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ORIGINAL RESEARCH

Effects of essential amino acid supplementation and rehabilitation on functioning in hip fracture patients: a pilot randomized controlled trial

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Abstract

Background Physical exercise and nutrition seem to have a key role in the management of hip fracture patients.

Aim To evaluate the impact of a 2-month rehabilitative protocol combined with dietetic counseling, with or without essential amino acid supplementation, on functioning in hip fracture patients.

Methods In this pilot randomized controlled study, we recruited patients aged more than 65 years, at 3 months after hip fracture. We randomly assigned the participants into two groups (A and B). Both groups performed a physical exercise rehabilitative programme (five sessions of 40 min/week for 2 weeks, followed by a home-based exercise protocol) and received a dietetic counseling; only group A was supplemented with two sachets of 4 g/day of essential amino acids (Aminotrofic®). We evaluated at baseline and after 2 months of intervention (T_1): hand grip strength, Timed Up and Go, and Iowa Level of Assistance scale (ILOA).

Results The 32 hip fracture patients (mean aged 79.03 ± 7.80 years) were allocated into two groups: group A ($n = 16$) and group B ($n = 16$). All the participants showed significant differences in all outcomes at T_1 ($p < 0.017$). Sarcopenic patients in group A ($n = 10$) showed statistically significant differences in all the primary outcomes at T_1 ($p < 0.017$), whereas sarcopenic patients in group B ($n = 13$) showed a significant reduction of ILOA only. In non-sarcopenic patients, we found no differences at T_1 in all outcome measures.

Discussion Hip fractures are a complex multifactorial condition of the elderly that determines devastating effects on functioning and independence.

Conclusion A multidisciplinary rehabilitative and nutritional intervention seems to be effective on functioning in hip fracture patients, in particular sarcopenic ones.

Keywords Hip fractures · Sarcopenia · Amino acids · Rehabilitation · Muscle strength · Nutrition

Marco Invernizzi, Alessandro de Sire, Giovanni Iolascon and Carlo Cisari contributed equally to this work.

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Introduction

Hip fractures are the most common osteoporotic fragility fractures that require hospitalization [1], with a high risk of mortality (33% at 1 year) [2], and limitation of function and independence in the activities of daily living (ADL) [3]. These fractures are expected to increase in the next years, in particular by 2020 [4], with an important economic burden in health care due to their treatment in hospital, the length of stay, and the higher consequent disability than other osteoporotic fractures [5, 6].

As showed by a recent study, over 50% of community-dwelling hip-fractured patients had a walking disability (unable to walk across a room—3 m), about 39% showed disability in transferring, and 18% in personal grooming [3].

Sarcopenia is a condition characterized by a decreased muscle mass with concomitant strength deficit and low physical performance [7]. It could be considered the analogous for muscle of what osteoporosis is to bone [8], sharing several pathogenic factors [9] and it might worsen the functional outcomes after osteoporotic hip fracture [10–12].

Previous studies showed a high prevalence of sarcopenia in hip fracture patients with important implications on disability and functional recovery [12, 13]. Moreover, general malnutrition has long been recognized as both highly prevalent (40–80% of hospitalized patients with hip fracture) and a strong predictor of poor outcomes after osteoporotic hip fracture [14], confirmed by the association between low serum levels of albumin (< 3 g/dl) and poor recovery after osteoporotic hip fracture [15]. Physical exercise is crucial in hip fracture rehabilitative management and it has been already shown that a robust, long-term supervised training is commonly associated with increasing muscle function in these patients. On the contrary, nutritional interventions have not shown significant impact on long-term outcomes after hip fractures [14], although micronutrients and, in particular amino acids, have been proven to play a key role in muscle metabolism and functioning in older people [16]. Thus, physical exercise and nutrition have a key role in the multidisciplinary management of elderly fractured patients, being two synergistic interventions able to modify rehabilitative outcomes in this condition [17, 18].

Recent randomized controlled trials (RCTs) showed that exercise plus supplementation with proteins and/or creatine [19] or with oral essential amino acids, whey proteins, and vitamin D [20] could induce significant improvements in muscle strength and physical performance in older frail individuals.

On the other hand, a previous meta-analysis affirmed that resistance training plus protein supplementation did not seem to increase muscle mass or strength in older adults [21].

Therefore, the aim of this pilot randomized controlled trial (RCT) was to evaluate the impact of a 2-month rehabilitative protocol combined with dietetic counseling, with or without essential amino acid supplementation, on functioning in hip fracture patients.

Methods

Participants

Osteoporotic hip fracture patients of both sex, aged more than 65 years referred to the Outpatient Service for the Management of Osteoporosis of the Physical Medicine and Rehabilitation Unit of University Hospital "Maggiore della Carità" in Novara, were consecutively enrolled 3 months after hip fracture, and having undergone a total hip replacement, from January to June 2015. Patients with dysphagia to liquids, traumatic hip fractures, secondary osteoporosis or cancer were excluded from the study. The study protocol was approved by the Local Committee and met the guidelines of the responsible governmental agency. At enrollment, all the participants were asked to carefully read and sign an informed consent, and researchers provided to protect the privacy and the procedures in this study were in accordance with the Declaration of Helsinki.

Intervention

After enrollment, all patients were randomly assigned to one of the two treatment arms (group A and group B) using a randomization scheme generated by software with a 1:1 allocation and without blocks.

Patients in group A were treated for 2 months with an essential amino acid supplementation (Aminotrofic®, Errekappa Euroterapici, Milan, Italy) two sachets of 4 g per day (1,250 mg of L-leucine, 650 mg of L-lysine; 625 mg of L-isoleucine, 625 mg of L-valine, 350 mg of L-threonine, 150 mg of L-cystine, 150 mg of L-histidine, 100 mg of L-phenylalanine, 50 mg of L-methionine, 30 mg of L-tyrosine, 20 mg of L-tryptophan; 0.15 mg of vitamin B6, and 0.15 mg of vitamin B1). At baseline (T_0), patients in group A were provided a container with 14 sachets of Aminotrofic® accounting for a full week of treatment. Every week during the whole study period, group A patients returned the container and were provided with a full one. Compliance to amino acid supplementation was evaluated through the number of sachets returned every week. Patients of group A did not take any other dietary supplements or nutraceuticals including amino acids. Moreover, patients in group A performed a concomitant specific physical exercise rehabilitative program,

consisting in five sessions of 40 min each per week for 2 weeks with the supervision of an experienced physiotherapist, and received a dietetic counseling.

On the other hand, patients in group B performed the same physical exercise rehabilitative program as group A and received only a concomitant dietetic counseling alone, without essential amino acid supplementation.

The physical exercise rehabilitative protocol, performed by both groups, consisted of different phases to address the maximum number of fitness components (aerobic, flexibility, resistance and neuromotor) according to healthy ageing indications in individuals with clinically significant chronic conditions or functional limitations [22]. The first phase of each session consisted of 15 min of walking training, the second phase consisted of 10 min of upper and lower limb strengthening and stretching, standing or at bed, and the fourth phase consisted of 10 min of balance exercises. Each session lasted 40 min and was performed with the supervision of an experienced physiotherapist. After these first 2 weeks of physical exercise rehabilitative program, all participants performed a home-based exercise protocol up to the end of the study period, after 2 months of intervention (T_1). The study flow chart is resumed in Fig. 1.

Outcomes

At baseline (T_0), we assessed demographic and anthropometric characteristics, mental status evaluation, using the Short Portable Mental Status Questionnaire (SPMSQ) [23], comorbidities, by the Cumulative Illness Rating Scale (CIRS) [24], and the skeletal muscle mass index (SMI), expressed as the ratio between skeletal muscle mass (SM) and height^2.

This index was obtained, according to the Janssen equation [25], through the whole-body tetrapolar bioelectrical impedance analysis (BIA). This device uses an alternating sinusoidal electric current of 400 mA at a single operating frequency of 50 kHz (BIA 101 Anniversary Sport Edition—ASE—Akern Srl; Florence, Italy). The device's precision was 1% for resistance (Rz) and 5% for reactance (Xc). BIA was performed on supine subjects with their limbs slightly away from their body, after an overnight fast, and bladder voiding. Active electrodes (BIATRODES Akern Srl; Florence, Italy) were placed on the right side on conventional metacarpal and metatarsal lines, recording electrodes in standard positions at the right wrist and ankle [26, 27]. All resistance measurements were normalized for stature (height in centimetres squared/Rz) to obtain the resistive index (RI).

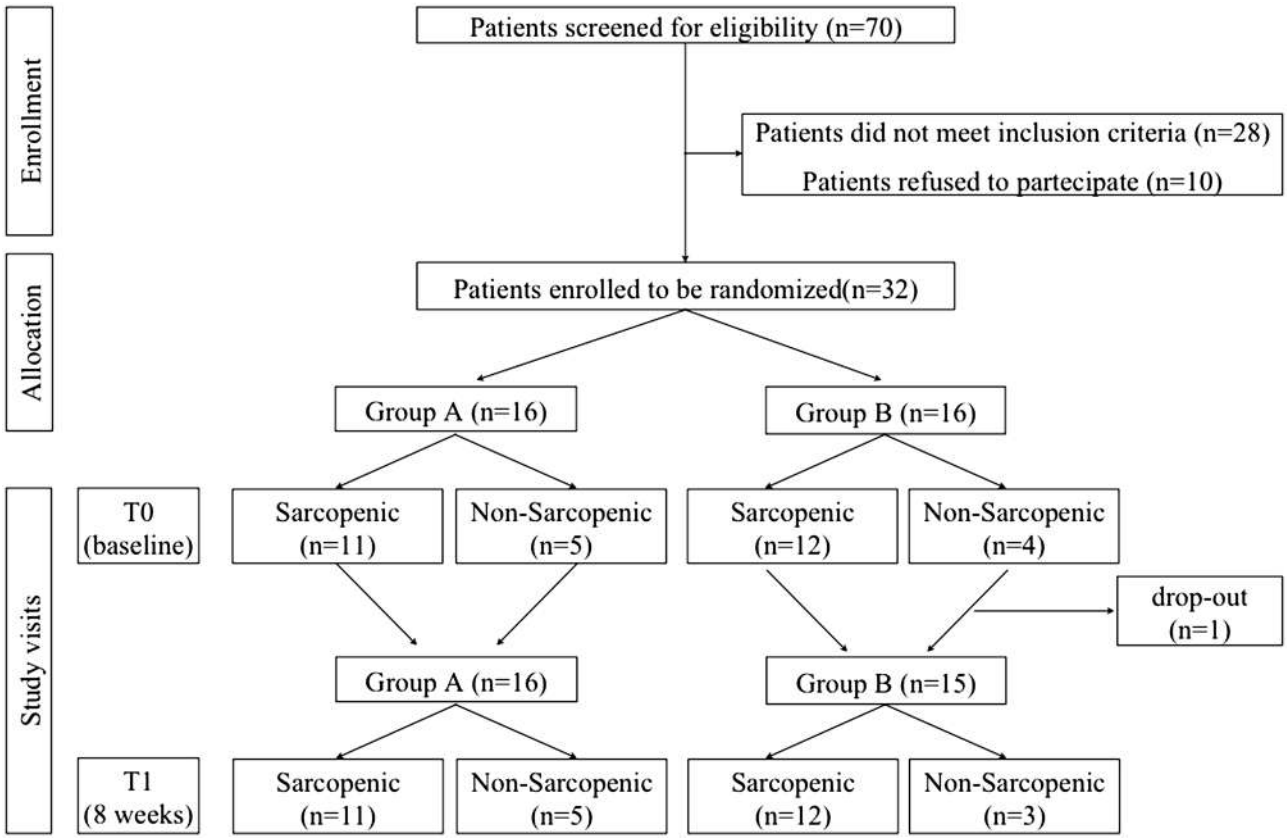

Fig. 1 Study flow chart

We evaluated as primary outcome measures: appendicular muscle strength, measured by hand grip strength test (HGS), through the hand-held Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL), considering the maximum value (in kilograms) of three consecutive measurements of the upper dominant limb (with a pause of 1 min after each measurement) [28]; physical performance, using the Timed Up and Go test (TUG) [29]; the level of assistance, measured by the Iowa Level of Assistance scale (ILOA) [30].

Secondary outcomes were nutritional assessment, with evaluation of daily caloric intake and daily protein intake, and the health-related quality of life (HRQoL), using the 12-Item Short Form Health Survey (SF-12), determining both Physical (PCS) and Mental Health Composite Scores (MCS) [31].

All the outcome measures were assessed at baseline (T_0) and after 2 months of treatment (T_1).

Patients in both groups were divided in sarcopenic and non-sarcopenic patients, according to Janssen criteria [32], reported by the European Working Group on Sarcopenia in Older People (EWGSOP) [7]. Therefore, we considered as sarcopenic: men with a SMI $\leq$ 8.51 kg/m^2 and women with a SMI $\leq$ 5.75 kg/m^2 [32]. Data analysis has been performed on whole groups A and B, and on sarcopenic and non-sarcopenic patients in both groups, as depicted by the study flow chart in Fig. 1.

Statistical analysis

Due to the small sample size, we supposed a non-Gaussian distribution of variables. Differences between each variable in each group have been evaluated with Wilcoxon's signed rank test. Differences between single variables in different groups were evaluated with the Mann–Whitney *U* test. A type I error level of 0.05 was chosen. The Bonferroni correction for multiple comparisons was applied considering three primary outcome variables (HGS, TUG and ILOA), which resulted in a new α error level of 0.017.

Results

Of the 32 hip fracture patients assessed (mean aged 79.03 ± 7.80 years), 16 (mean aged 80.33 ± 6.72 years) were allocated in group A and 16 (mean aged 77.65 ± 8.40 years) in group B.

There were no statistical differences between groups in terms of age, body mass index (BMI), sex, mental status, comorbidities, ASMMI, and prevalence of sarcopenic patients, as depicted by Table 1.

The prevalence of sarcopenic patients was 68.8% in group A and 75.0% in group B, and the whole prevalence was 71.9%.

A non-sarcopenic patient allocated in the group B dropped out between the two evaluations.

All patients in both groups showed statistically significant differences in all the primary outcome measures (HGS, TUG, ILOA) at T_1 evaluation ($p < 0.017$) (see Fig. 2 for further details).

Sarcopenic patients in group A ($n = 11$) showed statistically significant differences in all the primary outcomes (HGS, TUG, ILOA) at T_1 ($p < 0.017$), whereas sarcopenic patients in group B ($n = 12$) showed a significant reduction of ILOA at the end of treatment (see Fig. 3 for further details).

On the other hand, in non-sarcopenic patients we found no differences at T_1 in all the primary outcome measures.

Moreover, in both groups and in all the sub-groups (group A sarcopenic and non-sarcopenic and group B sarcopenic and non-sarcopenic), there were no differences at T_1 in all the secondary outcomes: daily caloric intake, daily protein intake, SF-12 PCS and MCS (data not shown). Furthermore, there were no differences between groups in all the outcome

Table 1 Baseline characteristics of study population

	Total ($n = 32$)	Group A ($n = 16$)	Group B ($n = 16$)	p value
Age (years)	79.03 ± 7.80	80.33 ± 6.72	77.65 ± 8.40	NS
BMI (kg/m^2)	23.10 ± 4.90	23.05 ± 4.77	23.15 ± 5.33	NS
Sex (male/female)	5/27	2/13	3/14	NS
SPMSQ	0.59 ± 0.34	0.60 ± 0.84	0.59 ± 0.71	NS
CIRS-CI	2.44 ± 1.33	2.10 ± 1.37	2.67 ± 1.29	NS
CIRS-SI	1.62 ± 0.49	1.51 ± 0.29	1.69 ± 0.58	NS
ASMMI	5.96 ± 1,32	6.03 ± 1,58	5.90 ± 1.06	NS
Sarcopenic patients	23 (71.88)	11 (68.75)	12 (75.00)	NS

Continuous variables are expressed as means ± standard deviations; categorical variables are expressed as counts (percentages); rates are expressed as *x*/*y*

BMI body mass index, *SPMSQ* Short Portable Mental Status Questionnaire, *CIRS-CI* Cumulative Illness Rating Scale-Comorbidity Index, *CIRS-SI* Cumulative Illness Rating Scale-Severity Index, *ASMMI* appendicular skeletal muscle mass index

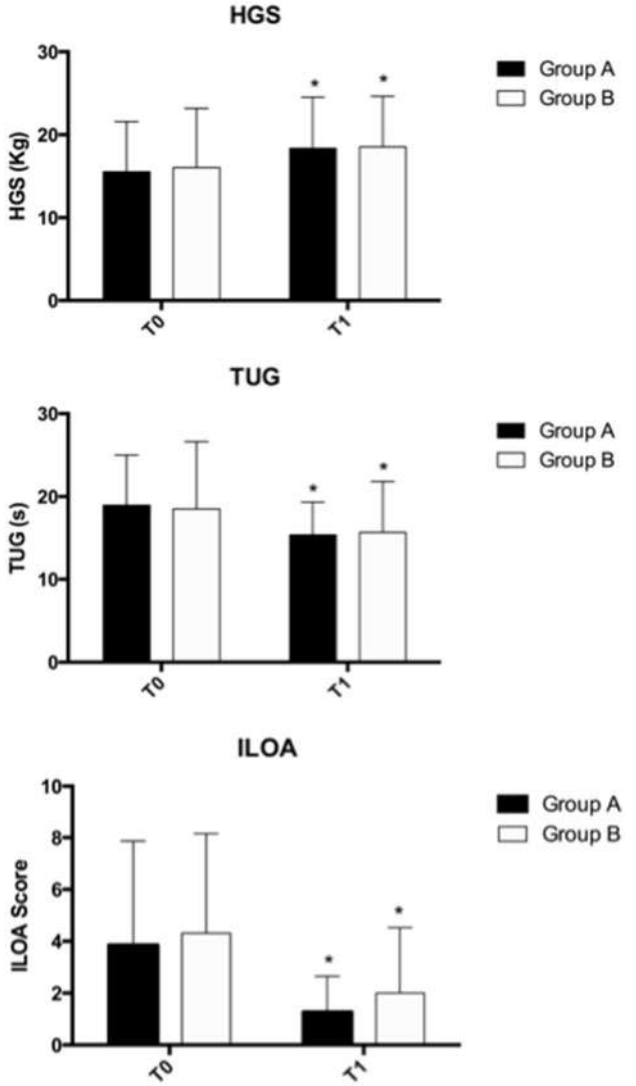

Fig. 2 Differences in primary outcomes after intervention (T_1–T_0) in both groups. *HGS* handgrip strength test, *TUG* Timed Up and Go, *ILOA* Iowa Level of Assistance scale

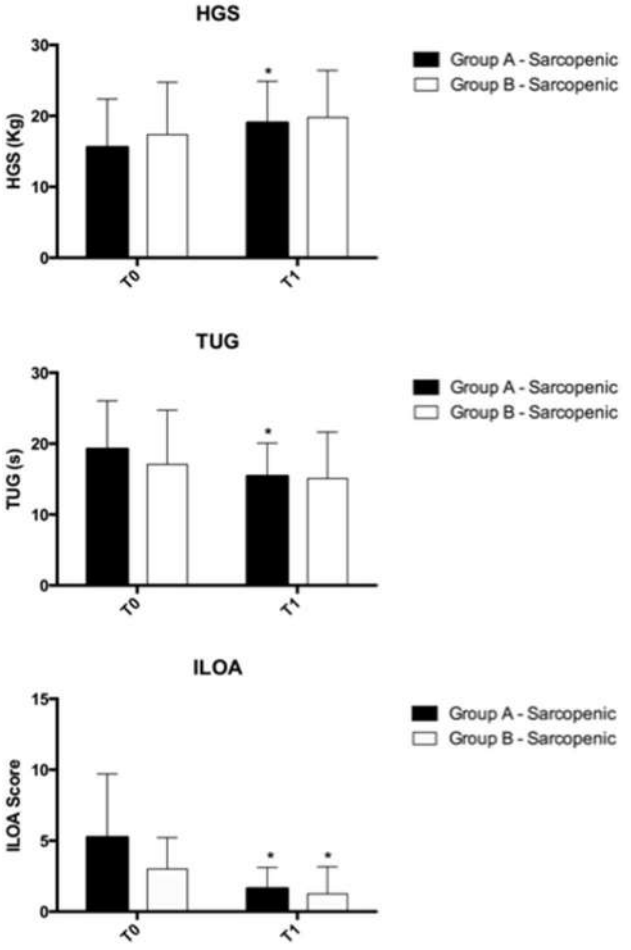

Fig. 3 Differences in primary outcomes after intervention (T_1–T_0) in sarcopenic patients of both groups. *HGS* handgrip strength test, *TUG* Timed Up and Go, *ILOA* Iowa Level of Assistance scale

measures both at baseline and after 2 months of treatment (data not shown).

Discussion

In this study, we showed that a 2-month multidisciplinary rehabilitative and nutritional approach starting 1 month after osteoporotic hip fracture provided significant improvements in function and disability reduction in these patients. Amino acid supplementation did not show greater improvements in primary outcome measures compared to nutritional counseling alone; however, after sarcopenia stratification, the sarcopenic subgroup treated with amino acid supplementation (group A) showed significant improvements in all the primary outcome measures (HGS, TUG, ILOA) at T_1 ($p < 0.017$), whereas non-supplemented sarcopenic patients (group B) reported only a significant reduction of ILOA score. Moreover, after the 2-month treatment period, a positive trend, although not significant, was observed in daily caloric and protein intake in both groups, testifying also the importance of an adequate dietetic counseling with potential clinical implications regarding nutritional indications and their positive impact in patients undergoing rehabilitative treatment after an osteoporotic hip fracture.

As previously noticed, sarcopenia is characterized by a decreased muscle mass with concomitant strength deficit and low physical performance, and is able to worsen functional outcomes and disability in hip-fractured osteoporotic patients [12, 13]. According to EWGSOP criteria [7], a prevalence of 71.9% of sarcopenia in the entire cohort of this study was found. Compared to the few reports in literature, this prevalence is higher and in particular a recent study reported a prevalence of 58% in a cohort of hip fracture

patients [12], even though this difference might be due also to the smaller sample size of our cohort. However, considering the few papers in literature and the low number of patients enrolled, robust and definitive data about the real impact of sarcopenia in subjects affected by this condition are still missing thus further evidences by larger prospective studies are needed.

Previous studies in general community-dwelling sarcopenic patients produced relevant data about the impact of synergistic interventions comprising both nutritional supplements and physical activity in the treatment of sarcopenic patients. Rondanelli et al. conducted a 12-week randomized double-blind placebo-controlled protein supplementation trial on 130 sarcopenic elderly subjects (53 men and 77 women; mean age 80.3 years) with a concomitant physical activity intervention, showing that protein supplementation in conjunction with physical exercise, increased significantly fat-free mass and strength, HRQoL and independence in ADL and reduced serum inflammatory markers in these patients [20]. Similarly, Ikeda et al., in a cross-over study investigated the effects and feasibility of a twice weekly 6-month therapeutic exercise combined to supplementation of branched chain amino acids (BCAAs) on physical function improvement in frail and pre-frail elderly people requiring long-term care, showing greater improvements in gross lower limb muscle strength and dynamic balance ability in patients treated with concomitant BCAA supplementation and structured physical exercise [33].

A recent review highlighted the strong correlation between poor nutritional status and frailty onset, evidencing that macro- and micronutrient deficit correction and concomitant physical exercise are the best non-pharmacological approach to maximize outcome in frail patients [18]. However, studies examined in the above-mentioned review were mainly conducted on community-dwelling patients, with great heterogeneity of outcomes and without any special focus on hip-fractured patients. A recent meta-analysis performed on nine RCTs aimed to quantify whether protein supplementation could optimize the effects of resistance training on muscle mass and strength in an aged population [21]. Authors stated that combining protein supplementation with resistance training is effective for eliciting gains in fat-free mass among older adults, but does not seem to increase muscle mass or strength. However, they underlined that due to the paucity of studies on very elderly patients and the variety of supplementation protocols, amounts and type of products made it hard to compare the results obtained by this review and the risk of bias in the studies examined remained quite high. Another review focused specifically on rehabilitative approach and nutritional supplements in hip-fractured patients, stressing the need to address several issues in these patients such as sarcopenia/dynapenia treatment, balance impairment, under-nutrition, vitamin D and calcium, depression, cognitive impairment, sensory impairment and social isolation through exercise, nutrition and other modalities [14].

Thus, several papers in literature underlined the need of a multidisciplinary therapeutic approach involving both nutritional and rehabilitative interventions to better address a complex and multifactorial geriatric syndrome such as osteoporotic hip fracture. However, at present, the number of studies and the heterogeneity of both elderly populations and interventional protocols hinder the overall evidence of combined nutritional and rehabilitative interventions in these patients.

The main limitation of this study is the low sample size; however, considering the few papers addressing this issue in literature and the pilot design, this study might be the starting point to a larger multicenter study on bigger samples to obtain more robust evidences about amino acid supplementation impact on functioning and HRQoL in hip fracture patients. Another limitation is the use of BIA instead of the dual X-ray absorptiometry (DXA) to calculate the SMI. The BIA, commonly used in our clinical practice, might be a good portable alternative to DXA that is the gold standard procedure as suggested by EWGSOP [7].

Conclusions

Considering the increasing lifespan [34], healthy ageing is one of the main targets in the near future to prevent disability and improve HRQoL for as long as possible [35]. Sarcopenia and osteoporotic hip fracture are two complex and multifactorial conditions of the elderly sharing several pathophysiological mechanisms. Recent evidences suggest that structured exercise programmes combined with nutritional assessment/intervention are mandatory to treat two complex and multifactorial condition such as sarcopenia and osteoporotic hip fracture in the elderly. The purpose of this pilot RCT was to apply a synergistic multidisciplinary rehabilitative and nutritional protocol in osteoporotic hip fracture patients. Even though performed on a small sample size, data emerging from this study showed a positive impact of this combined intervention on function and disability in hip fracture patients after 2 months of treatment. In particular, essential amino acid supplementation induced significant improvements in the sarcopenic sub-population of the study, suggesting a greater efficacy of this intervention in these patients, with possible important implications for the clinical management of this complex and burdensome condition.

Author contributions Each author is expected to have made substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data; or the creation of new software used in the work; or have drafted the work or substantively revised it; and has approved the submitted version (and version substantially

edited by journal staff that involves the author's contribution to the study); and agrees to be personally accountable for the author's own contributions and for ensuring that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and documented in the literature.

Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. Funding sponsors had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript, and in the decision to publish the results.

Ethical standards The experiments comply with the current laws of the country in which they were performed.

Statement of human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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