Maturitas 101 (2017) 42–50

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Effectiveness of nutritional supplementation on sarcopenia and recovery in hip fracture patients. A multi-centre randomized trial

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ARTICLE INFO

Keywords:
Sarcopenia
Oral nutritional supplementation
β-Hydroxy-β-methylbutyrate (HMB)
Hip fracture
Muscle mass

ABSTRACT

Background and objectives: Functional deterioration and reduced mobility in elderly patients with a hip fracture are associated with a loss of both muscle mass and function (sarcopenia). The aim of this study was to assess whether oral nutritional supplementation (ONS) improves muscle mass and nutritional markers (BMI, proteins) in elderly patients with hip fracture.

Methods: Patients aged 65 years and over with hip fractures admitted to either of two rehabilitation facilities were included. Patients with diabetes, with Barthel index scores < 40 prior to the fracture or with pathological fractures were excluded. A random-numbers generator was used to randomly allocate patients to the intervention group (IG) or the control group (CG). Those in the IG received a standard diet plus ONS in the form of two bottles a day of β-hydroxy-β-methylbutyrate (HMB), while those in the CG received a standard diet only. The intervention was not blinded.

In order to assess changes in body mass index (BMI), anthropometric parameters were recorded at both admission and discharge. Patients' functional situation was evaluated using the Barthel index (BI) and the Functional Ambulation Categories (FAC) score. Muscle mass was assessed using bioelectrical impedance analysis, which allowed us to calculate appendicular lean mass (aLM). The outcome variable was the difference between aLM upon discharge, minus aLM upon admission (Δ-aLM).

Results: Of the 107 randomised patients (IG n55, CG n52), 49 finished the study in the IG and 43 in the CG. BMI and aLM were stable in IG patients, whilst these parametres decreased in the CG. A significant difference was observed between the two groups ($p < 0.001$, and $p = 0.020$ respectively). The predictive factors for Δ-aLM were ONS ($p = 0.006$), FAC prior to fracture ($p < 0.001$) and BI prior to fracture ($p = 0.007$).

The concentration of proteins ($p = 0.007$) and vitamin D (p.001) had increased more in the IG than in the CG.

Conclusion: A diet enriched in HMB improves muscle mass, prevents the onset of sarcopenia and is associated with functional improvement in elderly patients with hip fractures. Orally administered nutritional supplements can help to prevent the onset of sarcopenic obesity.

Trial registration: www.clinicaltrials.gov identifier: NCT01404195, registered 22 July 2011, HYPERPROTGER Study.

1. Introduction

Hip fractures represent 14% of all fractures but they amount to 72% of all cost associated with fractures [1]. Maintaining functional independence is of paramount importance in the lives of patients with fractured hips and rehabilitation centres play a special role here [2,3].

Approximately 40% of elderly people with a fracture do not recover their previous functional status [4]. Functional loss is associated with institutionalization and increases mortality [5]. Bed confinement and the reduced mobility of hospitalized elderly patients are associated with

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http://dx.doi.org/10.1016/j.maturitas.2017.04.010
Received 11 November 2016; Accepted 18 April 2017
0378-5122/

loss of muscle mass and muscle function (sarcopenia) and loss of bone mineral density from the 10th day and up to 2 months after the fracture [6,7]. The prevalence of sarcopenia in elderly patients with hip fractures is up to 54%, and it is higher in men than in women [8]. The postoperative standard diet has been regarded as unsatisfactory to prevent weight loss in trauma patients [9,10], while physical rehabilitation and nutritional supplementation have proven to be effective strategies to reduce the loss of muscle mass in older people [11,12].

Elderly patients with a hip fracture who are well nourished are more independent in activities of daily living (ADL), while malnourished patients show worse functional recovery [13] and gait recovery. [14,15]

β-hydroxy-β-methylbutyrate (HMB) is a leucine metabolite that has been shown to improve the synthesis and to reduce the degradation of muscle proteins [16]. The endogenous output of HMB reduces with age and its levels are associated with the loss of appendicular lean mass and hand grip strength [17]. Supplementation with 3 g of HMB prevents the muscle loss associated with bed confinement [17]. Branched chain amino acids (e.g. leucine) are responsible for the activation of muscle metabolism by stimulating the mammalian target of rapamycin (mTOR) [18].

Prior studies have assessed the effects of oral nutritional supplementation only on issues such as weight [19], complications [20], and hospital stay [21].

The hypothesis of the present study is that a nutritional supplement enriched with HMB, calcium (Ca) and 25-hydroxy vitamin D (25(OH)D) taken during rehabilitation therapy will improves muscle mass and thereby functional recovery.

The purpose of this study is to assess whether oral nutritional supplementation (ONS) improves muscle mass and nutritional markers (BMI, proteins) in elderly patients with a hip fracture.

2. Methods

2.1. Study design and participants

Both the patient selection criteria and the study methodology have been previously described [22]. In a departure from the original protocol, a second recruitment centre was included, but otherwise none of the inclusion and exclusion criteria were modified. In short, the Hyperprotein Nutritional Intervention in Elderly Patients With Hip Fracture and Sarcopenia (HIPERPROT-GER) study is a multicentre randomized open-label study. Inclusion criteria were age ≥65, and a diagnosis of hip fracture. The study was carried out in two post-acute rehabilitation centres: 1) Hospital San Juan de Dios, Pamplona, Spain (2012 and 2013) and 2) Hospital Viamed Valvanera, Logroño, Spain (2014 and 2015). Exclusion criteria were diabetes (because the ONS is not suitable for diabetic patients), established disabilities, defined by a Barthel index score < 40 prior to the fracture, tumour treated with chemotherapy or radiotherapy, pathological fractures and high-impact fractures (car crashes).

This study was approved by the Comunidad Foral de Navarra Clinical Research Ethics Committee (62/2011) and was conducted following the Good Clinical Practice Standards set by the European Union and the Helsinki Declaration. Written informed consent was provided by all patients or their legal representatives.

2.2. Description of rehabilitation centres

In Navarra, there are some 600 hip fractures every year and a further 300 occur in a year in La Rioja [2]. Almost one-third of these patients with hip fractures are referred to either of two post-acute rehabilitation centres: Hospital San Juan de Dios (Navarra) and Hospital Viamed Valvanera (La Rioja). Reasons for referral are the high clinical complexity of patients due to their high comorbidity and the presence of complications at admission, or patients having only a partial response to the rehabilitation therapy provided in the trauma units. We recorded the variables for this study within the first 72 h after admission to the rehabilitation units (following randomisation) and again 48 h before discharge.

We recorded the type of fracture, the type of surgery and the duration of stay at the trauma unit and at the rehabilitation unit. We also recorded post-operative complications.

2.3. Nutritional intervention

Individuals included were randomized to either the intervention group (IG) or the control group (CG). The IG received a standard diet plus oral nutritional supplementation during their stay in the rehabilitation units, while the CG received a standard diet. The intervention did not change the length of stay. Patients were discharged from the rehabilitation units when the responsible physician considered that they had no more need of rehabilitation.

The nutritional characteristics of the standard diet are: 1500 kcal, 23.3% protein (87.4 g/day), 35.5% fat (59.3 g/day) and 41.2% carbohydrates (154.8 g/day). In addition, patients in the IG received two bottles a day (one in the morning and one in the afternoon) of pre-prepared oral liquid nutritional supplementation (220 ml x 2, total: 660 kcal) (Ensure® Plus Advance, Abbott Laboratorios S.A.) with the following nutritional characteristics: 1.5 kcal/mL, 24% protein (9.1 g/100 ml), 29% fat (5 g/100 ml) and 46% carbohydrates (16.8 g/100 ml). The supplement was enriched with CaHMB 0.7 g/100 ml, 25(OH)D 227 IU/100 ml and 227 mg/100 ml of calcium.

2.4. Sarcopenia diagnosis and study of body composition

The test to assess walking speed was performed by an experienced and trained physiotherapist (PT) over a distance of 4 m. We considered values < 0.8 m/s to be reduced walking speed (slowness). Grip strength of both hands was measured using a JAMAR digital dynamometer (Akern, Italy) based on the original protocol [23]; measurement that was taken twice with a 60-s break between the two measurements. We used the better of the two results. We considered values < 20 kg in women and < 30 kg in men to indicate weakness.

Muscle endurance was determined as fatigue resistance (FR), i.e. the time in seconds that each patient kept the dynamometer from points of maximum strength to less than 50% of that value. Grip work (GW) was calculated using the following formula: GW = (maximum strength x 0.75) x FR [24]. GW was divided by weight in kilograms to calculate the Grip Work Index.

For the Bioelectrical Impedance Analysis (BIA) we used a single-frequency tetrapolar BIA-101 device (Akern, Italy). BIA was carried out with the patient in the supine position on a nonconductive surface, in slight upper extremity adduction and with the lower limbs slightly separated, while the electrodes were placed on the side unaffected by the fracture. The BIA values were used in the equation described by Sergi et al. for predicting muscle mass (MM) [25]:

$$MM = -3.964 + 0.227 \times height^2/Resistance + 0.095 \times weight + 1.384 \times sex + 0.064 \times Reactance.$$

We measured height in centimetres, resistance and reactance in ohms; male sex = 1 and female sex = 0, and weight in kg. MM was converted to appendicular lean mass (aLM) using model 1 described by Kim et al. [26].

$$aLM = (Total\ body\ skeletal\ muscle\ mass)/1.19 + 1.65$$

Low aLM was defined as aLM ≤ 5.67 kg/m^2 for women, and aLM ≤ 7.25 kg/m^2 for men. We used delta-aLM (Δ-aLM) for the outcome variable, calculating the difference as aLM upon discharge minus aLM on admission. Sarcopenia was defined in accordance with the definition proposed by the European Working Group on Sarcopenia in Older

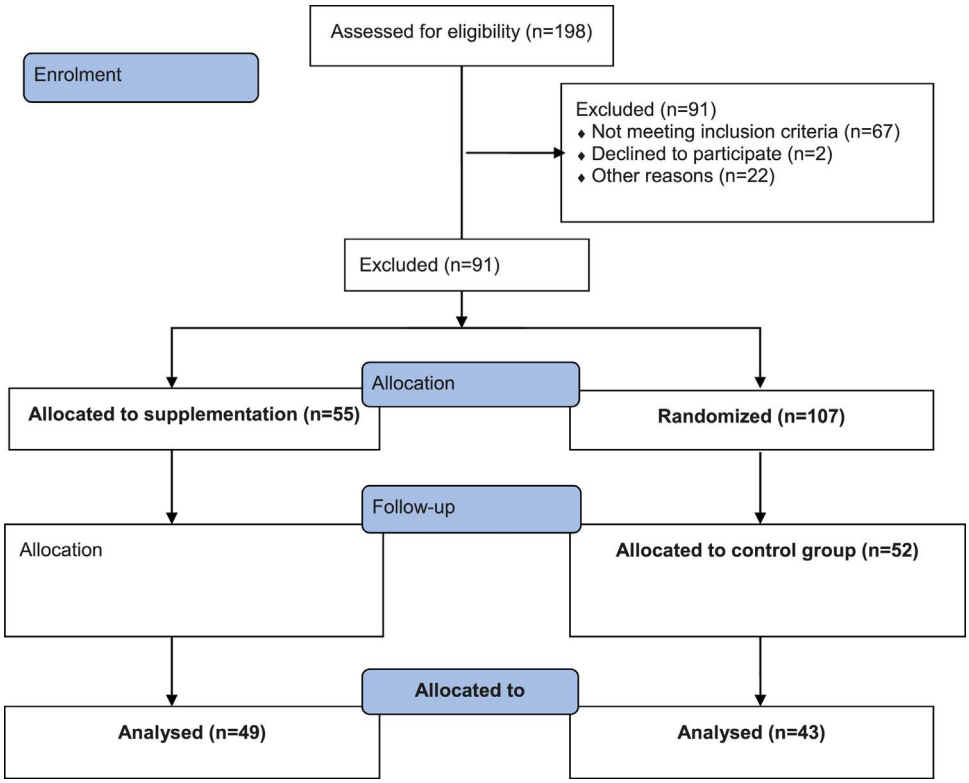

Fig. 1. CONSORT diagram of participants through the trial.a: patients who after beginning the study decided that they no longer wished to participate.b: patients who withdrew from the study after being referred to an acute care hospital due to complications.c: patients excluded for lacking compliance with the treatment − taking less than 50% of the indicated oral nutritional supplementation.d: patients whose intake was very small, for whom nutritional treatment wasindicated and who were therefore excluded from the study.

People (EWGSOP) [27].

2.5. Clinical characteristics

Weight was measured (in kg) by weighing patients on a wheel chair. Height (in cm) was measured with patients in the supine position. Body mass index (BMI) (weight/height^2) was calculated accordingly.

Nutritional assessment was carried out by a nutritionist who used the Mini Nutritional Assessment − Short Form (MNA-SF) based on the original classification: 12–14 points = well nourished; 8–11 points = -risk of malnutrition; and 0–7 points = malnutrition [28].

For the assessment of activities of daily living (ADL), an experienced trained PT used the Barthel index [29] (on which scores range from 0 points, indicating total dependency, to 100 points, indicating total self-sufficiency) and scores prior to the fracture (determined retrospectively via interview) and at discharge were taken into account.

The PT measured self-sufficiency while walking using the Functional Ambulation Categories (FAC) score, which ranges from 0, nonfunctional walking, to 5, independent walking on an even surface and stairs [30].

For the cognitive assessment the Mini Mental State Examination (MMSE) was used [31]. Comorbidity was defined on the basis of the Charlson index [32].

2.6. Blood tests and laboratory assessment

One blood test was carried out to record blood count and kidney function, total proteins, albumin, transthyretine, and 25(OH)D levels. Lipid metabolism was assessed by measuring the concentration of total cholesterol and triglycerides. For the study of glycemic metabolism, both the glycemic levels and the blood concentration of insulin were measured using the Homeostasis Model Assessment (HOMA) index to calculate insulin-resistance, using the original formula: HOMA = Insulin (mcU/mL) x [glycemia (mmol/l)/22.5] [33].

We measured the concentration of C-reactive protein (CRP) and blood concentrations of interleukin-1 (IL-1), interleukin −6 (IL-6) and tumour necrosis factor-alpha (TNF-α) in order to study the inflammatory state.

All tests took place in the morning after 8 h of fasting. Tests were repeated 72 h before discharge.

2.7. Social assessment

A social worker took the social history of patients, including their marital status, usual address and level of education, and used the Gijón scale [34] to score the patient's social-familial assessment, including family and economic situation, home, social relations and social support. Based on their Gijón scale score, patients were categorized as follows: low or normal social risk, for patients with values < 10; intermediate social risk, for patients with scores between 10 and 16; and high social risk for patients with scores ≥17. Destination upon discharge was recorded.

2.8. Rehabilitation therapy

Rehabilitation therapy comprised two distinct parts. The first part took place in the hospital ward (nursing staff and occupational therapist) and was based on moving patients early using technical aids (canes, crutches or walker), and rehabilitation of activities of daily living. The second part (physical therapy) took place at the hospital gym (PTs) and included exercises to strengthen the lower limbs, balance exercises and walking re-training in individual or group 50-minunte sessions, once a day five days a week (Monday to Friday).

2.9. Statistical analysis

Patient randomization was carried out with a random number generator, using R software and the 'runif' function, using a central

Table 1
Basal characteristics and discharge destination.

Variables	All patients n = 107	Control group n = 43	Intervention group n = 49	Drop-out n = 15
Age, years	85.4 ± 6.3	84.7 ± 6.3	85.7 ± 6.5	86.7 ± 5.7
Men	83.4 ± 7.7	82.5 ± 8.1	83.1 ± 7.4	86.5 ± 9.0
Women	86.1 ± 5.6	85.2 ± 5.8	87.0 ± 5.7	86.7 ± 4.7
Female	79 (73.8%)	35 (81.4%)	33 (67.3%)	9 (69.2%)
Gijon scale	9 (8–11)	9 (8–10)	10 (8–12)	9 (7–10)
Schooling				
Primary	99 (92.5%)	41 (95.3%)	43 (87.8%)	15 (100%)
Marital status				
Married	33 (30.8%)	16 (35.6%)	13 (26.5%)	4 (30.8%)
Single	16 (15.0%)	6 (13.3%)	10 (20.4%)	0
Widow	56 (52.3%)	20 (46.5%)	25 (51.0%)	11 (69.2%)
Social support				
Lives alone	35 (33%)	13 (33.3%)	18 (36.7%)	4 (15.4%)
Spouse	30 (28%)	13 (28.9%)	13 (26.5%)	4 (30.8%)
Son/daughter	28 (26.2%)	13 (28.9%)	8 (16.3%)	7 (53.8%)
Caregiver	5 (4.7%)	2 (4.4%)	3 (6.1%)	0
Other	7 (6.5%)	1 (2.2%)	6 (12.2%)	0
Type of fracture				
Intracapsular	46 (43%)	18 (41.9%)	24 (49%)	4 (26.7%)
Extracapsular	61 (57%)	25 (58.1%)	25 (51%)	11 (73.3%)
Surgical method				
Prosthetic replacement	32 (29.9%)	13 (30.2%)	16 (32.7%)	3 (20.0%)
Internal fixation	75 (70.1%)	30 (69.8%)	33 (67.3%)	12 (80.0%)
Time to surgery (d)	2.9 ± 2.0	3.1 ± 2.0	2.8 ± 4.1	2.9 ± 2.2
Length of Stay				
Orthopaedic wards[a] (d)	10.3 ± 3.8	10.1 ± 3.9	10.4 ± 4.0	10.7 ± 2.9
Rehabilitation units[b] (d)	42.3 ± 20.9	42.5 ± 19.4	41.9 ± 20.5	43.1 ± 27.0
Complication n (%)				
Anaemia Transfused	60 (56.1%)	21 (58.8%)	30 (61.2%)	9 (60.0%)
Delirium	26 (24.3%)	10 (23.3%)	14 (28.6%)	2 (13.3%)
Urinary Infection	5 (4.7%)	2 (4.7%)	3 (6.1%)	0
Urinary Retention	10 (9.3%)	1 (2.3%)	5 (10.2%)	3 (20.0%)
Respiratory Infection	7 (6.5%)	2 (4.7%)	5 (10.2%)	0
Heart Failure	5 (4.7%)	3 (7.0%)	1 (2%)	1 (6.7%)
Pressure Ulcers	1 (0.9%)	1 (2.3%)	0	0
No weight bearing	15 (14%)	7 (16.3%)	8 (16.3%)	0
MMSE	24 (19.5–27.5)	24 (21–28)	24 (19–26)	22 (19.5–26)
FAC Previous	5 (4–5)	5 (4–5)	4 (4–5)	5 (4–5)
FAC at discharge	3 (3–4)	3 (3–4)	3 (3–4)	–
Barthel Index				
Previous	95 (80–100)	90 (77.5–100)	95 (75–100)	100 (90–100)
At discharge	65 (40–85)	65 (40–82.5)	65 (30–90)	–
MNA-SF (n 71)	10 (8–12)	9 (8–12)	11 (9–12)	7 (7–12)
Discharge destination				
Home	84 (78.5%)	38 (88.4%)	40 (81.6%)	–
Nursing-home	9 (8.4%)	4 (9.3%)	4 (8.2%)	–

Results are expressed as Median (IQR), Mean ± SD or number of individuals (percentage).
FAC: Functional Ambulation Categories:
MMSE: Mini Mental State Examination; MNA-SF: Mini Nutritional Assessment-Short Form.
[a] Stay from ER admission to discharge from the acute orthopaedic wards.
[b] Length of stay from admission to discharge from the rehabilitation units (study time).

computer system. The principal investigator was responsible for randomization. Using the generated randomization list, the principal investigator assigned patients to one of two groups (intervention or control group). The intervention was not blinded. Quantitative variables were expressed as mean ± standard deviation (for normally distributed variables), and median and inter-quartile interval for non-normally distributed variables. The Shapiro-Wilk test was used to assess the normal distribution of the included variables. The Student *t*-test, and the Mann-Whitney *U* test were used for comparisons between variables. Categorical variables were expressed as number of subjects (percentage); and comparisons were done using the chi-square test.

The Student *t*-test was used for comparison within each group. The ANCOVA method was used in order to compare the results of both groups, for quantitative variables, correcting the analysis for the basal values. For the multivariate study, adjusted for possible confounding factors, we used the stepwise variable selection method. It was not possible to carry out an assessment with intention to treat groups, as designed in the original protocol, because it was not possible to record outcome variables upon discharge for patients who were referred to other hospitals for medical complications. The statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS), version 20.0 (IBM Corporation, Chicago, IL).

3. Results

During the study period, 198 patients with hip fractures admitted to the centres were screened for inclusion in the study and 107 (52%) patients were randomised (Fig. 1). Compared with participants, excluded patients (n 91, 72% women, mean age 85.7 ± 6.5) presented worse functional status (previous BI, $p < 0.001$), worse cognitive status (MMSE, $p < 0.001$) and a higher prosthetic replacement percentage (47%, $p = 0.008$), whilst no significant differences were found in the rest of variables assessed (e.g. sex, age, comorbidity, etc.).

The baseline characteristics of the included patients (age

Table 2
Nutritional and biochemical measurements.

Variables	Control group (CG)		Intervention group (IG)		p value
	Admission	Discharge	Admission	Discharge	
Height (m)	**n 45**		**n 49**		
	1.6 ± 0.1		1.6 ± 0.1		
Weight (Kg)		**n 44**		**n 42**	**< 0.001**
	63.2 ± 14.7	59.9 ± 14.1	62.7 ± 12.9	62.5 ± 12.7	
BMI (Kg/m^2)					**< 0.001**
	26.0 ± 5.4	24.7 ± 5.1	24.9 ± 4.4	24.6 ± 4.6	
Haemoglobin (g/dL)		**n 43**		**n 43**	**.240**
	10.5 ± 1.2	12.0 ± 1.2	10.6 ± 1.2	11.6 ± 1.0	
Total protein (g/dL)				**n 42**	**.007**
	5.7 ± 0.5	6.1 ± 0.5	5.8 ± 0.5	6.5 ± 0.5	
Albumin (g/dL)					**.118**
	3.0 ± 0.4	3.4 ± 0.4	3.1 ± 0.4	3.6 ± 0.3	
Prealbumin (mg/dL)		**n 38**		**n 35**	**.037**
	17.1 ± 4.8	19.8 ± 5.2	16.0 ± 5.9	21.9 ± 5.1	
Creatinin (mg/dL)	**n 44**		**n 49**		**.948**
	0.9 ± 0.3	0.9 ± 0.3	1.0 ± 0.4	0.9 ± 0.4	
Total Cholesterol (mg/dL)	**n 44**	**n 43**	**n 49**	**n 39**	**.336**
	169.5 ± 35.7	176.9 ± 39.6	155.0 ± 37.4	168.9 ± 35.5	
Triglycerides (mg/dL)		**n 42**			**.604**
	127.1 ± 45.4	125.3 ± 50.9	130.8 ± 53.5	131.1 ± 48.5	
25(OH)D (ng/mL)	**n 40**		**n 37**		**< 0.001**
	9.2 (5–14)	12.2 (7–19.6)	9 (7–12)	20.8 (16–30)	
CRP (mg/L)	**n 42**	**n 38**	**n 48**	**n 37**	**< 0.001**
	24 (7.2–36)	6.5 (2.2–10)	20.3 (4.5–35)	4 (1.8–11)	
IL-1 (pg/mL)	**n 36**		**n 35**		**.642**
	1.1 (0.4–5.8)	0.5 (0.4–4.8)	0.4 (0.4–4.5)	0.9 (0.4–3.6)	
IL-6 (pg/mL)					**.272**
	13.9 (8.6–21.1)	5.6 (2.5–8.4)	19.4 (13–24.1)	6.8 (4.2–9.2)	
TNF-alfa (pg/mL)					**.180**
	11.8 (6.8–18.5)	9.5 (5–14)	9.9 (5.4–14.8)	11.3 (7.7–15.1)	
Glycemia (mg/dL)	**n 45**	**n 40**	**n 49**	**n 43**	**.238**
	94.4 ± 11.1	88.5 ± 12.2	94.9 ± 12.3	91.9 ± 14.1	
Insulin (mcU/mL)	**n 45**	**n 39**	**n 48**	**n 36**	**.412**
	7.6 ± 5.2	6.9 ± 5.9	7.1 ± 8.1	8.3 ± 8.3	
HOMA					**.346**
	1.9 ± 1.4	1.6 ± 1.6	1.7 ± 2.2	2.1 ± 2.7	

Results are expressed as Median (IQR), Mean ± SD.
p Value: for parametric variables is the result of the ANCOVA test, the differences in the variables between the groups at discharge corrected by values and readings at admission. For non-parametric variables is the result of U-Mann Whitney test.
n = number of patients with all the information for each variable.
BMI: Body Mass Index, 25(OH)D: 25-Hydroxy-Vitamin D, CRP: C-Reactive Protein, IL-6: Interleukin-6, IL-1: interleukin-1, TNF-alpha: Tumour Necrosis Factor-alpha, HOMA: Homeostasis Model Assessment.
Bold values represent the number of patients with all the information for each variable.

85.4 ± 6.3, 74% female) are shown in Table 1. The average length of stay in the rehabilitation units was 42.3 ± 20.9 days (42.5 ± 19.4 days for the control group, and 41.9 ± 20.5 days for the intervention group) (Table 1). Almost all patients came from their own home (n 105), with good baseline functional status (prior BI 90 CI95% 80–100) and cognitive status (MMSE 24 CI95% 19.5–27.5).

During admission 6 patients died (5.6%). They were older patients (92.0 ± 3.6 years old, p = 0.009) with longer average stays in the trauma unit (14.8 ± 7.3 days, p = 0.003) but without any other differences with respect to the rest of the sample.

All of the subjects in the intervention group took more than 80% of the prescribed oral nutritional supplement, demonstrating good adherence to treatment.

3.1. Nutritional status

The MNA-SF was conducted on 71 patients and most of them (n 47, 66%) showed some degree of malnutrition (47.9% at risk of malnutrition and 18.3% with malnutrition).

More weight loss was observed in the control group than in the intervention group (p < 0.001) (Table 2 and Fig. 2 panel A). The results of the multivariate analysis show that the two predictive factors for BMI upon discharge were: 1) BMI upon admission, and 2) oral nutritional supplementation (Table 3). The ANCOVA, corrected for basal values, shows that in the intervention group total protein values, transthyretin and 25(OH)D upon discharge were significantly higher than in the control group (p = 0.007, p = 0.037 and p < 0.001, respectively) (Table 2).

The blood concentration of 25(OH)D increased significantly in the intervention group compared with the control group (p = 0.005) (Table 2). Only 5% of the individuals in the intervention group and 41% of the individuals in the control group had 25(OH)D values < 10 ng/mL at discharge.

3.2. Inflammatory markers

Fifty-seven per cent of the individuals in the intervention group and 43% of the individuals in the control group had CRP values ≤5 (p = 0.084) at discharge.

Also, a decrease in the levels of IL-1, IL-6 and TNF-alpha was reported − and this was more accentuated in the intervention group (Table 2).

In the intervention group there was a slight increase in the concentration of insulin and HOMA values − but this was non-

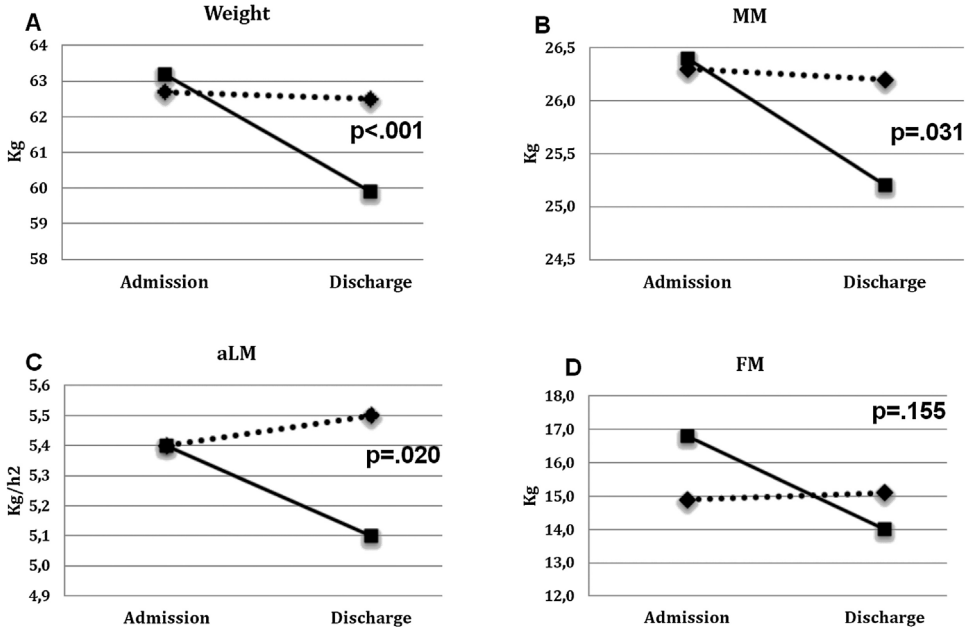

Fig. 2. Body composition study. Panel A: loss of weight among individuals in the control group (solid line), while in the intervention group weight was gained (dotted linen). Panel B and C: increases in muscle mass (MM) and in appendicular lean mass (aLM) in the IG (dotted line), compared with the CG (solid line), in which a decrease in both values was observed. Panel D: fat mass (FM) in both the IG (dotted line), and in the CG (solid line).

Table 3
Multivariable Models of Predisposing Factors.

	Adjusted Odds Ratio (95% Confidence Interval)		
	Δ-aLM[†]	BMI at discharge[§]	Barthel index at discharge[‡]
ONS	−0.35 (−0.60 to −0.11	0.79 (0.13–1.45)	–
Previous BI	−0.02 (−0.03–−0.01)	–	–
Previous FAC	0.40 (0.18–0.61)	–	12.20 (6.00–18.40)
BMI at admission	–	0.95 (0.88–1.02)	–
Age	–	–	−1.37 (−2.31 to −0.43)
Charlson index	–	–	−4.14 (−7.69 to −0.59)
MMSE	–	–	0.82 (0.03–1.61)

BI: Barthel index; BMI: Body Mass Index; Δ-aLM: delta-aLM (appendicular Lean Mass) difference between aLM upon discharge minus aLM on admission; FAC: Functional Ambulation Categories; MMSE: Mini Mentas State Examination; ONS: oral nutritional supplementation.
Adjusted Univariable Factors: [†] sex, age, ONS, previous BI, MMSE, previous FAC. [§] sex, age, ONS, previous BI, MMSE, previous FAC, admission BMI, admission total protein (g/dL), Charlson index, aLM at admission. [‡] sex, age, ONS, previous BI, MMSE, previous FAC, admission BMI, admission total protein (g/dL), Charlson index and rehabilitation length of stay.

significant compared with the control group.

3.3. Sarcopenia markers and body composition study

Table 4 shows the mean ± SD of the sarcopenia diagnostic markers (gait speed, hand grip strength, and body composition) at admission and discharge.

Gait speed was available only on discharge because on admission patients were unable to walk. No differences between the groups were observed.

Despite no differences having been found between the groups in terms of strength, measured with the GWI, an increase in GWI was observed in the intervention group, which did no occur in the control group.

As regards the muscle mass indices, a reduction in aLM was observed in the control group, whereas the values remained stable in the intervention group. The difference between values upon discharge, corrected to take into account basal values, was statistically significant (p = 0.020) (Table 4). We found three factors that predicted Δ-aLM: 1) oral nutritional supplementation, 2) previous Barthel index score, and 3) the previous FAC score (Table 3).

We used the criteria proposed by the EWGSOP to diagnose sarcopenia at discharge. Among the entire population, 24 (28%) individuals did not have sarcopenia, and 62 (72%) had sarcopenia.

3.4. Activities of daily living

The mean Barthel index at discharge was 61.9 ± 28.6.

A positive effect of oral nutritional supplementation on ADL recovery was reported. The recovery of ADL was more common in the intervention group (68%) than in the control group (59%) (p = 0.261). We found four predictive factors for the Barthel index score upon discharge: 1) FAC score prior to fracture; 2) age; 3) the Charlson index score; and 4) the MMSE score (Table 3).

4. Discussion

To our knowledge, this is the first study to assess the effects of an oral nutritional HMB supplement with in elderly patients with hip fractures admitted to rehabilitation facilities. This study demonstrates that patients who receive nutritional oral supplementation suffer fewer complications and less sarcopenia, and – conversely − undergo an improvement in body composition and have a better functional and nutritional status upon being discharged. Former studies showed the benefits of oral nutritional supplementation on weight [19] and complications [20].

The prevalence of sarcopenia was greater in the present study than is reported in studies conducted in the community (4–25%) [35], hospitals (25%) [36], or nursing homes (32%) [37]. Several factors may have influenced this. Firstly, the high degree of heterogeneity in the definition and the measurement of sarcopenia makes the results of different studies hard to compare [38]. Secondly, the average age of our

Table 4
Sarcopenia parameters, hand grip strength, gait speed and bioimpedance measurements.

Variables	Control group (CG)		Intervention group (IG)		p value
	Admission n 45	Discharge n 38	Admission n 49	Discharge n 36	
Gait-speed (m/s)	–	0.4 ± 0.3	–	0.4 ± 0.3	0.367
Hand-grip (Kg)	13.8 ± 6.2	14.6 ± 6.7	15.6 ± 7.6	16.8 ± 8.8	0.752
Grip work index	4.4 ± 3.7	6.3 ± 4.4	4.1 ± 2.7	6.8 ± 5.4	0.188
MM by Sergi et al. [24]	4.5 ± 1.6	4.1 ± 1.7	4.5 ± 1.4	4.6 ± 1.4	0.020
aLM by Sergi et al. [24]	5.4 ± 1.4	5.1 ± 1.4	5.4 ± 1.1	5.5 ± 1.2	0.020
SMM	23.6 ± 10.0	22.7 ± 7.9	25.5 ± 9.9	24.3 ± 8.6	0.368
ASMM	18.1 ± 5.6	17.1 ± 4.6	18.8 ± 5.3	18.1 ± 4.8	0.026
MM	26.4 ± 7.0	25.2 ± 5.3	26.3 ± 7.3	26.2 ± 6.4	0.031
FFM	46.8 ± 9.5	45.4 ± 7.7	47.8 ± 9.5	47.1 ± 8.2	0.016
FM	16.8 ± 13.4	14.0 ± 10.9	14.9 ± 10.6	15.1 ± 9.7	0.155

Results are expressed as Mean ± SD. p value = result of the t-Student test, of the result of the differences between values upon discharge minus values on admission.
aLM: appendicular lean mass, ASMM: appendicular skeletal muscle mass, FFM: fat free mass, FM: fatty mass, MM: muscle mass, SMM: Skeletal Muscle Mass.

patients (almost 86 years old) was greater than that in the earlier studies [36]. Thirdly, our study was conducted in rehabilitation centres to which the patients with most clinically complex conditions are admitted [39]. Lastly, in elderly patients with hip fractures the recovery of one of the diagnostic parameters of sarcopenia – gait – is slower than the recovery of other aspects of functional capacity (like dressing, continence, or eating) [40].

Yet despite the high prevalence of sarcopenia, 68% of the individuals in the intervention group recovered to the extent that their functional status matched what it had been before the fracture, which is a larger proportion than is reported in former studies without nutritional supplementation [5]. Several studies have shown the validity of BIA in assessing nutritional status, as well as measuring body composition in elderly patients with a hip fracture [41–43]. The novelty in this study is that it demonstrates how the observed increase in weight is due to a significant increase in muscle mass coupled with a non-significant change in fat mass. This research shows that hypercaloric and hyperproteic nutritional supplementation helps to preserve appendicular lean mass and can be effective in the treatment of sarcopenia. It would be interesting to conduct research into whether the decrease in the prevalence of sarcopenia and the better functional response in elderly patients with hip fractures is maintained over the long term.

In situations of fast or reduced intake compared with metabolic requirements, muscle can be viewed as the organism's "supermarket". When there is insufficient intake (as may happen in hospitalized elderly people) the body recovers necessary nutrients by metabolizing muscle tissue [44]. This study shows that when patients are given oral nutritional supplements their muscle mass increases and fat mass remains unchanged. In contrast, subjects in the control group lost muscle mass, developing a pattern known as sarcopenic obesity [45,46].

The low concentration of 25(OH)D is associated with a reduction in muscle mass and strength, and supplementation with 25(OH)D is effective in the prevention and management of frailty [47]. In this study we saw that the amount of 25(OH)D contained in the oral nutritional supplement was effective in restoring normal values of vitamin D in most patients treated.

The proinflammatory IL-6 cytokine is also known as myokine, since it is produced by muscle cells in response to regular physical exercise in the absence of muscle damage [48]. Yet despite the significant decrease in both groups in the concentration of IL-6 after admission, the persistence of relatively high values could be associated with the rehabilitation process and thus be considered a positive marker of muscle activation [49].

4.1. Limitations and strengths of the study

This study has a number of limitations. First, our patients received rehabilitation five days a week. It will be interesting to see whether participation in a programme of resistance exercises during patients' stay at a rehabilitation centre improves the functional results reported. Second, we could not do any follow-up of our patients after discharge to assess whether the benefits obtained were maintained. Third, the diagnostic criteria for sarcopenia proposed by the EWGSOP are difficult to apply in patients with hip fractures admitted to rehabilitation units, because most of the patients are unable to walk when they arrive. Despite this, the aforementioned criteria can be applied at the time of discharge from rehabilitation, whereby our research has shown a high prevalence of sarcopenia.

Yet despite these limitations, this research has some important strengths. Due to the characteristics of the patients included, we believe our study is representative of the geriatric population admitted to rehabilitation centres. The methodology used for this randomized multicentre study, whose protocol was registered, adds clinical significance to the results obtained.

5. Conclusions

In elderly patients with hip fractures, oral nutritional supplements with HMB improves muscle mass (sarcopenia), prevents weight loss and therefore the onset of malnutrition, and helps with functional recovery. ONS with HMB could be an effective intervention to reduce sarcopenia and malnutrition and could prevent the onset of disability secondary to hip fractures in elderly patients with hip fractures.

Contributors

VM was the principal investigator, wrote the study protocol, was involved in the training of the staff who took part in the study, conducted the statistical analysis and ultimately wrote this paper. This research is part of the VM's PhD project.

FU-O took part in the statistical analysis of the results and in the writing of the paper.

CM and JAM helped in the critical analysis of the findings, and in both the correction and the editing of the manuscript.

MAZ was the supervisor of the PhD project, and contributed to the critical analysis of findings and the writing and editing of this paper.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

No funding was received for this study.

Ethical approval

This study was approved by the Comunidad Foral de Navarra Clinical Research Ethics Committee (62/2011) and was conducted following the Good Clinical Practice Standards set by the European Union and the Helsinki Declaration. Written informed consent was provided by all patients or their legal representatives.

Provenance and peer review

This article has undergone peer review.

Acknowledgments

We wish to thank the medical doctors, nurses, nurses' aides, physical therapist, psychologist and social worker of Hospital Viamed Valvanera for their help in the acquisition of the data for this study.

We also wish to thank Fernando Martín Ciancas for his support in the whole process of preparing and conducting this study.

We are extremely thankful to all patients and their families for their participation in this study.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.maturitas.2017.04.010.

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