CLINICAL ARTICLE

Effect of Resistance Training Combined with Beta-Hydroxy-Beta-Methylbutyric Acid Supplements in Elderly Patients with Sarcopenia after Hip Replacement

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Abstract

Objectives: To evaluate the efficacy of resistance training (RT) combined with beta-hydroxy-beta-methylbutyric acid (HMB) in the treatment of elderly patients with sarcopenia after hip replacement.

Methods: From January 1, 2018 to December 31, 2018, 200 elderly patients (68 men, mean age 76.3 years and 137 women, mean age 79.1 years) who experienced femoral neck fracture with sarcopenia after hip arthroplasty were assigned to four groups: RT + HMB group, RT group, HMB group, and negative control group. Baseline data, body composition, grip strength, Barthel index (BI), Harris hip score (HHS), and visual analog scale score (VAS) were compared among the four groups before and 3 months after surgery.

Results: A total of 177 participants completed the trial, including 43 in the HMB + RT group, 44 in the HMB group, 45 in the RT group, and 45 in the negative control group. At the 3-month follow-up, the body composition and grip strength of the HMB + RT group and RT group were significantly improved compared with those before operation. The HMB group had no significant change, while the measures in the negative control group significantly decreased. Postoperative BI and HSS did not reach pre-injury levels in any of the four groups, but postoperative VAS score was significantly improved. However, there was no significant difference in BI, HSS, or VAS among the four groups.

Conclusion: RT, with or without HMB supplementation, can effectively improve body composition and grip strength in elderly patients with sarcopenia after hip replacement at short-term follow-up. Simultaneously, use of exclusive HMB supplementation alone may also help to prevent decreases in muscle mass and grip strength in these patients.

Key words: Beta-hydroxy-beta-methylbutyric acid; Femoral neck fracture; Hip replacement; Resistance training; Sarcopenia

Introduction

Sarcopenia, from Greek*sarx* ("flesh") and *penia* ("lacking"), is a geriatric syndrome characterized by progressive and widespread skeletal muscle loss[1]. The incidence of sarcopenia varies widely among the elderly population, ranging from 1% to 29% in the community population over 50 years of age and from 14% to 33% in those requiring long-term care[2]. Abundant evidence shows that sarcopenia is strongly associated with patients suffering from hip fractures, cognitive decline, and cardiovascular diseases[3,4]. These conditions frequently lead

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to decreased physical activity, resulting in decreased quality of life, increased medical costs, and higher mortality[5].

Femoral neck fracture is the most common fracture leading to disability in the elderly, accounting for 48.22% of hip fractures, and 3.13% of total adult fracture patients[6]. It is estimated that by 2050, the number of femoral neck fracture patients around the world will reach 6.3 million to 8.2 million[7]. Hip replacement is one of the most frequently performed and successful reconstructive procedures for elderly patients with femoral neck fracture[8]. Still, the mortality rate of elderly patients with femoral neck fracture within 1 year of surgery is up to 35.9%[9], and 25%–30% of patients are never able to recover the pre-injury physical state[10]. A growing number of studies have shown that sarcopenia is closely linked to femoral neck fractures in the elderly as both an independent risk factor and a common complication, with an incidence of about 37% in patients with femoral neck fracture[11,12]. Kim *et al.* showed that in patients with femoral neck fracture and sarcopenia, the 1-year and 5-year mortality rates were 22.2% and 82.7%, respectively[13]. Similarly, Malafarina *et al.* found that the mortality rate of patients suffering from both femoral neck fracture and sarcopenia was almost twice as high as that of patients without sarcopenia[14]. Therefore, femoral neck fracture with sarcopenia in elderly patients should be considered an urgent clinical problem to be solved.

Resistance training (RT), also known as strength training, refers to the process of the body overcoming resistance to achieve muscle growth and gain strength[15]. On a molecular level, this can also inhibit the expression of myostatin mRNA and stimulate myatin synthesis[16]. RT has been increasingly adopted for home-dwelling hip fracture patients, in addition to in supervised strength-training programs in a rehabilitation setting, with the goal of recovering physical function, muscle mass, strength, and balance[15]. Several clinical studies have shown that RT is an effective, easy-to-use, functional training program in maintaining functional strength and increasing muscle mass in older adults with sarcopenia[17]. Nevertheless, little is known about the specific roles of RT programs in older individuals with sarcopenia, especially those with a femoral neck fracture. Moreover, almost no studies have examined the effect of RT on femoral neck fracture patients with sarcopenia after hip replacement.

In addition to strength training, supplements are sometimes prescribed to patients with the goal of aiding in recovery, a common example of this is beta-hydroxy-beta-methylbutyric acid (HMB), a metabolite of the branched amino acid leucine[18]. HMB is thought to promote skeletal muscle protein synthesis and inhibit skeletal muscle protein decomposition, and may facilitate intracellular cholesterol synthesis to support sarcolemma integrity[18,19]. As an energy enhancing supplement, HMB has been widely applied to enhance increases in the mass and strength of skeletal muscles in both youths and the elderly, especially after endurance exercise or RT[18]. For example, Ellis *et al.* concluded that oral administration of HMB was able to increase muscle mass and improve physical function in healthy elderly people[20]. Besides, a number of studies have investigated the effect of HMB in chronic diseases correlation with muscle wasting, such as cancer, acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, and fractures that requires long-term bed rest[21]. Gratifyingly, growing evidence have certified that HMB supplementation is able to increase lean body mass and preserve muscle strength and function in elderly people[22]. Further, Malafarina *et al.* showed that a diet rich in HMB could improve muscle mass and function in elderly patients with hip fracture and prevent the occurrence of sarcopenia[23]. And excitingly, Phillips *et al.* found that HMB combined with RT could increase muscle mass in patients with sarcopenia[24]. However, there have been no reports of the effect on RT combined with HMB treatment in elderly patients with femoral neck fracture and sarcopenia after hip replacement.

The purpose of this study was as follows: (i) to investigate the therapeutic effect of body composition and muscle strength of RT combined with HMB in elderly patients with femoral neck fracture and sarcopenia undergoing hip replacement surgery; (ii) to identify the influence on postoperative recovery of hip function and quality of life on above participants after a short-term follow-up; and (iii) to compare the outcomes among the different interventions.

Materials and Methods

Study Design

The present investigation is a pragmatic, prospective observational study, which was in accordance with the Helsinki Declaration. All participants were fully aware of the nature, purpose, procedures, and risks of the study and signed informed consent.

Participants

A total of 200 participants was conducted in Tianjin Hospital (Tianjin, China) from January 1, 2018, to December 31, 2018. All participants received the same level of educational lectures after admission and were given a guide book including diet and exercise strategies. The flow chart of study participants is shown in Figure 1. The inclusion and exclusion criteria were described as follows:

Inclusion criteria: (i) patients with a first unilateral femoral neck fracture; (ii) ≥65 years of age; (iii) patients meeting the diagnostic criteria for sarcopenia (defined by Asian working group of sarcopenia [AXGS]): hand-grip strength (male at <26 kg, female at <18 kg) and high-adjusted skeletal muscle mass by dual-energy X-ray absorptiometry (male at < 7kg/m^2 and female at <5.4 kg/m^2)[25]; (iv) primary unilateral hip replacement employed by traditional posterior approach; and (v) consent to be included in the study.

Exclusion criteria: (i) accompanied by mental diseases, cognitive impairment, movement disorders, or postoperative

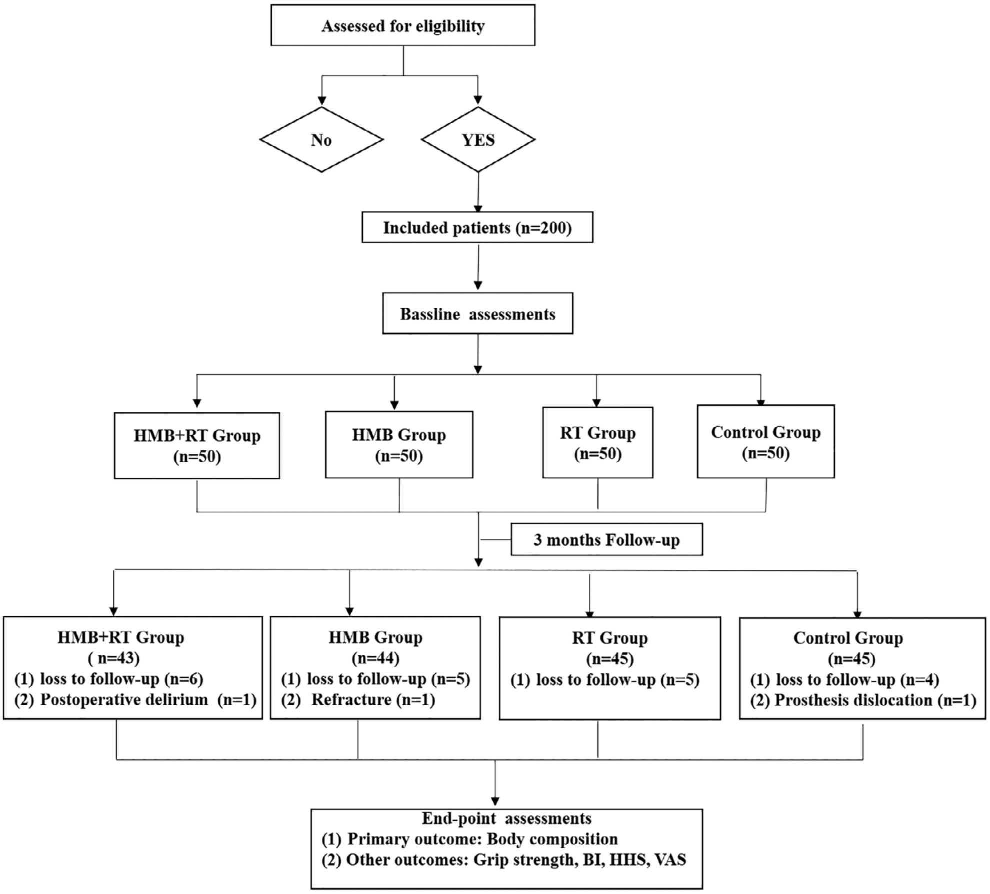

Figure 1 Flowchart of patients in four groups. BI, barthel; HMB, hydroxymethylbutyrate; HSS, Harris Hip Score; RT, resistance training; VAS, visual analog scale

complications; (ii) recent experience with a regular guided exercise program (more than three times per week); and (iii) oral protein-rich nutritional medications, bisphosphonates or vitamins, or any medication known to affect protein metabolism.

Interventions

All participants were given routine postoperative rehabilitation training[26], and were randomly assigned to four groups: (i) RT + HMB group;(ii) RT group; (iii) HMB group; and (iv) negative control group.

HMB Supplementation

Currently, there is no specified therapeutic dose of HMB supplement for patients with hip fracture and sarcopenia. However, numerous studies suggest that a dose of 3 g per day of HMB in older adults could treat muscle loss with no side effects[27,28]. Therefore, we supplemented HMB (3 g/day) for participants in two of the groups (RT + HMB group and HMB group) daily for 3 months after surgery. The patients' daily medication was strictly recorded as a basis for assessing compliance.

Resistance Training

Before RT, training logs were made for every participant, including training frequency, repetition times, training speed, and training intensity (non-maximum repetition amount including non-repetition maximum [NRM] and repetition maximum [RM]). In order to illustrate the concepts of RT intensity, how to evaluate the maximum intensity metric, and how to adjust the training intensity, we provide the following example: if a weightlifter can lift 100 kg at most with the correct method, then 1RM is 100kg for weight training, and a training intensity of 70%–80% 1RM would mean lifting 70–80 kg. Participants can freely choose the training intensity and the number of repetitions to achieve the desired training effect. The postoperative RT for patients were all under the guidance of professional rehabilitation instructors and training logs were recorded weekly by telephone interview.

The main muscle groups (hip flexor, hip adductor, hip abductor, and hip posterior extensor) were trained in stages according to the Progressive Resistance Training Model for Healthy Adults developed by the American College of Sports Medicine[29]. In the first stage (1 month after surgery, every 3 days), 60%–70% 1RM exercise intensity was used for eight to 12 repetitions in each set, with two to three sets of training each time and 3–5 min of rest between sets. In the second stage (2–3 months after surgery, every 2 days), 80%–90% 1RM exercise intensity was used for 15 repetitions in each set, two to three sets for each training, with 3–5 min of rest between sets[17,30,31].

Outcomes Measure

The following assessments will be taken at the baseline and endpoint of 3 months.

Primary Outcomes

Body Composition

Body composition was measured by a Dual Energy X-Ray Absorptiometry (DXA, HOLOGIC Discovery, USA) according to DXA standards[32–34], including: whole body fat-free mass (WBFFM); upper-extremity mass(UEM); healthy lower-extremity skeletal muscle mass (HLESMM); injured lower-extremity skeletal muscle mass (ILESMM); body skeletal muscle mass (BSMM); skeletal muscle mass index (SMI; the ratio of muscle mass of the limbs to the height squared); and fat mass (FM).

GS

The dominant side GS was measured using an electronic dynamometer (EH101, CAMRY, China). Participants first sat in a standard armchair with their upper arms in an adductive neutral position, elbows flexed 90°, and their forearms and wrists in a naturally relaxed position. The participants were then asked to hold a dynamometer in their hand and squeeze the device with maximum force, reaching the maximum smoothly without any twisting or twitching movement of the forearm or hand. The GS was measured three times for every participant with 1 min interval between each time, taking the maximum value of three trials as the final result[35].

Secondary Outcomes

BI

The daily quality of life of patients was assessed based on the improved BI, which has a high sensitivity and reliability, and includes eating, bathing, dressing, stool control, urination control, grooming, toilet use, bed chair transfer, physical activity (walking), and walking up and down stairs[36]. The total BI ranges from 0 to 100: a score below 20 indicates the patient is in complete disability and complete dependence on care; 20 to 40 indicates the patient is severely disabled and needs significant daily aid; 40 to 60 suggests the patient has moderate disability and requires some daily aid; above 60 indicates the patient has disability but can complete basic self-care; 100 means the patient has no reliance on aid for daily activities.

HHS

HHS is a measure employed to estimate recovery of hip function of patients receiving hip surgery. It consists of four dimensions (pain, function, deformity, and range of motion), with individual scores for pain (0 to 44), function (0 to 47), deformity (0 to 4), and range of motion (0 to 5), totaling to between 0 and 100[37]. The scoring system can be interpreted as: <70 is considered poor hip condition; 70–80 is considered as fair condition; 80–90 is considered as good condition; and 90–100 is considered as excellent condition.

VAS Score

Postoperative pain is a common complication of hip arthroplasty, so it is necessary to evaluate pain in the hip area to observe the efficacy of different interventions. VAS is identified as a simple, relatively objective, and sensitive method for pain assessment [37]. The basic method for measuring VAS is to use a vernier about 10 cm long, with 10 marks on one side and a "0" and a "10" on each end. A score of 0 indicates no pain and a score of 10 indicates the most intolerable pain. The participants were requested to mark the corresponding position on a scale that represents their level of pain. The scale of pain severity based on VAS score was 1–3 as mild pain, 4–6 as moderate pain, and 7–10 as severe pain.

The pre-fracture BI and HSS of all participants were evaluated retrospectively by patients or their family members, while VAS score was assessed after the injury. Postoperative BI, HSS, and VAS score were measured by a face-to-face interview at 3 months after surgery. Treatment compliance, any medications or nutritional supplements, and adverse events were recorded by telephone interview weekly and details were confirmed in the 3 months follow-up interview. Physical examinations and body composition tests for all participants were performed by the same professional treatment team preoperatively and 3 months postoperatively.

Statistical Analysis

Analyses were performed using SPSS version 25.0 statistical software (SPSS Inc., Chicago, Illinois, USA). The categorical variables of preoperative details and postoperative outcomes were assessed using Pearson's chi-squared test or Fisher's exact test. The continuous variable data were assessed for a fit to a normal distribution and for homogeneity of variance using the Shapiro–Wilk test and Bartlett test, which was represented as mean ± SD. Then, the paired-sample t-test was used for intra-group comparisons, and the analysis of variance (ANOVA) was used for inter-group comparisons. The test level α was 0.05 on both sides, and P value less than 0.05 was considered as statistically significant.

TABLE 1 Characteristics of participants

Variables	HMB + RT group (n = 43)	HMB (n = 44)	RT group (n = 45)	Control (n = 45)	F value/χ^2 value	P value
Age (years)	78.3 ± 5.9	77.1 ± 6.5	78.5 ± 6.5	76.8 ± 7.1	0.756	0.520
Female (%)	31(72.1%)	30(68.2%)	35(77.8%)	36(80.0%)	1.908	0.566
BMI (kg/m^2)	21.9 ± 5.8	23.1 ± 4.6	22.3 ± 4.1	22.4 ± 4.7	0.466	0.706
Fracture type					1.007	0.800
Garden I/II	7/1	5/0	6/0	6/1		
Garden III/IV	31/4	35/4	32/7	34/4		
ASA class					1.100	0.777
ASA I/II	23	20	25	22		
ASA III/IV	20	24	20	23		
Total protein (g/L)	64.4 ± 5.5	62.1 ± 6.0	63.4 ± 6.5	61.8 ± 6.4	1.696	0.170
Albumin (g/L)	37.1 ± 3.3	38.5 ± 5.2	39.1 ± 4.7	37.8 ± 3.6	1.803	0.149
Operation time(h)	1.6 ± 0.3	1.5 ± 0.4	1.6 ± 0.3	1.6 ± 0.3	1.026	0.383
Intraoperative blood loss (ml)	196.8 ± 43.6	202.1 ± 42.9	204.0 ± 45.4	201.0 ± 43.6	0.211	0.889
Time to surgery(d)	2.3 ± 0.9	2.1 ± 0.8	2.2 ± 0.8	2.4 ± 0.9	1.023	0.384
Surgical type					0.994	0.803
THA	11	11	15	12		
HA	32	33	30	33		
Length of hospital stay (d)	6.4 ± 2.1	6.1 ± 1.8	5.8 ± 1.9	6.2 ± 2.2	0.686	0.562

Note: Results are expressed as mean ± SD or number of individuals (percentages).; Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; HA, hemiarthroplasty; HMB, hydroxymethylbutyrate; RT, resistance training; THA, total hip arthroplasty.

Results

Database of Patients

A total of 177 participants completed the follow-up at 3 months after surgery, of which 43 patients were in the HMB + RT group, 44 in the HMB group, 45 in the RT group, and 45 in the negative control group. There were no significant differences in age, gender, BMI, fracture types, American Society of Anesthesiologists (ASA) class, total protein, albumin, operation time, intraoperative blood loss, time to surgery, operation methods, and length of hospital stay among the four groups ($P > 0.05$, Table 1).

Primary Outcomes

Body Composition

As shown in Table 2, there were no marked differences in preoperative WBFFM, UEM, HLESMM, ILESMM, BSMM, and SMI among the four groups ($P > 0.05$). However, compared with pre-operation state, the WBFFM, UEM, HLESMM, ILESMM, BSMM, and SMI of the HMB + RT group and the RT group were significantly improved after 3 months ($P < 0.05$), while there were no significant differences in those of the HMB group ($P > 0.05$). The WBFFM, UEM, HLESMM, ILESMM, BSMM, and SMI of the control group were significantly decreased ($P < 0.05$). Comparison among the four groups showed that there were no differences in the change of WBFFM, UEM, HLESMM, ILESMM, BSMM, and SMI between the HMB + RT group and the RT group postoperatively at 3 months ($P > 0.05$), which were higher than those of the HMB group ($P < 0.05$). In addition, the change of WBFFM, UEM, HLESMM, ILESMM, BSMM, and SMI in the HMB + RT group, the HMB group, and the RT group were all better than those in the control group ($P < 0.05$).

There was no statistical difference in FM among the four groups before surgery ($P > 0.05$). However, 3 months after operation, the FM in the HMB + RT group and the RT group was significantly lower than before operation ($P < 0.05$), while there was no significant change in the FM for the HMB or control groups ($P > 0.05$). The change of FM in the HMB + RT group and the RT group was significantly higher than that in the other two groups ($P < 0.05$). Compared with the RT group, the change of FM in the RT+ HMB group seemed no different ($P > 0.05$).

GS

Similar to the above findings, there was no marked discrepancy in preoperative GS among the four groups ($P > 0.05$, Table 2). The postoperative GS of the HMB + RT group and the RT group were significantly improved at 3 months follow-up ($P < 0.05$), whereas there was no change in the GS of the HMB group ($P > 0.05$). The GS of control group was significantly decreased when compared with preoperative condition

TABLE 2 Comparison of primary outcomes in different groups

Variables	HMB + RT group (*n* = 43)	HMB group (*n* = 44)	RT group (*n* = 45)	Control (*n* = 45)	*F* value	*P* value
WBFFM (kg)						
Baseline	36.38 ± 5.75	37.88 ± 6.56	37.96 ± 8.43	35.14 ± 6.22	1.738	0.161
3 months	38.09 ± 6.32[a]	37.26 ± 6.42	39.43 ± 7.92[a]	33.75 ± 5.83[a]	5.931	0.001
ΔWBFFM	1.71 ± 0.82[b,c]	−0.62 ± 0.91[b]	1.47 ± 0.78[b,c]	−1.39 ± 0.92	141.1	<0.001
UEM (kg)						
Baseline	3.98 ± 0.82	4.01 ± 1.12	4.05 ± 1.01	3.90 ± 0.84	0.198	0.897
3 months	4.26 ± 0.90[a]	3.91 ± 0.98	4.32 ± 1.20[a]	3.27 ± 0.64[a]	11.46	<0.001
ΔUEM	0.28 ± 0.35[b,c]	−0.19 ± 0.22[b]	0.27 ± 0.27[b,c]	−0.63 ± 0.39	84.90	<0.001
HLESMM(kg)						
Baseline	4.87 ± 0.85	5.05 ± 0.79	4.94 ± 1.27	4.91 ± 1.43	0.207	0.892
3 months	5.46 ± 1.03[a]	4.92 ± 0.81	5.31 ± 1.25[a]	4.40 ± 1.02[a]	9.189	<0.001
ΔHLESMM	0.39 ± 0.60[b,c]	−0.13 ± 0.45[b]	0.37 ± 0.52[b,c]	−0.51 ± 0.79	22.84	<0.001
ILESMM (kg)						
Baseline	4.80 ± 0.82	4.95 ± 0.79	4.98 ± 1.26	4.90 ± 1.19	0.251	0.861
3 months	5.35 ± 1.03[a]	4.86 ± 0.67	5.41 ± 1.24[a]	4.33 ± 0.94	11.46	0.001
ΔILESMM	0.55 ± 0.40[b,c]	−0.09 ± 0.44[b]	0.43 ± 0.58[b,c]	−0.57 ± 0.37	56.74	<0.001
BSMM (kg)						
Baseline	19.78 ± 3.34	20.21 ± 4.06	20.45 ± 4.62	18.78 ± 3.88	1.520	0.211
3 months	20.53 ± 3.65[a]	20.09 ± 3.87	21.13 ± 5.10[a]	17.92 ± 3.28[a]	5.378	<0.001
ΔBSMM	0.75 ± 0.82[b,c]	−0.12 ± 0.74[b]	0.68 ± 0.89[b,c]	−0.86 ± 1.07	32.37	<0.001
SMI (kg/m^2)						
Baseline	5.13 ± 0.66	5.23 ± 0.85	5.27 ± 0.96	5.13 ± 0.76	0.338	0.798
3 months	5.49 ± 0.86[a]	5.14 ± 0.95	5.59 ± 0.94[a]	4.70 ± 0.58[a]	10.14	<0.001
ΔSMI	0.36 ± 0.45[b,c]	−0.09 ± 0.42[b]	0.32 ± 0.53[b,c]	−0.43 ± 0.51	26.91	<0.001
FM (kg/m^2)						
Baseline	18.52 ± 5.29	19.66 ± 4.93	19.97 ± 4.97	19.76 ± 5.37	0.697	0.555
3 months	17.76 ± 4.79[a]	19.27 ± 5.08	19.14 ± 4.39[a]	19.33 ± 5.26	1.014	0.388
ΔFM	−0.76 ± 0.60[b,c]	−0.39 ± 0.71	−0.83 ± 0.66[b,c]	−0.43 ± 0.74	4.842	0.003
GS (kg)						
Baseline	15.18 ± 5.24	14.76 ± 5.13	13.59 ± 5.98	14.25 ± 5.26	0.707	0.549
3 months	17.23 ± 5.78[a]	15.64 ± 5.39[a]	15.43 ± 6.46[a]	13.14 ± 4.52	4.022	0.009
ΔHS	2.05 ± 1.98[b,c]	0.88 ± 1.65[b,c]	1.84 ± 1.79[b,c]	−1.11 ± 1.88	27.77	<0.001

Note: Results are expressed as mean ± SD.; Abbreviations: BSMM, body skeletal muscle mass; FM, fat mass; GS, grip strength; HLESMM, healthy lower-extremity skeletal muscle mass; HMB, hydroxymethylbutyrate; ILESMM, injured lower-extremity skeletal muscle mass; RT, resistance training; SMI, skeletal muscle index; UEM, upper-extremity mass; ΔWBFFM, whole body fat-free mass.; [a] Difference *vs*. baseline ($P < 0.05$).; [b] Difference *vs*. control group ($P < 0.05$).; [c] Difference *vs*. HMB group ($P < 0.05$).

TABLE 3 Comparison of secondary outcomes in different groups

Variables	HMB + RT group (*n* = 43)	HMB group (*n* = 44)	RT group (*n* = 45)	Control (*n* = 45)	*F* value	*P* value
BI						
Baseline	81.67 ± 11.16	83.27 ± 8.30	80.37 ± 10.1	80.22 ± 8.71	0.962	0.412
3 months	71.21 ± 5.41[a]	69.27 ± 6.19[a]	70.40 ± 5.26[a]	68.33 ± 7.82[a]	1.796	0.150
HSS						
Baseline	85.62 ± 13.22	84.37 ± 11.68	81.37 ± 18.31	84.12 ± 13.63	0.681	0.565
3 months	69.21 ± 7.93[a]	65.27 ± 8.75[a]	68.40 ± 7.46[a]	66.40 ± 9.98[a]	1.938	0.125
VAS						
Baseline	6.25 ± 2.61	5.49 ± 3.17	5.88 ± 2.50	6.10 ± 2.63	0.637	0.592
3 months	2.24 ± 1.56[a]	1.90 ± 1.52[a]	2.11 ± 1.46[a]	2.51 ± 1.77[a]	1.159	0.326

Note: Results are expressed as mean ± SD; Abbreviations: BI, barthel; HMB, hydroxymethylbutyrate; HSS, Harris Hip Score; RT, resistance training; VAS, visual analog scale.; [a] Difference versus baseline ($P < 0.05$).

($P < 0.05$). In a subsequent intergroup comparison of GS changing at 3 months after surgery, our results indicated that there was no significant distinction between the HMB + RT group and the RT group ($P > 0.05$), although both showed better improvements than that of the HMB group ($P < 0.05$). Furthermore, compared to the control group, the change of GS in the HMB + RT group, the HMB group, and the RT group were statistically different ($P < 0.05$).

Secondary Outcomes

BI

As illustrated in Table 3, there were no significant differences in BI among the four groups before injury ($P > 0.05$). However, the postoperative BI of all four groups failed to reach the pre-injury level 3 months later ($P < 0.05$). Simultaneously, there were no differences in BI among the four groups 3 months after surgery ($P > 0.05$).

HSS

The preoperative HSS did not differ significantly among the four groups ($P > 0.05$), nor did the postoperative HSS after 3 months ($P > 0.05$). Furthermore, the postoperative HSS did not reach the preoperative levels ($P < 0.05$; Table 3). Encouragingly, the HMB + RT group had a higher rate of excellent and good HSS than the other three groups.

VAS Score

There were no notable differences in the preoperative and postoperative VAS score among the four groups ($P > 0.05$, Table 3). However, our data showed that postoperative VAS score was effectively improved in all groups at 3 months follow-up ($P < 0.05$).

Discussion

To the best of our knowledge, this is the first study to investigate the effects of RT combined with HMB supplement on muscle strength, muscle mass, quality of life, hip function, and pain in elderly patients with both femoral neck fracture and sarcopenia after hip replacement. In our study, we found that both RT + HMB and RT could significantly improve body composition and GS of patients after 3 months, while HMB treatment by itself was able to alleviate the decline of muscle strength, muscle mass, and GS when compared with negative controls. However, none of the treatments were associated with improvements in the BI, HHS, or VAS scores of patients after 3 months later.

Effect of Interventions on Body Composition and Grip Strength

Numerous studies have shown that healthy muscle mass is conducive to maintaining glucose homeostasis, fatty acid metabolism, aerobic capacity, and the normal functions of bones and joints[38]. Muscle mass decreases associated with aging can lead to sarcopenia, resulting in decreased physical function, decreased quality of life, and higher mortality[13,39,40]. In addition, a prior study showed that for elderly patients with femoral neck fracture, increasing muscle mass and muscle strength helped to restore patients' balance and daily living activities, and reduce postoperative dislocation rate, risk of fall, risk of re-fracture, and mortality[41]. It has been suggested that HMB, a metabolite of leucine, could promote increases in skeletal muscles by stimulating protein synthesis through up-regulation of anabolic signaling pathways and down-regulation of catabolic signaling pathways, consequently reducing protein hydrolysis[41]. This has led to HMB being increasingly used in clinical practice[42]. However, several studies have concluded that HMB supplementation could not markedly improve body composition or performance in young adults and older adults who loves sports[43,44]. Still, increasing evidence suggests that HMB treatment can improve muscle mass in patients with chronic diseases such as chronic obstructive pulmonary disease, cancer, and malnutrition[45]. Wu *et al.* also found that HMB was beneficial to increase muscle mass in elderly people who were healthy or with various chronic diseases, and could alleviate muscle atrophies caused by being bedridden and other factors[28]. Additionally, a study by Malafarina *et al.* indicated that oral HMB could build muscle mass, improve physical function and prevent the occurrence of sarcopenia obesity in elderly patients with associated hip fracture [23]. In agreement with the above studies, our study also showed that HMB could effectively prevent the postoperative loss of muscle mass in patients with both femoral neck fracture and sarcopenia at 3 months follow-up.

RT programs have been clearly demonstrated to increase muscle mass, walking speed, and improve living quality in both young and older individuals[38,46]. Recent research has shown that RT was a safe and effective method of increasing muscle strength and preventing the development of severe sarcopenia, and has been widely accepted as a leading clinical intervention for sarcopenia[17,47]. In addition, Matheis *et al.* found that RT was able to improve thigh circumference, hip range of motion, walking speed, and muscle strength in patients with hip fractures after hip arthroplasty[48]. Lee *et al.* conducted a meta-analysis of the effects of RT on patients with hip fracture after surgery, concluding that RT contributed to improvements in muscle strength, daily activity ability, and balance ability[49]. Our own findings also clearly show that RT exerted a strong effect on promoting muscle strength in patients with sarcopenia associated with femoral neck fracture after joint replacement.

Growing evidence suggests that HMB could effectively promote the muscle strength of healthy people undergoing RT[50,51]. For example, Cermak *et al.* showed that long-term RT combined with HMB was more effective than long-term RT alone in enhancing the total body muscle and maximum leg strength of participants[52]. However, Din *et al.* found that RT combined with HMB-FA supplements in healthy older men did not increase muscle strength more than RT alone[53]. To further determine whether HMB supplementation could improve body composition, Jakubowski *et al.* performed a meta-analysis of 11 randomized controlled trials, which indicated that HMB supplementation did not significantly improve the body composition of healthy subjects aged 18–45 years who underwent RT[54]. Our study was the first to evaluate the effect of combined RT and HMB supplementation on changes in body composition in patients with sarcopenia following joint replacement. We found that RT combined with HMB treatment was effective in increasing muscle mass and improving functional strength in elderly people with sarcopenia after hip replacement, which suggests the benefits of HMB may be greater in elderly people compared to young people. However, we also found a limited effect of RT combined with HMB treatment on muscle mass and muscle power, when compared with RT alone. Data from animals and humans have shown that during exercise, protein synthesis in muscles remains unchanged or decreases, while protein decomposition remains unchanged or increases[55]. Recent evidence supported the idea that healthy adults need to consume at least 1.6 g/kg/day of protein during RT to support muscle protein anabolism, and as high as 2.2 g/kg/day for men who exercise regularly to achieve maximum fat-free mass gain throughout the body[56]. This means that for adults, higher HMB supplementation may be required if they need to improve their body composition and increase muscle mass. Therefore, the HMB dose we selected may explain why there was no significant difference in muscle mass increase between the RT + HMB group and the RT group.

Effect of Interventions on Postoperative Hip Function and Life Quality

Baumgarther *et al.* first proposed the concept of oligomuscular obesity, in which skeletal muscle loss is accompanied by an increase in body FM, and sarcopenia is strongly associated with FM[57]. Evidence has shown that reduced levels of physical activity and muscle mass contribute to reduced total energy expenditure, which in turn leads to the accumulation of adipose tissue.[58] In addition, more adipose tissue can result from the progression of sarcopenia, which stimulates muscle cell catabolism[59]. Chen *et al.* showed that RT could reduce the total FM of obese elderly people with sarcopenia, which increased the muscle mass and muscle strength of patients[60]. Our study also found that RT and RT + HMB treatment could effectively reduce the FM of patients with femoral neck fracture with sarcopenia after joint replacement. Holland *et al.* showed that HMB did not change the FM of young adults[43], and Wu *et al.* found that HMB treatment did not improve FM in older adults in a meta-analysis involving seven randomized controlled trials[28]. These previous results are consistent with our findings that HMB supplementation did not lead to a significant change in FM after joint replacement for femoral neck fractures with sarcopenia. Moreover, Shiina *et al.* found that amino acid intake combined with RT reduced the percentage of FM and increased skeletal muscle mass in patients with congenital heart disease with sarcopenia[61]. Similarly, our study showed that HMB supplementation combined with RT effectively reduced fat mass and increased systemic muscle mass in patients with sarcopenia after joint replacement for femoral neck fracture.

Martin *et al.* found that RT improved living ability and motor function in patients with sarcopenia[47]. Additionally, Singh *et al.* showed that high-intensity progressive RT could improve the daily living ability of patients with hip fracture, such as toilet use and turn around, reduce the reliance on nursing workers, and decrease postoperative mortality of patients[30]. A meta-analysis indicated that progressive RT was able to improve the balance force and ability of daily life of hip fracture patients[49]. Furthermore, Wu *et al.* showed that RT could significantly improve postoperative walking speed and HSS of patients undergoing total hip arthroplasty[41]. HMB supplementation was also found to increase the rate of improvement in postoperative daily life activities and physical function in elderly patients with sarcopenia following hip fracture[23]. However, our study is the first to report on the effects of HMB combined with RT treatment on the quality of life and hip function after hip replacement in elderly patients with femoral neck fracture and sarcopenia. Our results suggest that HMB + RT, RT alone, and HMB alone did not significantly improve patients' living ability, hip function, and pain compared with before injury. However, HSS ratings of "excellent" and "good" were more common in the HMB + RT, HMB, and RT groups than in the negative control group. We propose several possible explanations for this. First, the previous studies recorded the hip function and quality of life of the patients after the injury, while our study investigated the hip function and quality of life of the patients before injury. Second, compared with the previous studies, we followed up for a shorter period of time, which might have resulted in patients' hip function and quality of life not approaching pre-injury levels. And finally, all the patients included in our study were elderly patients with sarcopenia, and the postoperative recovery was somewhat different from that of healthy elderly people.

Study Limitations

Despite these promising results, our study still has several limitations. First, it is difficult to estimate the severity of sarcopenia for patients with femoral neck fracture due to most patients not being able to walk when they arrive at the hospital and their walking speed cannot be calculated. Second, the effects of HMB and RT treatments may become more pronounced over time, and our trial may not be able to detect these effects only 3 months after surgery. Additionally, this study was not a randomized controlled trial, which can lead to bias of the results. Despite these limitations, we believe that our patients were representative of the population of elderly patients with sarcopenia who underwent hip arthroplasty for femoral neck fracture. Still, a longer prospective randomized controlled trial should be conducted as soon as possible to fully evaluate the effectiveness of these treatments.

Conclusion

In this study, we found that RT with or without HMB supplementation significantly increased muscle mass and muscle strength after hip arthroplasty in elderly patients with femoral neck fracture and sarcopenia. In addition, we found that HMB supplementation alone may help to alleviate muscle loss. Therefore, we suggest that RT should be considered as an effective therapy in elderly patients with femoral neck fracture with sarcopenia. In addition, HMB supplements for these patients should also be considered in conjunction with RT. Even on its own, HMB supplementation may have a beneficial effect on preventing the decline of muscle mass and strength. Future long-term RCTs are still needed to assess treatment choices combining HMB and RT for elderly patients with femoral neck fractures and sarcopenia.

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