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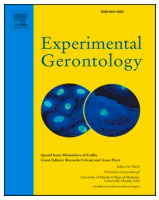

Optimizing recovery after a hip fracture: Protocol of a randomized controlled trial to study the effects, costs, and cost-effectiveness of a combined protein and exercise intervention in older adults after a hip fracture (ProBUS study)☆

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ABSTRACT

Background: Hip fractures are common among older adults and typically occur alongside accumulating comorbidities and age-related musculoskeletal decline. While nutritional or exercise interventions can support recovery, the effect of a combined approach during rehabilitation remains unclear. This study aims to evaluate the effects, costs, and cost-effectiveness of a high-protein diet plus exercise intervention on functional recovery after a hip fracture.

Methods: This randomized controlled trial will include 102 older adults (≥65 years) recovering in a rehabilitation centre after a hip fracture. Participants will be randomly assigned (1:1) to the intervention or control group, stratified by sex and hospital. The intervention group will receive weekly dietitian support to comply with a high-protein diet (≥1.2 g/kg body weight/day) and will participate in progressive resistance exercise training twice weekly for 3 months. The control group will receive usual care. Due to the nature of the intervention, participant and staff blinding is not feasible, but analyses will be performed blinded. Measurements will be performed in the first week after surgery, at rehabilitation discharge, and 3 months after baseline. The primary outcome is physical functioning using the Short Physical Performance Battery. Secondary outcomes include handgrip strength, muscle mass, bone density, quality of life, daily functioning, nutritional status, bone metabolism biomarkers, and costs.

Discussion: The intervention is expected to enhance recovery, attenuate postoperative bone and muscle loss, and improve quality of life. Implementation into standard care could improve efficiency and cost-effectiveness.

Abbreviations: ANCOVA, Analysis of covariance; BIS, Bioelectrical Impedance Spectroscopy; BMD, Bone Mineral Density; CCI, Charlson Comorbidity Index; CFS, Clinical Frailty Scale; DOS, Delirium Observation Screening; DEXA, Dual-Energy X-ray Absorptiometry; eGFR, Estimated Glomerular Filtration Rate; EQ-5D-5L, EuroQol-5 Dimensions-5 Levels; FES-I, Falls Efficacy Scale-International; IGF-1, Insulin-like Growth Factor 1; iMTA MCQ, iMTA Medical Consumption Questionnaire; iMTA PCQ, iMTA Productivity Costs Questionnaire; IQR, Inter-quartile range; MAR, Missing At Random; MI, Multiple Imputation; MNA, Mini Nutritional Assessment; NRS, Numeric Rating Scale; ONS, Oral Nutritional Supplements; P1NP, Procollagen Type 1 N-Propeptide; PRT, Progressive Resistance Training; PSS, Perceived Stress Scale; PTH, Parathyroid Hormone; QUS, Quantitative Ultrasound; RCT, Randomized Controlled Trial; SD, Standard Deviation; SNAQ, Simplified Nutritional Appetite Questionnaire; SPPB, Short Physical Performance Battery.

☆ *Trial registration:* CCMO-register (Protocol ID NL68932.081.19).

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1. Introduction

Hip fractures are common among older adults, with an incidence of 13.5 per 10.000 women and 7.7 per 10.000 men in the Netherlands in 2023, and a mean age of 78 years (Dutch Institute for Clinical Auditing (DICA), 2023). These fractures often require costly surgery followed by a prolonged recovery period, which may include several months of rehabilitation. In 2019, the annual costs were estimated at 607 million in the Netherlands, with 90% of these costs incurring in the year following the fracture (VZinfo, 2022). Less than one-third of patients regain their pre-fracture functional abilities within a year, and 24% die within a year (Medin et al., 2015; Moerman et al., 2018). The elevated risk of subsequent fractures and increased mortality persists for at least a decade (Hansen et al., 2015). Optimizing rehabilitation is therefore crucial, since this may result in a faster recovery and a reduced need for future healthcare.

While nutrition plays a crucial role in bone and muscle health, older adults recovering from a hip fracture often face malnutrition (Bonjour et al., 1996). Malnutrition is a condition resulting from inadequate intake or absorption of essential nutrients, leading to impaired bodily function and health (World Health Organization (WHO), 2025). Malnutrition impairs the recovery process following a hip fracture, resulting in slower functional recovery and a higher risk of complications (Avenell et al., 2016). Furthermore, proper nutrition is crucial for maintaining bone and muscle health, as inadequate nutritional intake increases the risk of age-related diseases such as osteoporosis and sarcopenia, which may worsen by the limited postoperative mobility after hip fracture surgery (Edwards et al., 2015). Osteoporosis is characterized by decreased bone mass and deterioration of bone tissue, while sarcopenia affects muscle health by a progressive loss of muscle strength and mass (Edwards et al., 2015).

An earlier observational study by our research group in two Dutch rehabilitation centres showed that 73% of older adults recovering from a hip fracture were classified as either malnourished or at risk of malnutrition (Groenendijk et al., 2020). The percentage of subjects with insufficient protein intake, defined as <1.2 g/kg body weight/day for older adults during periods of acute illness or rehabilitation (Deutz et al., 2014), amounted to 92% during inpatient rehabilitation (Groenendijk et al., 2020). When lowering the criterion for sufficient intake to >0.8 g/kg body weight/day (current recommended daily allowance), still only 46% of the subjects met this recommendation. Another observational study demonstrated that in a community-dwelling population, patients significantly worsen in nutritional status in 3 months after a hip fracture (Groenendijk et al., 2025). This decline was associated with decreased independence in activities of daily living, which underscores the importance of adequate nutrition during rehabilitation. Especially adequate protein intake is crucial for muscle health, as it supports muscle repair, growth, and maintenance, helping to prevent muscle loss and maintain strength (Nunes et al., 2022). The association between protein intake and bone health is less clear (Groenendijk et al., 2019). With respect to nutrition and bone health, calcium and vitamin D play a crucial role in bone density and strength. By enhancing bone mineralization, recovery and bone healing is improved, especially in patients with osteoporosis (Deutz et al., 2014; Fischer et al., 2018; Rizzoli et al., 2018).

In addition to nutrition, exercise is beneficial for muscle mass and strength and for bone health (Daly, 2017). Systematic reviews have assessed the optimal exercise-based strategy for patients recovering from a hip fracture, with progressive resistance training (PRT) emerging as the most promising approach for improving physical function, while balance exercises can enhance mobility (Pan et al., 2023; Zhang et al., 2022). PRT stimulates muscle protein synthesis by activating anabolic signalling pathways (Martone et al., 2017), and applies mechanical loading to bone, promoting bone remodelling and maintaining bone mass (Hong and Kim, 2018). The positive effect of exercise may be enhanced by a high protein intake, depending on characteristics of the population (Denison et al., 2015; Thomas et al., 2016). Specifically frail, sarcopenic, or older adults with a low protein intake may benefit from a combined intervention of protein supplementation and exercise compared to exercise alone (Denison et al., 2015; Thomas et al., 2016). Protein intake provides essential amino acids that further enhance muscle protein synthesis, creating a synergistic effect that supports the preservation and growth of muscle mass and strength (Martone et al., 2017). The evidence for synergistic effects of protein intake and exercise is limited for bone health (Wolf et al., 2025).

The ProBUS study is designed to evaluate the effects of a combined nutritional and exercise approach in a targeted intervention for older adults who require functional recovery in a rehabilitation centre after hip fracture surgery. This study will assess whether a combined high-protein diet and PRT can improve functional recovery over 3 months. By evaluating the clinical effects, costs, and cost-effectiveness of this approach, the ProBUS study aims to provide insights into optimizing rehabilitation strategies, potentially improving functional recovery, reducing long-term healthcare needs, and increasing overall quality of life for older adults recovering from a hip fracture.

2. Study design and methods

2.1. Design and setting

This study is a 3-month randomized controlled trial in older adults recovering from an acute hip fracture. Patients will be recruited during their hospital stay and followed for 3 months. After hospital discharge, patients will be admitted to a rehabilitation centre first and subsequently return home. The study will take place at three Dutch hospitals (Rijnstate in Arnhem, Gelderse Vallei in Ede, and Gelre in Apeldoorn) and eight regional rehabilitation centres (Attent, Charim, Liemerije, Opella, Pleyade, Vilente, Zinzia, and Zorggroep Apeldoorn). Additional centres may be included if recruitment at these sites is insufficient to reach the target sample size within the scheduled study timeline. The intervention group will receive a high-protein diet and a PRT program for 3 months, while the control group will receive usual care. Fig. 1 presents an overview of the study.

Before the start of the trial, a pilot study was conducted to evaluate the feasibility and acceptability of the proposed nutritional and exercise intervention. Based on practical experiences and feedback from patients and involved healthcare professionals, several adjustments were made to the protocol. These included modifications to the exercise protocol to better match individual physical capacities and adapting or omitting some measurements to reduce patient burden. The study is registered at the CCMO-register (Protocol ID NL68932.081.19).

2.2. Study population and recruitment

Older adults (aged $\geq$65 years) will be recruited in three hospitals after admission for an acute hip fracture. The study will focus on patients who are referred to a rehabilitation centre for further recovery and support after hospital discharge. In order to be eligible to participate in this study, the patient should meet the criteria presented in Table 1.

A treating healthcare professional and study team member will assess whether patients are eligible before showing the patients a short animated video about the study. Subsequently, the information brochure will be given to the patients and they will be asked if they consent to an appointment with a researcher, during which the patients will be able to ask questions. After patients are fully informed and have had 24 h to consider participation, first the patient and then the investigator will sign the informed consent form twice.

2.3. Sample size

Power calculations were made for both the primary as multiple secondary outcomes regarding physical functioning, muscle health, and

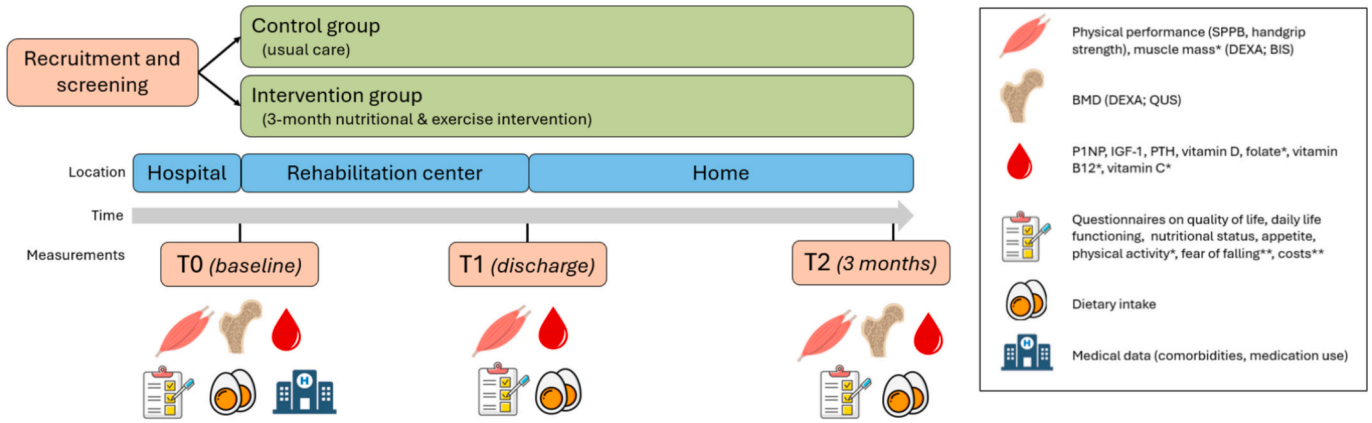

Fig. 1. Schematic overview of the ProBUS study design, with a control group receiving usual care and an intervention group receiving a 3-month nutritional and exercise intervention. Measurements visits are performed at baseline, at discharge of the rehabilitation centre, and after three months.
* = measurement is not performed at T1. ** = measurement is only performed at T2. BIS = Bioelectrical Impedance Spectroscopy; BMD = bone mineral density; DEXA = dual-energy x-ray absorptiometry; IGF-1 = insulin-like growth factor 1; P1NP = procollagen type 1 N-propeptide; PTH = parathyroid hormone; QUS = quantitative ultrasound; SPPB = short physical performance battery.

Table 1
Eligibility criteria of the ProBUS study.

Inclusion criteria	Exclusion criteria
• Aged ≥65 years • Acute hip fracture • Able to give written informed consent • Mentally competent, as judged by the treating physician • Admission to a rehabilitation centre that participates in this research	• Allergic, intolerant or hypersensitive to milk/lactose (self-reported) • Not willing to stop using dietary supplements with exception of calcium and vitamin D • Pathological fracture or periprosthetic fracture • Abnormal renal laboratory parameters (e.g. estimated glomerular filtration rate (eGFR) <30 mL/min/1,73 m^2) or diagnosis of conditions where a high protein intake can be harmful, such as renal impairment or failure, or liver disease • Diagnosis of bone metabolic disorders such as primary hyperparathyroidism, Paget's disease, or myeloma • Taking medication other than bisphosphonates known to strongly alter bone, calcium or muscle metabolism, such as oestrogens, hormone replacement therapy, corticosteroids, anabolic agents, or calcitonin • Disorders/diseases which may affect the ability to follow the study protocol and which cannot be overcome with help of a caregiver, such as (suspected) cognitive impairment or motivational disorders • Current participation in other scientific research

bone health. Conducting multiple power calculations was considered essential to ensure adequate power for the secondary outcomes as well. These outcomes are clinically and scientifically relevant, and reliable conclusions are intended to be drawn from the results. Effect sizes were calculated with the program G*Power 3.1.9.2. Sample sizes were calculated with a power of 80% and a significance level (α) of 0.05.

For the primary outcome, the power calculation was based on the recommended criterion for meaningful change on the Short Physical Performance Battery as described by Perera et al. (Perera et al., 2006). With a substantial meaningful change of 1.0 point and a SD of 1.48 points, a total sample size of 72 subjects was found. With an expected dropout of 25%, a sample size of 96 subjects is considered adequate.

Taking all power calculations for secondary outcomes into account as well, the power calculation for IGF-1 blood levels resulted in the highest number of patients needed to show a significant effect. This power calculation was based on a RCT of Schürch et al. (1998), which found an effect of protein supplements of 20 g/day for 6 months on IGF-1 levels with an effect size of 0.63 (Schürch et al., 1998). A required sample size of at least 82 patients, 41 per group, was found. With an expected dropout of 25%, a total sample size of 102 patients was considered adequate. Therefore, the ProBUS study aims to include 102 patients.

2.4. Intervention

When the screening is completed and the patient is eligible to participate, the patient will be randomized into either the intervention or control group. Block-randomisation with a block-size of four will be used and randomisation will be stratified for sex and hospital. Participant and staff blinding is not feasible, while analyses will be performed blinded. Baseline measurements will be conducted in the hospital and during the first days of the patient's stay at the rehabilitation centre. After completion of all baseline measurements, patients in the intervention group will start with the intervention program, receiving a high-protein diet and PRT in the rehabilitation centre. The control group will receive usual care, consisting of the standard diet provided by the rehabilitation centre and energy- and protein-dense oral nutritional supplements are prescribed only in case of (risk of) malnutrition. Exercise therapy is part of standard rehabilitation care, which focuses on mobility and activities of daily living. After discharge from the rehabilitation centre, the intervention will continue at home until the intervention is completed 3 months after its start.

2.4.1. Nutritional intervention

The aim of the nutritional intervention is to achieve a protein intake of at least 1.2 g/kg body weight per day. An additional target is to consume at least 25 g of protein during every main meal to stimulate muscle protein synthesis, as recommended by expert groups for both bone and muscle health (Bauer et al., 2013; Rizzoli et al., 2014). Furthermore, a leucine intake of 2.0–2.5 g per main meal is aimed for, as this amino acid is known to stimulate muscle protein synthesis (Wall et al., 2013). A dietitian will provide the patients with personalized recommendations during weekly counselling sessions. The use of both protein-rich and protein-enriched products, such as juice and bread, will be stimulated to achieve the dietary goals. This study is an intervention in practice; the exact intervention will be tailored to the individuals' wishes and needs and therefore may differ per patient to reach the target of at least 1.2 g/kg body weight per day. This is dependent on the habits

and preferences of the patients and their baseline protein intake. In the rehabilitation centre, both protein-rich and protein-enriched products will be provided. After discharge from the rehabilitation centre, the intervention continues and protein-enriched products will be delivered at home for the patients, while the dietitian will keep providing weekly support. The control group will receive the usual diet that is provided in the rehabilitation centres without further dietary support after discharge.

The beneficial impact of a high protein intake is enhanced with an adequate intake of vitamin D and calcium (Rizzoli et al., 2018). Vitamin D supplementation of 800 IU/day will be provided and an adequate calcium intake (1000 mg/day) will be assured via diet and/or supplements in patients of the intervention group (Rizzoli et al., 2014). The control group will also receive vitamin D supplementation of 800 IU/day and calcium supplementation as part of usual care.

2.4.2. Exercise intervention

At the start of rehabilitation, the primary focus will be on functional training to help patients regain their ability to perform daily activities. Once a week, very-low-intensity resistance exercises will be introduced to familiarize the patient with the movements. When patients reach a certain level of independence, classified as a Functional Ambulation Category (FAC) of 3, the focus will shift towards the PRT (Chau et al., 2013). Twice a week, the patient will perform the following four exercises: leg press, leg extension, abduction and knee raises. To determine the Rate of Perceived Exertion (RPE), the Borg category ratio (CR-10) scale is used, which is a subjective measure ranging from 0 (rest; no exertion) to 10 (maximal level of exertion) (Morishita et al., 2019). The first trainings will start on low intensity (exertion rate of 3 on the Borg CR-10 scale) by performing a small number of repetitions with low resistance. The intensity will be increased to an RPE of 7. This will be done by increasing the number of repetitions, gradually increasing the resistance, and extending the excentric phase of the movement. Resting periods with a minimum of 1–2 min are obligatory between sets and exercises. Even though the Borg CR-10 scale is a subjective measure of RPE, this scale is proven useful for older adults who perform resistance exercise (Morishita et al., 2019). All sessions will be supervised by experienced physiotherapists.

Patients will continue the PRT after discharge from the rehabilitation centre in two sessions each week, with a minimum of 48 h between sessions until the study period of 3 months is completed. These sessions will be supervised by experienced primary care physiotherapists and the first session will focus on habituation again. If the patient is not able to come to the training location, the exercise program will be continued from home with the physiotherapist visiting them. Alternative exercises that target the same muscle groups will be performed, typically using resistance bands or bodyweight exercises. While the absolute training stimulus may differ from machine-based exercises, the exercises are adapted to match intensity and perceived exertion as closely as possible. No strict criteria will be applied for stopping or modifying exercises, as exercise tolerance and safety are highly patient-dependent. Any modifications or temporary cessation of PRT are determined individually by the supervising physiotherapist, and will be closely monitored. Compliance and program modifications, including reasons for adjustments, will be documented in a personal logbook.

Patients in the control group will follow the usual rehabilitation training program. Under supervision of physiotherapists, the training program, which focuses on functional training restoring mobility and activities of daily living, is offered on average 3–5 times per week in the rehabilitation centre. Some patients continue with physiotherapy sessions once or twice a week in primary care after discharge.

2.5. Outcome measures and data collection

Measurements will be performed during screening, at baseline (in the hospital and first 5 days in the rehabilitation centre), when the patient is discharged from the rehabilitation centre to home, and 3 months after the baseline measurements (Table 2).

General information of the patients including sex, age (years), education (CBS; low, middle, high educated), smoking habits (frequency and number of cigarettes, cigars and/or tobacco-pipes) will be assessed with a questionnaire at baseline.

Hip fracture details (cause, location, type of surgery), length of hospital stay, number of fractures in the past, comorbidities, clinical frailty status (CFS) and medication and supplement use will be extracted from patient files. The Charlson Comorbidity Index (CCI, 0–37 points) will be used to determine the severity of comorbidities. The higher the score, the more comorbidities the patient suffers from (Charlson et al., 1987). Furthermore, the presence of delirium will be assessed by healthcare professionals according to Delirium Observation Screening (DOS, 0–13 points). A DOS score of 3 or greater indicates delirium (Schuurmans et al., 2003). It has been shown that a delirium increases the risk of malnutrition and consequently, lower intake can be expected (Vanderwee et al., 2010).

2.5.1. Primary outcome

2.5.1.1. Short physical performance battery. The short physical performance battery (SPPB) is a performance test that evaluates lower extremity function through assessments of standing balance, gait speed (over 4 m), and lower body strength. Balance will be tested through three stances: a side-by-side stance, a semi tandem stance, and a full tandem stance. The patients will be asked to balance in each stance for 10 s. Gait speed will be measured by timing patients as they walk a 4-m course at their usual pace. The fastest of two trials counts. Lower extremity strength will be assessed using the chair stand test, where patients are asked to cross their arms in front of their chest and rise from a chair as quickly as they can for five times. Each component is scored on a 0–4 point scale, with a possible score ranging from 0 to 12, where 12 represents the highest level of physical functioning. The SPPB has been shown to predict future disability, institutionalization, and mortality (Guralnik et al., 1994). When a patient is not able to complete a test, this is recorded, including the reason for not completing.

2.5.2. Secondary outcomes

2.5.2.1. Handgrip strength. Handgrip strength will be assessed with a JAMAR hydraulic handheld dynamometer. Patients will be seated with their elbow flexed at 90 degrees, holding the dynamometer unsupported. Patients will be verbally encouraged to achieve their maximum grip strength during three trials with each hand, with at least 30 s of rest between each trial. The highest value of three measurements will be used for analysis (Roberts et al., 2011). Cut-off values for low muscle strength will be used according to the EWGSOP2 recommendations: $<$27 kg for men and $<$16 kg for women (Cruz-Jentoft et al., 2019).

2.5.2.2. Muscle mass. Muscle mass will be quantified using dual-energy X-ray absorptiometry (DEXA) and bioelectrical impedance spectroscopy (BIS). DEXA measures muscle mass by analysing the attenuation of X-ray photons as they pass through the body, quantifying bone mineral and soft tissue composition (Messina et al., 2020). It is considered the gold standard for evaluating body composition, including muscle mass, fat mass, and bone mineral content (Cruz-Jentoft et al., 2019; Messina et al., 2020). DEXA scans are particularly valuable postoperatively, as body weight can be overestimated due to immobilisation and the inflammatory response following surgery, often resulting in oedema of the operated leg. By distinguishing between bone, fat, and lean tissue, DEXA provides a more accurate and objective measure of body composition. Appendicular lean mass (kg) is used as an approximation for muscle mass. BIS estimates muscle mass based on the resistance of body tissues to an electrical current, which is influenced by the amount of water and

Table 2
Overview of the assessments of the ProBUS study.

	Measure	Method	Screening	Baseline	Discharge	3 months
Primary outcome	Physical Performance	SPPB		x	x	x
Secondary outcomes	Handgrip strength	Hand dynamometer		x	x	x
	Muscle mass	DEXA		x		x
		BIS		x		x
	BMD	DEXA		x		x
		QUS		x		x
	Quality of life	EQ-5D-5L		x	x	x
	P1NP, IGF-1, PTH, vitamin D	Blood sample		x	x	x
	Inpatient rehabilitation time	Patient file			x	
	Daily life functioning	Barthel Index		x	x	x
	Nutritional status	MNA		x	x	x
	Costs	iMTA MCQ & PCQ				x
Additional outcomes	Dietary intake	Food records		x	x	x
	Frailty status	Fried criteria		x	x	x
	Body weight	Weighing scale		x	x	x
	Free vitamin D, folate, vitamin B12, vitamin C	Blood sample		x		x
	Physical activity	LAPAQ		x	x	x
	Appetite	SNAQ		x	x	x
	Fear of falling	FES-I				x
	Oral health	Questionnaire		x		
	Number of and time to new falls and fragility fractures	Questionnaire				x
	Pain	NRS		during every PRT session		
Socio-demographic characteristics	Patient characteristics	Questionnaire	x	x		
	Height	Stadiometer		x		
	Frailty Status	CFS		x		
	Fracture details	Patient file	x			
	Comorbidities	CCI & patient file	x	x		
	Medication & supplements	Questionnaire & patient file	x			
	Allergies & intolerances	Questionnaire & patient file	x			
	eGFR levels	Patient file	x			
	Length hospital stay	Patient file		x		
	Discharge location	Patient file		x		
	Number of fractures in the past	Questionnaire & patient file		x		
	Delirium	DOS		x		

Abbreviations: BIS = Bioelectrical Impedance Spectroscopy; BMD = bone mineral density; CCI = Charlson Comorbidity Index; CFS = Clinical Frailty Score; DOS = Delirium Observation Screening; DEXA = dual-energy x-ray absorptiometry; eGFR = estimated glomerular filtration rate; EQ-5D-5L = EuroQol-5 Dimensions-5 Levels; FES-I = Falls Efficacy Scale-International; IGF-1 = insulin-like growth factor 1; iMTA MCQ = iMTA Medical Consumption Questionnaire; iMTA PCQ = iMTA Productivity Costs Questionnaire; MNA = Mini Nutritional Assessment; NRS = Numeric Rating Scale; P1NP = procollagen type 1 N-propeptide; PRT = Progressive Resistance Training; PTH = parathyroid hormone; QUS = quantitative ultrasound; SNAQ = simplified nutritional appetite questionnaire; SPPB = short physical performance battery.

lean tissue in the body (Kyle et al., 2004). Although less precise than DEXA, BIS is a practical and easy-to-use method in clinical settings. The Sergi formula will be used to calculate appendicular skeletal muscle mass (Sergi et al., 2015).

The protocols of the DEXA manufacturer (GE Healthcare, Lunar iDXA) and BIS manufacturer (ImpediMed, BIS SFB7) will be followed, and the scans take approximately 30 and 5 min, respectively. DEXA measurements will be performed at baseline and after 3 months. When feasible, the BIS measurements will be performed at the same moment to allow for comparison between the two methods. BIS will not be performed in patients with a pacemaker, implantable cardioverter defibrillators and cardiac resynchronization therapy defibrillators (Kyle et al., 2004). BIS measurements will also adhere to key recommendations from Kyle et al. (2004), including supine positioning after ≥5 min of rest, standardized electrode placement on one side of the body, and documentation of hydration status and conditions potentially affecting measurement accuracy.

2.5.2.3. Bone mineral density. Bone mineral density (BMD) will be measured at baseline and after 3 months. BMD (g/cm^2) of the total hip, femoral neck and total body will be assessed using DEXA. The unfractured hip will be measured. DEXA is considered the "gold standard" for BMD measurements, as it is a non-invasive and safe procedure (Messina et al., 2020). In addition to DEXA, a quantitative ultrasound (QUS) of the calcaneus will be performed to assess bone health using the portable Osteosys Sonost 3000 ultrasonometer (Osteosys, Korea). The broadband ultrasound attenuation (BUA) and speed of sound (SOS) will be measured in duplicate in both the right and left calcaneus. This measurement is quick, cheap, radiation-free and portable.

2.5.2.4. Quality of life. Quality of life will be assessed with the EQ-5D-5L questionnaire (Herdman et al., 2011). This questionnaire consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression.

2.5.2.5. Blood sample. Several blood markers playing a role in bone turnover will be measured in serum: procollagen type 1 N-propeptide (P1NP), insulin-like growth factor 1 (IGF-1), parathyroid hormone (PTH), and vitamin D. P1NP is recommended as the reference marker for bone formation (Vasikaran et al., 2011), IGF-1 supports bone formation by stimulating osteoblast function (Langdahl et al., 1998) and PTH is associated with the stimulation of bone resorption (Vervloet et al., 2017). Vitamin D plays a crucial role in maintaining calcium homeostasis and promoting bone mineralization, and deficiency is associated with impaired bone health and increased fracture risk (Fischer et al., 2018). P1NP levels will be measured using chemiluminescent immunoassay (CLIA) (IDS-i10 Intact P1NP; CV% = 4.2–5.3%), IGF-1 levels will be assessed using CLIA (Liaison XL, Diasorin, CV% = 5.6–9.6%), PTH levels will be measured using CLIA (Attelica IM; CV% = 7.8%), and vitamin D levels will be measured using CLIA (Attelica IM; CV% = 2.8–6.9%).

2.5.2.6. Inpatient rehabilitation time, daily life functioning and nutritional status. The inpatient rehabilitation time will be documented as the number of days from admission to discharge at the rehabilitation centre. Daily life functioning will be assessed with the Barthel Index of Activities of Daily Living (Collin et al., 1988). The Mini Nutritional Assessment (MNA) will be used to evaluate nutritional status. Patients will be classified as having a normal nutritional status (24–30 points), having a risk of malnutrition (17–23.5 points), or being malnourished (0–16 points) (Vellas et al., 2006).

2.5.2.7. Costs. Patients will receive questionnaires about their health care use, out-of-pocket costs, and productivity losses. A health care use questionnaire based on the iMTA Medical Cost Questionnaire will be used, which includes cost categories that were deemed relevant for older adults (general practitioner, home care, informal care, dietitian, physiotherapist, hospitalization, residential care, rehabilitation care, outpatient clinic, and medication use) (iMTA, 2020). Out-of-pocket costs include sports club memberships, purchase of sport equipment, and other out-of-pocket payments related to the intervention. Productivity losses will be measured using questions from the iMTA Productivity Cost Questionnaire (iMTA, 2020). The Dutch guideline for economic evaluations in healthcare will be used to assess cost prices per unit for health care–related costs and productivity losses for unpaid work (Kanters et al., 2017; Zorginstituut Nederland, 2016). Costs for medication use, sports club membership, sports equipment, and out-of-pocket payments will be individualized. Bottom-up micro-costing will be used to estimate intervention costs. Intervention costs will be calculated per patient. Working hours of health care professionals will be multiplied by unit prices (hourly wage costs) for the specific professional. Intervention materials (e.g., protein-rich products) will be valued according to market prices.

2.5.2.8. Cost-effectiveness. Using the quality of life questionnaire EQ-5D-5L, quality-adjusted life year (QALY) will be determined. The incremental cost-effectiveness ratio (ICER) will be calculated by dividing the difference in costs by the difference in effects between the intervention and control group. The ICER will be calculated separately for effects in SPPB, handgrip strength, and QALY using bootstrap analyses with 5000 simulations. Data providing insights into perceived benefits will be extracted from interviews (separate study protocol will be prepared). Cost-effectiveness planes and cost-effectiveness acceptability curves will be plotted. The latter will indicate the probability of the intervention to be cost-effective compared to usual care, according to threshold values for willingness to pay (WTP). In the Netherlands, threshold values of €20.000 to €80.000 per QALY are used (van den Berg et al., 2008).

2.5.3. Additional outcomes

Additional outcomes include dietary intake, frailty status, body weight, levels of free vitamin D, folate, vitamin B12 and vitamin C, physical activity, appetite, fear of falling, oral health, number of and time to new falls and fragility fractures, and pain levels.

Dietary intake will be recorded over a period of three non-consecutive days at baseline, discharge and after 3 months with a combination of food records and observation. When the patient does not stay at the rehabilitation centre anymore during assessment of the dietary intake, patients will fill in the food record at home. The researchers will discuss the food records with the patients to clarify and collect all details of the dietary intake. Days for filling in the food records will be randomized. A weekend day is included to take into account possible variation in intake between week- and weekend days. Data is processed in ComplEat (Human Nutrition WUR, Wageningen, NL).

Frailty will be defined with the Fried criteria, as the presence of 3 or more of the following 5 criteria: unintentional weight loss (>4.5 kg in the last year), weakness (handgrip strength lowest 20% by sex and body mass index (BMI), based on handgrip strength reference values from Grgic et al. (2025), self-reported exhaustion, slow walking speed (slowest 20% by sex and height, based on gait speed reference values from Dommershuijsen et al. (2022), and low physical activity (Fried et al., 2001).

Body weight (kg) will be recorded in duplicate at baseline, discharge and after 3 months using a calibrated (chair) weighing scale. Height (cm) will be measured in duplicate at baseline with a wall mounted stadiometer. If standing height cannot be measured at baseline due to physical limitations, it will be assessed at discharge or after 3 months. If standing height cannot be measured during the entire study period, height will be estimated using knee height. Subsequently Body Mass Index (BMI) will be calculated as body weight divided by height in meters squared.

Levels of (free) 25(OH)D and folate in serum and vitamin B12 and vitamin C in plasma will be assessed at baseline and after 3 months to evaluate potential nutrient deficiencies and monitor changes in nutrient status. (Free) 25(OH)D, folate and vitamin B12 levels will be measured using CLIA (Attelica IM: CV% = 6.6%, CV% = 5.9–7.1% and CV% = 9.2%, respectively) and vitamin C levels will be measured using high-performance liquid chromatography (HPLC-Alliance 2695; CV% = 3.64%).

Physical activity will be assessed at baseline, at discharge, and after 3 months, using the LASA Physical Activity Questionnaire (LAPAQ). The level of habitual physical activity may influence outcomes of an exercise intervention and may vary highly when patients are at home. The LAPAQ is a validated questionnaire to measure physical activity in older adults and assesses frequency and duration of several activities of the last two weeks (Stel et al., 2004).

Since loss of appetite can be a reason that someone does not comply to the intervention, appetite will be assessed. The simplified nutritional appetite questionnaire (SNAQ) is a short tool to quantify appetite and includes four questions (maximum score of 20, score of ≤14 indicates poor appetite) (Wilson et al., 2005).

Fear of falling will be measured after 3 months with the Falls Efficacy Scale-International (FES—I). This questionnaire has 16-items, scored on a 4-point Likert scale, assessing concerns about falling related to physical and social activities. The total score ranges from 16 to 64, with higher scores indicating a higher level of fear of falling. The FES-I has good reliability and validity, and has been validated in Dutch older patients with hip fracture (Visschedijk et al., 2010).

An inadequate dental health status of older adults may affect dietary intake. Observational research has shown that intake of protein and calcium is significantly higher in people with 21 or more teeth compared to people who have few or no teeth (Sheiham et al., 2001). Therefore, number of teeth and presence of a dental prosthesis will be recorded.

Number of and time to new fragility fractures will be retrieved from a questionnaire and the patient file after 3 months. In addition, number of and time to new falls will be asked after 3 months.

As a result of the fracture and surgery, pain is a common complaint in patients after a hip fracture. Pain can negatively influence the adherence to exercise protocols. Therefore, changes in pain levels will be monitored by the physiotherapists using a Numeric Rating Scale (NRS).

2.5.4. Qualitative study alongside the study

Alongside the randomized controlled trial, a qualitative study will be conducted to explore patients' lived experiences during rehabilitation. Semi-structured interviews will be carried out with patients from both study arms to gain insight into perceived barriers and facilitators of the intervention, as well as overall experiences with recovery and care. This information will contribute to the development of recommendations for future implementation of the combined intervention in routine clinical practice.

2.6. Statistical analysis

Data will be expressed as mean ± standard deviation (SD), n (%), or as median with interquartile range (IQR) for non-normally distributed data. Data will be checked for normality using histograms and the Shapiro-Wilk test. If data distribution is skewed, data will be log-transformed and analysed as described hereafter. If data are still not normally distributed, nonparametric tests will be used. All statistical analyses will be performed using R and will be based on the intention-to-treat principle. Missing data will be assumed to be missing at random (MAR) and multiple imputation (MI) will be applied to handle missing data when appropriate.

After the intention-to-treat analysis including all patients, an additional per-protocol analysis will be conducted, if applicable, without the patients that did not adhere to the nutritional intervention (inadequate protein intake of <1.2 g/kg body weight/day). A two-sided *p*-value of 0.05 will be used to determine statistical significance. Baseline characteristics will be analysed by independent samples *t*-test for continuous variables and χ^2 for categorical variables.

2.6.1. Primary study parameter

Difference in SPPB score at discharge and after 3 months will be evaluated with linear mixed models with patients as random factor and time, treatment, and time*treatment interaction as fixed factors. Possible confounders include sex, age, BMI, change in body weight, physical activity, frailty, presence and severeness of comorbidities (CCI), pain levels and the use of a walking aid. Covariates will be retained in the final model if they show a significant association with the dependent variable and do not violate the assumption of homogeneity of regression slopes (i.e. no significant interaction with time or treatment group). Degrees of freedom are determined with the Kenward-Roger method.

2.6.2. Secondary study parameters

Difference in muscle mass and BMD after 3 months of intervention between the treatment groups will be evaluated with analysis of covariance (ANCOVA). The baseline values of the outcomes of interest, sex, and age will be entered as covariates in the basic model (primary analysis). Next, other potential confounders will be identified and entered in the models, including sex, age, BMI, change in body weight, energy intake, physical activity, frailty, smoking, alcohol use, comorbidities, and fracture history. Covariates will be handled in the same manner as for the analyses of the primary study parameter.

Differences in handgrip strength, quality of life, blood levels of P1NP, IGF-1 and PTH, daily life functioning and nutritional status at discharge and after 3 months will be evaluated with linear mixed models with patients as random factor and time, treatment, and time*treatment interaction as fixed factors. Potential confounders may be added to the models as fixed factors. The difference in inpatient rehabilitation time between the treatment groups will be evaluated with independent samples *t*-tests. To account for multiple testing, the Benjamini-Hochberg correction will be applied.

2.6.3. Additional study parameters

Difference in dietary intake, body weight, frailty status, physical activity and appetite at discharge and after 3 months between the treatment groups will be evaluated with linear mixed models. Differences in levels of free 25(OH)D, folate, vitamin B12, and vitamin C after 3 months will be evaluated with ANCOVA, with the baseline values of the outcomes of interest as covariates in the basic model. Other outcomes include fear of falling and oral health, the difference in these outcomes after 3 months between the groups will be evaluated with independent samples t-tests. Difference in the number of new fragility fractures and falls will be assessed with Fisher's Exact Test.

3. Discussion

This paper describes the study design of the ProBUS study that evaluates the effects, costs, and cost-effectiveness of a combined high-protein diet and exercise intervention for 3 months on functional recovery, bone and muscle health, and quality of life in older adults after an acute hip fracture. Despite growing evidence supporting combined nutrition and exercise strategies in older adults, to our knowledge no studies have applied this combined approach to patients recovering from an acute hip fracture. Moreover, this study will evaluate functional recovery, which is highly relevant for patients, rather than focusing solely on outcomes such as mortality or length of hospital stay.

Although several studies have demonstrated positive effects of oral protein interventions on complications, length of stay, and mortality in patients after a hip fracture (Espaulella et al., 2000; Myint et al., 2013), these effects could not always be confirmed in other studies (Wyers et al., 2018). A meta-analysis by Takahashi et al. (2020) found that interventions focused on high-protein supplements may reduce complications and mortality and improve muscle function, however, the overall quality of the evidence was rated as low (Takahashi et al., 2020). Another review also concluded that the evidence for the effectiveness of these supplements following hip fracture remains weak (Avenell et al., 2016). Combining high-protein nutritional support with exercise may offer a more effective strategy to enhance recovery after hip fracture. This combined approach has already shown clinical benefits in other older patient populations (Han et al., 2020).

To demonstrate the beneficial effects of this combined intervention, the study will focus on a carefully selected group of patients, since both the most fit and most vulnerable patients are excluded. The most fit patients are likely to recover well without additional intervention, limiting the potential to detect differences between groups. Conversely, the most vulnerable patients—often returning to a nursing home within days after surgery—are unlikely to benefit from the intervention due to their poor overall prognosis. By focusing on a more homogeneous group of community-dwelling older adults who are discharged to a rehabilitation unit after their hospital stay, the ProBUS study targets the population most likely to benefit from and respond to the intervention. Consequently, the results may have limited generalizability to the broader population of hip fracture patients. Furthermore, cognitive capacity of the patients will be clinically evaluated together with the patient and their family or caregiver during the informed consent process, in order to optimize compliance with the study intervention.

Nutritional interventions often face poor compliance in older adults (Chen et al., 2024). To optimize compliance with the nutritional intervention, patients will be offered protein and energy enriched bread, fruit juices, and dairy products as part of their regular diet, instead of nutritional supplements, as enriched foods are more easily integrated into daily eating habits and perceived as part of a normal diet. Previous studies have shown that such protein-enriched foods can be effective in improving protein intake in malnourished patients (Stelten et al., 2015; van Til et al., 2015). A personalized approach will be applied with weekly individual support from a dietitian to ensure the intervention meets each patient's personal needs and preferences.

Another strength of this study is that it will assess the quality of life and psychological effects of a hip fracture, such as the fear of falling. These psychological effects may lead to avoidance of risky actions, but also an increased risk of falling and refracturing. While rehabilitation focusses on restoring mobility and function, there is little time and opportunity to address the psychological impact of a hip fracture on the patient.

A potential limitation of the study is the risk of contamination. As part of usual care, participants in the control group may receive dietary advice (with or without oral nutritional supplements (ONS)) if clinically indicated or advice on physical activity from healthcare staff as part of usual care. This could dilute the observed between-group differences. Furthermore, performance bias may arise because participants and staff

are aware of group allocation, which could influence behaviour, motivation, or additional care, potentially affecting the observed outcomes. Nevertheless, the design reflects real-world clinical practice, and any contamination is likely to underestimate, rather than exaggerate, the intervention effect.

The results of this study will provide insights into the effects of a combined nutritional and exercise intervention on physical functioning following hip fracture surgery, compared to usual care. It is hypothesized that the intervention will attenuate functional decline and help preserve muscle mass in older adults. These findings may be essential for optimizing rehabilitation strategies and improving functional recovery, bone and muscle health, and quality of life after hip fracture surgery. If the intervention is effective and cost-effective, it will be considered for broader implementation in Dutch rehabilitation centres. Moreover, a successful outcome could pave the way for future studies exploring how elements of the intervention might be adapted for other populations after hip fracture surgery, such as individuals with dementia or those residing in nursing homes.

4. Conclusion

The results of this study will provide valuable information about whether a high-protein diet combined with progressive resistance exercise training is effective and cost-effective to implement in the rehabilitation process after a hip fracture in older adults.

Ethics approval and consent to participate.

The study and protocol are developed according to the Declaration of Helsinki guidelines. The protocol has been approved by the medical ethical committee of East-Netherlands (2021–12,993).

CRediT authorship contribution statement

Emma Treijtel: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Conceptualization. **Hugo H. Wijnen:** Writing – review & editing, Writing – original draft, Investigation, Funding acquisition, Conceptualization. **Nienke M.S. Golüke:** Writing – review & editing. **Marian A.E. de van der Schueren:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Lisette C.P.G.M. de Groot:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization. **Inge Groenendijk:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization.

Informed consent statement

All recruited individuals read and digitally sign an informed consent form prior to participation in the study.

Consent for publication

All authors provided their consent for publication.

Declaration of Generative AI and AI-assisted technologies in the writing process

Not applicable.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: This project received financial support provided by ZonMW. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The datasets generated and analysed during the current study are not publicly available due to privacy and ethical restrictions but can be made available from the corresponding author on reasonable request. Access will be provided in accordance with applicable privacy regulations, ethical approvals, and with a signed data-sharing agreement to ensure participant confidentiality.

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