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Effects of whey protein nutritional supplement on muscle function among community-dwelling frail older people: A multicenter study in China

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ABSTRACT

Background: Frailty, featured by the presence of fatigue, weight loss, decrease in grip strength, decline gait speed and reduced activities substantially increase the risk of falls, disability, hospitalizations, and mortality of older people. Nutritional supplementation and resistance exercise may improve muscle function and reverse frailty status.
Objective: To evaluate whether whey protein supplements can improve muscle function of frail older people in addition to resistance exercise.
Methods: 115 community-dwelling older adults who met the Fried's criteria for frailty from four hospitals' outpatients clinic in Beijing, China completed the study. It's a case–control study which whey protein was used as daily supplementation for 12 weeks for active group and regular resistance exercise for active group and control group. Handgrip strength, gait speed, chair-stand test, balance score, and SPPB score were compared in both groups during the 12-week follow-up.
Results: Overall, 115 subjects were enrolled for study with 66 in active group and 49 in control group. Handgrip strength, gait speed, and chair-stand time were all significantly improved in both groups with significant between-group differences. The active group improved significantly in handgrip strength compared with the control group, which between-group effect (95% confidence interval) for female was 0.107 kg (0.066–0.149), $p = 0.008$ and for male was 0.89 kg (0.579–1.201), $p = 0.007$. For chair-stand time, between-group effect (95% confidence interval) was −2.875 s (−3.62 to −2.124), $p = 0.004$ and for gait speed, between-group effect (95% confidence interval) was 0.109 m/s (0.090 to 0.130), $p = 0.003$.
Conclusions: The 12-week intervention of whey protein oral nutritional supplement revealed significant improvements in muscle function among the frailty elderly besides aiding with resistance exercise. These results warrant further investigations into the role of a multi-modal supplementation approach which could prevent adverse outcomes among frailty elderly at risk for various disabilities.

1. Introduction

Population is a global phenomenon that poses various challenges to the healthcare systems. Unlike most western countries, eastern Asian countries are experiencing much more rapidly aging in the demographic transition. Despite the optimal control of chronic conditions, geriatric syndromes, such as functional decline and frailty have become new healthcare challenges to individuals and the healthcare systems (Fried et al., 2001). Among geriatric syndromes, frailty may be the most characteristic feature that substantially increases the risk of

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falls, fractures, hospitalizations, disability and even mortality (Cederholm, Cruz-Jentoft, & Maggi, 2013; Guralnik, Ferrucci, Simonsick, Salive, & Wallace, 1995; Guralnik et al., 1994). Hence, maintaining physically fit and independent living is the utmost goal of the later life, which may be applied to the frailty prevention and management (Kalyani, Corriere, & Ferrucci, 2014). The development and progression of frailty is multidimensional, including physical inactivity, altered metabolism, neuromuscular deterioration, and marginal nutrient intakes and absorption (Fried et al., 2001).

Although frailty prevention and management depends on multimodal intervention, nutritional supplementation remains to be of critical importance. Maintaining sufficient skeletal muscle health may stop the frailty cycle, to promote better mobility and to reduce the risk of sarcopenia. Several previous studies have shown the potential benefits of nutritional supplementation in frailty intervention, as well as sarcopenia management. Overall, the PROT-AGE study recommended protein intake for 1.0–1.2 gm/kg/day to maintain muscle health, and resistance exercise may further enhance the clinical benefits of nutritional supplementation. In addition to sufficient protein intake, studies have shown that whey protein was superior to casein protein in the efficiency of muscle building. Whey protein has been described as the "fast protein" because it contains rich branch-chained amino acid that is better absorbed and utilized for muscle synthesis.

The Chinese Frailty and Sarcopenia Expert Consensus recommended resistance exercise and sufficient protein intake for 1.0–1.2 g/kg body weight/day; and whey protein supplementation was recommended if necessary (Chinese Nutrition Society Elderly Nutrition Branch, Chinese Nutrition Society Clinical Nutrition Branch, Chinese Medical Association Parenteral Enteral Nutrition Branch Elderly Nutrition Support Group, 2015; Deutz et al., 2014). Therefore, this study aims to provide a targeted nutritional supplement containing whey protein in a timely bolus amount, to investigate the potential benefits of whey protein on muscle function and mobility among pre-frail and frail older adults.

2. Methods

2.1. Study design

This was a 12-week, multicenter, interventional, 2 parallel-group case–control study among pre-frail and frail older participants. The study protocol was approved by the institutional review board of Peking Union Medical College Hospital. Study procedures were performed in accordance with the Declaration of Helsinki ethical principles for medical research involving human subjects.

2.1.1. Participants

Participants were recruited from 4 general hospitals in Beijing which are Peking Union Medical College Hospital, Tongren Hospital, Chaoyang Hospital and Aerospace Central Hospital investigated from August 30, 2017 to November 30, 2017. Overall, 200 participants with pre-frailty and frailty aged 60 years and older were screened for participation. Among them, 115 agreed to participate in this study, and they were assigned into the active or control groups. During the 12-week study period, participants received three tests at week 4, 8 and 12 after the baseline assessment before study. All the muscle functions were tested during the follow-up including grip strength and SPPB.

2.1.2. Inclusion criteria and rationale

Participants with the following conditions were considered for inclusion: (1) age ≥60 years, (2) meeting at least 2 of the 5 components of physical frailty: weakness (handgrip strength < 26 kg in men and < 18 kg in women), slowness (6-m usual gait speed < 1.0 m/s), unintentional weight loss (> 3 kg or 5% during half a year), fatigue over the past week from any activity, and < 1 h of outdoor activities per week, (3) able to communicate with the research team, and (4) able to understand and sign the informed consent. Moreover, subjects with the following conditions were excluded for study: (1) unable to stand from the chair independently, (2) unable to perform home exercise programs due to underlying diseases, (3) unable to perform usual daily activities due to cardiopulmonary distress, (4) with renal insufficiency (estimated glomerular filtration rate < 60 ml/min/1.73 m^2), (5) with active liver disease (serum levels of transaminase higher than 2 folds of normal reference value), (6) with malignancy, and (7) with milk allergy.

2.2. Intervention

Mini-Nutrition Short Form (MNS-SF) was done for every participant. Malnutrition was defined as MNA-SF ≦ 7 and risk of malnutrition for MNA-SF 8–11, no malnutrition as MNA-SF ≧ 12. All participants received home-based resistance exercise programs, and participants of the active group received daily whey protein supplementation. The 30-min home-based resistance exercise programs were taught by a professional physical therapist at the beginning and the participants also received an educational video to exercise twice a day. Specialized doctors conduct phone follow-up to ensure compliance for exercise intervention. Participants in both groups were given information regarding a diet that aimed to maintain their current weight and carry on daily resistance exercise programs. For participants in the active group, they were provided for whey protein (Nutrasumma brand), which contained 32.4 g of whey protein and should be administered with 100–150 ml warm water. Daily Whey protein supplementation (32.4 g) was provided and participants consumed them before breakfast and lunch or 30 min after resistance exercises in addition to their meals.

2.3. Outcome measures

Primary outcome indicators of this study were the handgrip strength, gait speed and the score of Short Physical Performance Battery (SPPB). The handgrip strength was measured using a digital dynamometer, and the maximum reading of two consecutive measurements of the dominant hand with participants at upright position was recorded as the handgrip strength. SPPB was consisted of 3 components: gait speed (4-m walk at a usual pace), chair stand test (time required to rise 5 consecutive times from a chair without arm rests), and balance (3 different standing balance tests) (Guralnik et al., 1994). Each component was scored from 0 (unable) to 4 (able) and the total score was summed of all components ranging from 0 to 12. Results of chair rise test and balance score from the SPPB were identified as the secondary outcomes.

A self-administered intake diary was provided for the participants to evaluate their compliance to the whey protein supplementation. Dietary assessment was done at baseline and weeks 4, 8 and 12 using 3-day prospective diet records. Glycated hemoglobin and C-reactive protein were measured for all participants at baseline and week 12. Comprehensive assessments including medical history, nutritional supplements, and medication use were collected for all participants. Information about adverse events were collected via telephone calls throughout the intervention and at each of the visits. Additional assessments were done at all return visits, which included monitoring vital signs, evaluating laboratory parameters related to liver and renal function and gastrointestinal tolerance.

2.4. Statistical analyses

All continuous variables were expressed by mean and standard deviation (SD), and categorical data were expressed by median and interquartile ranges (IQRs). Comparisons between continuous variables were done by independent samples t test and comparisons between categorical data were done by Wilcoxon rank-sum test (Table 1). Generalized linear mixed model (GLMM) estimation is performed in

Table 1
Baseline demographic and clinical characteristics.

	Control (n = 49)	Active (n = 66)	p value
Age, mean (SD)	78.04 (6.82)	76.79 (7.11)	0.405
Sex, female, n (%)	30 (61.2%)	41 (62.1%)	0.922
Mini Mental State Examination, median (IQR)	28.00 (25.00–29.00)	27.00 (24.25–29.00)	0.416
HGB, mean (SD)	122.87 (12.57)	118.40 (30.72)	0.451
BMI, mean (SD), kg/m^2	22.73 (4.40)	21.02 (3.45)	0.023
Mini Nutritional Assessment Short-Form (MNA-SF), n (%)			
Malnutrition (MNA-SF ≦ 7)	2 (4.1%)	3 (4.5%)	
Risk of malnutrition (MNA-SF: 8–11)	18 (36.7%)	25 (37.9%)	
No malnurtrition (MNA-SF ≧ 12)	29 (59.2%)	38 (57.6%)	
Charlson's Index, mean (IQR)	1.00 (0.00–2.00)	2.00 (1.00–3.50)	0.023
Calf circumference, mean (SD)	33.22 (3.12)	32.31 (3.07)	0.129

Table 2. All statistical analyses were performed using SPSS software Version 22.0 according to the predefined statistical analysis plan.

3. Results

Overall, 115 participants were enrolled with their mean age of 77.3 years, and 61.7% of them were females. Table 1 shows comparisons between active and control groups, and it revealed that participants have no significant difference between two groups except the baseline gender, body mass index and Charlson's comorbidity index. Participants of the active group tended to be thinner with more multi-morbidity.

Fig. 1 shows the improvement of handgrip strength between groups in the follow-up period.

During the second follow-up and the third follow-up, we found that handgrip strength and presence with family companion was significantly correlated with intervention effect ($r = 0.634$, 0.490, respectively, p both < 0.05) and handgrip strength had significant correlation with living with family ($r = 0.729$, 0.719, respectively, p both < 0.05). These indicated that presence with family companion and living with family may be predictors for the intervention effects.

For participants of the active group, we found that gait speed was progressively improved at the follow-up visits, but the gait speed remained similar in the control group (Fig. 2).

In the control group and the active group, only the third follow-up was significantly different from the baseline SPPB, and p values from Wilcoxon signed ranks tests were 0.034, 0.009, respectively, and there was no significant difference between the first two follow-ups in SPPB and the baseline.

For the secondary outcomes, there were significant differences in the active group among the three follow-ups in terms of the time of chair-stand test at baseline. All the p values in the active group were less than 0.05 which were 0.039, 0.000, and 0.000, respectively. While in the control group, There were no significant differences for the three follow-ups compared to baseline ($p > 0.05$) (Fig. 3). In the group comparison, the control group showed an upward trend from baseline to the first follow-up, while the active group showed a downward trend for all 3 follow-ups.

For the subjects in the control group and the active group, there was no significant difference in the balance test scores of the three follow-ups compared with the baseline (all p values > 0.05).

4. Discussion

Previous studies suggested that oral nutrition supplements containing quality protein like whey protein, or exercise alone may successfully reverse frailty (Antoniak & Greig, 2017; Bauer et al., 2015; Beaudart et al., 2017; Villareal et al., 2011, 2017). Nevertheless, the intervention effects of combined nutritional supplement and exercise were superior to that of either intervention alone. Results of these studies constructed the main strategy of frailty prevention and intervention. However, most previous studies were focused on the short-term effects of protein synthesis of muscle, but studies evaluating long-term muscle function and changes of frailty status were scarce (Cruz-Jentoft et al., 2014). In particular, in China, no well-established trial evidences were available to provide frailty prevention and intervention in such a rapidly aging country. Results of this study clearly established the intervention benefits of whey protein plus resistance exercise among pre-frail and frail older adults in China.

Table 2
Summarized results of intervention effects between active group and control group.

	Mean (SD)	Mean (SD)			Estimated between-group mean difference (95% CI) active–control	p (Time)
	Baseline	Week 4	Week 8	Week 12		
Handgrip strength, male, kg						
Control	25.50 (0.71)	26.60 (3.39)	26.20 (1.13)	27.65 (1.91)	0.050 (−11.947, 12.047)	0.007
Active	24.69 (7.71)	26.65 (7.06)	27.08 (7.14)	27.73 (8.07)		
Handgrip strength, female, kg						
Control	18.27 (5.45)	19.57 (5.26)	19.85 (4.88)	20.27 (5.30)	−1.048 (−4.356, 2.259)	0.008
Active	17.08 (2.62)	18.66 (2.06)	18.83 (2.07)	19.19 (2.46)		
Gait speed, m/s						
Control	0.71 (0.22)	0.74 (0.26)	0.72 (0.24)	0.77 (0.29)	0.097 (−0.087, 0.282)	0.003
Active	0.74 (0.20)	0.84 (0.22)	0.84 (0.25)	0.90 (0.27)		
Chair stand test, s						
Control	11.33 (1.84)	11.77 (3.54)	10.99 (2.41)	10.29 (2.61)	−1.596 (−5.377, 2.185)	0.004
Active	12.26 (6.86)	9.10 (4.39)	8.29 (4.06)	8.35 (4.19)		
SPPB						
Control	9.50 (8.25,11.00)	10.00 (8.25,11.00)	10.00 (8.50,11.00)	11.00 (9.25,11.75)	N.A.	0.101
Active	10.00 (8.00,11.00)	10.00 (8.00,11.00)	10.00 (9.00,12.00)	10.00 (9.00,12.00)		
Balance test						
Control	3.50 (3.00, 4.00)	3.50 (3.25, 4.00)	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)	N.A.	0.431
Active	4.00 (3.00, 4.00)	4.00 (3.50, 4.00)	4.00 (4.00, 4.00)	4.00 (4.00, 4.00)		
BMI						
Control	22.54 (4.43)	22.48 (4.32)	22.97 (4.72)	23.40 (4.636)	−1.783 (−4.892, 1.326)	0.000
Active	20.77 (3.58)	20.81 (3.48)	21.19 (3.51)	21.49 (3.32)		

N.A., not applicable; SPPB, Short Physical Performance Battery.
Muscle function including handgrip strength, gait speed and BMI were all improved in both groups, and the improvement of active group was more pronounced.

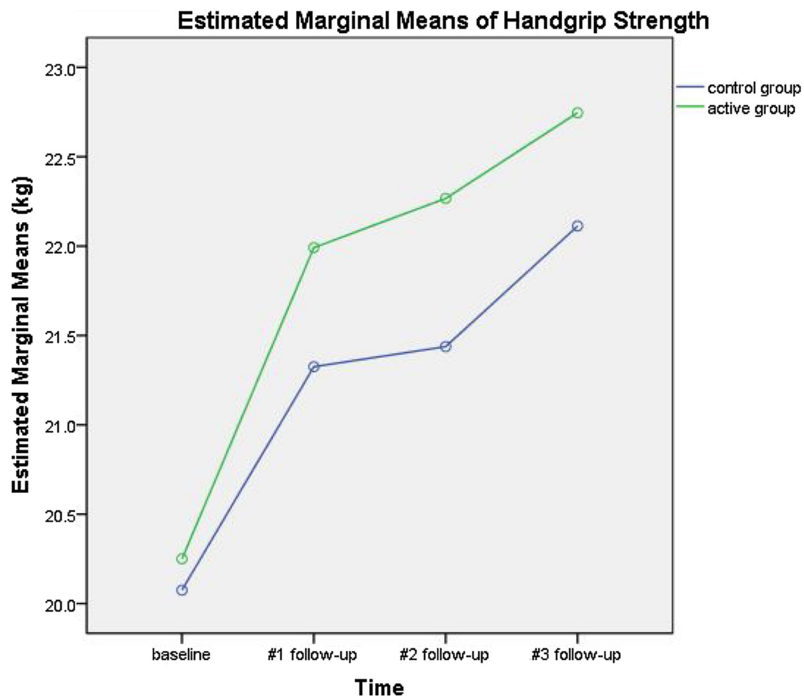

Fig. 1. Variation trend for handgrip strength.

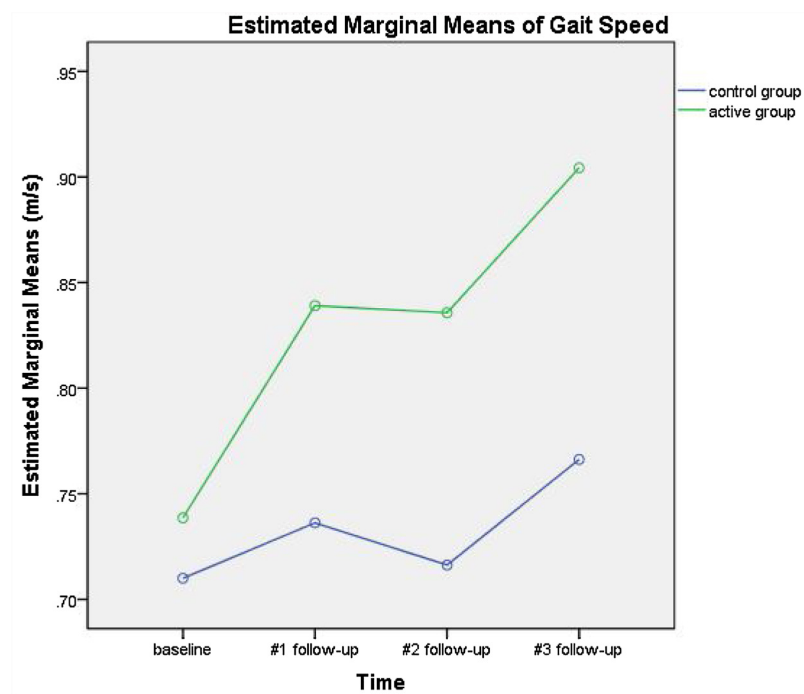

Fig. 2. Variation trend for gait speed.

Our current 12-week intervention composed of nutritional supplementation and resistance exercise among pre-frail and frail older adults significant increases in handgrip strength and improvements in chair-stand ability and walking speed in the active group versus control group. Results of this study suggested that whey protein-based nutritional supplement stimulated muscle synthesis in an acute setting (Kramer et al., 2014; Luiking, Deutz, Memelink, Verlaan, & Wolfe, 2014), and could improve frailty over a 3-month intervention. Resistance exercise could be set as a standard treatment for increasing muscle strength and improving physical performance among adults with frailty and sarcopenia (Pahor et al., 2014).

In our study, we selected frail elderly characterized by Fried's phenotype definition, using a nutritional supplement specifically targeted for aging muscle. During the intervention, we also observed something of clinical significance; patients with family members accompanying or supporting them showed better improvement than those without, especially in grip strength. We believe that's related with the monitoring support from the family members as participants with family members were more compliant. The chair-stand test is a robust measure of lower-extremity function because it requires lower-body

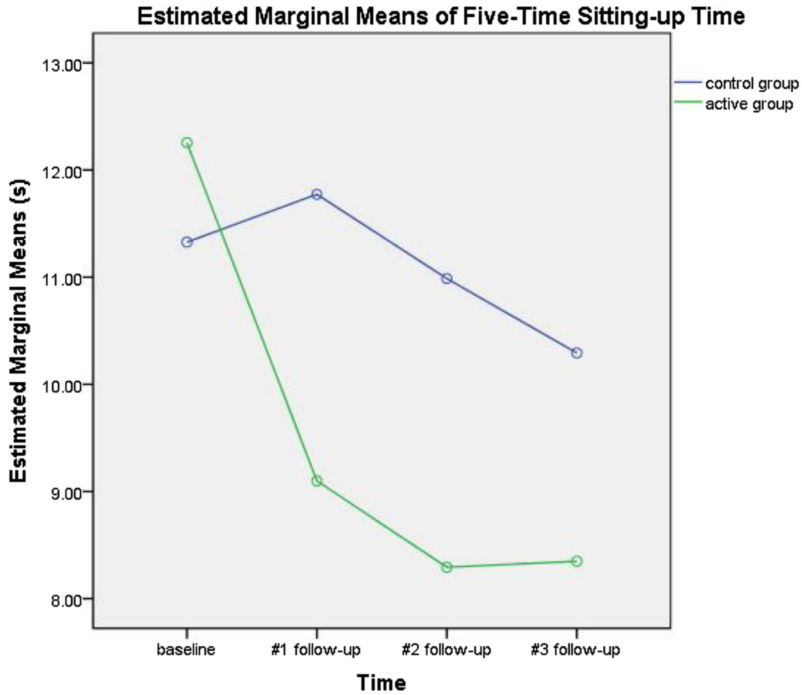

Fig. 3. Variation trend for the time of chair-stand test.

strength, power, and good balance and coordination (Hardy et al., 2010). Grip strength is a measure for upper extremity function, an independent risk factor for physical disability, hospitalization, and mortality (Leong et al., 2015). Improvement of muscle function can greatly aid to the quality of life for the elderly, just as some of our participants' feedback, "I could not take long walks before, but after the intervention, I can go by myself to the supermarket and buy what I need, then carry groceries by myself. I feel that I'm energetic again. That is really important to me." These results warrant further investigations into the role of a multi-modal approach to help prevent adverse outcomes among older adults with various disabilities.

This study is not without limitations. One of our primary outcome measurements, SPPB, we did not observe an intervention effect. This is likely to be explained that SPPB is by nature a categorical score and is therefore less sensitive to changes than a continuous numerical scale like the chair-stand test and gait speed. And the participants in the active group were thinner with more multi-morbidity, but their muscle function (grip strength and gait speed) improvement was more pronounced during the 12-weeks follow-up. Therefore, the difference in BMI and comorbidity between the two groups did not at least overestimate the conclusion of our study. Without a doubt, our study employed a robust sample of out-patient elderly and was unable to include the full spectrum of older adults in the population at large.

5. Conclusion

We present here a 12-week intervention of a whey protein oral nutritional supplement plus resistance exercise, which resulted in improvements in muscle function among pre-frailty and frailty older adults. This study shows that specific nutritional supplementation besides exercise could provide extra benefit to elderly patients. Groups such as those recovering from hospitalization and community could also benefit from nutritional supplementation and exercise. Nutrition intervention combined with structured physical activities overall can provide extra benefits to the elderly, improve physical frailty conditions and have the potential to enhance mobility, independence, and quality of life.

Author contribution

Term	Name
Conceptualization	Lin Kang, Xiaohong Liu
Methodology	Lin Kang, Haiyu Pang, Lu Zhang, Wei Chen, Xiaohong Liu
Software	Lin Kang
Formal analysis	Lin Kang, Haiyu Pang
Investigation	Ying Gao, YingHui Liang, Yiwen Chen, Yanhong Liang
Resources	Lin Kang, Ying Gao, Yanhong Liang
Data curation	Lin Kang
Writing – original draft	Lin Kang
Writing – review and editing	Lin Kang, Li-Ning Peng
Visualization	Lin Kang
Supervision	Lin Kang
Project administration	Lin Kang

Conflict of interest

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