Study protocol: High-protein nutritional intervention based on β-hydroxy-β-methylbutirate, vitamin D3 and calcium on obese and lean aged patients with hip fractures and sarcopenia. The HIPERPROT-GER study

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ARTICLE INFO

Article history:
Received 21 May 2013
Received in revised form 6 June 2013
Accepted 8 June 2013

Keywords:
Sarcopenia
Obesity
β-Hydroxy-β-methylbutirate
Hip fracture
Older people
High protein

ABSTRACT

Introduction: Loss of muscle strength is associated with falls, which, in turn, are the main cause of hip fractures in elderly people. The factors that most influence loss of strength in elderly people are a decrease in muscle mass, i.e. sarcopenia, and an increase in fat, i.e. obesity.

Methods: A prospective randomized clinical trial among patients who have undergone an operation for a traumatic hip fracture and who are aged 65 or above will be implemented. We shall compare a control diet against a high-protein diet enriched with β-hydroxy-β-methylbutirate, calcium and vitamin D. The diet will be administered during 30 days of hospitalization in the orthopaedic geriatric rehabilitation unit. There will be 50 patients in each arm of the study. The main objective is to assess whether the experimental diet, together with rehabilitation, improves functional recovery, measured on the Barthel index. Secondary objectives are to assess changes in body composition and the prevalence of sarcopenia, obesity and mortality one year after the hip fracture. We shall also assess whether there is a relationship between specific inflammatory markers, sarcopenia and functional recovery.

Conclusions: Ageing is accompanied by changes in body composition that increase the risk of falls and progressive functional loss. These factors are a public health problem because they are highly associated with disability in older people. The present study seeks to gain knowledge of those factors that are most often associated with the onset of disability and those that can be modified through diet.

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1. Introduction

Sarcopenia, defined as a loss of strength, function and mass of skeletal muscle, is associated with ageing [1]. Few studies have attempted to establish the ‘normal’ amount of muscle mass in elderly people who are independent or who have few functional limitations [2,3]; there are thus no universally accepted criteria or cut-off points for sarcopenia. Nevertheless, there is a consensus among most international groups on the following guidelines for the diagnosis: (1) a decrease in muscle mass, measured with dual-energy X-ray absorptiometry (DXA) or with bioelectrical impedance analysis (BIA); (2) a decrease in strength, measured with a dynamometer (hand grip strength); and (3) a decrease in muscle function, measured as walking speed [4,5].

Sarcopenia in elderly people is not always associated with a decrease in body mass index (BMI), because the loss of muscle mass is commonly accompanied by an increase in fat mass [6–8]. An increase with age in the proportion of people who are overweight is common in developed countries [9,10]. The combination in an individual of a decrease in muscle mass and an increase in fat mass is known as sarcopenic obesity (SO) [11]. SO has been shown to directly reduce the autonomy of elderly people, as it is broadly acknowledged as a risk factor for the onset of functional limitations [12,13]. The many studies that have assessed the effect of BMI on mortality in elderly people have tended to find either J-shaped or U-shaped relationships [14,15].
2. Subjects and methods

2.1. Inclusion and exclusion criteria

The inclusion and exclusion criteria used in the present study are listed in Table 1. The HIPERPROT–GER study has been approved by the appropriate ethics committee (Comité Ético de Investigación Clínica de la Comunidad Foral de Navarra) (62/2011) and has been designed in accordance with the European Union requirements for good clinical practice and the review of the Declaration of Helsinki. Informed consent will be obtained from all participants. This trial has been registered at www.clinicaltrials.gov with code NCT01404195.

2.2. Statistical analysis

2.2.1. Descriptive analysis

The data will be defined at the descriptive level, and presented according to the type of variable: using measures of centrality (mean and median) and measures of dispersion (standard deviation) for quantitative data; and using percentages (of the study group) for qualitative variables. The distribution of the data (normality) will be taken into account in the selection of the appropriate statistical tests.

2.2.2. Univariate analysis

A homogeneity analysis will be undertaken of the sample’s baseline characteristics. Any associations between different measurements taken at the scheduled times for the intervention group and the control group will be assessed using the appropriate parametric and non-parametric tests. All inter-subject quantitative comparisons will be carried out with the Student t-test for independent samples or the Mann–Whitney U-test. Associations between qualitative variables will be determined with the chi-square or Fisher’s exact test, depending on the distribution of the data. Intra-subject and within-group comparisons (longitudinal tests for changes over time) will be made using the paired Student t-test for quantitative variables or the McNemar test for qualitative variables.

2.2.3. Multivariate analysis

Multivariate models will be considered for the purpose of adjusting for confounding factors. Cross-sectional analyses will be adjusted using binary logistic regression models. The results will be presented as adjusted ORs (odds ratios), accompanied by p values and confidence intervals. Repeated-measures analysis of variance (ANOVA) will be used to assess longitudinal change; in particular, mixed-effects models (fixed and random) will be used. We will adjust for confounding variables in these models, and then examine time × group interaction terms. We plan to apply a statistical significance of 0.05 for population inference. The study design is intention to treat. Analysis will be carried out using SPSS 19 and R 2.13.0.

2.2.4. Estimation of sample size

Sample size has been calculated in terms of the main objective of this study: to find significant differences in functional improvement following a nutritional intervention for patients with a hip fracture, measured with the Barthel index. For the present study, we estimated that a sample size will be needed of 50 patients in the intervention group and 50 in the control group. The standard deviation in ratings of such patients on the Barthel index was around ±30 in a pilot study (unpublished data). Using this figure in the calculation of sample size, and a level of statistical significance set at 0.05 (5%), a sample made up of two groups of 45 patients has a statistical power of 80% to pick up a 10-point difference between groups on the Barthel index. Estimating a loss to follow-up of 10%, the total

Table 1

<table>
<thead>
<tr>
<th>Inclusion</th>
<th>Exclusion</th>
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<tbody>
<tr>
<td>≥65 years</td>
<td>Barthel index &lt; 40 in the previous six months</td>
</tr>
<tr>
<td>Traumatic hip fracture</td>
<td>IMC &lt; 21 kg/m², MNA &lt; 11 or serum albumin &lt; 2.1 g/dl</td>
</tr>
<tr>
<td>undergone surgery</td>
<td>Diabetés</td>
</tr>
<tr>
<td>Join for rehabilitation</td>
<td>Liquid dysphagia</td>
</tr>
<tr>
<td>Inadequate protein intake</td>
<td>Pathological hip fracture or cancer disease in active phase or undergoing treatment (radiotherapy or chemotherapy)</td>
</tr>
<tr>
<td>for sarcopenia</td>
<td>Serious clinical conditions that compromise and endanger the patient’s life</td>
</tr>
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</table>
| Hip fractures are a common health problem for elderly people. In Spain, there are between 50,000 and 60,000 hip fractures a year, representing an annual incidence rate of 100 cases/100,000 population [16]. The female: male ratio is 4:1 and the incidence of hip fractures increases with age. Hip fractures have important implications for the ability to walk but also greatly restrict many other daily activities. Inadequate protein intake is one of the main risk factors for sarcopenia [17]. The dietary intake of a group of patients undergoing orthopaedic surgery was shown to be insufficient in terms of energy, proteins and micronutrients [18]. This situation is often due to a hypermetabolic state secondary to inflammation, to a reduction of food intake due to lack of appetite and to patients being confined to bed. For all these reasons, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends, with the highest grade of evidence (grade A), the use of nutritional supplements in older people who have experienced a hip fracture [19]. Many studies have demonstrated that muscle metabolism improves with HMB supplements, and that there is also a decrease in protein deterioration and a significant increase in free fatty mass [20–22]. However, few studies have reported significant results in their assessment of functional parameters. A deficiency of vitamin D3 (vitD) (in its active form 1α, 25(OH)2D3) is very prevalent among elderly people [23,24]. Despite the fact that vitD receptors are present in many organs and tissues, recommendations about vitD intake refer only to bone tissue [25]. VitD plays an important role in protein synthesis and low levels are associated with a decrease in muscle strength and an increase of the risk of developing mobility limitations and disability [26]. VitD supplements may help to improve muscle function as well as strength and to reduce the risk of falls and mortality [27]. This paper describes a prospective randomized clinical trial presently being conducted among patients who have undergone an operation for a traumatic hip fracture and who are aged 65 or above (the HIPERPROT–GER study). We aim to compare a control diet against a high-protein diet enriched with β-hydroxy-β-methylbutirate (HMB), calcium and vitamin D3 (cholecalciferol). The diet will be administered during 30 days of hospitalization in the orthopaedic geriatric rehabilitation unit. There will be 50 patients in each arm of the study. The main objective is to assess whether the experimental diet, together with rehabilitation, improves functional recovery. The secondary aims are: (1) to gain knowledge of body composition and calculate the prevalence of sarcopenia and obesity; (2) to assess whether there is a relationship between inflammatory indexes and sarcopenia; (3) to evaluate whether there is an increase in muscle mass; and (4) to assess mortality and morbidity.

It is considered traumatic fracture resulting from an accidental fall, fall defining any unexpected event that determines that the patient reaches a lower level than where it was originally.
Table 2
Determinations and assessment scales in patients included.

<table>
<thead>
<tr>
<th></th>
<th>Admission</th>
<th>30 days</th>
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<tbody>
<tr>
<td>Weight</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Height</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Arm circumference</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Calf circumference</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Triceps skinfold</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Inflammatory markersa</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Hormonesb</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Hepatic functionc</td>
<td>X</td>
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<tr>
<td>Renal functiond</td>
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<td>Proteinsf</td>
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<tr>
<td>Lipt</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Blood count</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Vitaminsg</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Fast blood glycaemia</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Gijón scale</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MNA</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>SF-LLFDI</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>BARTHEL index</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>FAC</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>CHARLSON index</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

a IL1, IL6, PCR, TNF-a.
b TSH, FT3, FT4, cortisol, insulin.
c Cortisol, insulin.
d Transaminases, bilirubin total and fractions, alkaline phosphatase, lactic dehydrogenase, g-glutamyl transferase.
e Creatinine, ureaemia, uric acid, MDRD.
f Albumin, transtiretin.
g Cholesterol, HDL, LDL, triglyceride.
h B-12, 25-OH-Vit-D.
i Barthel index pre-fracture.

The sample size is about 100 individuals. The relatively low percentage loss is due to the fact that the patients will be in hospital for the duration of the study.

2.3. Study design

This is a prospective, randomized, controlled clinical trial. Patients admitted to the orthopaedic geriatric unit at the San Juan de Dios Hospital in Pamplona (Spain) from January 9, 2012 were due to be prospectively included.

Assessment shall be carried out within 72 h of admission and shall be repeated upon discharge (Fig. 1). After assessment and randomization, patients will begin their rehabilitation programme.

A summary of the assessments and scales used, and when, can be found in Table 2.

2.4. Hypothesis

The hypothesis for our study is that the addition of a hypercaloric and hyperproteic diet enriched with HMB, calcium and vitD is more effective than conventional methods alone in treating sarcopenia in older patients with hip fractures and improves recovery.

2.5. Intervention

Once patients are included in the study, they shall be randomly split into two groups. Group 1 (G1), the intervention group, will receive the nutritional intervention, which is an oral hypercaloric and hyperproteic liquid supplement enriched with HMB, calcium and vitD. Group 2 (G2), the control group, will receive standard care.

Patients in Group 1 shall be given two bottles of Ensure Plus Advance per day, one with breakfast and one mid-afternoon, 7 days a week, during the 30 days of their stay in hospital. Ensure Plus Advance 220 ml, Abbott Laboratorios SA (Avenida de Burgos 91, 28050 Madrid, Spain) has the following characteristics: 1.5 kcal/ml, 22% protein origin (8.3 g/100 ml), 29% fat (4.8 g/100 ml), 47% carbohydrates (17 g/100 ml), 1% FOS (0.75 g/100 ml). The supplement is enriched with HMB 0.55 g/100 ml, vitD 227 UI/100 ml and calcium 160 mg/100 ml. In order to assess whether the patients genuinely follow the treatment, they will be given a register on which to note their daily intake of the supplement.

2.6. Assessment of functional abilities

The scale used most often studies of autonomy in daily life activities is the Barthel index, which was developed in 1965 by Mahoney and Barthel [28]. It addresses 10 variables: feeding, bathing, dressing, grooming, urinary and faecal continence, toilet use, chair-to-bed transfer, walking and stairs. The score is on a scale of 0–100, where 100 indicates total independence and 0 total dependence.

Function will be assessed using the Short Form-Late Life Function and Disability Index (SF-LLFDI), which has a very low floor effect, whereas no ceiling effect has been observed in previous studies [29,30].

We will evaluate the ability to walk with the Functional Ambulation Category (FAC), which places patients into six categories: 0 = non-functional or no walking; 1 = walks with a lot of physical help from another person; 2 = walks with light manual contact from another person; 3 = requires supervision but no physical contact; 4 = independent on a flat surface; 5 = independent on flat surface and stairs. It can be applied via direct observation or via medical history [31].

Cognitive assessment will be carried out using the Mini Mental State Examination (MMSE) [32], which will be applied once the processes that may influence cognitive assessment have been stabilized, in order to ensure the validity of the results as far as possible.

2.7. Nutritional assessment

Nutritional assessment is key to the diagnosis of sarcopenia [33]. There are numerous scales for the nutritional assessment of older patients. The most widely used is the Mini Nutritional Assessment (MNA), which will be used in the present study [34,35]. Patients will be classified as malnourished (MNA score <17), as being at risk of malnutrition (score 17–23.5), or as having an adequate nutritional status (score ≥24) [36].

2.8. Assessment of comorbidity

The Charlson index, originally designed to predict mortality, is the comorbidity index most widely used in both Spanish and international studies. It has been translated into Spanish and validated for use with Spanish subjects [37,38].

2.9. Assessment of sarcopenia

To assess sarcopenia we shall use the criteria proposed by the European Working Group on Sarcopenia in Older People (EWG-SOP) [5]. Bioelectrical impedance analysis (BIA) will be carried out between 08:00 and 09:00 h, with patients in a fasting state, in a supine position and with an empty bladder. We shall use a BIA-101, RJL System, Akern SRL (Via Lisbona 32/34, 50 065 Pontassieve, Firenze, Italia). Measurements will be taken with the electrodes placed on the patients’ wrists and ankles on the same side. Muscle mass (MM) in kg shall be calculated as: MM = [(size^2/BIA-resistance × 0.401) + (sex × 3.825) + (age × -0.071)] + 5.102, where size is in centimetres, BIA-resistance is in ohms, sex is rated male = 1.
and female = 0, and age is in years [39]. Muscle mass will be normalized by size (muscle mass in kg/size in m²), to give the Skeletal Muscle Index (SMI).

We shall classify patients according to the criteria proposed by Janssen in 2006 defining, respectively for men and women: normal SMI values, ≥10.76 kg/m² and ≥6.76 kg/m², moderate sarcopenia, 8.51–10.75 kg/m² and 5.76–6.75 kg/m²; or severe sarcopenia, ≤8.50 kg/m² and ≤5.75 kg/m² [40].

We will measure strength in both hands with a JAMAR portable dynamometer. Patients will be asked to press for 3–5 s. The measure will be repeated after a 30-s rest. The highest score will be registered. In order to reduce variability, measurements will be taken in a standardized manner [41]. Grip work will be calculated according to the formula proposed by Bautmans and colleagues in 2011 in order to study resistance to fatigue [42].

Performance measurements will be carried out using the 4-m walking test, with values lower than 0.8 m/s considered to be a reduction in speed, and the FAC (see above).

3. Novelty of the study and discussion

Two studies have directly compared muscle mass in young and older people, measuring it with BIA. Thus, Schutz et al. in 2002 showed that muscle mass in older healthy people is similar to that in young subjects, both men and women [2]. They also observed that fat increases with age in both men and women. Masanes et al. in 2012 found similar results only in men, because the muscle mass in older women was significantly less than that in younger women [2].

Some authors have suggested that excess fat accompanied by loss of muscle (sarcopenic obesity) may negatively influence the ability to walk, whilst the loss of muscle mass (sarcopenia) is an important limiting factor for more tiring activities [43]. BMI is a risk factor for death and disability and many studies have shown that the relationship appears in the shape of a ‘J’ or a ‘U’, with BMI values of 28.2 kg/m² in men and 27.1 kg/m² in women associated with the lowest mortality rates [15]. This outcome could be at the root of the well known obesity paradox, whereby, especially in older people, being overweight (BMI between 25 and 30 kg/m²) may even become a protective factor. Nevertheless, a BMI above 30 kg/m², particularly with a fat percentage above 28% in men and 40% in women, is still a risk factor for disability and death [44].

Low intake of VitD has been shown to be a risk factor for the loss of muscle mass and function [26,45,46]. The mechanism probably involves myoblast proliferation and differentiation [23].

A recent review of studies assessing nutritional supplements in the treatment of loss of muscle mass in elderly patients with sarcopenia found that the reported results are not uniform, despite quite a high correspondence among them [47]. The main limitation in most of the reviewed studies was that they included older people living in the community, with whom the benefits of nutritional supplements are more difficult to prove. The present study, in contrast, will be carried out with an older population admitted to a specialist rehabilitation unit.

4. Conclusions

Dependency and disability are two public health problems with a large impact on the quality of life of older people. There are certain factors which can be modified to reduce their prevalence, such as loss of muscle mass and strength, sarcopenia, and excess fat or obesity. We have a duty to attempt to manipulate these factors in order to improve the health and well-being of older people.

Contributors

VM designed the study and he is the principal investigator and wrote the first draft. FJU, RI, LGG, MAZ and JAM collaborated actively in the scientific basis of the protocol, and in drafting and editing the manuscript.
Competing interest

VM has received grants from Abbott Nutrition SA, Avenida de Burgos 91, 28050 Madrid, España, and Nestle Health Care SA, Avenida Paíos Catalans 25-51, 08950 Esplugues de Llobregat, Barcelona. The sponsor of the study, not participate nor in the statistical analysis of the results, which are owned by Hospital San Juan de Dios of Pamplona, nor in the conclusions of this study. JAM and MAZ are members of CIBERObn, physiopathology of obesity and nutrition. Instituto de Salud Carlos III, Madrid, Spain.

Funding

The San Juan de Dios Hospital has received funding from Abbott Nutrition SA, Avenida de Burgos 91, 28050 Madrid, España.

Acknowledgments

The authors are grateful to the Head of staff of Hospital San Juan de Dios, Pamplona, and the staff of the Fundación Sant Joan de Deu, Barcelona, for their efforts and support in the development of this protocol. The authors thank specially to Pau Ferrer Salovans for advice and availability in the early stages of protocol development.

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