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Identifying Effective and Feasible Interventions to Accelerate Functional Recovery from Hospitalization in Older Adults: A Randomized Controlled Pilot Trial

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Abstract

Hospitalization induces functional decline in older adults. Many geriatric patients fail to fully recover physical function after hospitalization, which increases the risk of frailty, disability, dependence, re-hospitalization, and mortality. There is a lack of evidence-based therapies that can be implemented following hospitalization to accelerate functional improvements. The aims of this Phase I clinical trial are to determine 1) the effect size and variability of targeted interventions in accelerating functional recovery from hospitalization and 2) the feasibility of implementing such interventions in community-dwelling older adults. Older patients (≥ 65 yr, n=100) will be recruited from a single site during hospitalization for an acute medical condition. Subjects will be randomized to one of five interventions initiated immediately upon discharge: 1. protein supplementation, 2. in-home rehabilitation plus placebo supplementation, 3. in-home rehabilitation

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TRIAL STATUS

Recruiting was underway at the time of manuscript submission.

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

RRD, JMD, SRF, HJ, and EV participated in study conception and design. All authors read and approved the final manuscript.

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plus protein supplementation, 4. single testosterone injection, or 5. isocaloric placebo supplementation. Testing will occur during hospitalization (baseline) and at 1 and 4 weeks post discharge. Each testing session will include measures of muscle strength, physical function/performance, body composition, and psychological function. Physical activity levels will be continuously monitored throughout study participation. Feasibility will be determined through collection of the number of eligible, contacted, and enrolled patients; intervention adherence and compliance; and reasons for declining enrollment and study withdrawal. This research will determine the feasibility of post-hospitalization strategies to improve physical function in older adults. These results will also provide a foundation for performing larger, multi-site clinical trials to improve physical function and reduce readmissions in geriatric patients.

Keywords

Protein; exercise; testosterone; geriatrics; hospitalization; physical function

INTRODUCTION

Acute hospitalization can have catastrophic consequences for physical function and independence in older adults [1–3]. In addition to the disease burden, hospitalized older adults are profoundly inactive [4–6] and often malnourished [7–10], which significantly contributes to muscle dysfunction, increased falls, and loss of independence [1, 11, 12]. The negative impact of hospitalization on the physical function of older adults may be worsened by the presence of sarcopenia. Sarcopenia, a condition affecting many older adults, is characterized by diminished muscle health. It exacerbates disability, functional dependence, institutionalization, and mortality [13, 14]. Reductions in physical function and activities of daily living are commonly observed in geriatric patients admitted for acute hospital care [15–20]. These impairments often persist after discharge [16, 20, 21], with a poor prognosis for functional recovery [19, 22]. The deconditioning resulting from an acute hospitalization, often termed “post-hospital syndrome” [21], is now recognized as a strong risk factor associated with the development of frailty, disability, and dependence. It leads to poorer outcomes in this population, including re-hospitalization, reduced quality of life, and mortality [1, 21–25].

Reduced physical activity and malnutrition are independent predictors of impaired physical function, increased re-hospitalization, and mortality [9, 24, 26, 27]. Over the past decade, protein ingestion and exercise have been identified as major contributors to muscle anabolism and protein synthesis. However, we have found that older adults require more amino acids than younger individuals to maximally stimulate muscle protein synthesis [28–31] and that a bout of exercise enhances the anabolic efficacy of a subsequent meal in this population [32–34]. In addition, testosterone administration has been shown to increase skeletal muscle mass, lean mass, and strength while decreasing fat mass [35–40].

In this research, we are testing the hypothesis that targeted, age-appropriate strategies to improve nutritional status and/or physical activity following acute hospital care in the elderly

will improve physical function, activities of daily living, and quality of life, and may reduce rates of re-hospitalization within 30 days (Figure 1).

The specific aims of this randomized controlled pilot trial are twofold: 1) to determine the effect size and variability of protein supplementation, in-home rehabilitation, or testosterone on recovery of muscle mass and function after acute hospitalization in community dwelling older adults, and 2) to determine from an institutional and patient perspective the feasibility of implementing each of these interventions following acute hospital care in older adults.

METHODS/DESIGN

Study Overview

This 3 year, single site randomized controlled pilot trial is designed to determine the feasibility of post-hospital interventions aimed at accelerating functional recovery in community dwelling older adults after hospital discharge for acute medical care. We will enroll 100 older adults (>65 years of age) who are admitted to the Acute Care for Elders (ACE) unit at the University of Texas Medical Branch. Enrolled subjects will be randomly assigned into one of five treatment arms (n=20 per arm): 1) protein supplementation, 2) in-home rehabilitation and placebo supplementation, 3) in-home rehabilitation and protein supplementation, 4) single testosterone injection, or 5) isocaloric placebo supplementation (also serves as control/standard of care). A schematic of the general study design is depicted in Figure 2. All groups will receive the specific intervention to which they are randomized (1–5 as described above) in addition to any standard of care prescribed by their physician (home health, PT/OT, nutritional support, prescriptions/medications, etc.). Each intervention will be initiated upon discharge and will continue uninterrupted for 4 weeks post discharge unless a study endpoint is met (e.g., readmission, detailed below). This study has been approved by the University of Texas Medical Branch Institutional Review Board and is registered at clinicaltrials.gov (NCT02203656). Written informed consent will be obtained from each subject prior to any study procedures.

Participant recruitment and screening

Participants will be adults, 65 years of age or older, who are admitted to the UTMB ACE unit for acute medical care. Initial screening will take place with chart reviews of all admitted patients to identify those who initially qualify. The number of total admissions as well as the number of qualified and non-qualified subjects will be collected. Chart reviews will occur at 8am each weekday and eligible participants will be approached during their hospital stay.

Participants eligible for inclusion will meet the following general criteria: 1) admitted to the UTMB hospital with an admitting diagnosis of congestive heart failure, respiratory infection, kidney/urinary tract infection, gastrointestinal bleed, or metabolic disorder or other less common condition that would permit inclusion in the study; 2) residing at home before and after hospitalization; 3) aged 65 years or older; 4) self-reported ability to walk across a small room (with or without the aid of an assistive device) two weeks prior to hospitalization; 5) ability to stand without assistance at the time of baseline testing; 6) no medical

contraindication to wearing a loose fitting velcro strap of the step activity monitor on one ankle; and 7) living within 30 miles of UTMB.

Exclusion criteria will be: 1) nursing home resident or hospice patient; 2) uncontrolled blood pressure (systolic >150, or diastolic > 100); 3) history of stroke with motor disability; 4) eGFR <30 mL/min/1.73m² or evidence of kidney disease or failure; 5) liver disease (AST/ALT 2 times above the normal limit, hyperbilirubinemia); 6) recent (within 3 months) treatment with anabolic steroids; 7) planned or elective hospitalization within 30 days of discharge; and 8) any other condition or event considered exclusionary by the principal investigator or attending physician.

The inclusion criteria are the same for all groups. Additional exclusion criteria for subjects randomized to the testosterone group will include: 1) breast or prostate cancer; 2) palpable prostate nodule or induration or prostate specific antigen (PSA) ≥ 4 ng/ml; 3) PSA ≥ 3 ng/ml in men at high risk of prostate cancer, such as African Americans or men with first-degree relatives with prostate cancer; 4) hematocrit ≥ 50%, and 5) decompensated heart failure.

Randomization

Subjects will be stratified according to gender to ensure that an equal number of men and women are allocated to each arm, and randomized to one of the five study arms (n=20/group). If a subject is randomized to the testosterone group but does not meet the additional inclusion criteria, that subject will be re-randomized to one of the other groups. To maintain blinding, a master randomization list will be developed and maintained by the Research Operations Manager and investigators will be blinded to the treatment list.

Interventions

The five intervention arms include: 1) protein supplementation, 2) in-home rehabilitation and placebo supplementation, 3) in-home rehabilitation and protein supplementation, 4) single testosterone injection, or 5) isocaloric placebo supplementation (which also serves as control/standard of care). All primary and secondary outcomes will be identical for each intervention group (see below); however, each intervention group will undergo a unique intervention protocol. The intervention period will begin upon discharge and end 27–33 days after discharge.

Supplementation—Subjects randomized to receive supplements will be instructed to ingest the supplements twice daily, in the morning and evening. The supplements will be provided in pre-weighed containers, and the subjects will be asked to mix the supplement with approximately 8 fluid ounces of water prior to ingestion. Subjects randomized to receive protein supplements will ingest 20g of a whey protein supplement (BiPro, Eden Prairie, MN, USA). Subjects randomized to receive isocaloric placebo supplements will ingest 20g of maltodextrin. All supplements will be mixed with one packet of sugar free flavored drink mix to mask the flavor and color. All subjects will receive a phone call once a week to monitor adherence and answer any study-related questions. To confirm compliance, subjects receiving supplements will be asked to return all supplement containers (both empty and full).

In-Home Rehabilitation—Subjects randomized to perform directed in-home rehabilitation will take supplements (as described above) and undergo progressive in-home rehabilitation training 3 days per week throughout the intervention period. This experimental rehabilitation program will be added to any physical and/or occupational therapy ordered by the treating physician. A licensed physical therapist developed the in-home rehabilitation program and will oversee its implementation. All exercises will be performed within the subject's home and supervised by trained research staff 1–2 times per week; the remaining exercise session(s) will be performed independently by the subject, without the presence of research staff. The physical therapist will train and certify all those involved with delivery of the rehabilitation intervention.

Each home rehabilitation program will be individualized for the subject. Factors such as initial functional level, medical needs, contraindications noted by the physician upon hospital discharge, and any safety concerns noted by the physical therapist will inform the intensity and choice of exercises. Programs will emphasize progressive resistance exercise with a primary focus of strengthening the lower extremities. Functional activities (e.g., rising from a chair) and elastic resistance products (e.g., Thera-band, with increasing resistance including yellow, red, blue and black) will be used to design each individualized program, and will include activities that can be easily and safely done within the home and are adaptable to a wide range of physical functioning.

All programs will begin at a low or moderate intensity level depending on the subject's baseline abilities. The rehabilitation program will include a series of five exercises: chair rises (low intensity: 1 set of 5; moderate intensity: 2 sets of 5), toe stands (low intensity: 1 set of 10; moderate intensity: 2 sets of 10), seated knee extensions with Thera-band (low intensity: 1 set of 10 each leg; moderate intensity: 2 sets of 10 each leg), seated row with Thera-band (low intensity: 1 set of 10; moderate intensity: 2 sets of 10), and seated arm extensions with Thera-band (low intensity: 1 set of 10; moderate intensity: 2 sets of 10). Subjects will be provided the Thera-band to use with the resistance exercises. The resistance of the band will be changed throughout the intervention period to keep the program progressive in difficulty. A physical therapist will meet weekly with the research staff supervising the exercises to review reports on subject progress and make recommendations regarding intensity and exercise choice.

Testosterone—Subjects randomized to the testosterone intervention group will receive a single intramuscular injection of testosterone enanthate within 24 hours of discharge. The injection will be administered by a research nurse. The dose of testosterone will be 200 mg for men and 100 mg for women. The Endocrine Society's clinical guideline for testosterone injection in older males is 150–200 mg given every two weeks [41]. These doses have been previously and safely utilized by UTMB and other investigators in chronic studies involving weekly testosterone injections in older men and women [42]. A member of the research team will contact subjects in this group by phone once a week to monitor their progress and provide the same contact frequency as those in the other intervention groups.

Outcome Measures

Testing will be the same for all groups and will occur at three time points throughout the study period: 1) baseline (in hospital), 2) 1-week post discharge, and 3) 4-weeks post discharge. The testing windows have been designed to allow for 1-week (6–10 days) and 4-week post discharge (27–33 days) measures to be collected at UTMB or at the subject's home if transportation is an issue.

The first aim of this study is to test the effect size, variability, and safety of our interventions on muscle mass and physical function following an acute hospital stay in community dwelling older adults. The primary outcome measure will be the Short Physical Performance Battery (SPPB). Secondary outcome measures will include measures of muscle strength, physical function, body composition, and psychological well-being.

The second aim of our study is to investigate the institutional- and patient-based feasibility of these interventions. Outcome measures for institutional-based feasibility will be: total admissions, patient eligibility, and enrollment statistics. Outcome measures for patient-based feasibility will be: patient adherence, compliance, enrollment, and withdrawal statistics.

Outcome measure specifics – Aim 1 (Effect Size, Variability and Safety)—A complete list of outcome measures to be collected at each of the three designated time points is presented in Table 1 and is identical for each intervention group.

Physical Function Tests: A series of physical function tests will be performed to assess each subject's mobility, strength, and physical performance. These tests will be administered in an identical order for each a group and at all time points. Our primary outcome measure, the **Short Physical Performance Battery (SPPB)** test, has been previously used to successfully evaluate UTMB patients on the ACE unit and consists of three tests of lower body function: a short timed walk at usual gait speed, five repeated chair stands, and a standing balance exercise [43, 44]. Usual gait speed will be measured over a 3 meter course. Subjects will be permitted to use an assistive device (e.g., cane or walker) and will be asked to walk at their normal pace. This test will be repeated and the quickest time used for analysis. Cut points for the gait speed scores will be: 0: unable; 1: > 6.52 seconds; 2: 4.66–6.52 seconds; 3: 3.62–4.65 seconds; and 4: < 3.62 seconds[44]. For the repeated chair stands measure, subjects will be asked to fold their arms across their chest and stand up once from a straight backed, regular height chair. If successful, they will then be asked to stand up and sit down five times as quickly as possible from the chair. The five chair rises will be timed from the initial sitting position to the final standing position at the end of the fifth stand. Cut points for the chair stand scores will be: 0: >60 seconds or unable; 1: > 16.7 seconds; 2: 13.70–16.69 seconds; 3: 11.20–13.69 seconds; and 4: 11.19 seconds[44]. For tests of standing balance, participants will be asked to maintain three positions (side-by-side, semi-tandem, and tandem) for 10 seconds each. Cut points for the balance tests will be: 0: unable to hold the side-by-side for 10 seconds; 1: able to hold the side-by-side for 10 seconds; 2: able to hold the side-by-side and semi-tandem for 10 seconds; 3: able to hold the side-by-side and semi-tandem for 10 seconds each, and tandem stand for 3.00–9.99 seconds; and 4: able to hold the side-by-side, semi-tandem, and tandem for 10 seconds each[44]. To assess

gait speed reserve, a **Fast Gait Speed** test will be used. Fast gait speed will be measured over a 3 meter course. Subjects will be permitted to use an assistive device if needed and will be asked to walk the course as quickly as they safely can. This test will be repeated and the quickest time will be used for analysis. **Timed Up and Go (TUG)** is a simple test in which the subject will be asked to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down [45]. Subjects will be permitted to use an assistive device and will be asked to walk at their normal pace for the TUG. The **hand grip strength test** will be performed on both dominant and non-dominant hands. While in a seated position, subjects will hold the dynamometer in their hand with the elbow bent to 90° and wrist in a comfortable position (typically around 30° wrist extension). Subjects will be asked to squeeze the dynamometer as hard as they can (for about 15 seconds). The subject will be allowed to rest (30–45 seconds) between the three tries on each hand. Maximum grip strength will be used for analysis. This test will not be performed on a given hand if the patient has had hand or wrist surgery within the past 3 months. For the **lower extremity knee extension strength test**, subjects will be seated in a straight back chair without arms. During the test, subjects will not get support from the other leg (it should be hanging unsupported in a relaxed position). The dynamometer will be placed just above the ankle on participant's shin and the subject will be asked to push against the dynamometer as hard as they can (for about 15 seconds). The subject will be allowed to rest (30–45 seconds) between the three tries on each leg. Maximum knee extension strength will be used for analysis. Hand grip and lower extremity knee extensor extension strength will be measured as a continuous variable in kilograms using hand held dynamometers. The **stair climb test** will assess the time taken to ascend up four steps in a single flight of stairs. Subjects will be asked to climb up four steps as quickly as they safely can. Timing will begin when the first foot touches the first step and end when both feet are on the fourth step. This test will be repeated and the fastest time will be used for analysis. This test will not be performed in subjects who reported the inability to climb a flight of stairs in the IADL questionnaire. If the participant reports chest pain, tightness or pressure, significant shortness of breath or difficulty breathing, feeling faint, lightheaded or dizzy, the test will be stopped and the reason for stopping will be recorded. Also, if the patient is unable to climb four stairs within approximately 30 seconds, the test will be stopped.

Body Composition Assessments: Body composition (lean mass, body fat) will be determined by dual-energy X-ray absorptiometry (DEXA; GE Lunar iDXA) and bioimpedance (Tanita; BF-350). Segmental and whole body analysis will be examined with DEXA to determine appendicular and whole body composition. The coefficient of variation for repeated measures of lean tissue is <1% [46]. Bioimpedance will be used to measure weight and body fat percentage [47]. The results obtained with bioimpedance will be compared to the DEXA results to test the accuracy and validity of bioimpedanciometry as a potential portable means to measure changes in body composition for future clinical trials utilizing an in-home setting.

Questionnaires: A series of questionnaires will be administered to assess patient-based physical and psychological function. The questionnaires are related to physical function and well-being. Questions will be read to the subject by a study coordinator and their answers

recorded. **Activities of Daily Living (ADL)** is comprised of: bathing, using the toilet, transferring from bed to chair, walking across a small room, personal grooming, dressing, and eating [1]. Scoring will be 0–7 points with a higher score for subjects requiring more help with ADLs. **Instrumental Activities of Daily Living (IADL)** is comprised of: using the telephone, driving a car, shopping, cooking, cleaning, taking medication, handling money, climbing stairs, and walking ½ mile. Scoring will be 0–10 points with a lower score indicating subjects needing more help with IADLs. The **Geriatric Depression Scale** includes 15 yes/no questions about feelings and mood. A score of 5 or greater suggests depression. The **Iowa Fatigue Scale** asks subjects to rate 11 sentences (e.g., “I feel worn out”, “I feel energetic”) using the following responses: not at all, a little, moderately, quite a bit, or extremely. A score of 30–39 indicates substantial fatigue and >40 indicates severe fatigue. The **Falling and Balance** questionnaire asks subjects about any falls they have had within the past year and if as a result of any of those falls they had to visit their physician or be hospitalized. Scoring will be: 0: no falls; 1: one fall; 2: two falls; 3: three or more falls.

Physical Activity Levels: During the study period, physical activity level (e.g., number of daily steps, bouts of activity, etc.) will be monitored using a StepWatch Activity Monitor (SAM; Modus Health LLC). The SAM is a waterproof dual-axis accelerometer which the subject will wear on his/her ankle with a Velcro strap beginning on the day of baseline testing and continuing throughout the intervention period to monitor daily activity. Our research group has utilized SAMs to monitor physical activity in both inpatient and in-home settings [26, 43].

Outcome measure specifics – Aim 2 (Feasibility)

Institutional-based feasibility: The number of admitted, eligible, contacted, excluded, enrolled, randomized, and retained (at time of discharge) patients will be collected and analyzed to determine institutional-based feasibility. These feasibility measures will be assessed based on percentages of total admitted patients, eligible patients, contacted and enrolled patients that initiated each intervention. Reasons for exclusion will be recorded.

Patient-based feasibility: We will assess adherence and compliance to each intervention, as well as reasons for declining enrollment and for study withdraw. Dependent upon subject availability at the study endpoint, a post-intervention questionnaire focused on subjective patient-centered outcomes will also be administered. This questionnaire is designed to provide patient-centered feedback/data on perceived satisfaction of the intervention, facilitators of the intervention, and barriers to the intervention (adherence and compliance).

Data safety and monitoring plan (DSMP)

The risk level associated with this study is estimated to be moderate and reasonable. The DSMP includes careful monitoring of the recruitment, enrollment, retention, adverse events, and study procedures to help protect the safety of study subjects, the quality of data, and the integrity of the study. A designated study physician will be responsible for the medical management of the subjects during study participation. The study physician will review each subject's records to ensure that appropriate mechanisms to protect the safety of study participants are being followed and that protocol requirements related to inclusion/exclusion

criteria are being adhered to. A quarterly review of data safety and interim data analysis will be performed by the PI and study physician, a semi-annual review of patient safety will be conducted by an independent geriatrician, and an annual review of adverse events will be performed by the UTMB Institutional Review Board. The study physician and independent geriatrician will be responsible for making any recommendations about starting, continuing, or stopping the study and for making recommendations, as appropriate, to the UTMB Institutional Review Board.

Study endpoints

The primary endpoint for the study will be the completion of the 30 day post-hospital intervention and associated tests. Additional endpoints of study participation will include: 1) subjects who met the inclusion/exclusion criteria at the first screening but did not meet the inclusion/exclusion criteria at time of discharge (i.e., not discharged home, not alert and oriented, etc.); 2) subjects who experienced an adverse event such as a traumatic fall, re-hospitalization, or death during the intervention period; 3) subjects who choose to withdraw from the study prior to completion of the intervention period; and 4) subjects for whom the study physician or primary care physician determine that participation in this study will interfere with their safety and well-being. A chart review will occur at all study endpoints.

Statistical analyses and sample size

Data for aim 1 will be analyzed using a repeated Analysis of Variance (ANOVA) with two factors (time $\times$ group) to compare our primary outcome at all time points among the five groups. Post-hoc comparisons will be conducted using Tukey-Kramer test with multiple hypothesis testing adjustment. All data will be tested for normality and equal variance. In the absence of normality or constant variance, the data will be transformed using natural log (ln) or appropriate transformation. To account for differences between populations and increase power, an Analysis of Covariance modeling approach will be considered to take into account possible covariate adjustments of baseline characteristics (i.e., disability score, length of stay, diagnosis). Data for aim 2 will be analyzed with independent t-tests or ANOVA and Tukey-Kramer post-hoc tests as described above for aim 1. Institutional-based feasibility will be assessed using descriptive data and patient characteristics collected from medical records on admitted patients, eligible patients, enrolled patients, patients retained at discharge, and patients no longer eligible at discharge (i.e., not discharged to home). Patient-based feasibility will be assessed by comparing intervention compliance and adherence and drop-out/withdrawal rate among each intervention. All values will be reported as mean $\pm$ SEM. Nominally significant differences will be considered at $P < 0.05$. All statistical analyses will be performed using SAS (version 9.2, SAS Inst. Inc., Cary, NC).

Sample Size and Power Calculations

Due to the paucity of comparable studies, we have selected a reasonable sample size for a pilot/feasibility study of 20/group and calculated power using the estimated change and standard deviations reported in post bed rest rehabilitation studies in healthy older adults and the existing literature on hospitalized geriatric patients [43, 48, 49]. The outcomes for calculating power are presented in Table 2. These calculations are based on $N=20$ /group using the estimated changes from discharge to 4-weeks post discharge in the intervention

groups. Power calculations for the future larger trials will be carried out using the effect size and variability collected during this pilot study. Nonetheless, we cannot exclude the possibility that we may be able to provide efficacy information regarding one or more of the tested interventions if the effect size is large enough relative to the placebo/standard of care group.

DISCUSSION

It is well documented that acute hospitalization can substantially reduce physical function in older adults [1–3]. Yet, very little evidence is available on potential interventions that accelerate recovery of physical function following acute hospitalization. The findings from this project will determine the effect size, variability, and safety of post-hospitalization strategies targeting recovery of muscle mass and physical function in older adults. These results will provide 1) pilot data regarding the effect size, variability, and safety of practical post-hospitalization strategies for accelerating muscle recovery and 2) institutional- and patient-based feasibility information to develop larger, multi-site clinical trials employing the most promising interventions to improve physical function and reduce readmissions in geriatric patients after acute hospitalization.

Interventions to Enhance Muscle Growth in Healthy Older Adults

Protein ingestion, physical activity and testosterone represent powerful therapies to preserve or improve physical function in older adults. However, most studies investigating the potential benefits of these treatments have been tested in healthy older adults [28–30, 32–34]. We have previously conducted mechanistic-based studies demonstrating that: 1) aging attenuates the meal stimulated increase in skeletal muscle protein synthesis [50], 2) anabolic resistance of skeletal muscle to nutrients with aging is associated with endothelial dysfunction and blunted mammalian/mechanistic target of rapamycin complex 1 (mTORC1) signaling [51, 52], 3) acute exercise improves endothelial function and muscle perfusion, and enhances skeletal muscle protein synthesis after nutrient ingestion in older adults [31–34], 4) older adults require more amino acids (or protein) than younger individuals to stimulate skeletal muscle protein synthesis [28–30], 5) the response of skeletal muscle protein synthesis to essential amino acids depends on a high leucine dose (~3 g) with maximal stimulation occurring when ingesting approximately 30 g of whole protein per meal [29, 53–55], 6) inactivity (short-term bedrest) blunts skeletal muscle mTORC1 activation by amino acids, increases anabolic resistance of skeletal muscle, and is associated with reduced skeletal muscle amino acid transporter expression in older adults [56–58] and 7) muscle anabolism in response to resistance exercise is reduced in older adults but this problem is mitigated by protein intake after the exercise bout. These data show that, relative to younger individuals, older adults require more protein and physical activity to achieve an anabolic response in skeletal muscle. They also underscore that inactivity (e.g. hospitalization) worsens the muscle anabolic resistance of aging.

Testosterone has also been shown to stimulate skeletal muscle protein synthesis and increase skeletal muscle mass. In younger men, androgen hormone therapy enhances skeletal muscle strength and size [59–61]. In older men, findings have been more variable. However, in

numerous studies, testosterone treatment has been shown to increase lean mass, decrease fat mass, and increase strength [35–38]. In addition, testosterone has been shown to have positive effects on quality of life, and enhance energy, mood, and appetite [60, 62]. Whereas the use of exercise and nutritional strategies following hospitalization is dependent upon subject adherence and compliance, implementing the administration of a single dose of testosterone upon discharge is not dependent upon patient adherence and compliance in the weeks following discharge. Thus, the inclusion of a testosterone intervention arm will provide important preliminary data to compare and contrast the efficacy of interventions that require very different degrees of patient adherence and/or compliance.

Improving Physical Function in Clinical Populations

Previous studies have examined whether nutritional supplementation post-hospitalization can improve physical function [63–65]. Results from these investigations suggest that nutritional supplementation after hospitalization can lower the incidence of falls [64], reduce inflammation (during concomitant rehabilitation) [66], and increase handgrip strength [63, 65]. However, these previous studies have not observed benefits of protein supplementation on measures of physical function or muscle size. A limitation of many of the previous studies is that subjects were not provided or did not consume a sufficient amount of protein in a given meal [30, 67, 68]. The inadequate distribution of protein might have reduced the benefits of protein supplementation on muscle strength and function [69, 70]. Older adults require a greater amount of protein, in particular the amino acid leucine, than younger individuals to adequately stimulate muscle protein anabolism [29, 30, 54, 71–75]. One clinical trial carried out in frail, yet otherwise relatively healthy, older adults has reported that adequate doses of high quality protein throughout the day (15 g protein supplement at breakfast and lunch) can increase measures of physical function [76]. These studies highlight the potential for protein supplements to improve physical functioning in community dwelling frail older adults. Recent data also indicate that the benefits of protein/ amino acid supplementation on skeletal muscle health can be achieved during a 2–3 week time frame in clinical populations[77] or models of clinical settings[49]. However, it is still unclear whether nutritional supplementation can also accelerate the functional recovery of older adults following acute hospitalization.

Why Should We Focus on Post-Hospitalization Interventions?

In-hospital interventions are extremely difficult to implement due to the disease severity and the complexity of medical care during hospitalization. Regardless, deconditioning during hospitalization occurs, and there is a need for novel interventions to accelerate recovery of physical functional after hospital discharge. It is also important to identify potential barriers to implementation of post-hospital interventions in order to devise solutions. There is a considerable lack of well-designed, randomized clinical studies that have investigated potential strategies to restore and recover muscle strength and physical function in older adults following an acute hospital stay. The need to identify and develop practical, feasible, and cost-effective approaches to improve function following hospitalization in older adults is underscored by several important healthcare and health cost related issues. For instance: 1) older adults admitted to the hospital experience severe reductions in physical function [1–3], 2) recent data indicate that more than one-third of hospitalizations are comprised of patients

65 years and older [78] despite the fact that this group accounts for only 13 percent of the population, 3) by the year 2030, it is estimated that 20% of the US population will be comprised of persons aged 65 years or older (U.S. Census Bureau; National Institutes on Aging statistics), 4) estimates indicate that 1 in 5 older adults discharged from the hospital will be readmitted within 30 days [79], and 5) the Centers for Medicare and Medicaid Services initiatives penalize hospitals with higher 30-day readmission rates [80].

Acute hospitalization represents a key factor contributing to accelerated morbidity in our expanding aging population. There is a lack of evidence-based strategies to improve recovery after hospital discharge. In addition, little attention has been directed toward assessing the feasibility of such interventions or identifying barriers or facilitators to the implementation of post-hospital care. This project is designed to simultaneously identify the effect size, variability, and safety and determine the feasibility of unique and practical approaches to help older adults recover physical function and preserve independence following acute medical care. We recognize that patients for this study will be recruited from a hospital unit specifically designed for the multidisciplinary care of older adults (ACE Unit), and therefore, there may be limitations in the ability to translate our findings to elderly patients treated in other hospital units. However, given the specific care provided on the ACE unit, we anticipate that patients in this study will not demonstrate as much hospital-associated functional decline as patients in other hospital units, and consequently we believe that these interventions would have larger effects on other patient populations acutely treated at the hospital. Nonetheless, this pilot study will provide necessary data to design larger, multi-site clinical trials to test the effectiveness of the proposed interventions in geriatric patients acutely treated in various hospital units. The long-term goal of this research is to improve overall health outcomes and reduce the costs associated with post-hospital care and re-hospitalization in geriatric patients.

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LIST OF ABBREVIATIONS

ACE	acute care for elders unit
ADL	activities of daily living
ANOVA	analysis of variance
DSMP	data safety and monitoring plan
Ex	exercise/rehabilitation session
IADL	instrumental activities of daily living

mTORC1	mammalian/mechanistic target of rapamycin complex 1
SAM	step activity monitor
SPPB	short physical performance battery
T	testosterone
TUG	timed up and go
UTMB	University of Texas Medical Branch

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Figure 1.

Schematic representation of the relationship between acute hospitalization, the loss of muscle size and function, post-hospital syndrome (red arrow to left of descriptions), the inability to recover muscle size and function, decreases in independence, and re-hospitalization. We hypothesize that post-hospitalization interventions involving protein supplementation (#1, green), in-home rehabilitation (#2, blue), in-home rehabilitation plus protein supplementation (#3, orange), or a single testosterone injection (#4, purple) will accelerate functional recovery in previously hospitalized older adults relative to control/standard of care (placebo supplementation only).

Figure 2.

Schematic of general study design. Subjects will be recruited during an acute hospitalization. Once consented, subjects will be randomized to one of the five groups. Baseline testing will occur in the hospital and follow-up testing will occur 1- and 4-weeks after hospital discharge. Subjects will begin the intervention protocol the day following discharge. ACE, acute care for elders unit; Ex, exercise/rehabilitation session; T, testosterone injection.

Table 1
List of functional outcome measures

All measures will be performed, if possible, in each of the five groups at the indicated time points.

Functional Outcome Measures	Baseline testing	1 week testing	4 week testing
<i><u>Physical Function Tests</u></i>			
* Short Physical Performance Battery	X	X	X
Fast Gait Speed	X	X	X
Hand Grip Strength	X	X	X
Knee Extension Strength	X	X	X
Timed Up and Go	X	X	X
Stair Climb	X		X
<i><u>Body Composition Assessments</u></i>			
DEXA Scan	X		X
Bioimpedance	X	X	X
<i><u>Questionnaires</u></i>			
Activities of Daily Living	X	X	X
Instrumental Activities of Daily Living	X	X	X
Geriatric Depression Scale	X	X	X
Iowa Fatigue Scale	X	X	X
Falling and Balance	X	X	X
<i><u>Physical Activity Levels</u></i>			
StepWatch Activity Monitor	continuous monitoring throughout study period		

* primary outcome; DEXA, dual-energy X-ray absorptiometry

Power calculations based on a sample size of n=20/group and expected effect sizes and variability estimated from published studies of bed rest in healthy older adults and in geriatric patients.

Table 2

Intervention N=20/group	Sit to stand SD= 3.2 sec		8 ft walk SD =2.5 sec		Hand Grip [*] SD= 25%	
	Change	Power	Change	Power	Change	Power
1. Protein supplementation	-3.1 sec	0.85	-2.8 sec	0.93	35%	0.99
2. In-home rehabilitation + placebo supplementation	-3.1 sec	0.85	-2.8 sec	0.93	35%	0.99
3. In-home Rehabilitation + protein supplementation	-3.4 sec	0.91	-3.1 sec	0.97	45%	0.99
4. Single testosterone injection	-3.4 sec	0.91	-3.1 sec	0.97	45%	0.99

^{*} Note: Percent change used due to absolute difference between sexes [48].