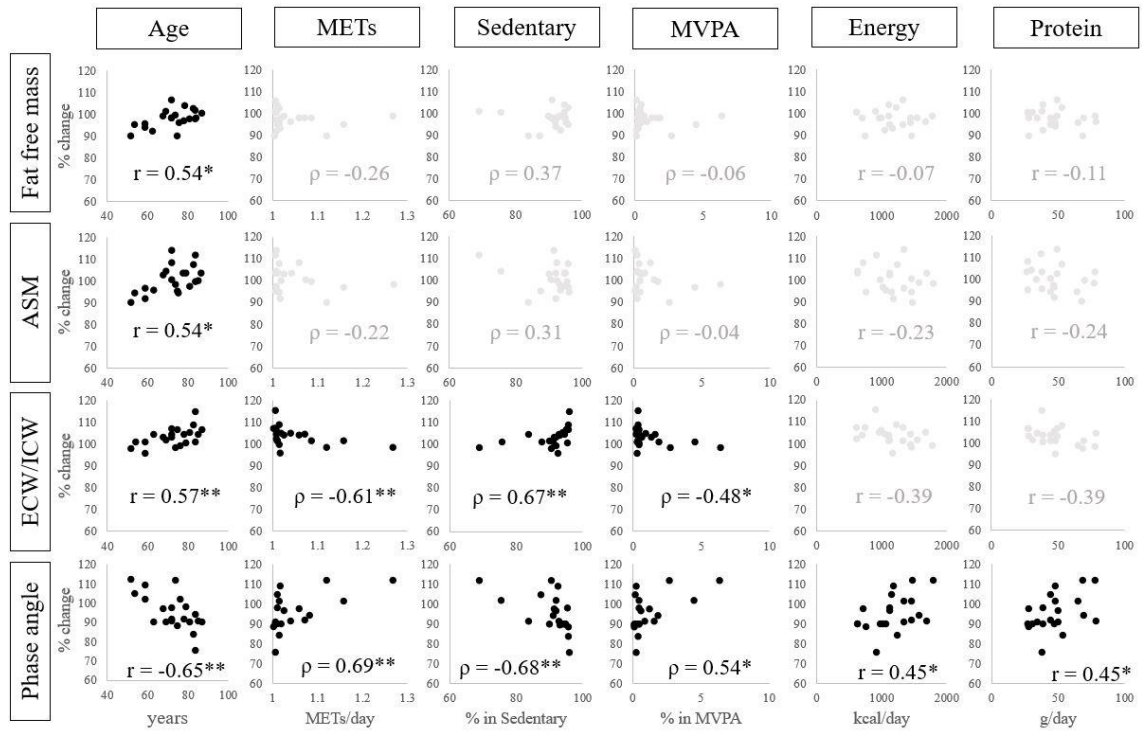
	Baseline		Post		Mean difference [95% CI]	
Duration from onset, days	1.9	± 1.0	14.4	± 1.0		
Weight, kg	62.7	± 12.6	60.6	± 12.1*	-2.13	[-2.91, -1.35]
Fat free mass, kg	43.4	± 8.0	42.2	± 7.6*	-1.18	[-2.06, -0.30]
Fat mass, kg	19.3	± 9.3	18.4	± 8.4	-0.95	[-2.08, 0.18]
Skeletal muscle mass						
- Appendicular, kg	17.8	± 4.2	17.7	± 4.0	-0.06	[-0.59, 0.46]
- Paresis side, kg	9.0	± 2.1	8.9	± 2.0	-0.06	[-0.37, 0.25]
- Non-paresis side, kg	8.8	± 2.1	8.8	± 2.0	0.00	[-0.37, 0.25]
SMI, kg/m ²	6.7	± 1.2	6.7	± 1.1	-0.02	[-0.22, 0.18]
TBW, L	32.0	± 5.9	31.2	± 5.6*	-0.77	[-1.43, -0.10]
ECW/ICW ratio, a.u.	0.63	± 0.02	0.65	± 0.03**	0.02	[0.01, 0.03]
- Paresis side, a.u.	0.64	± 0.02	0.66	± 0.03**	0.02	[0.01, 0.03]
- Non-paresis side, a.u.	0.63	± 0.02	0.65	± 0.03**	0.02	[0.00, 0.03]
Phase angle, °	5.2	± 0.6	4.9	± 0.8*	-0.25	[-0.47, -0.03]
- Paresis side, °	5.1	± 0.7	4.8	± 0.8**	-0.33	[-0.56, -0.10]
- Non-paresis side, °	5.1	± 0.7	5.0	± 0.9	-0.19	[-0.45, 0.07]

Asterisks indicate significant changes compared to the baseline (*, $p < 0.05$; **, $p < 0.01$).

Abbreviations: SMI, skeletal muscle mass index; TBW, total body water; ECW, extracellular water;

ICW, intracellular water

Fig. 1. Correlation between body composition changes and age, activity, or nutrition status



Asterisks indicate a significant correlation (*, $p < 0.05$; **, $p < 0.01$).

Abbreviations: MET, metabolic equivalent; MVPA, moderate-to-vigorous physical activity; ASM,

appendicular skeletal muscle mass; ECW, extracellular water; ICW, intracellular water