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Protein supplementation improves muscle mass and physical performance in undernourished prefrail and frail elderly subjects: a randomized, double-blind, placebo-controlled trial

Yongsoon Park,[1] *Jeong-Eun Choi,*[1] *and Hwan-Sik Hwang*[2]

[1]Department of Food and Nutrition, Hanyang University, Seoul, Republic of Korea and [2]Department of Family Medicine, Hanyang University College of Medicine, Seoul, Republic of Korea

ABSTRACT

Background: Age-related loss of muscle mass and function is a major component of frailty. Nutrition supplementation with exercise is an effective strategy to decrease frailty by preventing sarcopenia, but the effect of protein alone is controversial.

Objective: The present study was performed to investigate a dose-dependent effect of protein supplementation on muscle mass and frailty in prefrail or frail malnourished elderly people.

Design: A 12-wk double-blind randomized controlled trial was conducted in elderly subjects aged 70–85 y with ≥1 of the Cardiovascular Health Study frailty criteria and a Mini Nutritional Assessment score ≤23.5 (n = 120). Participants were randomly assigned to 1 of 3 groups: 0.8, 1.2, or 1.5 g protein · kg^{-1} · d^{-1}, with concealed allocation and intention-to-treat analysis. Primary outcomes were appendicular skeletal muscle mass (ASM) and skeletal muscle mass index (SMI) measured by dual-energy X-ray absorptiometry.

Results: After the 12-wk intervention, the 1.5-g protein · kg^{-1} · d^{-1} group had higher ASM (mean ± SD: 0.52 ± 0.64 compared with 0.08 ± 0.68 kg, $P = 0.036$) and SMI (ASM/weight: 0.87% ± 0.69% compared with 0.15% ± 0.89%, $P = 0.039$; ASM/BMI: 0.02 ± 0.03 compared with 0.00 ± 0.04, $P = 0.033$; ASM:fat ratio: 0.04 ± 0.11 compared with −0.02 ± 0.10, $P = 0.025$) than the 0.8-g protein · kg^{-1} · d^{-1} group. In addition, gait speed was improved in the 1.5-g protein · kg^{-1} · d^{-1} group compared with the 0.8-g protein · kg^{-1} · d^{-1} group (0.09 ± 0.07 compared with 0.04 ± 0.07 m/s, $P = 0.039$). There were no significant differences between the 1.2- and 0.8-g protein · kg^{-1} · d^{-1} groups in muscle mass and physical performance. No harmful adverse effects were observed.

Conclusions: The present study indicates that protein intake of 1.5 g · kg^{-1} · d^{-1} has the most beneficial effects in regard to preventing sarcopenia and frailty compared with protein intakes of 0.8 and 1.2 g · kg^{-1} · d^{-1} in prefrail or frail elderly subjects at risk of malnutrition. This trial was registered at cris.nih.go.kr as KCT0001923. *Am J Clin Nutr* 2018;108:1026–1033.

Keywords: protein supplementation, muscle mass, frailty, elderly, clinical trial, malnutrition

INTRODUCTION

Frailty is characterized by unintentional weight loss, weakness, exhaustion, slowness, and low physical activity and is related to high risk of incident falls, worsening mobility and physical disability, hospitalization, and death (1). Korea is known as the fastest-aging nation in the world (2), and the prevalence of frailty has been reported as 13% in the Korean Longitudinal Study on Health and Aging (KLoSHA) (3).

One of the major causes of frailty is sarcopenia, defined as an abnormal loss of muscle mass and strength (4). Declines in muscle mass and strength are expected with aging, but physical inactivity and low protein intake have been suggested as risk factors for both sarcopenia (5) and frailty (6). A meta-analysis of clinical trials showed that protein intake ≤1.6 g · kg^{-1} · d^{-1} improved resistance training–induced gains in muscle

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Address correspondence to YP (e-mail: yongsoon@hanyang.ac.kr).

Abbreviations used: ASM, appendicular skeletal muscle mass; BUN, blood urea nitrogen; CHS, Cardiovascular Health Study; HGS, handgrip strength; ITT, intention-to-treat; KLoSHA, Korean Longitudinal Study on Health and Aging; MNA, Mini Nutritional Assessment; SMI, skeletal muscle mass index; SPPB, Short Physical Performance Battery; TUG, timed up-and-go.

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mass and strength in healthy adults (7). In addition, clinical trials with a combination of exercise and protein supplementation improved frailty scores (8, 9) and physical frailty in a frail elderly population (10) and in a sarcopenic elderly population (11).

Epidemiologic studies have shown that protein intake is positively associated with appendicular skeletal muscle mass (ASM) in the elderly (12). Supplementation with whey protein (13) and leucine-enriched whey protein (14) also resulted in improvements in muscle mass compared with isocaloric control supplementation in an elderly population. However, 3 other clinical trials failed to show beneficial effects of protein supplementation on muscle mass in frail or sarcopenic elderly subjects (15).

In addition, epidemiologic studies (16) and clinical trials (15, 17) have suggested that protein supplementation significantly improved physical frailty in the elderly. However, Smoliner et al. (18) reported that protein supplementation of 1.3 g · kg^{-1} · d^{-1} with the use of hydrolyzed milk protein did not improve handgrip strength (HGS) and physical functioning compared with 1.1 g protein · kg^{-1} · d^{-1} in frail elderly nursing home residents at risk of malnutrition. Thus, the effect of protein alone on muscle mass and frailty is unclear.

The European Society for Clinical Nutrition and Metabolism expert group suggested daily amounts of protein intake of 1.0–1.2 g · kg^{-1} · d^{-1} for healthy elderly people and 1.2–1.5 g · kg^{-1} · d^{-1} for malnourished elderly people with illness (19). However, the existing evidence of the effect of protein on muscle mass and physical frailty is inconsistent. To our knowledge, there has been no study to determine the exact amount of protein beneficial for muscle mass and physical frailty in frail elderly people. Thus, the purpose of the present study was to investigate the hypothesis that protein intake of 1.2 g · kg^{-1} · d^{-1} and 1.5 g · kg^{-1} · d^{-1} increases muscle mass and physical performance dose dependently in prefrail or frail community-dwelling elderly people at risk of malnutrition.

METHODS

Study design

This study (KCT0001923) was conducted according to the guidelines laid out in the Declaration of Helsinki, and all procedures involving human subjects were approved by the Hanyang University Institutional Review Board (HYI-15–228). Written informed consent was obtained from all participants before enrollment in the study.

A total of 120 participants were enrolled in this randomized, double-blind, placebo-controlled, 3-parallel-group trial, and concealed allocation and intention-to-treat (ITT) analysis were applied. Eligible participants were randomly assigned to 1 of 3 groups: 0.8, 1.2, or 1.5 g protein · kg body $weight^{-1}$ · d^{-1} in the ratio of 1:1:1 for the 12-wk trial (20).

There was 1 screening visit and 3 visits at weeks 0 (baseline), 6, and 12. During the screening visit, Cardiovascular Health Study (CHS) frailty criteria, the Mini Nutritional Assessment (MNA), demographic and medical information, BMI, and 3-d dietary intake were measured. Within 4 wk of the screening visit, the intervention was initiated in eligible participants. At weeks 0, 6, and 12, medical and clinical information, KLoSHA frailty criteria, the timed up-and-go (TUG) test, and hematologic and urinary measurements were assessed. At weeks 0 and 12, muscle mass was measured; at week 12, the MNA was administered. In addition, 3-d dietary intake and adverse effects were assessed at weeks 2, 4, 6, 8, 10, and 12.

Participants

Participants aged 70–85 y who were prefrail or frail and at risk of malnutrition were recruited consecutively at 4 welfare centers in Seoul, Korea between May 2016 and August 2017. Prefrailty and frailty were defined as meeting ≥1 and ≥3 of modified CHS frailty criteria, respectively (1, 21), and risk of malnutrition was defined as MNA score ≤23.5 (22). Participants were excluded if they had comorbidities such as kidney or liver failure, if they were participating in another clinical trial, if they were unable to walk, or if they were unable to communicate.

Out of the 355 screened individuals, 120 were enrolled. Participants were excluded owing to possessing <1 CHS frailty criterion ($n = 117$), >23.5 score on the MNA ($n = 56$), inability to communicate ($n = 2$), or consent withdrawal ($n = 60$) (**Figure 1**).

Interventions

Participants were asked to maintain their usual diet and physical activity during the 12-wk intervention. All participants were provided a total of 5 × 10-g packs containing placebo or protein powders (Korean Medical Food, Seoul, Korea). Protein powder contained 0.5 g fat, 0.2 g cocoa powder, and 9.3 g whey protein/10-g pack, whereas placebo powder contained 0.5 g fat, 0.2 g cocoa powder, and 9.3 g maltodextrin/10-g pack. Both protein and placebo powders contained 200 kcal/d and were provided with 340 mL of corn silk tea (Kwangdong Pharmaceutical, Seoul, Korea). The 0.8-g protein · kg^{-1} · d^{-1} group consumed only placebo powder, and the 1.2- and 1.5-g protein groups consumed a combination of protein and placebo powder based on their usual intake of protein estimated by 3 d of 24-h recall during screening. Participants in both the 1.2- and 1.5-g protein · kg^{-1} · d^{-1} groups received an individually adjusted amount of protein powder to fulfill 1.2 or 1.5 g · kg^{-1} · d^{-1}. Placebo and protein supplements were provided at weeks 0, 6, and 12.

Primary outcome measure: muscle mass

Muscle mass was measured by dual-energy X-ray absorptiometry (Hologic, Marlborough, MA) after a 12-h fast. ASM was calculated as the sum of muscle mass in the arms and legs. There were 4 types of skeletal muscle mass index (SMI): ASM adjusted for height (ASM/$height^2$) = ASM (kg)/height (m^2), ASM adjusted for weight (ASM/weight, %) = ASM (kg)/weight (kg) × 100, ASM adjusted for BMI (ASM/BMI) = ASM (kg)/BMI (kg/m^2) (23), and ratio of skeletal muscle to body fat (ASM:fat ratio) = ASM adjusted for body fat mass (kg) (24).

Secondary outcome measure: frailty

Modified CHS frailty criteria included unintentional weight loss ≥4.5 kg during the last year, exhaustion, low physical activity, slowness, and low HGS (1). Exhaustion was evaluated

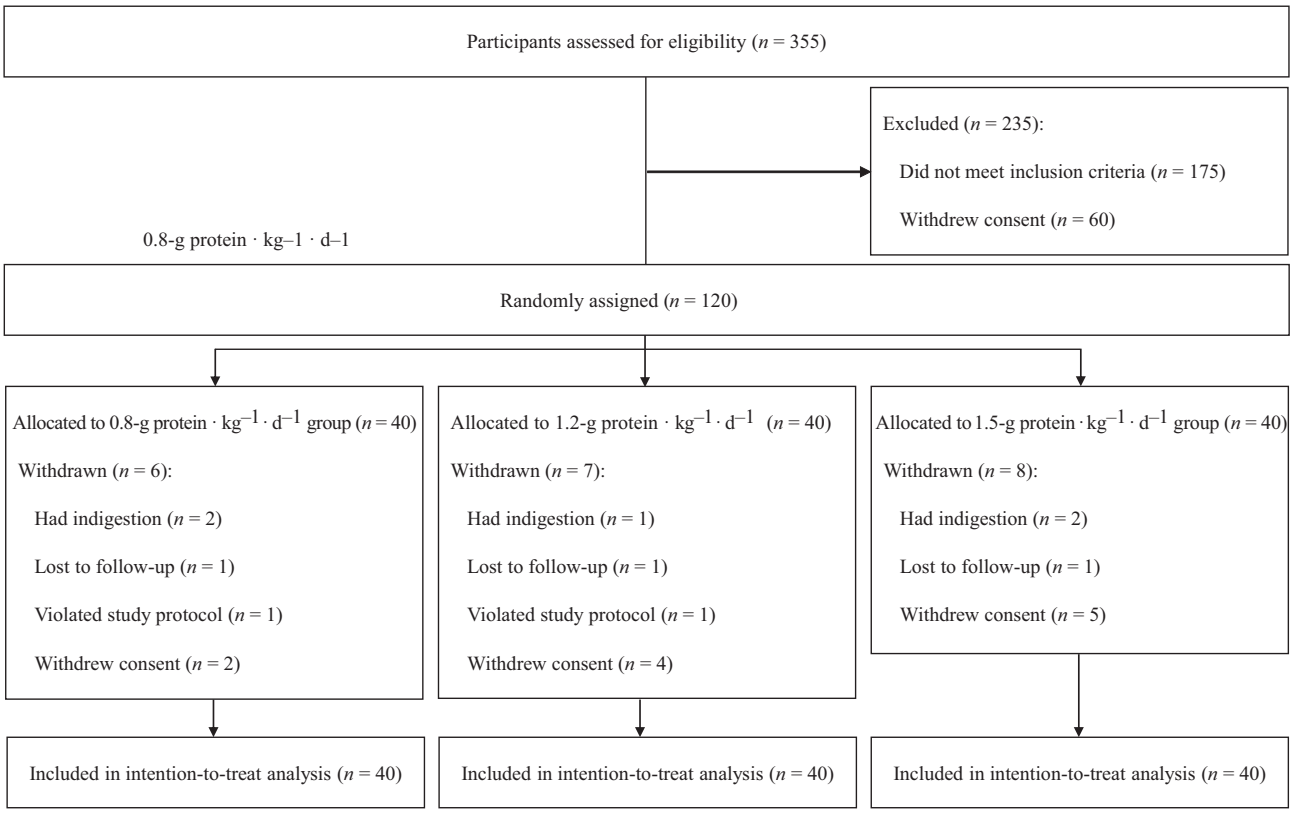

FIGURE 1 Participant screening, randomization, and follow-up during the 12-wk intervention. The intention-to-treat population comprised the included participants who underwent randomization.

through the use of the Center for Epidemiological Studies Depression scale, and physical activity was calculated as energy expended over the course of 1 wk by the International Physical Activity Questionnaire. Slowness was defined as ≤0.8 m/s taken from the average of three 4-m walks, with 1.5 m walked both before and after the walkway to allow for acceleration and deceleration. In addition, HGS of both hands was measured twice in the standing position with outstretched arms at a 30-degree angle with the use of a hand dynamometer (Takei, Niigat, Japan), and adjusted for sex and BMI.

KLoSHA frailty criteria were composed of the Short Physical Performance Battery (SPPB) score, Korean Activity of Daily Living score, Korean Instrumental Activity of Daily Living score, Korean Mini-Mental State Examination score, and serum albumin concentration (3). The SPPB consisted of balance, gait speed, and sit-to-stand ability: balance tests comprised the duration of each of side-by-side stand, semitandem stand, and tandem stand; the gait speed test the time to complete a 4-m walk (repeated 3 times); and the sit-to-stand test the time to rise from sitting (repeated 5 times) (25). In addition, a TUG test was performed to determine the time needed to rise from a chair, walk 3 m, turn around, walk back to the chair, and sit down (26).

MNA

The MNA includes anthropometric measurements, general assessments, and dietary questionnaires (22). Body weight was measured with an electronic scale (BioSpace, Chungcheong-do, Korea) to the nearest 0.1 kg, and body height was measured with an extensometer (Samhwa, Incheon, Korea) to the nearest 0.1 cm. With a nonelastic tapeline, midupper arm circumference was measured on the nondominant arm, relaxed, midway between the tip of the acromion and the olecranon process, and calf circumference was measured on the nondominant calf, undressed, at the thickest part.

Compliance, adverse effects, and safety assessment

Compliance and adverse effects were monitored biweekly. An adverse effect was regarded as a sign or symptom about which the participants complained after initiation of the protein supplement or placebo.

Fasting blood and urine samples were sent to Korea Biomedical Laboratory (Seoul, Korea). Serum concentrations of high-sensitivity C-reactive protein, C-peptide, and insulin-like growth factor 1 were measured by a hematology analyzer (Quintus, Stockholm, Sweden). Complete blood cell count and biochemical variables, and urinalysis were measured by a hematology analyzer (Quintus) and a portable urine chemistry analyzer (YD diagnostics, Gyeonggi-do, Korea), respectively.

Sample size

Sample size was calculated based on the findings of Candow et al. (27), considering a mean ± SD increase in lean tissue mass of 3.2 ± 1.9 kg in the protein supplement group and

2.1 ± 1.4 kg in the nonprotein supplement group, with a power of 80% and an α level (2-tailed) of 5%. This gave a sample size of 30 participants/group. With an expected dropout rate of 25%, a sample size of 40 participants/group was considered adequate.

Random assignment

An independent external researcher prepared a computer-generated randomization scheme in blocks (block size 3) with the use of Random Allocation Software (Microsoft Visual Basic 6; Microsoft, Redmond, WA). After random assignment, the external researcher newly assigned a subject ID to each participant, calculated the required number of protein powder packages for each participant, and managed the identity codes. All other study personnel and participants remained blinded to the identity codes throughout the course of the study. When participants withdrew from or completed the study, researchers were provided with the participants' identities, and the participants were told what supplement they had received.

Statistical analysis

All data are presented as means ± SDs for continuous variables or as numbers (percentages) for categoric variables. In the ITT analyses, missing data were primary endpoints of 21 participants at week 12 and secondary endpoints of 12 participants at week 6 and 21 participants at week 12. We used multiple imputation to handle missing data. To impute the missing data, we constructed multiple regression models including variables potentially related to the fact that the data were missing and also variables correlated with that outcome. These variables included baseline characteristics, such as age, sex, height, weight, frailty status, medical history, and MNA score, and the baseline value of each outcome. Ten multiply imputed datasets were generated with the use of PROC MI, and then results were combined with the use of PROC MIANALYZE. To confirm that no selection bias was present, we used ANOVA to compare continuous variables in accordance with the central limit theorem (28) and a chi-square test or Fisher's exact test to compare categoric variables between the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups of the ITT population. ASM, SMI, and dietary intake at week 12 were compared between the 3 groups by ANCOVA with adjustment for baseline values, sex, CHS frailty, diabetes, and osteoporosis. In addition, physical performances and safety assessments between and within groups were compared by repeated measures with a linear mixed model, including group, time, and group × time interaction as fixed factors and sex, CHS frailty, diabetes, and osteoporosis as covariates. P values <0.05 were considered statistically significant. Statistical analyses were performed with the use of SAS version 9.4 (SAS Institute Inc.).

RESULTS

Baseline characteristics of participants

During the intervention, 21 participants did not complete the study owing to indigestion ($n = 5$), loss to follow-up ($n = 3$), study protocol violation ($n = 2$), and consent withdrawal ($n = 11$), but a total of 120 participants were included for the ITT analyses (Figure 1). There were no significant differences on baseline characteristics between the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups (**Table 1**). Mean adherence to the supplementation based on nonconsumed supplements was 97%, 98%, and 96% in the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} protein groups, respectively.

Body composition, dietary intake, and physical performance

After the 12-wk intervention, ASM and SMI indicators, such as ASM/weight, ASM/BMI, and ASM:fat ratio, were significantly higher in the 1.5-g protein · kg^{-1} · d^{-1} group than in the 0.8-g protein · kg^{-1} · d^{-1} group (**Figure 2**). However, there were no significant differences between the 1.2- and 0.8-g protein · kg^{-1} · d^{-1} groups in ASM and SMI.

Protein intake was higher in the 1.2-g protein · kg^{-1} · d^{-1} group than in the 0.8-g protein · kg^{-1} · d^{-1} group, and in the 1.5-g protein · kg^{-1} · d^{-1} group than in the 0.8- and 1.2-g protein · kg^{-1} · d^{-1} groups (**Table 2**). Carbohydrate intake was higher in the 0.8-g protein · kg^{-1} · d^{-1} group than in the 1.2- and 1.5-g protein · kg^{-1} · d^{-1} groups. Intakes of energy, lipids, vitamins, and minerals were not significantly different between the 3 groups (Table 2 and **Supplemental Table 1**).

For gait speed, there was a significant group × time interaction between the 3 groups; thus, gait speed was significantly higher in the 1.5-g protein · kg^{-1} · d^{-1} group than in the 0.8-g protein · kg^{-1} · d^{-1} group at week 12 (**Table 3**). There was no significant group × time interaction for other physical performance metrics between the groups, although there was a time effect on frailty index, SPPB, balance test, TUG time, sit-to-stand time, Korean Mini-Mental State Examination score, and HGS (Table 3).

Safety assessment

There was a significant group × time interaction on the concentrations of blood urea nitrogen (BUN), calcium, and γ-guanosine triphosphate, but only BUN was significantly increased by protein intake of 1.2 and 1.5 g · kg^{-1} · d^{-1} compared with protein intake of 0.8 g · kg^{-1} · d^{-1} at weeks 6 and 12 (**Supplemental Table 2**). However, the changes in blood concentrations occurred within normal limits. None of the urine measurements significantly changed during the intervention in any of the 3 groups (**Supplemental Table 3**).

DISCUSSION

The present 12-wk, randomized, double-blind, placebo-controlled, 3-parallel-group trial showed that protein intake of 1.2 and 1.5 g · kg^{-1} · d^{-1} did not dose-dependently increase muscle mass or physical performance in prefrail and frail elderly subjects at risk of malnutrition compared with protein intake of 0.8 g · kg^{-1} · d^{-1}. However, protein intake of 1.5 g · kg^{-1} · d^{-1} improved ASM, SMI, and gait speed, whereas protein intake of 1.2 g · kg^{-1} · d^{-1} had effects on neither muscle mass nor physical performance.

Similar to the present study, it was previously shown that 1.3–1.5 g · kg^{-1} · d^{-1} of protein supplementation provided by whey protein increased muscle mass compared with protein consumption of 1.0 g · kg^{-1} · d^{-1} in elderly people (13, 14). A recent meta-analysis reported that protein intake ≤1.6 g · kg^{-1} ·

TABLE 1
Baseline characteristics of participants in the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups[1]

Characteristics	Protein intake of 0.8 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.2 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.5 g · kg^{-1} · d^{-1} ($n = 40$)
Age, y	76.83 ± 3.86	77.30 ± 3.67	76.80 ± 3.70
Men, *n* (%)	16 (40)	14 (35)	12 (30)
Height, m	1.56 ± 0.10	1.56 ± 0.09	1.54 ± 0.08
Weight, kg	58.73 ± 9.71	59.73 ± 9.98	56.28 ± 8.67
BMI, kg/m^2	24.16 ± 33.82	24.36 ± 3.04	23.65 ± 2.53
ASM, kg	15.19 ± 3.10	15.53 ± 3.56	14.19 ± 2.78
ASM/$height^2$, kg/m^2	6.19 ± 0.79	6.29 ± 0.93	5.93 ± 0.71
ASM/weight, %	26.00 ± 3.99	26.03 ± 3.89	25.19 ± 2.74
ASM/BMI	0.64 ± 0.16	0.64 ± 0.14	0.60 ± 0.11
ASM:fat ratio	1.08 ± 0.46	1.08 ± 0.57	0.98 ± 0.49
CHS score	1.70 ± 0.83	1.78 ± 0.89	1.93 ± 0.94
Frailty status, *n* (%)	5 (13)	8 (20)	12 (30)
Medical history, *n* (%)			
Hypertension	22 (55)	28 (70)	23 (58)
Hyperlipidemia	7 (18)	10 (25)	8 (20)
Diabetes	11 (28)	18 (45)	9 (23)
Osteoporosis	7 (18)	2 (5)	7 (18)
Arthritis	2 (5)	5 (13)	5 (13)
MNA score	20.04 ± 2.40	20.69 ± 2.11	20.89 ± 1.93

[1] Values are means ± SDs for continuous variables or *n* (%) of participants for categoric variables. ASM, appendicular skeletal muscle mass; CHS, Cardiovascular Health Study; MNA, Mini Nutritional Assessment.

d^{-1} improved resistance training–induced gains in muscle mass in healthy adults, but older people had an increased need for higher protein intakes to see gains in muscle mass (7). Thus, in the present study, protein intake of 1.2 g · kg^{-1} · d^{-1} was not sufficient to improve muscle mass compared with isocaloric intake of 0.8 g protein · kg^{-1} · d^{-1}.

Contrary to the present study, protein supplementation that used milk protein (15), hydrolyzed milk (18), and cheese (12) had no significant beneficial effects on muscle mass in other elderly populations. A meta-analysis of clinical trials suggested that whey protein was best to support muscle protein synthesis owing to its high leucine content compared with milk and

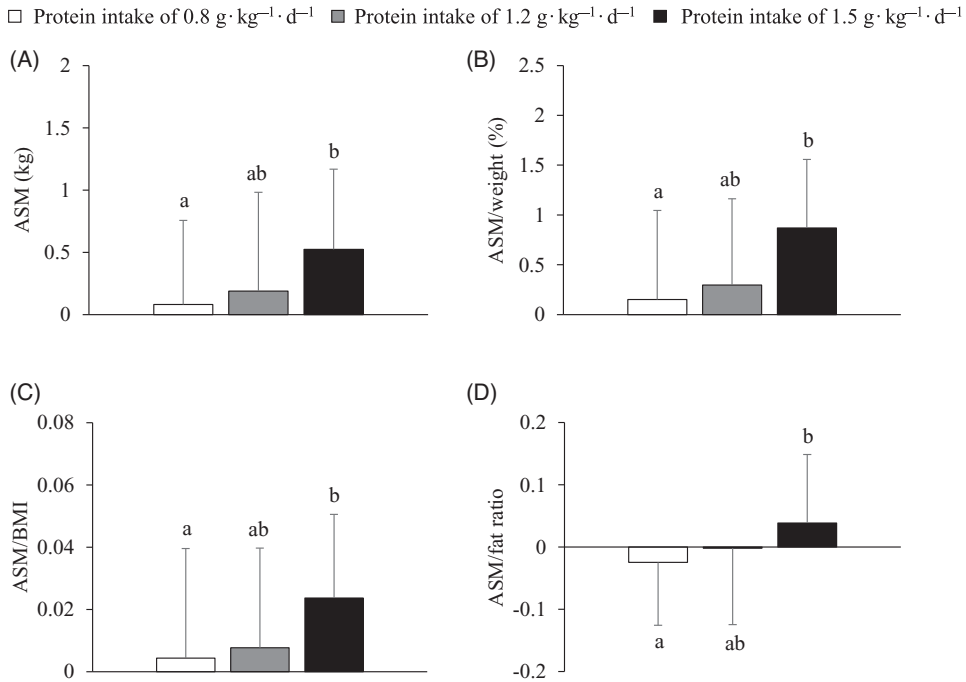

FIGURE 2 ASM (A) and SMI (B–D) in the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups. Data were analyzed with ANCOVA with adjustment for baseline values, sex, Cardiovascular Health Study frailty, diabetes, and osteoporosis. Values are means ± SDs; $n = 120$ (40/group). Different letters indicate a statistically significant difference between the 3 groups ($P < 0.05$). ASM, appendicular skeletal muscle mass; SMI, skeletal muscle mass index.

TABLE 2
Dietary intake during the 12-wk intervention in the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups[1]

Outcome variable	Protein intake of 0.8 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.2 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.5 g · kg^{-1} · d^{-1} ($n = 40$)	P[2]
Energy, kcal				
Baseline	1233.49 ± 296.31	1216.28 ± 290.01	1224.43 ± 263.03	
Week 12	1470.02 ± 343.40	1392.22 ± 277.22	1386.21 ± 272.23	0.194
Carbohydrate, g				
Baseline	202.19 ± 49.36	203.52 ± 47.97	204.60 ± 39.02	
Week 12	248.68 ± 54.30	215.70 ± 39.19	214.80 ± 44.42	<0.001
Protein, g				
Baseline	48.36 ± 15.54	45.18 ± 12.73	44.84 ± 11.58	
Week 12	52.28 ± 21.83	69.91 ± 16.98	76.36 ± 16.69	<0.001
Protein, g/kg				
Baseline	0.84 ± 0.28	0.77 ± 0.24	0.80 ± 0.21	
Week 12	0.90 ± 0.38	1.18 ± 0.23	1.37 ± 0.26	<0.001
Lipid, g				
Baseline	26.61 ± 12.21	26.55 ± 11.41	23.38 ± 9.37	
Week 12	24.43 ± 11.36	22.74 ± 9.65	19.05 ± 8.11	0.267
MNA score				
Baseline	20.04 ± 2.40	20.69 ± 2.11	20.89 ± 1.93	
Week 12	23.10 ± 2.76	23.91 ± 2.51	24.11 ± 2.25	0.421

[1]Values are means ± SDs. Values in a row without a common superscript letter are significantly different, $P < 0.05$. MNA, Mini Nutritional Assessment.
[2]P values are from ANCOVA with adjustment for baseline values, sex, Cardiovascular Health Study frailty, diabetes, and osteoporosis.

soy protein (29). This difference in leucine content might have an important mediating influence on maintaining and possibly increasing muscle mass with age, because leucine is able to stimulate the activation of proteins that regulate muscle protein synthesis (30). In the present study, leucine intake from the background diet was similar in the 3 groups (2.9–3.1 g/d), but supplemented leucine intake was 3.1 g/d in the 1.2-g protein · kg^{-1} · d^{-1} group and 4.3 g/d in the 1.5-g protein · kg^{-1} · d^{-1} group.

In addition to the type of protein, the increased deviation from normal protein intake (g · kg^{-1} · d^{-1}) could affect gains of muscle mass. Moore et al. (14) showed a breakpoint for the stimulation of muscle protein when consuming protein at 0.4 g/kg in older people. In the studies by Smoliner et al. (18) and Tieland et al. (15), 1.3–1.4 g milk protein · kg^{-1} · d^{-1} did not improve muscle mass because the deviation from baseline was <0.4 g · kg^{-1} · d^{-1} with a baseline protein intake of 1.0–1.1 g · kg^{-1} · d^{-1}. Our participants in the 1.5-g protein · kg^{-1} · d^{-1} group consumed ∼0.7 g · kg^{-1} · d^{-1} more protein compared with the baseline protein intake of ∼0.8 g · kg^{-1} · d^{-1}; however, the deviation of protein intake from baseline was <0.4 g · kg^{-1} · d^{-1} in the 1.2-g · kg^{-1} · d^{-1} group.

The other major finding of this study was that prefrail and frail elderly subjects at risk of malnutrition experienced improvement in some aspects of physical performance, such as gait speed, beyond the significant gain in muscle mass after consumption of 1.5 g protein · kg^{-1} · d^{-1} compared with consumption of 0.8 g protein · kg^{-1} · d^{-1}. Changes in physical performance are generally observed before measurable changes in skeletal muscle mass become apparent (31). Consistent with the present study, previous clinical trials that used protein supplements also observed significant increases in SPPB scores in frail elderly participants (15) as well as decreased chair-stand time in elderly patients with sarcopenia (32). However, supplementation with hydrolyzed milk (18) and cheese (12) did not improve functional frailty in frail and sarcopenic elderly patients, although energy intake was not monitored during the study. This discrepancy in previous studies could be due to the amount of supplemented protein, as well as changes in energy intake during the study period. Previous studies suggested that not only protein intake after adjusting for energy, but also energy intake itself was associated with frailty (16, 33).

Concerns are frequently raised regarding the impact of high-protein diets on renal function in the elderly, because aging itself is known to negatively affect kidney function (34). In the present study, BUN was significantly increased in the elderly consuming 1.2 and 1.5 g protein · kg^{-1} · d^{-1} compared with 0.8 g protein · kg^{-1} · d^{-1}, but was within normal limits. Kerstetter et al. (13) also reported an increase in glomerular filtration rate in an elderly population supplemented with protein, but their measures were also within normal limits. Thus, these studies suggest that protein supplementation has no detrimental effect on kidney function in elderly people with normal kidney function.

The present study has several strengths. The study participants accurately reflect an elderly population with risk of frailty and malnutrition, and baseline characteristics of the participants were similar between groups. Dietary intake and adherence to the intervention were carefully monitored by dietitians with independent validation with the use of repeated 24-h recall. Thus, mean protein intake of the present study was very close to the target protein intake, and energy intake was maintained among groups during the intervention. However, this study has a few limitations. First, participants could have become more familiar with the repetitive physical function tests during the 12 wk, and the familiarity could have led to an improvement in test scores in all groups. However, the effect of repetition was not biased to any specific treatment group. Second, the time of protein administration (with meals or between meals) could be an important factor in enhancing muscle mass and strength, but

TABLE 3
Physical performance during the 12-wk intervention in the 0.8-, 1.2-, and 1.5-g protein · kg^{-1} · d^{-1} groups[1]

Outcome variables		Protein intake of 0.8 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.2 g · kg^{-1} · d^{-1} ($n = 40$)	Protein intake of 1.5 g · kg^{-1} · d^{-1} ($n = 40$)	P[2]		
					Group	Time	Group × time
CHS frailty criteria score	Baseline	1.70 ± 0.82	1.78 ± 0.89	1.93 ± 0.94	0.881	<0.001	0.530
	Week 6	1.13 ± 1.14	1.04 ± 1.05	1.22 ± 1.02			
	Week 12	1.00 ± 1.05	0.96 ± 0.89	0.99 ± 0.88			
KLoSHA frailty criteria score	Baseline	0.19 ± 0.06	0.22 ± 0.08	0.21 ± 0.08	0.488	<0.001	0.948
	Week 6	0.18 ± 0.06	0.20 ± 0.08	0.18 ± 0.07			
	Week 12	0.16 ± 0.05	0.19 ± 0.08	0.18 ± 0.06			
SPPB score	Baseline	10.22 ± 1.79	9.88 ± 1.91	9.95 ± 1.95	0.924	<0.001	0.365
	Week 6	10.88 ± 1.50	10.64 ± 1.55	10.74 ± 1.68			
	Week 12	11.31 ± 1.37	10.70 ± 1.78	11.10 ± 1.45			
Gait speed, m/s	Baseline	0.99 ± 0.33	1.01 ± 0.34	1.00 ± 0.32	0.540	0.102	0.007
	Week 6	1.02 ± 0.28	1.03 ± 0.28	1.03 ± 0.28			
	Week 12	1.03 ± 0.26[a]	1.02 ± 0.30[ab]	1.09 ± 0.26[b]			
Balance test	Baseline	3.60 ± 0.84	3.68 ± 0.66	3.70 ± 0.56	0.168	0.002	0.319
	Week 6	3.77 ± 0.55	3.86 ± 0.44	3.95 ± 0.25			
	Week 12	3.92 ± 0.39	3.87 ± 0.42	3.97 ± 0.27			
Sit-to-stand, s	Baseline	12.61 ± 5.66	13.34 ± 6.46	13.95 ± 6.44	0.359	0.008	0.881
	Week 6	10.40 ± 3.01	11.84 ± 4.78	11.64 ± 4.68			
	Week 12	9.77 ± 3.17	10.69 ± 4.43	10.88 ± 4.21			
K-MMSE score	Baseline	25.30 ± 2.81	24.03 ± 3.55	24.40 ± 4.09	0.350	0.012	0.702
	Week 6	26.03 ± 3.11	24.86 ± 3.46	25.35 ± 3.40			
	Week 12	26.38 ± 2.64	25.50 ± 2.85	25.92 ± 3.14			
TUG test, s	Baseline	9.73 ± 3.02	10.09 ± 3.77	9.74 ± 3.25	0.859	<0.001	0.207
	Week 6	8.42 ± 2.32	9.06 ± 3.15	8.79 ± 2.85			
	Week 12	8.36 ± 2.23	8.93 ± 3.51	7.90 ± 2.38			
HGS, kg	Baseline	20.01 ± 6.18	20.65 ± 7.86	18.80 ± 7.10	0.604	<0.001	0.553
	Week 6	21.40 ± 6.29	20.47 ± 7.77	19.38 ± 6.80			
	Week 12	21.80 ± 6.03	21.91 ± 7.35	20.29 ± 6.41			
PA, kcal/wk	Baseline	1496 ± 1482	1437 ± 1254	1374 ± 1396	0.813	0.782	0.733
	Week 6	1458 ± 1364	1570 ± 1649	1181 ± 1006			
	Week 12	1532 ± 1330	1373 ± 1427	1212 ± 1011			

[1] Values are means ± SDs. Values in a row without a common superscript letter are significantly different, $P < 0.05$. CHS, Cardiovascular Health Study; HGS, handgrip strength; K-MMSE, Korean Mini-Mental State Examination; KLoSHA, Korean Longitudinal Study on Health and Aging; PA, physical activity; SPPB, Short Physical Performance Battery; TUG, timed up-and-go.

[2] P values are from linear mixed-effects models for repeated-measures data with covariates of sex, CHS frailty, diabetes, and osteoporosis.

was not controlled here. Last, the type I error might have been increased due to comparison of multiple outcome variables.

The present study demonstrates that protein intake of 1.5 g · kg^{-1} · d^{-1} improves muscle mass and physical performance compared with an isocaloric protein intake of 0.8 g · kg^{-1} · d^{-1} or 1.2 g · kg^{-1} · d^{-1} without adverse effects in prefrail or frail elderly people at risk of malnutrition. Thus, the present study suggests that protein intake of 1.5 g · kg^{-1} · d^{-1} could be beneficial for geriatric patients.

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