Review

EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly

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Summary

Background & aims: Older individuals are more likely to experience extended hospitalization and become protein malnourished during hospitalization. The concomitant compulsory inactivity results in functional decline. Increasing protein intake in hospitalized patients improves nitrogen balance, but effects on function are unknown. In the present study, we examined the effects of increasing protein intake by essential amino acid (EAA) supplementation in older individuals subjected to 10 d bed rest on LBM and muscle function.

Methods: Subjects were given a placebo (n = 12, 68 ± 5 (SD) yrs, 83 ± 19 kg) or 15 g of EAA (n = 10, 71 ± 6, 72 ± 8 kg) 3 times per day throughout 10 d of bed rest. LBM, muscle protein synthesis, and muscle function were determined before and after bed rest. Due to an imbalance in randomized gender distribution between groups, gender and beginning functional and LBM measures were utilized for analyses by repeated measures analysis of covariance (RMANCOVA).

Results: Analyses revealed the potential for the preservation of functional outcomes with EAA supplementation.

Conclusions: Increasing protein intake above the RDA may preserve muscle function in the elderly during compulsory inactivity. EAA supplementation is potentially an efficient method of increasing protein intake without affecting satiety.

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1. Introduction

The elderly represent the majority of hospitalized patients and the number of hospitalized elderly is projected to double by 2030. Physical inactivity, or compulsory bed rest during hospitalization, has long been proposed as a primary factor contributing to the functional decline of older hospitalized patients. Duration of hospitalization tends to be longer in the elderly, in part due to the loss of functional capacity with depleted muscle mass. Between 30 and 55% of older patients realize a decline in activities of daily living, and up to 65% experience a decrease in ambulatory function with hospitalization. Inadequate dietary intake prior to, and during, hospitalization is common in this population and may lead to depleted mass and subsequent loss of function. Many elderly are institutionalized prior to hospitalization, and as many as 50% are protein malnourished. While hospitalized, the stress response coupled with inactivity and inadequate protein intake results in a further loss of muscle mass and delayed functional recovery. It has been demonstrated that 21% of elderly patients receive less than 50% of their daily dietary requirement (including protein), and that this shortfall increases the risk of mortality.

Increasing dietary protein intake is beneficial in patients. An increase of dietary protein from 0.5 to 1.0, 1.5, and 2.0 g protein/kg/d in malnourished hospitalized patients resulted in progressively greater rates of whole-body protein synthesis and improved nitrogen balance. A traditional means of increasing dietary protein intake in an older population is the addition of popular
liquid meal replacements. However, our group has demonstrated that the elderly often reduce their dietary intake by the caloric equivalent of the supplement. Thus, an ideal supplement would confer benefits to skeletal muscle without interfering with meal intake or meal effects. High quality protein such as whey or casein stimulates muscle protein synthesis in proportion to the amount of ingested essential amino acids. We have previously demonstrated that the essential amino acids (EAA) alone are primarily responsible for the stimulation of net protein synthesis in skeletal muscle. The increase in protein synthesis, or protein turnover, has functional implications. The rate of muscle protein synthesis, in particular myofibrillar protein synthesis, is related to muscle strength. Thus, it is conceivable that with increased protein intake and muscle protein turnover muscle function will be affected.

In younger subjects, increasing dietary protein intake from 0.6 to 1.0 g/kg/d prevented the decrease in whole-body protein synthesis from 7 d of bed rest alone. It has recently been suggested that the RDA for protein intake (0.8 g/kg/d) may be inadequate in the elderly and that an intake of 1.5 g/kg/d is more reasonable for optimal health and function. Traditionally, protein intake declines over the lifespan, and may be a consequence of factors such as cost, altered taste perception with aging, difficulty with chewing and swallowing, and difficulty in food preparation. Increasing protein intake entails the concern of increased saturated fat intake with animal proteins. These issues can be circumvented with effective protein supplementation. We have previously demonstrated the anabolic effect of EAA in elderly muscle, and therefore reasoned that increasing dietary protein intake with an EAA supplement would provide an opportunity to efficiently augment protein intake. Thus, we investigated the supplementation of EAA to a diet containing the RDA for protein in the elderly during 10 d of bed rest and hypothesized that EAA supplementation would maintain lean mass and muscle function.

2. Materials and methods

2.1. Subjects

Twenty-five older subjects who were moderately active were recruited for this study. Twenty-one subjects completed the study, and were either given a placebo (Control Group; n = 11, 68 ± 5 (SD) yrs, 83 ± 19 kg) or 15 g of EAA (EAA Group; n = 10, 71 ± 6, 72 ± 8 kg). The EAA were delivered by mixing the free-form amino acids with a non-caloric diet soda 3 times per day throughout 10 d of bed rest. The placebo consisted of just the non-caloric diet soda. Subjects were blinded to treatment and were not studied in more than one treatment group. The control group was studied and completed first, and data related to this portion was previously reported. The composition of the EAA drink is outlined in Table 1. Subjects were recruited from advertisements and compensated for their participation, and the studies were approved by the IRBs at the University of Arkansas for Medical Sciences and The University of Texas Medical Branch. Exclusion criteria included body mass index (BMI) < 35 kg/m², diabetes (determined by history and physical or glucose greater than 200 mg/dl at 2 h of OGTT), current smoking, active malignancy, uncontrolled hypertension, history of cardiovascular disease including stroke, history of deep vein thrombosis/pulmonary embolism or hypercoagulability disorder, significant hepatic or renal disease, chronic inflammatory disease (e.g., rheumatoid arthritis), and a short physical performance battery (SPPB) score less than 9. Potential subjects were also excluded if they were taking any medications known to affect protein metabolism (e.g., corticosteroids, anabolic steroids). There was no attempt to match or stratify groups based on gender or outcomes variables.

2.2. Experimental protocol

The experimental protocol is depicted in Table 2. Subjects consumed a lacto-ovo vegetarian diet providing the RDA for protein (0.8 g/kg of protein per day) during diet stabilization and bed rest. The non-protein component of the menu was adjusted to provide approximately 60% energy from carbohydrate and 40% from fat. The diet consisted of a 3-d rotation based on the Harris–Benedict equation designed to maintain body weight throughout the study. An activity factor (AF) of 1.6 during diet stabilization (study days 1–8; Table 2) and 1.3 during bed rest (study days 9–19) was used to estimate daily energy requirement according to the following equation: weight requirement (kcal) = [66 + (13.7 × weight in kg) + (5 × height in cm) – (608 × age in yr)] × AF. After a diet stabilization period of 8 days, subjects remained in bed continuously for 10 days, except for toileting. Water was provided ad libitum. The EAA group was given a supplemental 45 g (15 g TID) of amino acids in addition to the dietary intake. Supplements were ingested between meals, at 1100, 1600, and 2100 h. Prophylactic measures were performed to prevent deep vein thrombosis, and ultrason examination results were negative for all participants at

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### Table 1

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Amount (g)</th>
<th>Proportion of total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histidine</td>
<td>0.488</td>
<td>3.26</td>
</tr>
<tr>
<td>Isoleucine</td>
<td>1.286</td>
<td>8.57</td>
</tr>
<tr>
<td>Leucine</td>
<td>5.382</td>
<td>35.88</td>
</tr>
<tr>
<td>Lysine (HCl)</td>
<td>2.561</td>
<td>17.08</td>
</tr>
<tr>
<td>Methionine</td>
<td>0.538</td>
<td>3.59</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>0.698</td>
<td>4.65</td>
</tr>
<tr>
<td>Threonine</td>
<td>1.435</td>
<td>9.57</td>
</tr>
<tr>
<td>Valine</td>
<td>1.116</td>
<td>7.44</td>
</tr>
<tr>
<td>Arginine</td>
<td>1.495</td>
<td>9.97</td>
</tr>
<tr>
<td>Total</td>
<td>15.000</td>
<td>100.00</td>
</tr>
</tbody>
</table>

Caloric content – 45 kcal.

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### Abbreviations

- DEXA: Dual-Energy X-ray Absorptiometry
- DVT: Deep Vein Thrombosis
- OGTT: Oral Glucose Tolerance Test
- POMS: Profile of Mood States
- REE: Resting Energy Expenditure Test
- SPPB: Short Physical Performance Battery
the conclusion of the bed rest. Outcome testing is also depicted in Table 2. Results of other experimental tests will be presented elsewhere. Nitrogen balance, changes in lean body mass, and muscle protein synthetic rate for the control group have been previously reported. Muscle protein synthesis and lean body mass for the control group are included here for comparisons with the EAA group.

2.3. Methods

Measurements before and after bed rest included the fractional muscle protein synthesis rate over 24 h, lean and fat body mass by dual-energy X-ray absorptiometry (DEXA), standing plantar flexion strength, and functional assessments of stair ascent power, stair descent power, and floor transfer time. Strength and functional measures were performed on Study Day 1 as a familiarization and again on Study Day 3 for evaluation purposes to minimize a learning effect (Table 2).

Body composition was determined by DEXA on a QDR 4500 W (Hologic, Inc., Bedford, MA.). Regional (leg) determination of lean mass was accomplished with APEX software, V 2.2.

Muscle protein synthesis was determined by 24-h incorporation of ring-13C6-phenylalanine. A primed (4.2 μmol/kg), constant (0.07 μmol/kg/min) infusion was initiated after 8 h in the fasted state and the first biopsy of the vastus lateralis was conducted after 2–3 h of tracer infusion. A second biopsy was taken approximately 24 h later, again after 8–10 h in the fasted state. Biopsy samples were immediately rinsed, blotted, and frozen in liquid nitrogen. Upon thawing, proteins were precipitated with 800 μl of 14% perchloroacetic acid. Tissue was homogenized, centrifuged, and free cell free amino acids (labeled phenylalanine) were extracted from the supernatant by cation exchange chromatography (Dowex AG 50W-8X, 100–200 mesh H+ form; Bio-Rad Laboratories, Richmond, CA) and dried under vacuum (Savant Industries, Farmingdale, NY). The remaining muscle pellet was washed and dried, hydrolyzed in 6 N HCl at 50 °C for 24 h. Muscle free and protein-bound ring-13C6-phenylalanine enrichment were determined using the tert-butyl-dimethylsilyl derivative and GCMS (HP model 5973, Hewlett-Packard Co.) with electron impact ionization and selective ion monitoring for ions 234 and 242. Fractional synthetic rate (FSR) was determined as the incorporation of tracer over a 24 h period. For each group, supplement/placebo was given according to the time schedule previously described (1100, 1600, and 2100 h). Though this represented an integrated value of muscle protein synthesis which included fed and fasted periods, biopsies were taken after 8–10 h of fasting, thus alleviating confounding effects of nutritional intake and non-steady state tracer kinetics. Given that intracellular enrichment would most likely decrease during periods of feeding, this measure represents an underestimate of 24 h muscle protein synthesis because of possible overestimation of precursor enrichment. FSR was calculated according to the following precursor-product model: FSR = [(Ept2 - Ept1)/(Em × t)] × 60 × 100, where Ept1 and Ept2 are the enrichments of bound ring-13C6-phenylalanine in the first and second biopsies, respectively, t is the time in minutes between biopsies, and Em is the mean ring-13C6-phenylalanine enrichment in the intracellular pool.21 The factors of 60 (min/h) and 100 (%) are for conversion to percent per hour.

Stair ascent/descent power was determined as described by Fiatarone et al.11 For the stair ascent test, subjects were asked to start from a standing position and walk up 10 steps as quickly as comfortably possible. Subjects were instructed to place one hand close to the handrail for balance if necessary, but not on the handrail. The time to walk up 10 steps was determined by using a stopwatch. After a short rest period, the subject was repositioned at the top of the stairs, and the stair descent test was performed in a similar fashion. Pre- and post-bed rest stair tests were conducted on the same flight of stairs. Power was calculated as work (force [subjects' body mass in kg × g (9.8 m/s²)] × the vertical height of the stairs in meters) divided by time in seconds.

Floor transfer time was performed as described by Wang et al.22 The time for a subject to move from a complete standing to a long-sitting position on a mat (i.e., legs extended in front of the body) and then back up to complete standing was measured using a stopwatch. A chair was placed nearby to be used for support, if needed, during this task.

Standing plantar flexion strength was determined by asking subjects to stand on their right leg while lightly resting their hand on a counter and applying no more than 20 lbs of force as measured by a scale. The subject was then instructed to rise onto the ball of their foot and then lower their heel back down as many times as possible in a 30 s period. Subjects were encouraged to maintain an erect posture and straight knee throughout the movement, and instructed to complete each repetition using a full range of motion.

2.4. Statistical analysis

The difference in pre- and post-bed rest measures between groups was tested statistically by repeated measures analysis of variance (RMANOVA) and Tukey's post hoc test. Because of the initial differences in several of the pre-bed rest values, a 2-sample t-test was performed to ascertain initial group differences. Further, a RMANCOVA was performed in order to account for the effects of the pre-bed rest outcome values (including LBM) and gender. A Bonferonni correction was made for multiple comparisons and significance is reported for each parameter. The statistical software package utilized was SAS 9.1 (SAS Institute Inc., Cary, NC). Outcome measures are reported as mean ± SEM.

3. Results

3.1. Subjects

Twelve control subjects began the study; however, one subject withdrew after the first metabolic study. Thirteen subjects were enrolled in the EAA group. Two subjects stated that they were too weak to perform post-bed rest function measures, and one subject was not tested in these functional outcomes. There were no adverse events associated with bed rest in these subjects. The gender distribution of each group, as a result of recruitment and subject qualification, was 6 male/6 female in the control group, and 1 male/9 female in the EAA group. A 2-sample t-test of pre-bed rest values of FSR, LBM, and functional measures revealed no initial differences between groups. Despite this finding, ANCOVA results utilizing the disparate initial values as a covariate are presented in Table 3.

3.2. Muscle protein synthesis

Twenty-four hour FSR was determined on 10 control subjects and 7 EAA subjects (Fig. 1). In control subjects, FSR decreased 30% from 0.077 ± 0.008%/h to 0.051 ± 0.007%/h, while FSR was maintained in the EAA group (0.069 ± 0.005%/h pre-bed rest to 0.070 ± 0.008%/h post-bed rest). There was a significant group by time interaction by ANOVA (P = 0.025); however, when adjusting for pre-bed rest value and gender (ANCOVA), there was a trend towards a significant interaction (P = 0.065). When adjusting for pre-bed rest values and leg LBM, there was no significant interaction of treatment and time (P = 0.283).
intake was large enough to induce the negative nitrogen balance; however, a greater period of accommodation may have resulted in eventual adaptation and balance. A previous study in frail women indicated that their normal dietary protein intake by 5 g food diary was near the RDA and further, and that they were able to maintain nitrogen balance on a 9 g diet at this intake (0.87 g protein/kg/d).24 In any event, protein intake at the RDA resulted in a loss of muscle mass and function during inactivity/bed rest in these elderly subjects.

Our results indicate that additional protein alone is not capable of reducing the loss of lean mass during inactivity in the elderly. It is likely that the calculated loss of lean mass by DEXA was accurate, as the losses in body weight closely agree with losses in total lean mass and there were no changes in urine specific gravity. A previous study demonstrated that the abrupt interruption of normal activity with rigorous bed rest of 7 d induces a loss of fluid from all compartments; however, they also demonstrated a decrease in urine osmolality.25 We have previously demonstrated that bed rest is associated with a loss of muscle volume in younger subjects.26 Thus, while it is possible that the loss of lean mass as determined by DEXA was in part reflect of a loss of body fluid in these older subjects, a loss of lean tissue is likely and is consistent with the loss of muscle function. Our previous bed rest studies in young subjects utilized a diet containing 1.1–1.2 g protein/kg/d and also demonstrated losses in lean mass.27,28 When this diet was augmented in young subjects with an EAA plus carbohydrate supplement, lean mass was preserved.26 Provision of EAA supplementation in the young resulted in a total protein intake of approximately 1.5 g/kg/d.28 In the current study, EAA supplementation increased the protein intake from the 0.8 g/kg/d to approximately 1.4 g/kg/d. Though the addition of carbohydrate to EAA stimulates muscle anabolism to a greater degree in the young, this response is not present in the elderly.29 Thus, it appears that during bed rest, a protein intake that preserves the loss of lean mass in the young is ineffective in the elderly.

The aspect of increased protein intake by EAA supplementation which may be relevant in both young and elderly subjects during bed rest is the potential for ameliorating functional loss. Increasing protein intake to 1.4 g/kg/d in the elderly with EAA supplementation indicates the potential for preserving muscle function. Given the statistical treatment for group imbalance and gender, the differences in absolute change in several outcomes and statistical treatment(s) indicate the potential for preservation of functional outcomes. Amelioration of the loss of function with increased protein intake is likely related to the maintenance of protein turnover. The value of muscle protein synthesis was maintained with EAA supplementation in these elderly subjects, and depending on the covariate utilized, indicated a trend towards a significant interaction. These data are consistent with other investigations. In frail elderly women, increasing protein intake from 0.87 to 1.23 g

### Table 3

Body mass and muscle function outcomes.

<table>
<thead>
<tr>
<th>Parameter/group</th>
<th>Pre-bed rest</th>
<th>Post-bed rest</th>
<th>% Change</th>
<th>p&lt;sub&gt;1&lt;/sub&gt;</th>
<th>p&lt;sub&gt;2&lt;/sub&gt;</th>
<th>p&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total lean mass (kg)</td>
<td>46.8 (0.3), N = 9</td>
<td>45.3 (0.3), N = 11</td>
<td>−2.9 (0.9)</td>
<td>−2.0 (0.7)</td>
<td>0.29</td>
<td>0.465</td>
</tr>
<tr>
<td>Leg lean mass (kg)</td>
<td>145.0 (41.2), N = 9</td>
<td>133.0 (41.2), N = 11</td>
<td>−9.1 (1.6)</td>
<td>−8.3 (1.8)</td>
<td>0.77</td>
<td>0.931</td>
</tr>
<tr>
<td>Total fat mass (kg)</td>
<td>27.0 (0.3), N = 9</td>
<td>27.0 (0.3), N = 11</td>
<td>0</td>
<td>0</td>
<td>0.86</td>
<td>0.950</td>
</tr>
<tr>
<td>Standing plantar flexion (rep/30 s)</td>
<td>21.8 (3.4), N = 7</td>
<td>20.9 (2.8), N = 12</td>
<td>−0.19 (0.04)</td>
<td>−0.19 (0.10)</td>
<td>0.054</td>
<td>0.200</td>
</tr>
<tr>
<td>Floor transfer time (s)</td>
<td>8.3 (1.1), N = 11</td>
<td>12.8 (2.3), N = 12</td>
<td>51 (17)</td>
<td>51 (17)</td>
<td>0.027</td>
<td>0.016</td>
</tr>
</tbody>
</table>

The N for each measure/group is included. Numbers are mean ± (SEM); p<sub>1</sub> is statistical significance (P value) for group by time interaction (RM ANOVA with Tukey's post hoc test); p<sub>2</sub> is statistical significance by ANCOVA considering the baselines measures and gender effects in each parameter. p<sub>3</sub> is statistical significance by ANCOVA adjusting for baseline measures and leg LBM. There were no significant differences between groups in pre-bed rest variables.

### 3.3. Body mass changes

Table 3 summarizes changes in total lean, fat, and leg lean masses. There was no effect of EAA on the maintenance of total or leg lean mass. Fat mass was maintained equally, indicating adequate caloric intake in each group. Weight loss in the control group was 2.66 ± 0.51 kg, while the EAA group lost 1.59 ± 0.18 kg. A t-test of the weight loss revealed a P = 0.059. There were no changes in urine specific gravity throughout the protocol in either group (control pre = 1.013, post = 1.010; EAA pre = 1.012, post = 1.012), indicating an absence of diuresis due to bed rest.

### 3.4. Strength and functional changes

Table 3 summarizes changes in strength and function measures. With ANCOVA analysis considering gender, pre-bed rest values and leg LBM, floor transfer time was impaired in the CON group and maintained with EAA supplementation. There was a trend towards the maintenance of stair ascent power and standing plantar flexion with EAA supplementation.

### 4. Discussion

An important finding of this study is that the RDA for protein is inadequate in the elderly, and that this inadequacy is exacerbated with inactivity. We had previously reported that prior to bed rest our subjects were in negative nitrogen balance.20 Our group has previously demonstrated that healthy subjects similar to those studied on this protocol consume approximately 0.94 g protein/kg/d. Augmentation of the weight loss revealed a P = 0.059. There were no changes in urine specific gravity throughout the protocol in either group (control pre = 1.013, post = 1.010; EAA pre = 1.012, post = 1.012), indicating an absence of diuresis due to bed rest.

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![Fig. 1. Twenty-four hour muscle protein synthesis (fractional synthetic rate; FSR) before and after 10 d of bed rest in elderly subjects. Control – (n = 110); placebo drink of non-caloric diet soda); EAA – (n = 87; 3 drinks of 15 g/d of amino acids (listed in Table 1)). There were no significant pre-bed rest differences between groups by t-test.](image-url)
protein/kg/d also increased whole-body protein synthesis and protein balance.24 Increasing dietary protein intake from 0.5 to 1.0, 1.5, and 2.0 g protein/kg/d in malnourished elderly hospitalized patients resulted in progressively improved rates of whole-body protein synthesis and improved nitrogen balance.10 Our previous investigation in young subjects during bed rest is not directly analogous, since carbohydrate was co-administered resulting in a greater caloric intake.25 However, the study in young subjects indicated that similar protein intake to the current study preserved muscle protein synthesis and ameliorated the decline in muscle strength.28

The amelioration of functional decline in the young was the result of improved function at the single fiber level.30 Single fiber function was maintained through the protection of peak force in Type I fibers and peak power in Type II fibers.30 Thus, it is plausible that the maintenance of protein turnover via the maintenance of protein synthesis leads to the maintenance of more functional fibers. Additional evidence is provided in the demonstrated relationship between myofibrillar protein synthesis and muscle strength.16 Though we did not measure myofibrillar protein synthesis in these elderly subjects, Glover et al. have recently demonstrated that the provision of amino acids to subjects after unilateral knee immobilization (muscular inactivity) resulted in an increase in myofibrillar protein synthesis.31 Taken together, these data are consistent with the proposal that increased protein intake maintains muscle protein turnover and protects fiber function during muscular inactivity.

It has been suggested that optimal health status, reduced risk of chronic disease and improved outcomes can be realized in the elderly with a protein intake of approximately 1.5 g protein/kg/d (reviewed by Wolfe et al.18). This level of protein intake may be particularly relevant to the elderly during compulsory inactivity. However, the straightforward provision of dietary and protein supplements is often not effective in improving lean mass or muscle function in the elderly.11,32 The failure of these nutritional supplements is related in large part to the fact that subjects decrease dietary intake by a caloric amount equivalent to the calories contained in the supplement.11 The supplements, which are most often liquid meal replacements, induce satiety and affect subsequent intake. This may be one of several reasons why elderly hospitalized patients often eat only one-half of their required dietary intake.28 On the contrary, constituent amino acid administration does not affect satiety, and further, does not alter the metabolic effects of subsequent meals.33 Increasing protein intake by EAA supplementation may be a promising means of improving protein intake in the elderly. Assuming a complete protein contains about 40–45% essential amino acids, the current provision of 3 x 15 g of EAA would entail a dietary intake of approximately 3 x 35 g of whey protein. The simple addition of bulk protein to the diet is not an optimal solution and entails a large energy component. Increasing protein intake with EAA supplementation is advantageous in terms of efficacy, convenience, flexibility of delivery (capsules, drink) and rapid absorption.

**Conflict of interest**

There is no conflict of interest.

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**Statistical Analysis:** Hays

**Funding:** Ferrando, Wolfe, Evans

**References**


