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Applied nutritional investigation

Effects of a leucine-enriched amino acid supplement on muscle mass, muscle strength, and physical function in post-stroke patients with sarcopenia: A randomized controlled trial

Yoshihiro Yoshimura M.D. [a,*], Takahiro Bise P.T. [b], Sayuri Shimazu R.D. [c], Maiko Tanoue P.T. [b], Yuko Tomioka P.T. [b], Mai Araki P.T. [b], Takafumi Nishino P.T. [b], Aomi Kuzuhara P.T. [b], Fumihiko Takatsuki [d]

[a] Department of Rehabilitation Medicine, Kumamoto Rehabilitation Hospital, Kumamoto, Japan
[b] Department of Rehabilitation, Kumamoto Rehabilitation Hospital, Kumamoto, Japan
[c] Department of Nutritional Management, Kumamoto Rehabilitation Hospital, Kumamoto, Japan
[d] Department of Consumer Foods & Seasonings, Food Products Division, Ajinomoto Co., Inc., Tokyo, Japan

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ABSTRACT

Objectives: The aim of this study was to investigate the effects of a leucine-enriched amino acid supplement on muscle mass, muscle strength, and physical function in post-stroke patients with sarcopenia.
Methods: We conducted an eight-wk, two-parallel group intervention, randomized controlled, blinded outcome assessment among 44 post-stroke older patients with sarcopenia. Sarcopenia was defined as a loss of skeletal muscle mass and decreased muscle strength according to the Asian Working Group for Sarcopenia criteria. The intervention group (n = 21) received a leucine-enriched amino acid supplement; the control group (n = 23) did not. Both groups performed low-intensity resistance training in addition to a post-stroke rehabilitation program. A primary outcome of physical function by using the motor domain of Functional Independence Measure (FIM), and secondary outcomes of appendicular muscle mass (skeletal muscle mass index [SMI]) measured via bioelectrical impedance analysis and muscle strength as handgrip strength were measured at baseline and at the end of the intervention.
Results: The FIM score increased significantly in both groups over time ($P < 0.01$), with significantly greater improvement in the intervention group than in the control group ($P < 0.045$). Handgrip strength also increased significantly over time ($P < 0.05$), with significantly greater improvement in the intervention group ($P < 0.01$). The SMI increased significantly in the intervention group but not in the control group over time, with significantly greater improvement in the intervention group (median estimated difference, 0.50 kg/m^2; 95% confidence interval, 0.01–2.11).
Conclusions: We demonstrated that an eight-wk intervention consisting of a leucine-enriched amino acid supplementation and low-intensity resistance training increased muscle mass, strength, and physical function in post-stroke patients with sarcopenia.

Introduction

Stroke is a leading cause of death in many countries, with many survivors experiencing persistent difficulty with activities of daily living (ADLs) as a direct consequence [1]. More than two-thirds of stroke survivors receive rehabilitation after hospitalization [2]. Approximately 8.2% to 49% of stroke patients are malnourished [3]. Malnutrition increases disease severity, mortality rates, and the incidence of infectious complications and swallowing difficulties and hampers the performance of ADLs after stroke onset; hence, intensive nutritional support during stroke rehabilitation is important [3–7]. Unlike other aspects of stroke treatment (e.g., establishment of designated stroke centers, recognition of stroke symptoms, and delivery of rehabilitation care), little attention has been paid to nutritional support during post-stroke rehabilitation. An effective combination of nutritional support and rehabilitation is thought to be an essential component of stroke care.

All authors contributed substantially to the conception and design of the study or the acquisition, analysis, or interpretation of data and the drafting or the revision of the article. All authors approved the final version of the manuscript for submission. The authors have no conflicts of interest to declare.

* Corresponding author: Tel.: +81 96 232 3111; Fax: +81 96 t 232 3119.
E-mail address: hanley.belfus@gmail.com (Y. Yoshimura).

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Sarcopenia, the age-related loss of muscle mass, strength, and physical function, largely accounts for physical frailty. Stroke-related sarcopenia is an emerging concept that has garnered much interest in the stroke field [8–11]. The onset and progression of stroke-related sarcopenia is multidimensional, involving muscle fiber-type shifts, bilateral differences in physical function, dysphagia and subsequent malnutrition, disuse atrophy, and complex systemic metabolic changes, as well as various comorbidities and premorbid factors such as older age, physical inactivity, and poor nutritional status [8]. The factors responsible for poor nutritional status, both premorbid and post-stroke, are of interest because they may be modifiable risk factors for stroke-related sarcopenia. Recent recommendations for preventing and treating sarcopenia include daily or supplemental intake of protein and vitamin D [12,13]. Furthermore, given the blunted sensitivity of older muscles to low doses of amino acids, a leucine-enriched amino acid supplement should be administered to stimulate muscle protein synthesis [14–17]. Based on a recent systematic review and meta-analysis [13] that provides evidence of the effectiveness of combining exercise and nutritional interventions for treating sarcopenia, resistance training should be added to maximize the effects of the nutritional intervention.

We hypothesized that combining resistance training with a timely bolus of a leucine-enriched amino acid supplement would increase muscle mass, strength, and physical function in post-stroke hospitalized patients with sarcopenia at high risk for disability. This randomized controlled trial determined the potential efficacy and safety of this combination and its effects on muscle mass (appendicular muscle mass measured via bioelectrical impedance analysis [BIA]), muscle strength (handgrip strength), and physical function (performance of ADLs).

Materials and methods

Design and setting

This was an eight-wk, two-parallel group, single-center, randomized, controlled, open-label, blinded outcome assessment study of older post-stroke patients with sarcopenia. It was conducted at Kumamoto Rehabilitation Hospital, Kumamoto, Japan, between September 2014 and April 2017.

The study protocol was approved by the Institutional Review Board and registered in the UMIN Clinical Trials Registry. Study procedures were performed according to the ethical recommendations of the Declaration of Helsinki. All participants were fully informed and written consent was obtained.

Patients

Consecutively admitted post-stroke patients in the convalescence rehabilitation wards served as the recruitment pool. Older patients (≥65 y of age) in the pool were screened for eligibility. Patients undergoing convalescent rehabilitation who were medically stable and able to stand up with or without aid were eligible. Eligible patients had a diagnosis of sarcopenia based on the cutoff value for older Asians [18], a skeletal muscle index (SMI) of ≤7 kg/m^2 (men) or ≤5.7 kg/m^2 (women) as determined via BIA (InBody S10; InBody, Tokyo, Japan), and a handgrip strength of <26 kg (men) or <18 kg (women). Eligible patients were currently receiving appropriate nutrition (i.e., had adequate energy intake according to the requirements set by a registered dietitian) and had provided informed consent. The exclusion criteria were as follows: unconsciousness; advanced dementia (Mini-Mental State Examination score ≤23) or delirium; an implanted pacemaker; obesity or overweight (body mass index [BMI] >25 kg/m^2]; an estimated glomerular filtration rate <30 mL/min/1.73 m^2; swallowing difficulties; inability to rise from a chair with or without aid; inability to communicate or understand the purpose of the study; a contraindication for a high-protein diet such as severe renal dysfunction; and comorbidities such as kidney, liver, or heart failure.

Within 7 d of admission to convalescent wards, patients were randomly assigned to an intervention group or a control group using a simple randomization method (Excel 2010, Microsoft, Washington, DC, USA). Baseline evaluation was carried out by members of the rehabilitation staff and registered dietitians and nurses who were not coinvestigators.

Rehabilitation program

Patients in both groups underwent an eight-wk post-stroke rehabilitation program that included physical, occupational, and speech-language therapy. Rehabilitation was conducted according to a standard protocol under the guidance of the rehabilitation team [19,20]. The rehabilitation program (≤3 h/d) was tailored to the functional abilities and disabilities of the patient, for example, physical therapy included paralyzed limb facilitation (for leg paralysis), range of motion exercises, basic movement training (mainly for the legs), walking training, and ADL training.

In addition to participating in the post-stroke rehabilitation program, patients in both groups performed the sit-to-stand exercise. This exercise has slow movements and low intensity (20–30% of one repetition maximum) and hence is useful for increasing muscle mass and strength in older adults [21,22]. For the sit-to-stand exercise, the patients were allowed to use a handrail or parallel bars as necessary, and a physical therapist assisted patients who had difficulty standing up on their own. Patients started performing two sets of 10 repetitions of the sit-to-stand exercise on the first day. The number of repetitions gradually increased as muscle strength and durability improved; the maximum daily sit-to-stand workout was two sets of 120 repetitions, one set of which took about 20 min.

Appropriate current nutritional management was defined as the amount of nutrition that provided adequate energy intake. It was calculated for each patient by experienced registered dietitians and was based on a nutritional evaluation on the day of referral. Energy expenditure was measured by using the Harris–Benedict equation. It was adjusted for the height, weight, age, and sex of the patient and multiplied by a physical activity factor and a stress factor to estimate energy need [23].

Intervention

The intervention group received a leucine-enriched amino acids containing jelly-type supplement; the control group did not. The supplement comprised 3 g of leucine 40% enriched essential amino acids (Amino L40, Ajinomoto Co., Inc., Tokyo, Japan) [15,24] and 9.7 g of carbohydrate. It did not contain any lipids and was 30 kcal/100 g (product details are presented in Table 1). Beginning on the first day of the study, the supplement was ingested once daily within 30 min after the end of the sit-to-stand exercise. Registered dietitians who were blinded to the group allocations supervised the daily diets. The supplement had low-calorie and low-protein content with little influence on daily dietary intake; hence, there seemed to be no sizeable difference in nutritional management between the two groups.

Outcome assessments

Blinded medical staff assessed the outcomes. Physical or occupational therapists blinded to the group allocations evaluated the physical conditions of the patients at baseline and at the end of the intervention. All patients were evaluated at baseline before allocation to their respective group.

The primary outcome measure was the physical function score (performance of ADLs). It was determined by using the Functional Independence Measure (FIM) [25], which is one of the most common measurement tools for ADL performance. The FIM consists of a motor domain (FIM-M) with 13 items and a cognitive domain (FIM-C) with 5 items. Tasks are rated on an ordinal scale that ranges from 1 (*total assistance*) to 7 (*complete independence*). The FIM, FIM-M, and FIM-C scores ranged from 18 to 126, 13 to 91, and 5 to 35 points, respectively. Lower scores indicated poorer performance of ADLs.

The secondary outcome measures were the SMI and handgrip strength. The SMI was determined in patients who were properly hydrated. Patients had their last meal 9 h before assessment and rested in bed for 1 h before the assessment. At the time of assessment, they were fever free, did not exhibit any tremors, and

Table 1
Micro- and macronutrients of the adopted nutritional supplementation

30 kcal/100 g	
Leucine-enriched essential amino acid (Amino L40) (%)	
Leucine	1.2 g (40)
Isoleucine	0.32 g (10.7)
Valine	0.33 g (11.1)
Others	1.15 g (38.2)
Lipid	0 g
Carbohydrate	9.7 g
Water	87.2 g
Sodium	75 mg
Vitamin B_1	0.2 mg
Vitamin B_6	0.2 mg
Vitamin B_{12}	0.4 μg
Vitamin D	20 μg

were not in poor physical condition. We used the latest version of a validated InBody system, and estimation of muscle mass was considered to be minimally affected by fluid overload [26]. Handgrip strength was measured using a Smedley hand dynamometer (TTM, Tokyo, Japan) in the non-dominant hand (or in case of hemiparesis, the non-paralyzed hand), with the patient in a standing or seated position, depending on their ability, and with their arms straight at their sides. The higher value from two consecutive measurements was recorded.

Other outcomes included nutritional status, serum albumin level, calf circumference, and BMI. Nutritional status was determined by using the Mini-Nutritional Assessment-Short Form (MNA-SF) [27]. Dietary assessments were performed by registered dietitians. Daily energy intake and protein intake were calculated by multiplying the ratio of the actual food intake and provided food with provided energy and protein. All food delivered to the patients was provided by the hospital; no additional food was provided by the families of the patients. Actual food intake was based on the ingestion ratio of staple foods, side dishes, and nutritional supplements as recorded by nurses and registered dietitians.

Basic information was collected at screening. It included the premorbid ADL level, stroke type, stroke severity score at onset, lower limb paralysis stage (Brunnstrom recovery stage) [28], and serum levels of albumin (g/dL) and C-reactive protein (mg/dL). The ADL level and stroke severity score were determined by using a modified Rankin scale [29] and the National Institute of Health Stroke Scale [30], respectively. Any adverse events were recorded throughout the intervention period.

Statistical analysis

This study was powered to detect an effect size of a score of 15 in the FIM-M [9,31,32]. Assuming an α error of 0.05 and a two-sided effect, a sample size of 23 per group provided 80% power to observe the effect.

Baseline characteristics were compared between the two groups using Student's t test, the Mann–Whitney U-test, and the χ^2 test. Postintervention characteristics were assessed using analysis of covariance; the baseline characteristics were included as covariates, and P-values, means, and 95% confidence intervals (CIs) were calculated. Group differences in terms of change from baseline were analyzed by using the Mann–Whitney U-test, with median values and corresponding 95% CIs determined by using the Hodges–Lehman estimator. Two-sided $P < 0.05$ were considered significant. All analyses were conducted using SPSS version 21 software.

Results

We screened 113 post-stroke patients for eligibility, 49 of whom were randomly placed in the intervention or control group (Fig. 1). Five participants withdrew from the study: two who were discharged before the end of the study, and three who refused to continue the study. The final intervention and control groups consisted of 21 patients (mean age of 80 ± 7 y) and 23 patients (mean age of 78 ± 6 y), respectively.

The baseline characteristics of the patients are shown in Table 2. None of the items that were examined differed significantly between the two groups at baseline. The mean age of the entire study cohort was 79.8 y. Most patients were women (68.2%), physically disabled (median FIM-M score, 26), and at risk for malnutrition (median MNA-SF score, 8). Intervention compliance was 100% from baseline to follow-up for all patients in both groups.

All patients performed two sets of 10 repetitions of the sit-to-stand exercise on the first day of the intervention. The number of repetitions gradually increased, and by the fourth week, all patients performed two sets of 120 repetitions sets per day until the end of the study. The FIM-M score increased significantly in both groups over time ($P < 0.01$), with significantly greater improvement in the intervention group than in the control group ($P < 0.045$; Table 3). Handgrip strength also increased significantly over time ($P < 0.05$), with significantly greater improvement in the intervention group ($P < 0.01$). The SMI increased significantly in the intervention group but not the control group over time, with significantly greater improvement in the intervention group (median estimated difference, 0.50 kg/m^2; 95% CI, 0.01–2.11).

No treatment × time effects were observed in cognitive levels (FIM-C scores), nutritional status (MNA-SF scores), or serum albumin levels. Daily protein and energy intake increased significantly in both groups over time (both $P < 0.05$), but the treatment × time effect was not significant ($P = 0.142$ and 0.256, respectively; Table 3).

There were no adverse effects reported throughout the intervention in regard to the nutritional supplement or the sit-to-stand exercise.

Discussion

Eight weeks of administration of a leucine-enriched amino acid supplement to older post stroke patients with sarcopenia significantly improved the performance of ADLs and increased muscle mass and strength. This finding suggests that this supplement,

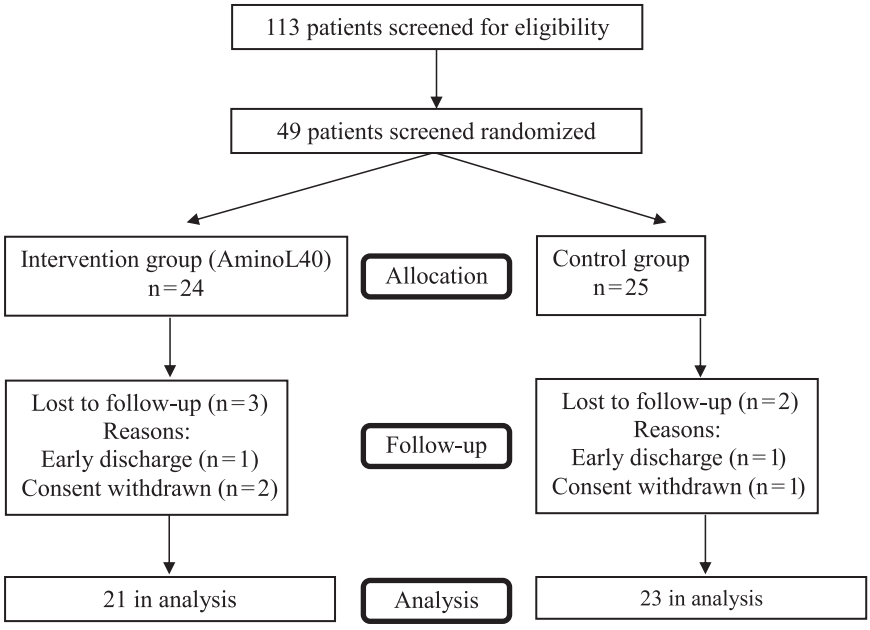

Fig. 1. Participant screening, randomization, and follow-up.

Table 2
Baseline demographic and clinical characteristics

Baseline characteristics	Intervention group (n = 21)	Control group (n = 23)	*P*-value
Age, y, mean (SD)	80.8 (7.1)	78.9 (6.3)	0.33*
Sex, female, n (%)	14 (66.7)	16 (69.5)	0.20†
Premorbid modified Rankin Scale, median (IQR)	0 (0–2)	0 (0–2)	0.61‡
FIM-motor, median (IQR)	25 (13–52)	26 (13–55)	0.41‡
FIM-cognitive, median (IQR)	18 (10–25)	19 (11–27)	0.55‡
Handgrip strength, male, kg, median (IQR)	12.5 (6–18)	14 (10–18)	0.37‡
Handgrip strength, female, kg, median (IQR)	9.5 (4–12)	10.1 (6–14)	0.27‡
SMI, male, kg/m^2, mean (SD)	6.2 (5.7–6.7)	6.3 (5.5–6.8)	0.45*
SMI, female, kg/m^2, mean (SD)	4.9 (4–5.1)	5 (4–5.2)	0.65*
Calf circumference, male, cm, median (IQR)	29.1 (26.3–31.3)	29.8 (26–32.1)	0.22‡
Calf circumference, female, cm, median (IQR)	26.1 (24.3–29.3)	26.3 (23–29.1)	0.42‡
MNA-SF, score, median (IQR)	8 (6–10)	9 (6–12)	0.57‡
Daily protein intake, g/kg BW, median (IQR)	1.1 (0.9–1.3)	1.1 (0.9–1.3)	0.41‡
Daily energy intake, kcal/kg BW, median (IQR)	27.7 (23.3–31)	28.2 (23.9–31.4)	0.33‡
Serum albumin level, g/dL, median (IQR)	3.3 (3–3.5)	3.4 (3–3.7)	0.87‡
Serum CRP level, mg/dL, median (IQR)	0.2 (0.1–0.4)	0.3 (0.1–0.9)	0.22‡
Stroke type, n (%)			
Brain infarction	12 (57.1)	12 (52.2)	0.41†
Brain hemorrhage	7 (33.3)	10 (43.5)	
Subarachnoid hemorrhage	2 (9.5)	1 (4.3)	
Onset NIHSS, score, median (IQR)	9 (6–19)	8 (5–15)	0.48‡
Lower limb paralysis stage (BRS), median (IQR)	4 (2–6)	4 (2–6)	0.51

BRS, Brunnstrom stage; BW, body weight; CRP, C-reactive protein; FIM, Functional Independence Measure; IQR, interquartile range; MNA-SF, Mini Nutritional Assessment-Short Form; NIHSS, National Institute of Health Stroke Scale; SMI, skeletal muscle index
*t test.
†χ^2 test.
‡Mann–Whitney U test.

Table 3
Function, muscle mass and strength, and nutritional outcomes

	Intervention group (n = 21)		Control group (n = 23)		Estimated between-group difference Mean (95% CI)*	*P*
	Baseline (IQR)	Post (IQR)	Baseline (IQR)	Post (IQR)		
FIM-motor, score, median	25 (13–52)	62 (41–82)	26 (13–55)	53 (38–75)	9.2 (1.5–15.8)	0.045
FIM-cognitive, score, median	18 (10–25)	26 (12–31)	19 (11–27)	27 (16–32)	1.1 (−2.4 to 7.03)	0.561
SMI (kg/m^2), median	5.4 (4.8–6.2)	5.9 (5.1–6.8)	5.5 (4.9–6.1)	5.6 (4.9–6.4)	0.50 (0.01–2.11)	0.041
Handgrip strength, kg, median	12.1 (4.2–19.3)	21.1 (15.2–25.8)	13.2 (5.1–19.2)	16.3 (10.2–21.8)	3.80 (1.09–7.22)	0.002
MNA-SF, score, median	8 (6–10)	9 (8–11)	9 (6–12)	9 (7–13)	0.9 (−1.5 to 4.6)	0.841
Protein intake including supplement, g/kg BW/d, median	1.1 (0.9–1.3)	1.4 (1.1–1.7)	1.1 (0.9–1.3)	1.3 (1–1.5)	0.11 (−0.12 to 0.51)	0.142
Energy intake including supplement, kcal/kg BW/d, median	27.7 (23.3–31)	34.3 (28.5–37.1)	28.2 (23.9–31.4)	31.1 (27–35.6)	3.54 (−1.14 to 8.27)	0.256
Serum albumin level, g/dL, median	3.3 (3.0–3.5)	3.5 (3.2–3.8)	3.4 (3–3.7)	3.6 (3.3–4)	0.21 (−0.81 to 0.58)	0.521

BW, body weight; FIM, Functional Independence Measure; IQR, interquartile range; MNA-SF, Mini Nutritional Assessment-Short Form; SMI, skeletal muscle index
Differences between the groups in postintervention values, analyzed with analysis of covariance with each baseline values as covariates
*Hodges-Lehma median estimator.

which stimulates muscle protein synthesis in older adults, counteracts muscle loss in these patients.

Exercise or resistance training is considered the standard method for increasing muscle mass and strength and improving physical function. In this clinical trial, however, we aimed to investigate the isolated effect of a specific nutritional intervention. Information on the effects of nutritional supplements on muscle mass, strength, and physical function in older adults with sarcopenia is limited and somewhat contradictory. Bauer et al. [33] found that nutritional supplements increased muscle mass and chair-stand ability but not handgrip strength or Short Physical Performance Battery scores. Fiataron et al. [34] reported that nutritional supplementation per se did not affect muscle mass or physical function. In a recent systematic review and meta-analysis, Yoshimura et al. [13] provided evidence of the effectiveness of nutritional supplements for increasing muscle mass, strength, and physical function, but the evidence was not robust. In this study, we selected post-stroke patients diagnosed with sarcopenia as defined by the Asian Working Group for Sarcopenia [18]. To our knowledge, this is the first interventional trial including nutritional supplementation in such patients.

Approximately 50% of stroke patients are malnourished [9], and malnutrition is a potential predictor of adverse post-stroke outcomes (e.g., physical dependency, muscle weakness, longer hospital stays, and poorer quality of life) [3–7,35]. When combined with malnutrition, sarcopenia might further worsen the prognosis of stroke patients. The present study is beneficial because it identified a viable means of increasing muscle mass, strength, and physical function in stroke patients with sarcopenia, and also because it focused on issues that have been largely overlooked by clinicians.

Stroke-related sarcopenia is another point worth discussing [36]. We previously reported a high rate (≤50%) of sarcopenia in stroke patients undergoing rehabilitation [9]. Factors underlying stroke-related sarcopenia may include malnutrition [8]. Moreover,

the clinical outcomes of stroke patients may largely depend on premorbid nutritional status, as well as nutritional management after stroke onset. Therefore, further clinical and basic research studies are needed to elucidate the etiology of stroke-related sarcopenia and to develop effective prevention and treatment strategies including nutritional support.

High daily protein intake can increase the mass of the appendicular muscles. In the present study, daily protein intake increased significantly over time in both groups: Both groups had a median daily intake of 1.1 g/kg of body weight at baseline, and both groups had a median daily intake of 1.4 (intervention) and 1.3 (control) g/kg of body weight at the end of the study. Although no treatment × time effects were observed for daily protein intake (including supplements), muscle mass and strength were significantly greater in the intervention than the control group.

In addition to quantity, the quality of the supplement is also a crucial determinant of muscle mass and strength [37–39]. Leucine is a key trigger of postprandial muscle protein synthesis, acting via the mTOR pathway [40], and consumption of essential amino acids enriched for leucine, as described in this trial, increases muscle protein synthesis and alleviates muscle soreness after exercise [24]. Therefore, leucine-enriched amino acid supplements appear to preserve muscle mass and physical function in older sarcopenic adults with decreased food intake.

To maximize the effects of the nutritional intervention, the patients in the present study also received low-intensity resistance training as part of their rehabilitation therapy. Because the patients in this study were older adults with physical limitations, we chose the sit-to-stand exercise from among the many resistance training exercises because it is easy to perform and assistance can be provided if necessary. Low-intensity resistance training with slow movements (e.g., the sit-to-stand exercise) has been shown to be a safe and effective way to increase muscle mass and strength in frail older adults [21,22].

The present study had some limitations. First, its relatively small sample size, selection bias, and single-center design might limit the generalizability of the results. Second, a control group that did not perform resistance training was lacking. Thus, the present study did not address the separate effects of nutrition and exercise.

Conclusions

The present study showed that an eight-wk intervention consisting of a leucine-enriched amino acid supplement and low-intensity resistance training increased muscle mass, strength, and physical function in post-stroke patients with sarcopenia. The study highlighted the efficacy and safety of this approach, which is especially suitable for older patients with physical limitations. Further studies are needed to determine how the nutritional supplement improves the outcomes of stroke patients with sarcopenia in combination with other rehabilitation procedures.

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Supplementary materials

Supplementary data related to this article can be found at https://doi.org/10.1016/j.nut.2018.05.028.

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