Journal of Aging Research & Clinical Practice©
Volume 2, Number 4, 2013

INCREASED NITROGEN INTAKE FOLLOWING HIP ARTHROPLASTY EXPEDITES MUSCLE STRENGTH RECOVERY

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Abstract: *Background: Objectives:* The aim of this study was to investigate the effects of increased nitrogen intake, via amino acid supplementation, on strength and functional recovery after THA. *Design:* Prospective, randomized clinical trial. *Setting:* Academic medical center; orthopedic clinic. *Participants:* Patients scheduled to receive elective hip arthroplasty. *Intervention:* Patients were randomly assigned to receive usual care (UC; n = 8, 55 ± 7 (SD) y) or 15 g of essential amino acid supplementation 3 times per day (EAA; n = 8, 55 ± 8 y) for 8 weeks. *Measurements:* Leg strength (maximal voluntary contraction of the quadriceps) was measured by hand-held dynamometer, and function by 4 meter walk and a chair stand test pre-surgery, 2, and 8 weeks post-surgery. *Results:* Improvement in leg strength was greater in the EAA group, as was the rate of improvement from weeks 2 to 8 post-surgery. Improved strength was realized without an increase in lean mass. Both groups improved chair stand and 4 meter walk times. EAA supplementation increased total protein intake by 0.6g/kg/d (EAA 1.7 g/kg/d vs UC 1.1 g/kg/d). *Conclusions:* Increased nitrogen intake via amino acid supplementation improves the rate of recovery of leg muscle strength following THA.

Key words: Essential amino acids, hip arthroplasty, paximal voluntary contraction, leg strength and function.

Abbreviations: EAA: essential amino acids; MVC: maximal voluntary contraction; UC: usual care rehabilitation; THA: total hip arthroplasty.

Background

Although total hip arthroplasty (THA) is the final treatment to counteract compromised mobility function resulting from osteoarthritis or other chronic disease (e.g., avascular necrosis), the great irony in far too many cases is that THA leads to muscle atrophy (1, 2) and dismobility (3, 4) that persist for extended periods and impose significant burden on both the individual's quality of life and healthcare utilization. For example, compared to a non-surgical population, total hip arthroplasty (THA) patients are 2- to 10-fold more likely to suffer functional impairment two years post-surgery (3). Five years after hip surgery, 35% of patients report moderate to severe mobility limitation; many with frank disability (unable to walk or entirely dependent on aids) (4). When compared with an age-matched general population, THA patients experience more difficulty in performing activities of daily living such as bending forward, climbing stairs, getting in and out of a chair, dressing, and walking more than 300 meters (4). This loss of muscle function is often not corrected indicating that a more effective rehabilitative strategy is required to improve outcomes. Failure to address the losses of muscle strength and function during rehabilitation limits the long-term functionality of THA recipients (4).

Previous work from our laboratory (5) and others (6) demonstrated the efficacy of supplementation with essential amino acids (EAA) on strength and functional outcomes in older individuals. Supplementation with EAA is an effective means of experimentally increasing nitrogen intake, since only the EAAs are required for the stimulation of muscle protein anabolism (7). During the catabolic condition of chronic inactivity, EAA supplementation preserved functional parameters in both young (8) and older subjects (5). The metabolic mechanism responsible for preservation of function (5) and strength (8) during inactivity appears to be the

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Received May 16, 2013
Accepted for publication May 20, 2013

maintenance of muscle protein synthesis. We have also demonstrated that EAA stimulation of muscle protein synthesis is consistent across age groups (9). Rehabilitation from THA entails predominant inactivity, especially early in the post-surgical period. Pain resolution with joint replacement/repair and the healing of soft tissue permit increased activity. Patient recovery; however, is entirely dependent upon their rehabilitative efforts, which is highly variable. Given this variability and the absence of standardization in exercise/strengthening rehabilitation programs, we endeavored to determine the effects of a simple nutritional formula on the recovery of muscle strength and function after THA. Due to the consistent findings on the effects of EAA on muscle protein synthesis, we hypothesized that increasing protein/nitrogen intake via EAA supplementation throughout 8 weeks of rehabilitation would increase muscle anabolism and translate to improved recovery of strength and functional outcomes.

Methods

Subjects

Subjects were recruited from the University of Arkansas for Medical Sciences (UAMS) Orthopedic Clinic once scheduled for hip replacement, hip resurfacing, or THA revision surgery. The study was approved by UAMS IRB. Subjects were recruited by the attending surgeon (RPE) and consented by the study nurse (SES) after the study was described and discussed in detail. While the initial subject age range was set between the ages of 40 and 80 y, our surgical population was generally younger than 60 yr of age (Table 1). This is consistent with future projections for THA in younger populations[10]. Subjects were randomly assigned to a usual care group (UC; n = 8, 55 ± 7 (SD) y; range 45-65 y) or a group that received 3 doses per day of 15g of EAA capsules (n = 8, 55 ± 8 y; range 45-68 y) for 8 weeks post-surgery. Patients were excluded if they were taking

Table 1
Subject Characteristics

	Subject ID	Age	Gender	Surgical Procedure	[1]Rehab Info
Group					
Usual Care	1	59	M	Hip Resurfacing	NFR
	5	56	M	Total Hip	1/wk, 45min, 12 wk
	9	45	M	Total Hip	3/wk, 1hr, 8 wk
	10	57	F	Total Hip	3/wk, 1hr, 4 wks
	14	62	F	Hip Resurfacing	3/wk, 45min, 16wk
	16	65	F	Hip Resurfacing	3/wk, 1.5hrs, 10 wk
	23	50	M	Total Hip	1/wk, 45min, 6wk
	27	47	M	Total Hip	3/wk, 1hr, 8wk
N		8			
Mean		55.1			
SD		7.2			
Supplement	3	52	M	Total Hip	NFR
	4	52	M	Total Hip	2/wk, 1-2hr, 8wk
	6	51	F	Total Hip	NFR
	7	45	M	Total Hip	3/wk, 30min, 6wk
	11	53	M	Total Hip	3/wk, 1hr, 6wk
	17	52	M	Hip Resurfacing	3/wk, 30min, 6wk
	18	68	F	Hip Revision	1/wk, 1hr, 8wk
	22	64	F	Total Hip	3/wk, 1hr, 8wk
	45	53	M	Total Hip	3/wk, 30min, 1wk
N		8			
Mean		54.6			
SD		7.5			

Definition of Terms. Total Hip: replacement of the hip joint with an artificial prosthesis; Hip Revision: removal of previously implanted artificial hip joint, or prosthesis, and replacement with a new prosthesis; Hip Resurfacing: placement of a metal cap over the head of the femur and a matching metal cup (similar to a total hip) is placed in the acetabulum. 1 Characterization of formal (rehabilitation facility) rehabilitation as number of sessions per week, session duration, and total weeks of rehabilitation. NFR – no formal rehabilitation.

insulin, on thiazolidinedione (TZD) drugs, or metformin; had a history of chronic renal insufficiency/disease or liver disease; had uncontrolled hypertension at the time of pre-surgical screening; had any history of hypo- or hyper-coagulation disorders including the taking of Coumadin; had a history of atrial fibrillation, angina or congestive heart failure; had recently (6 months or less) been treated for cancer other than basal cell carcinoma, or if they were pregnant. Bilateral joint replacement patients were excluded due to the confounding effects on strength and functional measures, as well as the different rehabilitation requirements. The UC group was not given placebo capsules for 2 primary reasons. First, this group represents the "standard" of care, though our experience (Table 1) indicates no standardization of rehabilitation. Second, work from our laboratory utilizing placebo treatment in young (9) and older (5) subjects indicates that EAA supplementation is effective in the catabolic circumstance of inactivity. In addition, work from former colleagues in older women supplemented with EAA or placebo for 3 months demonstrated that supplementation resulted in an increase in muscle protein synthesis and lean mass (6). We have also demonstrated increased strength and function in free-living elderly with EAA supplementation (11). Thus, in circumstances representative of recovery from THA, namely initial inactivity and worse case, an older population, EAA supplementation has proven to be efficacious. While rehabilitation in UC was neither controlled nor standardized, the number of sessions per week, the average session duration, and the total weeks of rehabilitation were recorded by questionnaire. Rehabilitation exercises generally included exercises for leg strengthening (e.g., therabands, leg lifts, isotonic weight lifting) and ambulation (e.g., treadmill walking, stationary cycling, balance exercises). The EAA group also had access to UC rehabilitation. Subject characteristics and rehabilitation profiles are outlined in Table 1 for each group.

Experimental Protocol

After consent and prior to surgery, all subjects were brought to the UAMS Reynolds Institute of Aging (RIOA) for dual-energy x-ray absorptiometry (DXA; Hologic Discovery QDR; Hologic, Inc. Bedford, MA) determination of body composition, as well as strength and function measures. Unilateral maximum voluntary isometric knee extensor strength was determined separately for surgical and non-surgical legs with a hand-held dynamometer (Manual Muscle Tester, Lafayette Instrument Co., Lafayette, IN). While the reliable isokinetic dynamometry is currently the gold standard for strength measures (12), limited access and complication with patient/subject adaptability have seen an increasing number of recent clinical studies rely upon strength measures from hand-held dynamometers (13-15). Our subjects were unable to physically arrange themselves on our isokinetic dynamometer 2 wks post-THA. Given recent findings on the reliability of hand-held dynamometry in patients awaiting joint arthroplasty (15) and the determination of muscle strength in rehabilitation unit patients (13), this measurement method was chosen on the basis of its efficacy and practicality. Subjects were seated in the same chair and were allowed to stabilize themselves with the chair armrests. The dynamometer was placed 6 inches (measured) below the tibial tuberosity and the subject was verbally encouraged to give a maximal knee extension effort. Three trials were performed with each leg, with the best effort (kg) recorded. The dynamometer recorded maximal force generated over a 3 sec interval to mitigate peak force derived from rapid acceleration. The measure of MVC is a sensitive indicator of functional strength and is responsive to differences in strength resulting from training and aging (16). Joint and ambulatory function was determined by the 5-repetition sit-to-stand (chair stand) test and the 4-meter gait speed test. To perform the chair stand test, subjects were seated in a chair and were timed performing 5 repetitions of standing and return to the seated position. Time (secs) began upon the first iteration of standing and finished when seated the 5th time. Subjects were not allowed to use their arms for assistance and were instructed to cross their arms across their chest. Four-meter gait speed (m/sec) was determined by time to walk a designated 4-meter course. Subjects started with their toes on the first line and time began when they crossed this line and ended when they crossed the second line. The 4-meter walk and chair stand measures are sensitive predictors of independent living in older people (17), and the sit-to-stand is a sensitive predictor of mortality (18).

These measurements were repeated for all subjects during routine clinical follow-up visits 2 and 8 wks post-surgery. Clinical visits were scheduled for early morning hours. Upon conclusion of conference with the surgeon (RPE), subjects were again brought to the RIOA for repeat DXA, strength, and functional tests.

Immediately following surgery, the EAA group was given pre-packaged dosages of amino acid capsules. The amino acid capsules were formulated by the AminoScience Laboratories at Ajinomoto Co (Ajinomoto Inc, Kawasaki, Japan), and pre-packaged into individual doses by the UAMS Research Pharmacy. Each 15g dose was packaged in 20 gelatin capsules. The composition of each 15g dose is outlined in Table 2. This formulation was very similar (by compounding methods) to the formula previously utilized to maintain muscle protein synthesis and muscle function in elderly subjects during 10d of inactivity (5). Subjects were given adequate doses to span from immediate post-surgery to their scheduled 2 wk clinical visit (plus one week in case a scheduling difficulty occurred). At the 2 wk follow-up visit, subjects were again given adequate doses for the interim 6 wks until their scheduled 8 wk clinical visit. Subjects were instructed to take their dosages between meals, as we demonstrated this paradigm to maximize daily stimulation of muscle protein synthesis (9) without interfering with the effects of subsequent meals (19). In addition, due to the interactive effects of exercise and EAA (20), subjects were instructed to take one of their daily dosages prior to their rehabilitation session, when/if appropriate. Subjects were given instructions to return all used and unused dosage bottles, and compliance was determined accordingly. Subjects were also given 4-d dietary records to complete every 2 weeks. Subjects were instructed to record diet during 4 consecutive days including 2 weekend days (e.g. Thur-Sun or Fri-Mon) during each record period. During post-surgical hospitalization, a research dietitian (AD) instructed each subject on the proper recording of dietary intake. Dietary records were utilized to determine protein and caloric intake throughout rehabilitation. The study coordinator made weekly calls to each subject to encourage supplement (EAA group only) compliance, dietary record keeping, check on rehabilitation progress, and to coordinate return visits.

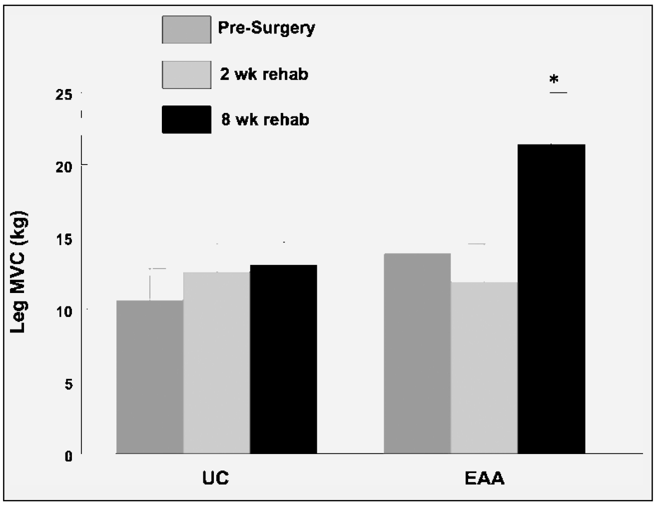
Statistical Analysis

Repeated measures analysis of variance (RM-ANOVA) models were used to compare leg MVC, chair stand time, and 4-m walk time among arthroplasty patients/subjects receiving EAA or UC. The models consisted of treatment (EAA or UC), time (pre-surgery, 2 and 8 weeks post-surgery), and treatment-by-time interaction effects. Analysis of covariance was also performed utilizing gender and age as covariates. Changes in total and leg lean mass from pre-surgery to 8 weeks, and differences in dietary intake were compared by students' t-test. The statistical software package utilized was SAS 9.3 (SAS Institute Inc, Cary, NC). Outcome measures are reported as mean ± SEM, except where otherwise delineated.

Results

Strength/Function: Recovery of leg MVC was greater in the EAA group. The group-by-time interaction approached significance ($P = 0.06$); however, the change over time was significant ($P < 0.02$) for the EAA group only. Further, the rate of improvement from 2 to 8 weeks post-surgery was significant for the EAA group ($P = 0.025$), while the UC group realized no significant improvement over pre-surgical strength after rehabilitation (Figure 1). When the covariates of gender and age were added, there was again a trend towards a group by time interaction ($P = 0.07$), with a highly significant time effect for the EAA group only ($P<0.001$). There were no differences in the chair stand between groups in pre-surgical (14.4 ± 1.7 sec for UC vs 14.0 ± 1.3 sec for EAA) or 8 wk (10.9 ± 1.7 vs 10.9 ± 1.3, respectively) times. The improvement over time was significant in both groups ($P = 0.035$). Four-meter walk speed also improved over time in both groups ($P = 0.041$), again without differences between groups in pre-surgical (5.1 ± 0.7 m/sec for UC vs 4.1 ± 0.6 m/sec for EAA) or 8 wk (2.9 ± 0.7 vs 3.7 ± 0.6, respectively) values.

Figure 1
Leg strength of surgically repaired limb measured by maximal voluntary contraction (MVC) at each clinical time point. The usual care (UC; n=8) group did not improve beyond pre-surgical values after 8wk of rehabilitation, while essential amino acid supplementation (EAA; n= 8) improved by approximately 35%. *Significant improvement with time ($P < 0.02$)



Dietary Intake: Averaged over the 8 weeks, the caloric intake by dietary record was similar between groups (24.3 ± 1.6 kcal/kg UC vs 27.1 ± 3.2 kcal/kg EAA). However, average protein intake was greater in the EAA group when the EAA supplement was added to the protein intake (1.1 ± 0.2 g/kg/d UC vs 1.7 ± 0.2 g/kg/d EAA; $P = 0.035$ by t-test). Further analysis of protein intake in subjects over 60 yrs in each group (Table 1) revealed that those subjects in the UC group consumed 1.42 ± 0.42 g/kg/d of protein, considerably above the RDA and not common among older individuals (21). Compliance with supplement ingestion after 8 weeks was 83% (range 48-98%). While our method of compliance monitoring could not preclude multi-dosing of EAA supplements, the consensus of our work indicates that 15g of EAA produces a maximal anabolic response in skeletal muscle (22). Thus, multi-dosing of EAA would provide no further anabolic benefit and the demonstrated positive relationship to strength outcome would exist with fewer episodes of stimulated muscle anabolism.

Lean body mass: Eight-week changes in leg and total lean mass were highly variable within each group, and not significantly different between groups. Due to the overestimation of lean mass in the affected limb from edema and/or the metal implant (23), we compared changes in lean mass of the unaffected leg. By week 8, the change in leg lean mass of the unaffected leg (8 wk value minus pre-surgical value) in the UC group was -129.6 ± 152.1 g, and in the EAA group -353.6 ± 138.5 g. The change in total lean mass after 8 wks, minus the affected limb (subtracted due to confounders), was 152.3 ± 438.9g in the UC group and -140 ± 336.2 g in the EAA group. Absolute strength changes in the affected limb measured by MVC are shown for THA subjects (Figure 1).

Discussion

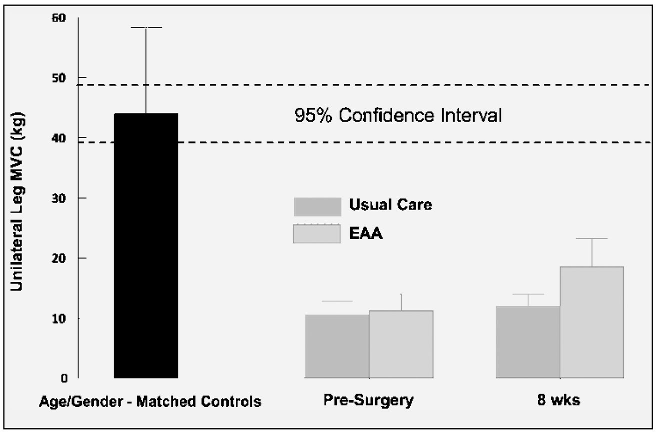
The principal finding of this study is that nutritional supplementation can improve muscle strength after THA. EAAs were utilized as nutritional supplementation in this study for several reasons. First, a 15g dose of EAA has been demonstrated to be anabolic in both younger and older populations (9). Second, this administration regimen ameliorated certain strength and functional losses with strict inactivity in young (8) and older (5) individuals, while maintaining muscle protein synthesis in each case. Though inactivity prevails shortly after THA, we reasoned that with continued healing and rehabilitation, EAA supplementation would help to increase muscle strength due to the interactive effect of EAA and exercise on muscle protein metabolism (20). For this reason, subjects in the EAA group were instructed to take a dose prior to their rehabilitation session. Third, EAA administration equates to complete protein ingestion, as only the essential amino acids required for muscle anabolism (7) were present in the formula (Table 2). Fourth, ingestion of the amino acid constituents minimizes the confounding potential for caloric substitution that often accompanies complete protein and/or supplement ingestion in older people (24). While the EAA group's total protein intake was 0.6 g/kg/d greater than the UC group, caloric intake was the same between groups. Thus, a greater portion of discretionary caloric intake was comprised of protein/amino acids. These data hint to the possibility that protein intake approximately twice the RDA can improve muscle strength without a concomitant gain in LBM after THA. The improvement in strength without a concomitant improvement in LBM is not unusual in an older population. We have previously demonstrated the maintenance of function without a concomitant maintenance of LBM in elderly during inactivity (5). Further, in a free-living elderly population, 16 wk of EAA supplementation improved leg strength by over 22% without a concomitant increase in leg or total lean mass (11). The improvement in strength is also consistent with the positive effects of providing a protein-rich supplement after hip fracture on activities of daily living and grip strength (25). Despite the potential problems associated with caloric substitution, the evaluation of complete protein supplementation on strength and function after THA would be beneficial, as it constitutes a pragmatic treatment option for broad application.

Table 2
EAA Supplement Composition

Amino Acids	Amount (g)
Histidine	0.225
Isoleucine	1.455
Leucine	5.46
Lysine	2.28
Methionine	0.45
Phenylalanine	0.915
Threonine	1.275
Valine	1.5
Tryptophan	0.09
Arginine	1.35
TOTAL	15.0

The improvement in muscular strength with EAA likely resulted from the known effects of EAA on muscle protein turnover, primarily the stimulated increase in muscle protein synthesis (9). Supplementation of a similar EAA formula for 16 weeks in community-dwelling older subjects also improved leg strength (11). Further, the stimulation of protein turnover with EAA during inactivity ameliorated the loss of muscle strength (8), which was likely due, at least in part, to protective effects on peak power generation in the type II muscle fibers (26). The absence of improved mobility function with EAA, which is not consistent with our findings during inactivity in the elderly (5), may be due in part to the higher functionality and generally younger age of our subjects. While there is little epidemiological data on the functionality of 45-60 yo adults, walking speed and chair stand performance from the Health, Aging, and Body Composition Study (Health ABC) indicate that the mean performance values of our subject pool prior to surgery were at or above these cross-sectional norms (27). This was particularly true in the few subjects over 60 in our study, as their scores on the chair stand and walking speed were at or above Health ABC norms, despite compromised joints. Further, while rehabilitation was not controlled or standardized, rehabilitation for THA generally entails exercises designed to increase capacity for the weight-bearing activities of daily living, specifically walking and stair climbing. Thus, functional capacity in these THA patients may have been above a threshold that might otherwise respond to nutritional intervention.

Figure 2
Comparison of leg strength (MVC) with 81 age- and gender-matched subjects from our cross-sectional database. EAA supplementation results in a restoration of approximately 50% of our population data strength value



The question arises as to the capability of nutritional supplementation to fully restore limb strength. The 8-week supplementation period was arbitrarily chosen as it coincided with scheduled patient clinical follow-up. Whether increased time of supplementation would result in further improvements is not known. In 8 weeks the EAA group realized an approximate 35% improvement in leg strength over the pre-surgical value. This improvement is similar to that demonstrated previously with 16 wks of EAA supplementation in community-dwelling elderly (11). Limb strength of THA patients is obviously compromised due to joint deterioration and pain. Thus, one would expect a greater rate of improvement over non-surgical or non-arthritic subjects. However, despite this improvement, the resultant strength after 8 weeks of supplementation is clearly not a full restoration of pre-joint deterioration strength levels. Despite a difference in dynamometer methodology in the determination of strength, when our subjects were age-matched with 81 (45 females and 36 males, ages 45-68 yrs) de-identified healthy, untrained subjects (16, 28) (and unpublished data by MMB), EAA supplementation resulted in leg strength that approximates only 50% of the maximal strength in these healthy controls (Figure 2). Whether a longer period of supplementation would completely restore strength values is uncertain. Generally speaking, once the joint has been replaced and pain is no longer an issue, the expectation of complete functional recovery is realistic. Additional studies are required to determine the capability of EAA or protein supplementation over the long term, or more appropriately, the combination of protein supplementation with standardized and perhaps more intensive rehabilitative exercise dosing.

There are potential limitations to these findings. First, patient presentation to our clinic tended to be younger than 60 years old. While the age for joint replacement is becoming increasingly younger (10), these results indicate that a population under 60 yo can benefit from nutritional supplementation. However, recent findings that older subjects were resistant to the anabolic effects of EAA after inactivity (29) indicate that these results may not translate to older populations. Our data indicates a less-robust rate of recovery in the EAA subjects over 60 years of age (subjects 18 and 22) when compared to those under 60 years.

A second potential limitation is absence of a placebo-controlled treatment group. While the placebo affect cannot be discounted, the only real difference between groups, given similar age, rehabilitation, and caloric intake, was nitrogen intake. Our previous placebo-controlled studies investigating the effects of EAA during inactivity in older subjects (5) elucidated the metabolic mechanism, namely the maintenance of protein synthesis, and functional outcomes that can be ascribed to each treatment. Given that free-living subjects show no increase in MVC over a 3-month period (30) and that the EAA group demonstrated a 64% greater recovery than the UC group, the improvement was most likely due to the increased amino acid/nitrogen intake.

In summary, our findings indicate that the provision of additional nitrogen by amino acid supplementation after THA improves muscle extensor strength and the rate of recovery of muscle strength; however, after 8 weeks, strength remains significantly depressed as compared to a healthy standard.

Conflict of Interest: No conflicts to declare.

Author's Contributions: All authors have made substantial contributions to this manuscript as outlined: AAF and RRW contributed to the conception and design of the project and manuscript preparation. MMB and AAF contributed to collection, analysis, and interpretation of the data. SES and RPE contributed to identification and consent of subjects, SES performed all endpoint measurements and consolidated results. HJS contributed to statistical analyses and interpretation of the data.

Acknowledgements: This project was funded by NIH grant R01 AR052293 (Ferrando, AA), with support from Translational Research Institute NIH grant UL1RR029884 and the Claude D. Pepper Older Americans Independence Center grant RFA-AG-11-002. The essential amino acid formula was prepared and encapsulated by the AminoScience Laboratories at Ajinomoto Co, Ajinomoto Inc, Kawasaki, Japan.

ClinicalTrials.gov Identifier: NCT00393848

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