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Original Article

Whey protein-enriched high-protein diet combined with sustained musculoskeletal rehabilitation improves muscle and bone mass in central nervous system injury patients

Li-Yen Tsao [1,2,†], Stella Chin-Shaw Tsai [3,4,5,†], Su-Ju Tsai[6,7], Frank Cheau- Feng Lin[7,8,9,*]

[1] *Department of Nutrition, Chung Shan Medical University Hospital, Taichung City, Taiwan*
[2] *Department of Nutrition, Chung Shan Medical University, Taichung City, Taiwan*
[3] *Superintendent Office, Tungs' Taichung MetroHarbor Hospital, Taichung City, Taiwan*
[4] *Department of Post-Baccalaureate Medicine, College of Medicine, National Chung Hsing University, Taichung City, Taiwan*
[5] *Department of Food and Nutrition, Providence University, Taichung City, Taiwan*
[6] *Department of Physical Medicine and Rehabilitation, Chung Shan Medical University Hospital, Taichung City, Taiwan*
[7] *School of Medicine, Chung Shan Medical University, Taichung City, Taiwan*
[8] *Department of Thoracic Surgery, Chung Shan Medical University Hospital, Taichung City, Taiwan*
[9] *Department of Parenteral Nutrition, Chung Shan Medical University Hospital, Taichung City, Taiwan*
[†] *These authors contributed equally to this work.*

Purpose: Convalescent stroke and traumatic brain injury (TBI) patients have special nutritional needs during rehabilitation training. Here, we investigated the administration of a whey protein-enriched high-protein feeding and rehabilitation program (WHRP) and its correlation with body composition changes in stroke and TBI patients.

Methods: Fifty patients with stroke and TBI (mean age: 64.6±15.02 years) were enrolled. Patients received tube feeding and texture-modified diet training, combined with rehabilitation exercise training. Diet in the WHRP was calculated for five daily meals; total daily caloric intake was 29.8±6.1 kcal/kg/day, total protein intake was 1.41±0.18 g/kg/day, and whey protein 15.7±10.9g/day. Medical dietary records were maintained for each participant.

Results: Body composition analysis was performed before and after the intervention and showed that muscle mass increased from 42.0±7.40 kg to 42.7±7.05 kg (P=0.029), whereas bone mass increased from 2.37±0.37 kg to 2.41±0.34 kg (P=0.042). Muscle mass associated more strongly with post- vs. pre-intervention protein and whey protein, with r values of 0.705 vs. 0.410 and 0.335 vs. 0.163, respectively, and the strongest effect was observed with post-intervention protein. Bone mass also associated more strongly with protein and whey protein after the WHRP intervention than before, with r of 0.699 vs. 0.291, and 0.463 vs. 0.117, respectively. The highest correlation was similarly observed for protein after the intervention.

Conclusion: This WHRP intervention program was beneficial for tube-fed stroke and TBI patients undergoing inpatient rehabilitation. Our study serves as a reference for clinical healthcare workers when incorporating nutritional supplementation into treatment plans for inpatient convalescent stroke and TBI rehabilitation patients.

Keywords: nutritional supplements; whey protein tube-feeding; rehabilitation; muscle mass; bone mass

* Corresponding Author: Frank Cheau-Feng Lin
Address: No. 110, Sec. 1, Jianguo N. Rd., Taichung City, 40201, Taiwan
Tel: +886-4-24739595 ext 34610
E-mail: frankcflin3@gmail.com

1. Introduction

Strokes and traumatic brain injuries (TBIs) often impair neurologic functions and long-term rehabilitation is required to alleviate such disabilities and restore normal function (1, 2). Once stroke patients' neurological functions and vital signs have stabilized, they are transferred to post-acute care, where they can begin stroke rehabilitation. At this point, professional multidisciplinary medical care is initiated, including disability assessment, treatment plan development, and effectiveness evaluation for each case (3, 4).

Nutrition is essential during the post-acute rehabilitation period because chronic stroke patients are usually older adults (5, 6), and the effects of age-related factors must be considered when designing rehabilitation exercises and nutritional supplementation strategies. Several studies have demonstrated that dietary supplementation strategies such as carbohydrate, protein, or amino acid supplements can significantly stimulate skeletal-muscle protein synthesis and muscle growth, promote muscle strength, and improve physical performance (5, 7). High-protein supplements, especially whey protein or branched-chain amino acids (BCAA), proved beneficial for increasing muscle mass in elderly patients undergoing rehabilitation (8). Similarly, Rabadi et al. (9) showed intensive nutritional supplementation for stroke patients in an inpatient acute-stroke rehabilitation setting facilitated recovery of motor function. Recently, Honaga et al. (10) reported suppression of fat infiltration into the muscle with whey protein and vitamin D diet supplementation in post-stroke patients.

This study aimed to investigate whether the implementation of a combined nutritional supplementation strategy using a whey protein-enriched high-protein feeding and rehabilitation program (WHRP) can improve the muscle and bone mass of stroke and TBI rehabilitation patients to achieve better rehabilitation efficacy.

2. Methods

2.1. Participants

Patients with stroke and TBI who received tube feeding and were admitted to the rehabilitation ward of a medical center for rehabilitation were enrolled. Each patient had a different rehabilitation schedule, starting from the onset of the disease. Patients received a rehabilitation plan during inpatient rehabilitation prescribed by the attending physician. The attending physician also prescribed tube feeding performed by a dietitian as well as texture-modified diet training performed by a speech therapist. The dietitian explained the WHRP to the patient’s family members and caregivers, and patients were enrolled only after providing written informed consent. The study was conducted between April 2018 and June 2019. The following exclusion criteria applied for participation in the survey: 1) inability to receive enteral nutrition; 2) inability to maintain a stable posture during standing exercises for successful completion of the body composition analysis; and 3) patients with diseases requiring restricted protein intake, such as renal diseases.

2.2. Experimental design

A longitudinal self-controlled case series study (11) was adopted in which dietitians administered nasogastric tube feedings to patients in the rehabilitation unit, implemented the nutrition care process, and completed nutrition care medical records in the Hospital Information System. Data collection included participants' baseline demographics from their inpatient electronic medical records, as well as previous nutritional intake and body weight data, including patient data before the brain injury. Anthropometric measurements were performed to determine body fat and muscle composition. The day of admission was considered day 0 of the intervention, and the day of discharge was the last day (i.e., case closed). At admission, preadmission data were queried, including anthropometric and dietary data, specifically total calories and amounts of protein and whey protein in the previous tube-feeding formula. These served as internal controls for each participant. This study was approved by the institutional review board of the CSMU Hospital (CS18071).

2.3. Whey protein-enriched high-protein feeding and rehabilitation program (WHRP)

During inpatient rehabilitation, the attending physician prescribed tube feeding. The tube-feeding schedule (five meals per day) and formula were determined by a dietitian based on the patient's body weight, nutrient requirements, gastrointestinal tolerance, rehabilitation training activity level, and weekly weight changes monitored by a nurse. Each participant received an individualized tube-feeding formula that contained the appropriate calories and was rich in whey protein. The formula contained 30 kcal total calories and 1.4 g protein per kg body weight. A high protein ratio was achieved by adding a BCAA-enriched whey protein supplement (Protison® whey protein powder and RESOURCE® fruit-flavored beverage). Because participants received different types of commercial tube formulas for their five daily meals (with varying calorie and protein content), different amounts of whey protein were provided to each participant. The dietitian prepared appropriate tube feedings throughout the study period to maintain adequate body weight, ensure good nutritional status, and improve the effectiveness of muscle-strength rehabilitation. The dietitian also educated patients and their family members about health issues and communicated and discussed with the medical team under the attending physician. When the patients' chewing and swallowing functions showed good progress in swallowing training, they were gradually prescribed oral diets on the ward. At this point, the dietitian was responsible for monitoring the type, frequency, amount, and nutrient content of food intake while continuously adjusting the tube feedings to ensure that the patients' total daily calories and total protein content were within the range provided by the experimental plan.

All patients were managed by a multidisciplinary post-stroke rehabilitation team at a dedicated stroke inpatient unit according to the guidelines (1, 12). The rehabilitation program included intensive rehabilitation training, physiotherapy, occupational therapy, swallowing therapy, and speech therapy. The prescribed exercise protocol included muscle-strength training, resistance training, orthoses for the upper arm and ankle-foot, constraint-induced movement therapy, repetitive task training, endurance exercises using bicycles, treadmills, cross-trainers, and handcycles, with three to four sessions per week for four weeks.

2.4. Anthropometric measurements

The TANITA® BC-545N 10-in-1 segmental body composition scale (eight hand-electrodes for detailed measurements of five body segments, including the trunk, left arm, right arm, left leg, and right leg) was used to measure the patient's body fat percentage, muscle mass, bone mass, and basal metabolic rate along with body weight. The accuracy of the bioelectrical impedance anthropometric measurement devices has been validated for research purposes (13-15). Patients' anthropometric measurements were compared before (day of admission, day 0) and after (day of discharge, week 4) the intervention.

2.5. Statistical methods

Statistical analyses were performed using IBM SPSS version 20 (IBM Corp., published 2011. IBM SPSS Statistics for Windows, version 20.0. Armonk, NY: IBM Corp.). Comparisons were performed on the data collected before and after intervention with whey protein supplementation via tube feeding. The Kolmogorov-Smirnov test for normality was performed, which indicated that the data were normally distributed. Continuous variables were analysed using paired t-tests and expressed as means and standard deviations (SD), with $P<0.05$ indicating statistical significance. Categorical variables were summarized using frequency distribution tables and expressed as the number of cases and percentages. Due to the non-normal distribution of the data, values for the interval from disease onset to rehabilitation were expressed as medians (interquartile range, IQR). For body fat and muscle composition, four male and two female patients had a missing value. Therefore, to avoid the influence of missing values, another chi-square test was performed to determine whether there were significant differences between the characteristics of the missing values and the study sample. The results revealed no significant differences in the distribution of men/women ($P=0.885$) and age, indicating that the missing values did not affect the overall results. Linear correlations were used to test the relationships between the nutrient intake and body composition, and the correlation figures were completed using the linear curve estimate function of SPSS.

Table 1. Demographics and nutritional intake of rehabilitation patients

		N (%)	
Total		50 (100)	
Male, n (%)		32 (64%)	
Disease type, n (%)	Ischemic stroke	23 (46%)	
	Hemorrhage stroke	19 (38)	
	TBI	8 (16%)	
Hemiplegia, n (%)	Bilateral hemiplegia	7 (14%)	
	Right hemiplegia	24 (48%)	
	Left hemiplegia	19 (38%)	
		Mean (SD)	
Age, year		64.6	(15.02)
Height, cm		162.4	(7.93)
Admission weight, kg		59.4	(8.89)
Admission BMI		22.5	(3.05)
Length of hospital stay, days		26.8	(2.43)
Interval from onset to rehabilitation, days		29.0	(15.8-46.3)*
Cumulative duration of inpatient rehabilitation, months		2.87	(1.02)
Nutritional intake	Calories, kcal/kg	29.8	(6.1)
	Protein, g/kg	1.41	(0.18)

BMI, Body mass index; TBI, Traumatic brain injury.
* Data are expressed as median (interquartile range, IQR).

3. Results

3.1. Participant demographics (Table 1)

In total, 56 patients were initially enrolled, of whom six were withdrawn from the study because they did not complete body composition analyses, which meant that 50 patients were included in the final data analysis. The participant included 32 (64%) men, with a mean age of 64.6±15.02 years. The mean height was 162.4±7.93 cm, mean admission weight 59.4±8.89 kg, and admission body mass index (BMI) 22.5±3.05, which was considered normal.

Among the 50 patients, 23 (46%) had an ischemic stroke, 19 (38%) had a hemorrhagic stroke, 8 (16%) had TBI. Seven (14%) had bilateral hemiplegia, 24 (48%) had right hemiplegia, and 19 (38%) had left hemiplegia.

Based on interviews with the patients' primary caregivers, the interval from onset to rehabilitation was 29 (15.8-46.3) days, the cumulative duration of inpatient rehabilitation was 2.87±1.02 months, and the length of this hospital stay was 26.8±2.43 days.

3.2. Nutritional intake in the whey protein-enriched high-protein feeding and rehabilitation program (Tables 1 and 2)

During hospitalization, daily target caloric and protein intakes were 30 kcal/kg and 1.4 g/kg, and actual intakes were 29.8±6.1 kcal/kg and 1.41±0.18 g/kg, respectively. The total mean caloric intake of the participants was 1752.5±214.9 kcal; the mean total protein intake was 84.1±11.1 g. The mean daily amount of whey protein added to the tube-feeding formula was 15.7±10.9g. Calorie, protein, and whey

Table 2. Body composition and nutrition intervention of rehabilitation patients

	Day 0 *Mean (SD)*	Week 4 *Mean (SD)*	*P value*
Body Composition			
Body weight, kg	59.4 (8.89)	59.3 (8.64)	0.703
Body fat percentage, %	24.8 (7.96)	24.3 (9.11)	0.417
Fat mass kg	14.6 (5.2)	14.4 (6.0)	0.552
Bone mass, kg	2.37 (0.37)	2.41 (0.34)	0.042*
Muscle mass, kg	42.0 (7.40)	42.7 (7.05)	0.029*
BMR, kcal	1229.8 (191.16)	1251.1 (181.28)	0.021*
Nutrition Intervention			
Calories, kcal/day	1669.8 (259.7)	1752.5 (214.9)	<0.001*
Protein, g/day	68.7 (12.0)	84.1 (11.1)	<0.001*
Whey protein g/day	1.2 (0.3)	15.7 (10.9)	<0.001*

BMI, Body mass index; BMR, Basal metabolic rate
Statistical analyses were conducted using Pair-t test: * P < 0.05.

protein amounts were significantly higher during the intervention than before, with mean values of 82.7 kcal, 15.4 g, and 14.5 g, respectively, P<0.001. As expected, whey protein increased the most, and protein-energy increased to 74.5% of total energy increase. During rehabilitation training, the proportion of oral food intake gradually increased from 25% of total caloric intake before the intervention to 37% at the end (P=0.001).

3.3. Body composition changes

Based on interviews with primary caregivers, the normal body weight of rehabilitation patients before onset was 62.8±10.36 kg, which had decreased to 59.4±8.89 kg at the time of admission (Day 0, Table 2). During hospitalization, patients' body weights were measured and recorded weekly. Patients showed stable body weights during these four weeks.

Body fat percentage decreased from 24.8±7.96% before the intervention to 24.3±9.11% after (P=0.417), which was not statistically significant (Table 2). Muscle mass increased significantly from 42.0±7.40 kg

Table 3. The correlations of muscle, bone, fat mass and body weight

		Body weight		Muscle mass	
		r	*P*	*r*	*P*
Muscle mass	Day 0	0.685***	<0.001	1	/
	Week 4	0.674***	<0.001		
Bone mass	Day 0	0.797***	<0.001	0.962***	<0.001
	Week 4	0.779***	<0.001	0.959***	<0.001
Fat mass	Day 0	0.562***	<0.001	-0.160	0.271
	Week 4	0.490**	0.001	-0.251	0.096

* Correlation is significant at P <0.05, **P<0.01, ***P<0.001.

before intervention to 42.7±7.05 kg after intervention (P=0.029), whereas bone mass also increased significantly from 2.37±0.37 kg before intervention to 2.41±0.34 kg after intervention (P=0.042).

Muscle mass and bone mass were closely associated with each other, with r=0.962 before and r=0.959 after the intervention (Table 3). Both were associated with body weight with r values of approximately 0.68 and 0.78 for muscle mass and bone mass, respectively. Fat mass also correlated with body weight, with r values of 0.562 before and 0.490 after the intervention, respectively. It was negatively associated with muscle and bone mass, without statistical significance.

In sum, bone and muscle mass increased synergistically, and fat mass decreased slightly, so the body weight remained stable due to the one-month WHRP intervention.

3.4. The influence of nutritional supply on the body composition of the rehabilitation patients (Table 4 and Figure 1)

The energy provided was designed to be 30 kcal of Day 0 body weight (BW), with a resultant mean of 29.8 close to the target, but a wide SD of 6.1 kcal/day. The protein should be provided according to the BW at Day 0 of 1.4 g/kg/day, and was actually 1.41±0.18 during the WHRP intervention. The nutrients given was according to Day 0 BW.

After 26.8±2.43 days of WHRP, the results were

Table 4. The correlations of nutrient supply and body compositions in rehabilitation patients

		Energy		Protein		Whey protein	
		Before	After	Before	After	Before	After
Body composition before WHRP intervention							
Body weight	*r*	-0.130	-0.068	0.016	0.662***	0.046	0.674***
	P	0.369	0.637	0.912	<0.001	0.749	<0.001
Muscle mass	*r*	0.324*	0.407**	0.410**	0.659***	0.163	0.289*
	P	0.023	0.004	0.004	<0.001	0.264	0.044
Bone mass	*r*	0.203	0.282	0.291*	0.675**	0.117	0.442**
	P	0.162	0.051	0.045	<0.001	0.422	0.001
Fat mass	*r*	-0.573***	-0.630***	-0.530***	0.164	-0.119	0.652***
	P	<0.001	<0.001	<0.001	0.258	0.414	<0.001
Body composition after 4 weeks WHRP intervention							
Body weight	*r*	-0.103	-0.054	0.031	0.655***	0.028	0.636***
	P	0.478	0.709	0.833	<0.001	0.848	<0.001
Muscle mass	*r*	0.393**	0.510***	0.465**	0.705***	0.115	0.335*
	P	0.008	<0.001	0.001	<0.001	0.454	0.024
Bone mass	*r*	0.293	0.405**	0.373*	0.699***	0.061	0.463**
	P	0.051	0.006	0.013	<0.001	0.690	0.001
Fat mass	*r*	-0.505***	-0.590***	-0.464**	-0.022	-0.050	0.489***
	P	<0.001	<0.001	0.001	0.885	0.742	<0.001

* Correlation is significant at P <0.05, **P<0.01, ***P<0.001.
Before and after, Nutrients and body components before (Day 0) and after WHRP.

demonstrated (Table 4). Body weight correlated with post-intervention protein and whey protein with r values of 0.655 and 0.636, respectively, but not with pre-intervention values. Muscle mass associated strongly with post- vs. pre-intervention energy, protein, and whey protein, with r values of 0.510 vs. 0.324, 0.705 vs. 0.410, and 0.335 vs. 0.163, respectively, and the strongest effect was observed with post-intervention protein (Figure 1). Bone mass was also synergistic with muscle mass in the correlation of nutrients. It correlated more strongly with energy, protein, and whey protein after the WHRP intervention than before, with r of 0.405 vs. 0.203, 0.699 vs. 0.291, and 0.463 vs. 0.117, respectively. The highest correlation was also observed for protein after the intervention (Figure 1). Fat mass was positively correlated with whey protein (p=0.489) and negatively correlated with energy before (r=-0.573) and after (r=-0.590) the intervention, and protein before the intervention (r=-0.530).

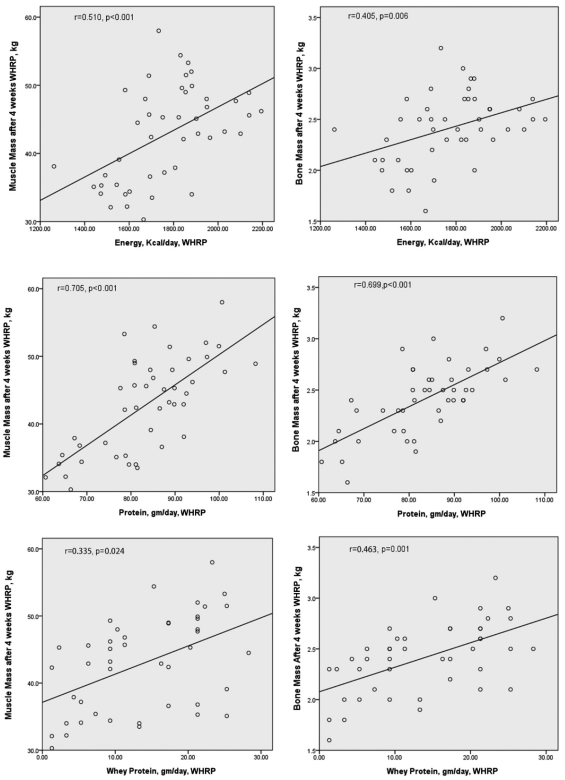

Figure 1. The effect of nutrients on the muscle and bone mass. For muscle mass, the effect of protein intake > energy intake > whey protein intake; for bone mass, the effect of protein intake > whey protein intake > energy intake. All nutrient intakes correlated with muscle and bone growth with statistical significance. WHRP: Whey protein-enriched high-protein feeding and rehabilitation program.

4. Discussion

Our WHRP study demonstrated that 1) the energy, protein, and whey protein supplements were increased after the intervention, mostly due to the whey protein added; 2) the rehabilitation was persistent; 3) the muscle mass and bone mass increased synergically, but the fat mass decreased rendering the BW stable; 4) the interventional energy, protein and whey protein were supplied according to the body weight at the beginning of the WHRP intervention, but they correlated better with the post-intervention muscle and bone mass. The high-protein, whey protein-enriched tube feeding combined with the non-interrupted standard rehabilitation program increased the muscle and bone mass in the post-stroke and post-brain injury patients.

When developing tube feeds for rehabilitation patients, the nutritional goals should account for the fact that the majority of stroke patients are older adults (8). Thus, excessive supplementation or imbalanced dietary intake combined with mobility problems due to limitations in physical performance may lead to an imbalance between energy expenditure and caloric intake, which may accelerate the development of obesity (16). This, in turn, can lead to excessive fat storage, which further impairs the patient's cardiorespiratory fitness and muscle function (17), while increasing the risk of metabolism-related chronic diseases (18). In a study of patients with hemiparetic chronic stroke, Serra et al. (19) found that resting metabolic rate measured with indirect calorimetry was lower, suggesting that muscle atrophy may be related to the decrease in resting metabolic rate. Houdijk et al. (20) demonstrated that patients expended 125% more energy than controls in various upright balance tasks. Therefore, it is important to determine the actual caloric and protein requirements of stroke rehabilitation patients.

The European Union Geriatric Medicine Society, in collaboration with other scientific organizations, established an international study group (the PRevention in Older people- Assessment in GEneralists' practices, PROT-AGE, study) to assess the impact of aging on dietary protein requirements (21). The PROT-AGE study group recommended an average protein intake of 1.0-1.2 g/kg BW/day to help maintain and restore lean body mass and function. In addition, a higher protein intake (1.2 g/kg BW/day) was recommended for older adults who exercised or were otherwise active, and more dietary protein (i.e., 1.2-1.5 g/kg BW/day) was required for older patients with acute or chronic diseases. Gaillard et al. (2008) suggested that the caloric intake of elderly hospitalized patients should be 1.31 times that of BMR, and protein intake should be 1.06±0.28 g/kg BW/day to maintain a positive nitrogen balance. Furthermore, older adults with acute or chronic diseases should increase their protein intake to 1.2-1.5 g/kg BW (22), while their caloric intake should be 30-40 kcal/kg BW, again adjusting for individual differences (23). In recent years, several nutritional studies in older adults have been published, showing that increased protein or whey protein intake did not worsen glomerular filtration rate (24, 25). However, given the risk of worsening renal function with age, comprehensive screening of older adults is recommended. In this study, participants received a protein intake of 1.4 g/kg BW, which was the standard dose for older adults with acute and chronic diseases recommended by PROT-AGE (21) and Gaillard et al. (26). Furthermore, participants' creatinine and estimated GFR were 122.5±36.65 mL/min/1.73 m2, which was within the normal range. Body weight monitoring is an important nutritional indicator in patients undergoing rehabilitation during hospitalization. The weekly measurements of body weight showed a steady trend. For the stroke and TBI patients with limited physical activity, moderate caloric intake (29.8±6. 1 kcal/kg BW) and high-protein intake (1.41±0.18 g/kg BW) were sufficient to maintain a stable body weight during the study period. Moreover, high-protein and whey protein intake had moderate positive correlations with body weight (r=0.655 and r=0.636; $P<0.001$). This may be attributed to the study design, in which most of the energy supplied was protein based.

In a study of elderly hospitalized patients with acute stroke (mean age: 74 years), de Aguilar-Nascimento et al. (2011) compared the effect of a whey protein supplement (35 kcal/kg/day, protein 1.2 g/kg/day) with that of an isocaloric formula containing casein. They found that the nasogastric enteral formula with whey protein was more effective in reducing the systemic inflammatory response, improving antioxidant defence, and attenuating anabolic resistance in elderly patients with acute stroke. Thus, the anti-inflammatory effect of whey protein was superior to that of casein. In our study, patients were given a daily tube feed that contained an average of 15.7±10.9 g of added whey protein. The average amount of fortified BCAA calculated on the basis of the amount of added whey protein was 3109 (1943-4981) mg, which was consistent with the dose-response results of the above-mentioned study. After the supplementation intervention, participants' muscle mass increased by 0.7 kg during the 4-week study period, from 42.0±7.4 kg to 42.7±7.05 kg (P=0.029, Table 2), whereas bone mass increased from 2.37±0.37 kg to 2.41±0.34 kg (P=0.042, Table 2). Moreover, muscle mass was strongly correlated with bone mass after the 4-week intervention, as a significant increase in muscle mass was associated with a significant increase in bone mass (r=0.959, $P<0.001$, Table 3). Similarly, after the 4-week WHRP intervention, protein intake was strongly correlated with muscle mass (r=0.705, $P<0.001$, Table 4, Figure 1)) and bone mass (r=0.699, $P<0.001$, Table 4, Figure 1); whey protein intake was moderately correlated with muscle mass (r=0.335, P=0.024) and bone mass (r=0.463, P=0.001) (Table 4 and Figure 1). This was due to the increase in protein content from oral intake of a textured diet, which decreased the added amount of WHRP but did not affect the total protein content. The results showed that the amount of protein was more important than the amount of whey protein for the growth of muscle and bone mass.

A limitation of this study was in the design of the control group. Instead of designating the WHRP (-) as the control group, internal controls of before and after WHRP intervention were used due to recruitment difficulty. The variations in whey protein intake were not negligible in the commercial feeding diet, and oral diet was vastly different among patients; occasionally even the designed whey protein supplements could be skipped for oral feeding training. Another limitation was that only patients who could maintain a stable standing posture on the body composition scale for anthropometric measurements could be recruited, which was troublesome as many subjects were excluded. Yet another limitation was presented by the longer nutrition interventional duration before an effect could be observed, frequently requiring an interventional period of 3 months. But we had only an average of 26.8 days due to the regulation on hospital stay posed by the National Health Insurance. Finally, some of the bioelectrical impedance data were generated through statistical calculations rather than from direct measurements.

5. Conclusion

The WHRP nutrition intervention, consisting of a high-protein, whey protein-enriched formula and an intensive exercise rehabilitation, achieved the end-points of a stable body weight, increased muscle and bone mass, and decreased fat mass in stroke and TBI rehabilitation patients. Future studies should include rigorous randomized controlled trials to understand the dose-effect of WHRP on improving muscle mass, bone mass, and physical performance in rehabilitation patients.

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Conflict of Interest

The authors declare no conflicts of interest.

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