Maturitas 93 (2016) 89–99

Contents lists available at ScienceDirect

Maturitas

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

Review article

The relationship between nutrition and frailty: Effects of protein intake, nutritional supplementation, vitamin D and exercise on muscle metabolism in the elderly. A systematic review

Iñaki Artaza-Artabe[a], Pilar Sáez-López[b], Natalia Sánchez-Hernández[c], Naiara Fernández-Gutierrez[a], Vincenzo Malafarina[d,*]

[a] Geriatric Department, Igurco Servicios Socio Sanitarios, Grupo IMQ, Bilbao, Spain
[b] Geriatrics Unit, Complejo Asistencial de Ávila, Ávila, Spain
[c] Unit of Orthopaedics Surgery, Complejo Asistencial de Ávila, Ávila, Spain
[d] Geriatric Department, Clinica Los Manzanos, Grupo Viamed, Lardero, Spain

ARTICLE INFO

Article history:
Received 21 January 2016
Received in revised form 5 April 2016
Accepted 11 April 2016

Keywords:
Frailty
Nutrition
Protein intake
Vitamin D
Sarcopenia

ABSTRACT

Background: Frailty is a geriatric syndrome that predicts the onset of disability, morbidity and mortality in elderly people; it is a state of pre-disability and is reversible.

The aim of this review is to assess how nutrition influences both the risk of developing frailty and its treatment.

Data sources: We searched two databases, PubMed and Web of Science. We included epidemiologic studies and clinical trials carried out on people aged over 65 years. We included 32 studies with a total of over 50,000 participants.

Results: The prevalence of frailty is ranges from 15% among elderly people living in the community to 54% among those hospitalized. Furthermore, the prevalence of frailty is disproportionately high among elderly people who are malnourished. Malnutrition, which is very prevalent in geriatric populations, is one of the main risk factors for the onset of frailty.

A good nutritional status and, wherever necessary, supplementation with macronutrients and micronutrients reduce the risk of developing frailty. Physical exercise has been shown to improve functional status, helps to prevent frailty and is an effective treatment to reverse it. Despite the relatively large number of studies included, this review has some limitations. Firstly, variability in the design of the studies and their different aims reduce their comparability. Secondly, several of the studies did not adequately define frailty.

Conclusions: Poor nutritional status is associated with the onset of frailty. Screening and early diagnosis of malnutrition and frailty in elderly people will help to prevent the onset of disability. Effective treatment is based on correction of the macro- and micronutrient deficit and physical exercise.

Contents

* Corresponding author at: Department of Geriatrics, Clínica los Manzanos, Calle Hermanos Maristas, Lardero, La Rioja 26140, Spain.
E-mail address: vmalafarina@gmail.com (V. Malafarina).

http://dx.doi.org/10.1016/j.maturitas.2016.04.009
0378-5122/

1. Introduction

Frailty is a state of increased vulnerability to stress. When frail subjects are exposed to a stress factor they are less able to recover and are at a higher risk of developing disability and secondary effects (such as admission to hospital, institutionalization or death) [1]. Frailty is a state of pre-disability; it could be described as a situation between normal ageing and disability (or even death) [2].

The two main instruments used to diagnose frailty are an index of frailty [3] and the frailty phenotype [4]. The former is a measure of the accumulation of deficits in the various body systems, whilst the latter defines subjects as frail if 3 or more of the following 5 criteria are present: weight loss, weakness, exhaustion, slow walking speed, and low physical activity.

The prevalence of frailty varies widely depending on the population under study, and it is higher among institutionalized elderly people [5]. The prevalence of frailty in nursing homes has been reported to be 52%, in contrast to about 10% in the community [6] (the same study also reported prevalence rates of 'pre-frailty' at around 40% in both settings [6]). It is very important to be able to correctly identify frailty, because it has been shown to be a predictor for mortality in institutionalized elderly people [7], but especially because it is a reversible state.

The pathophysiology of frailty is complex and multi-factorial, and nutrition is an important mechanism in its onset and a specific target for treatment [8,9].

In spite of increasing interest in the relationship between frailty and nutrition, we could not find any recent systematic reviews.

The main aim of this review is to assess the association between nutritional status and frailty. Its secondary aim is to assess the effects of nutritional intervention on the reversibility of frailty.

2. Methods

We performed this systematic review in accordance to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines for systematic reviews [10].

2.1. Search strategy

We searched two electronic databases: PubMed and Web of Science. The following terms were used: older/elderly, frail*, sarcopeni*, muscle metabolism/loss/mass, nutrition*, amino acid, protein metabolism/intake, vitamin D, body composition, supplement* (*and all variations on these terms). The search was restricted to articles that contained these terms in their title or abstract. In addition, we reviewed the references of the selected articles. Papers published in English, Italian and Spanish were reviewed in detail.

	Category of evidence
Class I	Evidence from meta-analysis of randomised controlled trials
Class II	Evidence from at least one controlled study without randomisation or quasi - experimental study
Class III	Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies, and case-control studies
Class IV	Evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
	Strength of recommendation
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Fig. 1. Categories of evidence and strength of recommendations adapted from Shekelle et al. [11].

2.2. Eligibility criteria

We included studies carried out on people aged 65 or above, regardless of study design. Reviews were excluded. Eligible studies were those which assessed: 1) the nutritional status of frail subjects; 2) the effects of nutritional supplementation (whether or not it was combined with physical exercise); 3) protein metabolism in frail elderly subjects; 4) the association between frailty and vitamin D levels and vitamin D supplementation.

The main aim of this review is to describe, classify and explore the various studies, rather than to carry out meta-analysis of their results. We therefore did not assess either bias or the quality of the studies. Nevertheless, in order to take possible bias into account, each study was assigned an evidence level score (I to IV) and a recommendation strength (A, B, C, D) using the guidelines proposed by Shekelle et al. (Fig. 1) [11]. Overall, the results from randomized controlled trials (I, A/B) were considered less susceptible to bias, whereas results stemming from expert opinions (IV, D) were considered more susceptible to bias.

2.3. Data extraction

The following information was extracted from each included study: 1) country in which it took place; 2) design; 3) sample size; 4) age and sex distribution of the population studied; 5) frailty and malnutrition screening tools (where used); 6) anthropometric parameters; 7) method used to measure muscle and protein metabolism; 8) type of nutritional supplementation and its combination with physical exercise or otherwise; 9) main results.

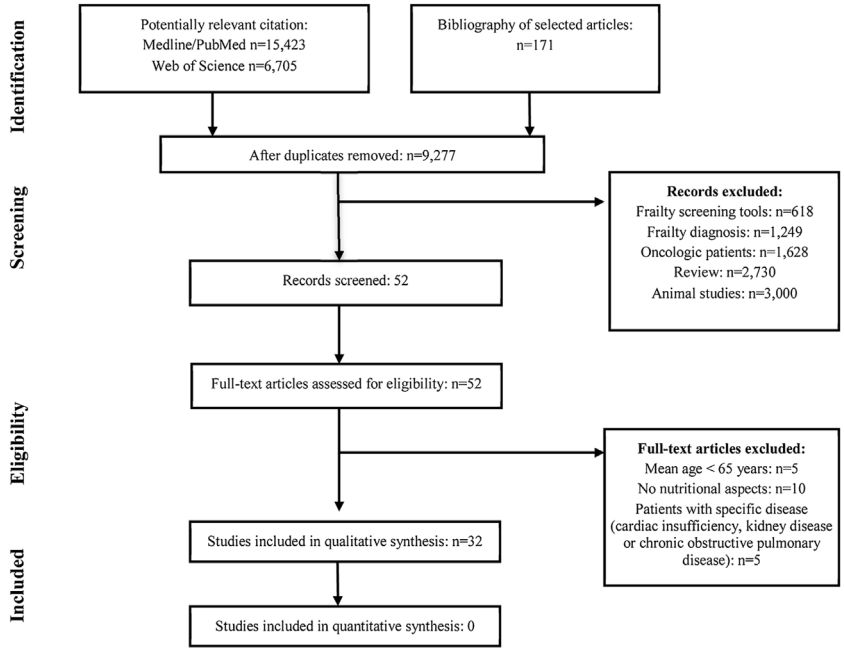

Fig. 2. Flow-diagram of literature search.

3. Results

Fig. 2 represents the flow chart of the paper selection process.

We included 32 studies (11 cross sectional, 9 trials, 5 quasi-experimental and 7 observational), with a total of 50,056 participants. Thirteen studies were carried out in Europe: one was multi-centre, 3 each in Germany and Spain, 2 in France and 1 each in Austria, the UK, Sweden and Denmark. Five studies took place in Canada, eight in the USA. Four were done in Asia: one each in Lebanon, the Republic of Korea, Japan and Taiwan. Two studies took place in Australia.

According to our main objective, we divided the studies into four major thematic groups: 1) association between nutritional status and frailty; 2) the treatment of frailty with nutritional intervention, alone or in combination with physical exercise; 3) protein metabolism and frailty; and 4) vitamin D status and frailty.

3.1. Association between nutritional status and frailty

Nutrition has been recognized as being of fundamental importance to healthy ageing [12]. Despite this, the lack of effective measures to prevent malnutrition makes it a serious health problem [13]. This association is evident in elderly people, and especially in institutionalized elderly people, among whom malnutrition is very common [14]. We found six papers that assessed the link between nutritional status and frailty (Table 1). Malnutrition, defined with the Mini Nutritional Assessment-Short Form (MNA-SF), is directly related to changes in body composition, such as fat-free mass and fat mass, measured with the Bio-impedance Analysis (BIA) [15]. Frail hospitalized elderly people are usually older than their community-dwelling counterparts and also have a significantly higher prevalence of malnutrition [16]. The prevalence of malnutrition in institutionalized elderly people is lower than in hospitalized elderly people, at around 30%, half of whom are frail [17].

Malnutrition significantly influences the development of frailty, because weight loss (one of the five criteria in the frailty phenotype) leads to the onset of exhaustion, weakness, slow walking speed, and low levels of physical activity [18].

Malnutrition and frailty are not equivalent, but malnourished elderly people are usually frail. This is why nutritional screening (medical history, nutritional history, anthropometry and blood tests) is of the utmost importance in frail elderly people [19].

Almost half of frail elderly people in the community present a high risk of malnutrition; conversely, 90% of elderly people with malnutrition are at high risk of being frail or 'pre-frail' [20].

There are many validated scales for frailty screening of elderly people in nursing homes [5] or in the community [21]. Malnutrition (diagnosed with the MNA) is associated with frailty but the sensitivity of this association is low (90% of robust people are well nourished, whilst only 64% of frail people have malnutrition) [22].

Nutrition is an important potentially modifiable factor that influences the development of frailty in elderly people [8]. In addition, nutrition plays a fundamental role in the design of intervention strategies aimed at re-establishing robustness [23].

Hypoalbuminemia, as a malnutrition marker, is associated with a significant loss of muscle mass and is a prognostic factor for mortality in elderly people, whether in the community or in hospital or other institutional settings [24].

Despite the difficulty of prospectively studying the relationship between low nutritional intake and frailty, and thereby determining cause and effect, evidence from population studies of these groups is strong [25]. Fifty-three percent of subjects defined as frail in the InCHIANTI study had lower nutritional intake than those classed as not frail: a caloric intake lower than 21 Kcal/kg was associated with an almost 25% increase in the risk of developing frailty [26].

3.2. Nutritional treatment of frailty

The effects of nutritional intervention on the functional status of frail elderly people are controversial. The aim of treatment is to reduce the progression of functional decline. Therefore, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends, with an evidence level A, the use of nutritional supplements to improve or maintain the health status of frail elderly people [27].

Table 1
Association between nutritional status and frailty in different geriatric settings.

Author Origin Publication year	Design n Women (%)	Evidence and Recommendation	Age (mean) Settings	Nutritional characteristics	Frailty screening tool	Main results
Slee A. UK 2015 [15]	Cross-sectional n 78 37%	IIID	82 y Hospitalized	MNA-SF 91% < 12 points	Not available	Body composition by BIA 100% of MN or RMN men have low FFMI 66% of MN and 33% of normal nourished women have low FFMI
Dorner T.E. Austria 2014 [16]	Cross-sectional n 133 61%	IIIC	74 y Hospitalized	MNA-SF 77% < 12 points	SHARE-FI 54% frail 22% pre-frail	Frail were older ($p < 0.001$) (83% of frail patients are over 85). 76% of malnourished were frail.
Martinez-Reig M. Spain 2014 [17]	Prospective n 678 58%	IIIC	78 y Community	MNA-SF 26% < 12 points	Fried's phenotype 18% frail 56% pre-frail	54% of MN or with RMN were frail.
Lilamand M. France 2015 [18]	Cross-sectional n 267 67%	IIIC	81 y Outpatients	MNA-SF 25% < 12 points	Fried's phenotype 37% frail 52% pre-frail	97% of robust has good nutritional status Frailty: 38% has RMN, 5% were MN
Bollwein J. Germany 2013 [20]	Cross-sectional n 206 66%	IIIC	83 y Community	MNA 0% MN 15% RMN	Fried's phenotype 15% frail 40% pre-frail	47% of frailty, 12% of pre-frail and 2% on non-frail were MN ($p < 0.001$). Frail were older, more often women, lived alone, had lower education, higher depression and lower ADL score.
Boulos C. Lebanon 2016 [22]	Cross-sectional n 1200 59%	IIIC	75.7 y Community	MNA 8% MN 29% RMN	SOF frailty index 36% frail 30% pre-frail	18% of frail were MN, 86% of robust were well-nourished MN were related to higher risk of frailty: OR 3.72 (95%CI-1.40–9.94)

ADL: activities of daily living; BIA: bio-impedance analysis; FFMI: fat free mass index; MNA: mini-nutritional assessment; MNA-SF: mini-nutritional assessment-short form; MN: malnourished; RMN: risk of malnutrition; SHARE-FI: survey of health, ageing and retirement in europe-frailty index; SOF: study of osteoporotic fractures.

Table 2 describes the design and main results of the research papers on the nutritional treatment of frailty.

Nutritional supplementation for frail elderly people has been shown to slow their functional decline (as measured using the Short-Physical Performance Battery [SPPB] and hand grip strength) [28]. However, there is no consensus on the effects of nutritional supplementation and no uniformity in study results. Smoliner et al. [29] studied a group of elderly people resident in care homes, at risk of malnutrition, and found no significant differences between the nutritional intervention group and the control group, either in their MNA scores or in their Body Mass Index (BMI) at the end of the study. Despite this, the authors observed that, as in other studies [28,30], there was functional loss in the control group, in terms of a statistically significant reduction in hand grip strength. It is important to highlight that the subjects included did not fulfil a set of criteria for 'frailty' and the sample size was small.

Nutritional supplementation for elderly people who are malnourished or who have lost weight is associated with improvements in both nutritional and functional status [31]. Both muscle mass and muscle strength improve with nutritional supplementation and improve even further if it is combined with a program of physical activity [32].

Recent Spanish research has shown that, in frail elderly people in nursing homes, nutritional supplementation combined with physical exercise stabilizes functional (hand grip strength) and nutritional status (BMI) and positively influences quality of life (as self-reported on the EuroQoL-5 Dimensions visual analogical scale, EQ5DVAS) [33].

In frail elderly people in the community treated with a programme of physical activity, an increase in the resting metabolic rate was observed, although no changes in body composition were detected [34]. This might indicate an improvement in muscle metabolism and in the ability to use micronutrients.

Bonnefoy et al. [35] included frail elderly subjects with a basal BMI of 27 kg/m^2 in their study and demonstrated an increase in weight after 3 and 9 months in subjects treated with nutritional supplements, but they did not report the frailty criteria they used.

The principal limitation of nutritional treatment is that it has relatively low adherence over the long run. A healthy diet combined with a physically active lifestyle and possibly aerobic resistance exercise is the basis of healthy ageing [32].

3.3. Proteins and muscle

Frailty exacerbates the effects of age on the metabolism of proteins through a series of factors such as reduced muscle mass and an increase in muscle catabolism, which means that supplementation is insufficient to counteract this effect if its use is limited over time [36].

Amino-acid supplementation improves the synthesis of muscle proteins in both young and elderly people [32,37]. The main factor limiting muscle synthesis in elderly people is a low concentration of proteins in their diet [38].

The daily protein intake (Recommended Dietary Allowance, RDA) of 0.8 g/kg currently recommended is insufficient for the maintenance of muscle mass [39]. Actual intake in the USA is even lower than this figure in one-third of women and one-quarter of men above the age of 50 [40,41].

In frail elderly people, the administration of moderately hyperproteic diets (1.5 g/kg/day), with a balanced spread of protein throughout the three main meals (25–30 g/meal), combined with high doses of calcium (1000–1200 mg/day) and vitamin D (more than 800 UI/day), improves bone and muscle health and reduces the risk of falls and fractures [42,43].

In order to achieve a muscular anabolic response, protein synthesis must exceed degradation. However, protein degradation is

Table 2
Effects of nutritional supplementation with or without physical exercise on frail elderly people.

Author Origin Publication year	Design n Women (%)	Evidence and Strength of Recommendation	Age (mean) Settings Inclusion criteria	Nutritional characteristics and intervention	Frailty screening tool	Main results
Kim C.O.	RT	IA	78.6 y	MNA: 17.9	Interventions on Frailty Working Group	Completed follow-up: n 84
Republic of Korea 2013 [28]	n 87 79%		Community Frail	CG: advise, n 44 IG: +400 Kcal/12 Wk, n 43		SPPB: ↔ in IG, ↓ 12% in CG (p = 0.039) Gait Speed: ↓ 1% in IG, ↓ 11% in CG (p = 0.039)
Smoliner C. Germany	RT n 52	IB	83 y Nursing-Home	MNA (mean) = 21 BMI = m 21.6, w 22.5	NA	Intervention group ↑ MNA: m 22.4 (p = 0.025), w 22.9 (p < 0.001)
2008 [29]	73%		MNA < 23.5	CG: standard diet, n 30 IG: +300 Kcal/12wk		↑ BMI: m 22.4 (p = 0.007), w 22.9 (p = 0.005)
Payette H.	RT	IA	80 y	BMI: 20 kg/m^2	NA	Body weight: CG ↔, IG ↑ 54.1 kg (p < 0.001)
Canada 2002 [31]	n 83 71%		Community home care Weight loss or BMI < 24 kg/m^2	Body weight: 52.5 kg CG: any treatment, n 41 IG: +500 Kcal/16 wk, n 42		TUG: ↓ IG from 24 to 21 s (p = 0.04)
Abizanda P.	Observational	IIID	85.6 y	MNA-SF (mean) 10.2	Fried's phenotype	Completed: n 69
Spain 2015 [33]	n 91 70%		Nursing-Home Frail and able to walk 50mt	BMI: 26.4 +300 Kcal and exercise, 12wk		Adherence rate: in 63% of sample > 80% MNA-SF: ↔ 10.5 BMI: ↔ 26.5 kg/m^2 Hand-grip strength: baseline 16.2 kg ↔ 16.5 kg
Lammes E.	RT	IA	82.8 y	MNA: 23.5	Chin A Paw criteria	Completed: at 3 months n 79; at 9 months n 64.
Sweden 2012 [34]	n 96 60%		Community Frail	BMI: 21.7 kg/m^2 N = 1.4 × RMR NT = 1.5 × RMR T and CG = advise		In T group: ↑ RMR (p < 0.05)
Bonnefoy M. France 2003 [35]	RT n 57 90%	IB	83 y Retirements home Frail	MNA: 24.5 BMI: 27 N = +400 Kcal NT = N + T T = 3 times/wk, 60 min CG = any treatment	NA	Completed follow-up: n 42 N group: ↑ BMI (p < 0.05)

BMI: body mass index; CG: control group; IG: intervention group; m: men; MNA: mini-nutritional assessment; MNA-SF: mini-nutritional assessment-short form; MN: malnourished; N: nutrition group; NA: not available; NT: nutritional + training group; RMN: risk of malnutrition; RMR: resting metabolic rate; RT: randomized trial; SPPB: short physical performance battery; T: training group; TUG: timed up-and-go; w: women; ↑: increase; ↓: decrease; ↔: unchanged.

often not taken into account in the assessment of anabolic response [44].

A large body of research has attempted to calculate the amount of protein intake necessary to stimulate protein synthesis efficiently. These studies propose amounts of between 1.2 and 1.5 g/kg/day [45,46].

Table 3 summarizes the main characteristics of these papers and classifies them into those which assess the amount of protein in people's diets, and those which take account of the added effect of physical activity.

3.3.1. *Protein intake and frailty*

An assessment of 2066 elderly people in the Health, Aging and Body Composition (Health-ABC) Study demonstrated the association between protein intake and changes in lean mass (LM) [47]. Elderly people in the highest quintile in terms of protein intake lost 40% less LM and appendicular lean mass (aLM) over three years than those in the lowest intake quintile [47]. Other studies have observed that a higher intake of amino acids and proteins is associated with a lower prevalence of frailty in women [48,49].

Based on a small cross-sectional study, Bollwein et al. reported that where an intake of 1.1 g/kg/day protein is achieved (15% of the total energy intake), its distribution over the three main meals of the day may be a factor that influences the development of frailty [86]. Fig. 3 plots the results from Bollwein et al. where an increase in the amount of protein consumed at breakfast and a slight reduction at lunchtime is associated with a lower prevalence of frailty [86]. This is an interesting result but the role of the distribution protein intake during the day in the causation of frailty requires confirmation in further research.

A diet with a high protein content makes a positive contribution to good health, helps in recovery from illness and helps maintain functional status in elderly people [50,51].

A very interesting study has looked into how protein metabolism is modified in frail and robust women in response to short-term nutritional supplementation [52]. Despite not specifying the frailty criteria used, the results clearly demonstrate that in frail women there is an increase in muscle catabolism and that an increase in protein intake leads to an increase in muscle metabolism [52]. It is essential that the protein supplementation is long term for it to result in an increase in muscle mass and lean mass.

Table 3
Relationship between frailty and protein metabolism, alone or combined with physical exercise.

Author Origin Publication year	Design n Women (%)	Evidence and Strength of Recommendation	Age (mean) Settings Cohort study	Nutritional characteristics, intervention and IC	Frailty screening tool	Main results
Protein intake and frailty						
Houston D.K.	Prospective	IIIA	74.5 y	BMI 27.5 kg/m^2	Not frail	Higher protein intake: less sedentary, higher BMI.
USA	n 2066		Community	Prot (% of energy): Q1 11, Q5 19		aLM were decreases 1.3 kg in weight losers, and 0.35 in weight maintainers.
2008 [47]	53%		Health-ABC	Prot (g/kg/d): Q1 0.8, Q5 1.2		Highest protein quintile lost 43% less of LM and 39% less of aLM over the 3 years of follow-up than those in the lowest quintile.
Kobayashi S.	Cross-sectional	IIIA	74.7 y	BMI 22.7 kg/m^2	Adapted Fried's criteria	Frail were older ($p < 0.0001$), have lower protein ($p = 0.0003$) and energy intake ($p < 0.0001$).
Japan 2013 [48]	n 2108 100%		Community	EI 1737 Kcal/d Tot Prot 74 g/d	23% frail	
Beasley J.M.	Prospective	IIIA	65–79 y	Not frail	Adapted Fried's criteria	20% greater protein intake → 9% lower risk of Pre-Frail and 12% lower risk of Frail.
USA	n 24,417		NA			At 3 years follow-up: 13% frail, 30% pre-frail.
2010 [49]	100%		WHI-OS			
Bollwein J.	Cross-sectional	IIIC	83 y	BMI: 27 kg/m^2	Fried's phenotype	Frail were older, higher percentage of female.
Germany	n 194		Community	EI: 0.12 KJ/kg of BW	15% frail	Protein%: morning, non-Frail 17%, Frail 11.9% ($p = 0.012$)
2013 [86]	66%				40% pre-frail	Noon, Non-Frail 55.3%, Frail 61.4% ($p = 0.041$)
Chevalier S.	Clinical trial	IIB	Frail 84 y; Healthy 71 y.	BMI: F 19, H 22.6 kg/m^2	NA	Frail were older, had lower BMI, lower FFM and MM.
Canada 2003 [52]	n 8 frail (F) n 13 healthy (H) 100%		Community	9 days: 12% of energy from protein (ISO); 12 days: 17% of energy from protein (PED)		Protein flux increased with PED
Luiking Y.C. USA	RT n 19	IC	69 y Healthy	BMI 26.6 kg/m^2 1 session of unilateral leg resistance exercise (15 min).	Not frail	EXP group: • higher FSR ($p = 0.049$) • higher peak plasma leucine ($p < 0.001$)
2014 [53]	53%			EXP: 20 g of whey protein + 3 g of leucine Control: 6 g milk protein		Not interaction between treatment and exercise was observed ($p = 0.52$)
Protein, exercise and frailty						
Bell K.E.	RT	IA	67 y	BMI 27 kg/m^2	NA	Myofibrilar FSR ↑ with HIIT and RE, response was greatest following RE.
Canada	n 22		Community	n 7: RE		Myofibrilar FSR is stable following AE.
2015 [57]	100%			n 8: HIIT n 7: AE		Sarcoplasmatic protein FSR ↑ by 25% following HIIT
Yang Y.	RT	IA	71 y	BMI 26 kg/m^2	Not frail	Non-exercise leg: myofibrilar FSR ↑ with W20 and W40.
Canada	n 37		Community	Unilateral leg resistance exercise.		Exercise leg: myofibrilar FSR ↑ compared to non-exercise leg; W40 = 32% greater than W20
2012 [58]	0%			Immediately after exercise drink contain 0 (W0 = n10), 10 (W10 = n7), 20 (W20 = n9), or 40 g (W40 = n10) of whey protein.		

Table 3 (*Continued*)

Author Origin Publication year	Design n Women (%)	Evidence and Strength of Recommendation	Age (mean) Settings Cohort study	Nutritional characteristics, intervention and IC	Frailty screening tool	Main results
Burd N.A. Canada 2012 [59]	Quasi-Experimental n 14 0%	IIA	72 y Healthy volunteers	BMI 26.6 kg/m^2 Unilateral resistance exercise n 7 = 20 g casein n 7 = 20 g whey	Not frail	MPS were greater in exercise leg than after feeding alone. MPS were greater in whey protein ingestion group than in casein ingestion group.
Drummond M.J. USA 2008 [60]	Quasi-Experimental n 14 0%	IIB	n 7 = 30 y n 7 = 70 y Healthy	Young = 21 kg/m^2 Old = 20 kg/m^2 8 sets of 10 repetition of 2-legged extension exercises (70% of 1RM) 1 h after exercise: 500 ml of ONS (20 g of EAAs)	Not frail	MPS significantly elevated in the young 1–3 h compared with baseline and old men. MPS significantly elevated in the old men at 3–6 h compared with baseline.
Esmarck B. Denmark 2001 [61]	Quasi-Experimental n 13 0%	IIB	74 y Community	BMI 25 kg/m^2 3 times/wk, 12 wk of resistance training. Supplementation: 10 g of protein (420 KJ) n7 P0 group = 5 min after each training session n6 P2 group = 2 h after	Not frail	CSA ↑ 7% ($p < 0.01$) and MFA ↑ ($p < 0.05$) in P0 from pre to post-exercise. MFA-1 and MFA-2 ↑ 18 and 29% in P0. P2: CSA, MFA-tot, MFA-1 and MFA-2 no significant changes.

1RM: one-repetition maximum; AE: aerobic exercise; aLM: appendicular lean mass; BMI: body mass index; CSA: muscle cross-sectional area; EAA: essential amino acids; EI: energy intake; EXP: experimental group; F: frail; H: healthy; FFM: fat free mass; FSR: fractional synthetic rate; Health-ABC: health aging and body composition study; HIIT: High-intensity interval exercise: ISO: isonitrogenous diets; LM: lean mass; MFA: mean fibre area, total, type 1 and type 2; MM: muscle mass; MPS: myofibrillar protein synthesis; NA: not-available; ONS: oral nutritional supplementation; PED: protein enriched diet Q: quintile; RE: Resistance exercise; RT: randomized trial; WHI-OS: women's health initiative – observational study; W0, W10, W20, W40: 0, 10, 20 or 40 g of whey protein; ↑: increase; ↓: decrease; ↔: unchanged.

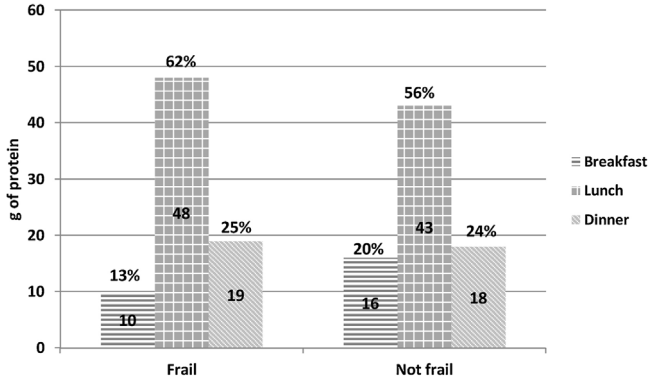

Fig. 3. Distribution of protein intake during the day in frail and not-frail subjects. A small increase in the concentration of protein of the breakfast, and a minimum reduction of protein for lunch, are associated with a significant reduction of the prevalence of frailty [86].

Intake of serum protein plus leucine was associated with a significantly greater increase in muscular protein synthesis than was the intake of milk protein [53].

3.3.2. *Protein, exercise and frailty*

Physical exercise in elderly people is associated with a reduction in mortality [54].

In elderly women, physical activity directly influences body composition and the quality of their muscles and is therefore a mechanism whereby to maintain physical ability, particularly in the lower limbs [55].

There is disagreement regarding the effects of protein intake on muscle synthesis. Some authors use a concept termed "anabolic resistance" to refer to an insufficient metabolic response to protein intake combined with physical exercise [56]. We included five studies on the muscle metabolic response to exercise combined with protein supplementation (Table 3).

Exercise brings about an increase in microfibrilar protein synthesis in elderly men and this increase is greater after resistance exercise (RE) than after high-intensity interval training (HIIT) [57].

In elderly men, the intake of 20 g of serum protein increases muscle protein synthesis (MPS) above fasting basal levels [58,59]. Combining resistance exercise with the protein intake enhances this effect and 40 g of serum protein, following resistance exercise, was found to be the quantity that most increases MPS [58].

Once the amount of protein that stimulates MPS most efficiently was determined, and the synergic effect of physical exercise had been demonstrated, it was still necessary to establish whether early supplementation following physical exercise was more effective than late supplementation in treating muscle trophism in elderly people. Drummond et al. [60] observed that the combination of physical exercise and supplementation with essential amino acids (EAA) leads to a significant increase in muscle protein synthesis, which in young people occurs immediately (within 1–3 h) and is maintained for up to 6 h after exercise, whereas in elderly people it begins later (after 3–6 h).

A very interesting piece of research demonstrated how after 12 weeks of resistance exercise, the muscle surface area and the sur-

Table 4
Relationship between vitamin D and frailty, disability and movement alterations.

Author Publication origin Publication year	Design n Women (%)	Evidence and Strength of Recommendation	Age (mean) Settings Cohort study	Nutritional characteristics and intervention	Frailty screening tool	Main results
Alvarez-Rios A.I.	Cross-sectional	IIIC	74 y	BMI: 30.3 kg/m^2	Fried	Frail were older and more dependent ($p < 0.001$)
Spain	n 592		Institutionalized and community	25(OH)D: 38.0 ng/mL	10% frail	Frail and pre-frail had: higher PINP, β-CTX and PTH levels, and lower 25(OH)D.
2015 [73]	100%		TSHA		39% pre-frail	High PINP and low 25(OH)D: OR of frailty 6.37 (95%CI 2.33–17.41).
Ensrud K.E. USA	Cross-sectional n 9704	IIIC	76.7 y Community	BMI: 26.4 kg/m^2 25(OH)D: 23.2 ng/mL	Fried 17% frail	Prevalence of frailty/25(OH)D: 23%/<15 ng/mL; 17%/15–20; 14%/20–30; 16%/≥30 ($p < 0.001$)
2010 [74]	100%		SOF		48% pre-frail	
Bird M. Australia	Observational n 98	IIID	69.2 y Community	BMI: 27.4 kg/m^2	NA	Completed follow-up: n 88 Seasonal variations in ankle muscle strength, serum 25(OH)D levels, physical activity and time spent outside ($p < 0.001$)
2013 [75]	NA					48 falls = 30 falls in autumn/winter Serum 25(OH)D variation (15%), highest values at the end of summer ($p < 0.001$).
Houston D.K.	Observational	IIIC	74.6 y	25(OH)D:	NA	Over 6 y: 738 mobility limitation (incidence 36%), 245 disability (incidence 22%).
USA	n 2099		Community	36% < 75 nmol/L (BMI 27 kg/m^2)		25(OH)D < 75 nmol/L: two-fold increase mobility disability.
2013 [76]	48%		Health ABC	29% < 50 nmol/L (BMI 28 kg/m^2)		PTH ≥ 70 pg/mL ↑ risk mobility limitation.
Zhu K. Australia	RT n 302	IA	76.9 y Community	BMI: 28.8 kg/m^2 25(OH)D: CG 17.7 ng/mL, IG 18.1 ng/mL	NA	Completed follow-up: n 261 25(OH)D at 1y: CG 18 vs IG 24 ng/mL ($p < 0.05$ from baseline for IG).
2010 [77]	100%			Calcium citrate 1000 mg/d + placebo (CG) or + 1000UI/d ergocalciferol (IG), for 1y		Lowest tertile of the IG was significantly faster at 1y, than the CG ($p = 0.02$)
Tajar A.	Cross-sectional	IIIC	69.5 y	BMI: 27.8 kg/m^2	Fried	Prevalence of 25(OH)D < 50 nmol/L: 62% F, 46% PF, 33% R
Europe	n 1504		Community	25(OH)D: 39% < 50 nmol/L	5% frail	For each 1 SD decrease in 25(OH)D, the odds of being pre-frail increase by 1.47, and by 1.85 for being frail.
2013 [80]	0%		EMAS		37% pre-frail	Higher PTH associated with pre-frail and frail.
Ensrud K.E. USA	Prospective n 5995	IIIC	73.8 y Community	BMI 27.4 kg/m^2	Fried 8% frail	Completed follow-up: n 1606 13% of men with 25(OH)D < 20 ng/mL were frail, vs 5% of men with > 30 ng/mL.
2011 [81]	0%		MrOS		45% pre-frail	Odds of greater frailty for 25(OH)D < 20 ng/mL: 1.03 (0.72–1.46) ($p = 0.88$)
Chang C.I. Taiwan	Cross-sectional n 548	IIIC	71.5 y Community	BMI: 25.4 kg/m^2 25(OH)D: 39.9 ng/mL	Fried 10% frail	Completed follow-up: n 215 Frail (n20): 71% women, lower MMSE (23), lower BI (92.6), 25(OH)D 30.8 ng/mL (62% < 20 ng/mL)
2010 [82]	59%				55% pre-frail	
Shardell M. USA	Observational n 1260	IIIC	75 y Community	Men: BMI 27 kg/m^2 25(OH)D 48.5 nmol/L	Fried F%: 11 W, 9 M.	Completed follow-up: n 980 Frail were: older, had lower MMSE, 25(OH)D and higher PTH.
2009 [84]	55.8%		InCHIANTI	Women: BMI 27.8 kg/m^2 25(OH)D 33 nmol/L	PF%: 44 W, 36 M	

25(OH)D: 25-hydroxy-vitamin D; BMI: body mass index; CG: control group; F: frail; EMAS: European male ageing study; Health-ABC: health aging and body composition study; IG: intervention group; MrOS: osteoporotic fractures in men study; NA: not-available; PF: pre-frail; PTH: parathyroid hormone; RT: randomized study; SD: standard deviation; SOF: study of osteoporotic fractures; TSHA: toledo study for healthy aging; ↑: increase.

face area of muscle fibres increased 7% and 22% respectively when subjects received a supplement of 10 g of proteins immediately after their training session, whereas no significant changes were observed when the intake was carried out 2 h after exercise [61].

Further research is needed to assess the impact of the timing of intake on the adaptive response of skeletal tissues to physical exercise. It is clear that the combination of resistance exercise and protein supplementation after exercise is an effective strategy to increase muscle mass and strength, and physical ability more generally, in elderly people.

3.4. Vitamin D

The importance of vitamin D in calcium homeostasis and its link to bone turnover are well known [62]. Colecalciferol, synthesized in the skin by the action of ultraviolet rays or taken in as part of people's diet, is hydroxylated in the liver [63]. Low levels of 25-hydroxi-vitamine D (25(OH)D) determine a decrease of intestinal absorption and in the blood calcium concentration, causing an increase in the levels of parathyroid hormone (PTH), and this – in turn – causes an increase of bone turnover and therefore an increase in the risk of fracture [64]. Levels of 25(OH)D above 30 ng/mL are considered normal; levels below 12 ng/mL are diagnosed as 25(OH)D deficiency and levels between 12 and 30 ng/mL indicate 25(OH)D insufficiency. Vitamin D deficiency is common in elderly people and especially in institutionalized elderly people, with a lack of 25(OH)D in itself being a risk factor for institutionalization [65]. Low levels of 25(OH)D are associated with alterations in balance [66], falls [67], fractures [68] and pain [69]. All this may contribute to a sedentary lifestyle and immobility and, therefore, to frailty [70,71].

The presence of 25(OH)D receptors in the skeletal muscle myocites could explain the association between low serum concentrations of 25(OH)D, reduced muscle synthesis and alterations in contractility [72].

Table 4 describes the design and main results of the research studies of potential links between vitamin D and frailty.

In frail and 'pre-frail' women, high levels of N-terminal propeptide of type I procollagen (PINP), C-terminal telopeptide of type I collagen, beta-CTX and PTH and low levels of 25(OH)D were found [73]. Women with high PINP and low 25(OH)D were at almost six times more at risk of becoming frail than were women who had only one of the two.

There is no agreement on how sex influences the association between 25(OH)D levels and the prevalence of frailty. In a cohort study of 6307 women in the community, a U-shaped association pattern was observed [74]. That is, the prevalence of frailty was greater in women with 25(OH)D levels lower than 15nmol/L and in women with a 25(OH)D level over 30 nmol/L, compared with women with values between 20 and 29.9 nmol/L.

Seasonal variation in the serum concentration of 25(OH)D is associated with variations in ankle muscle strength and a decrease in the latter is associated with an increase in the incidence of falls [75]. Low levels of 25(OH)D are associated with an increase in the risk of developing mobility limitations and disability over 6 years in elderly people in the community with a good basal level [76]. Zhu et al. [77] demonstrated improvements in muscle strength and function measured with the timed up-and-go test (TUG) in women treated with calcium and 25(OH)D for one year. Several studies showed that vitamin D supplements at doses of 700–1000 UI per day increased muscle mass and strength in elderly people [78], as well as improving balance and reducing the number of falls [79].

Low levels of 25(OH)D and high concentrations of PTH are associated with frailty in elderly men [80–82] and with an increase in mortality [83]. Despite the prevalence of frailty and 25(OH)D deficiency being higher in women than in men, it is only among men that a strong independent association between low serum levels of 25(OH)D and frailty was observed [84].

Low levels of 25(OH)D are associated with a decrease in muscle strength and with myopathy secondary to statins [83]. Di Monaco et al. demonstrated that 25(OH)D levels are associated with recovery after rehabilitation in women with a hip fracture, but are not significantly associated with an increase in fat free mass [85].

In summary, it is difficult to demonstrate the significance of the association between low levels of 25(OH)D and frailty with the data currently available. Low levels of 25(OH)D may be a marker of risk to health. But, on the other hand, frailty may contribute to the development of low levels of 25(OH)D due to a reduction in outdoor activity, facilitating a sedentary lifestyle and thereby reducing exposure to sunlight.

4. Conclusions

In geriatrics overall, but especially in care homes, nutritional screening is essential for the early diagnosis of malnutrition. Periodic monitoring of intake and body weight is a straightforward and inexpensive way to carry out basic screening. Malnutrition is significantly associated with frailty. Both malnutrition and frailty are reversible and if not correctly identified they can determine the onset of disability, which is for the most part not reversible. Prevention is the most effective and least costly way to maintain and promote elderly people's health. Nutritional treatment, a protein-rich diet, correction of micronutrient deficits, such as vitamin D, and physical activity all constitute fundamental aspects of the multidisciplinary treatment that is typical of geriatric medicine.

Conflict of interest

None declared.

Provenance and peer review

This article has undergone peer review.

Funding

No funding was received for the preparation of this review. NUTRICIA gave the funds to have this paper translated. None of the authors received payment for this paper.

Contributors

IA-A and VM were responsible for the idea and the objectives of this review, carried out the bibliographic research and wrote the manuscript.

PS-L, NS-H and NF-G contributed with critical analysis of the results and helped with the drafting of the manuscript.

All the authors approved the final version of this paper.

Acknowledgments

The authors wish to thank NUTRICIA, especially Chelo Martinez and Koldo Rodriguez, for their support and the funds to have this paper translated.

References

[1] B.J. Messinger-Rapport, J.K. Gammack, M.O. Little, J.E. Morley, Clinical update on nursing home medicine: 2014, J. Am. Med. Dir. Assoc. 15 (2014) 786–801.
[2] G. Abellan van Kan, Y.M. Rolland, J.E. Morley, B. Vellas, Frailty: toward a clinical definition, J. Am. Med. Dir. Assoc. 9 (2008) 71–72.
[3] K. Rockwood, A. Mitnitski, Frailty in relation to the accumulation of deficits, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 62 (2007) 722–727.

[4] L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, T. Seeman, R. Tracy, W.J. Kop, G. Burke, M.A. McBurnie, Cardiovascular health study collaborative research group, frailty in older adults: evidence for a phenotype, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 56 (2001) M146–M156.
[5] E. Kaehr, R. Visvanathan, T.K. Malmstrom, J.E. Morley, Frailty in nursing homes: the FRAIL-NH scale, J. Am. Med. Dir. Assoc. 16 (2) (2015) 87–89.
[6] G. Kojima, Prevalence of frailty in nursing homes: a systematic review and meta-analysis, J. Am. Med. Dir. Assoc. 16 (2015) 940–945.
[7] M. Tabue-Teguo, E. Kelaiditi, L. Demougeot, J.F. Dartigues, B. Vellas, M. Cesari, Frailty index and mortality in nursing home residents in france: results from the INCUR study, J. Am. Med. Dir. Assoc. 16 (2015) 603–606.
[8] A. Clegg, J. Young, S. Iliffe, M.O. Rikkert, K. Rockwood, Frailty in elderly people, Lancet 381 (2013) 752–762.
[9] V. Malafarina, F. Uriz-Otano, R. Iniesta, L. Gil-Guerrero, Sarcopenia in the elderly: diagnosis, physiopathology and treatment, Maturitas 71 (2012) 109–114.
[10] A. Liberati, D. Altman, J. Tetzlaff, C. Mulrow, P. Gøtzsche, J.P.A. Ioannidis, M. Clarke, P.J. Devereaux, J. Kleijnen, D. Moher, The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration, Ann. Intern. Med. 151 (2009) W65–W94.
[11] P.G. Shekelle, S.H. Woolf, M. Eccles, J. Grimshaw, Clinical guidelines: developing guidelines, BMJ 318 (1999) 593–596.
[12] E. Topinkova, Aging, disability and frailty, Ann. Nutr. Metab. 52 (Suppl. 1) (2008) 6–11.
[13] K. Norman, C. Pichard, H. Lochs, M. Pirlich, Prognostic impact of disease-related malnutrition, Clin. Nutr. 27 (2008) 5–15.
[14] C.L. Bell, B.K. Tamura, K.H. Masaki, E.J. Amella, Prevalence and measures of nutritional compromise among nursing home patients: weight loss, low body mass index, malnutrition, and feeding dependency a systematic review of the literature, J. Am. Med. Dir. Assoc. 14 (2013) 94–100.
[15] A. Slee, D. Birch, D. Stokoe, A comparison of the malnutrition screening tools, MUST MNA and bioelectrical impedance assessment in frail older hospital patients, Clin. Nutr. 34 (2015) 296–301.
[16] T.E. Dorner, E. Luger, J. Tschinderle, K.V. Stein, S. Haider, A. Kapan, C. Lackinger, K.E. Schindler, Association between nutritional status (MNA(R)-SF) and frailty (SHARE-FI) in acute hospitalised elderly patients, J. Nutr. Health Aging 18 (2014) 264–269.
[17] M. Martinez-Reig, L. Gomez-Arnedo, S.A. Alfonso-Silguero, G. Juncos-Martinez, L. Romero, P. Abizanda, Nutritional risk, nutritional status and incident disability in older adults. the FRADEA study, J. Nutr. Health Aging 18 (2014) 270–276.
[18] M. Lilamand, E. Kelaiditi, M. Cesari, A. Raynaud-Simon, A. Ghisolfi, S. Guyonnet, B. Vellas, G.A. van Kan, Toulouse frailty platform team, validation of the mini nutritional assessment-short form in a population of frail elders without disability. analysis of the toulouse frailty platform population in 2013, J. Nutr. Health Aging 19 (2015) 570–574.
[19] M.A. Camina-Martin, B. de Mateo-Silleras, V. Malafarina, R. Lopez-Mongil, V. Nino-Martin, J.A. Lopez-Trigo, M.P. Redondo-del-Rio, Nutritional status assessment in geriatrics: consensus declaration by the spanish society of geriatrics and gerontology nutrition work group, Maturitas 81 (2015) 414–419.
[20] J. Bollwein, D. Volkert, R. Diekmann, M.J. Kaiser, W. Uter, K. Vidal, C.C. Sieber, J.M. Bauer, Nutritional status according to the mini nutritional assessment (MNA(R)) and frailty in community dwelling older persons: a close relationship, J. Nutr. Health Aging 17 (2013) 351–356.
[21] J. Woo, J. Leung, J.E. Morley, Defining sarcopenia in terms of incident adverse outcomes, J. Am. Med. Dir. Assoc. 16 (2015) 247–252.
[22] C. Boulos, P. Salameh, P. Barberger-Gateau, Malnutrition and frailty in community dwelling older adults living in a rural setting, Clin. Nutr. 35 (2016) 138–143.
[23] E. Kelaiditi, S. Guyonnet, M. Cesari, Is nutrition important to postpone frailty, Curr. Opin. Clin. Nutr. Metab. Care 18 (2015) 37–42.
[24] S. Cabrerizo, D. Cuadras, F. Gomez-Busto, I. Artaza-Artabe, F. Marin-Ciancas, V. Malafarina, Serum albumin and health in older people: review and meta analysis, Maturitas 81 (2015) 17–27.
[25] H.A. Bischoff, H.B. Staehelin, W.C. Willett, The effect of undernutrition in the development of frailty in older persons, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 61 (2006) 585–589.
[26] B. Bartali, E.A. Frongillo, S. Bandinelli, F. Lauretani, R.D. Semba, L.P. Fried, L. Ferrucci, Low nutrient intake is an essential component of frailty in older persons, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 61 (2006) 589–593.
[27] D. Volkert, Y.N. Berner, E. Berry, T. Cederholm, P.C. Bertrand, A. Milne, J. Palmblad, S. Schneider, L. Sobotka, Z. Stanga, R. Lenzen-Grossimlinghaus, U. Krys, M. Pirlich, B. Herbst, T. Schutz, W. Schroer, W. Weinrebe, J. Ockenga, H. Lochs, ESPEN guidelines on enteral nutrition, Geriatrics 25 (2006) 330–360.
[28] C.O. Kim, K.R. Lee, Preventive effect of protein-energy supplementation on the functional decline of frail older adults with low socioeconomic status: a community-based randomized controlled study, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 68 (2013) 309–316.
[29] C. Smoliner, K. Norman, R. Scheufele, W. Hartig, M. Pirlich, H. Lochs, Effects of food fortification on nutritional and functional status in frail elderly nursing home residents at risk of malnutrition, Nutrition 24 (2008) 1139–1144.
[30] J. Edington, R. Barnes, F. Bryan, E. Dupree, G. Frost, M. Hickson, J. Lancaster, S. Mongia, J. Smith, A. Torrance, R. West, F. Pang, S.J. Coles, A prospective randomised controlled trial of nutritional supplementation in malnourished elderly in the community: clinical and health economic outcomes, Clin. Nutr. 23 (2004) 195–204.
[31] H. Payette, V. Boutier, C. Coulombe, K. Gray-Donald, Benefits of nutritional supplementation in free-living, frail, undernourished elderly people: a prospective randomized community trial, J. Am. Diet Assoc. 102 (2002) 1088–1095.
[32] V. Malafarina, F. Uriz-Otano, R. Iniesta, L. Gil-Guerrero, Effectiveness of nutritional supplementation on muscle mass in treatment of sarcopenia in old age: a systematic review, J. Am. Med. Dir. Assoc. 14 (2013) 10–17.
[33] P. Abizanda, M.D. Lopez, V.P. Garcia, D. Estrella Jde, A. da Silva Gonzalez, N.B. Vilardell, K.A. Torres, Effects of an oral nutritional supplementation plus physical exercise intervention on the physical function, nutritional status, and quality of life in frail institutionalized older adults: the ACTIVNES study, J. Am. Med. Dir. Assoc. 439 (2015), e9–439. e16.
[34] E. Lammes, E. Rydwik, G. Akner, Effects of nutritional intervention and physical training on energy intake resting metabolic rate and body composition in frail elderly. a randomised, controlled pilot study, J. Nutr. Health Aging 16 (2012) 162–167.
[35] M. Bonnefoy, C. Cornu, S. Normand, F. Boutitie, F. Bugnard, A. Rahmani, J.R. Lacour, M. Laville, The effects of exercise and protein-energy supplements on body composition and muscle function in frail elderly individuals: a long-term controlled randomised study, Br. J. Nutr. 89 (2003) 731–739.
[36] J.A. Morais, R. Ross, R. Gougeon, P.B. Pencharz, P.J. Jones, E.B. Marliss, Distribution of protein turnover changes with age in humans as assessed by whole-body magnetic resonance image analysis to quantify tissue volumes, J. Nutr. 130 (2000) 784–791.
[37] D. Paddon-Jones, M. Sheffield-Moore, X.J. Zhang, E. Volpi, S.E. Wolf, A. Aarsland, A.A. Ferrando, R.R. Wolfe, Amino acid ingestion improves muscle protein synthesis in the young and elderly, Am. J. Physiol. Endocrinol. Metab. 286 (2004) E321–8.
[38] S. Stenholm, T.B. Harris, T. Rantanen, M. Visser, S.B. Kritchevsky, L. Ferrucci, Sarcopenic obesity: definition, cause and consequences, Curr. Opin. Clin. Nutr. Metab. Care 11 (2008) 693–700.
[39] Joint FAO/WHO/UNU Expert Consultation, Protein and amino acid requirements in human nutrition: Report of a joint FAO/WHO/UNU expert consultation [homepage on the Internet]. http://apps.who.int/iris/bitstream/10665/43411/1/WHO_TRS_935_eng.pdf, 2007.
[40] V.L. Fulgoni 3rd, Current protein intake in America: analysis of the national health and nutrition examination survey, 2003–2004, Am. J. Clin. Nutr. 87 (2008) 1554S–1557S.
[41] R.E. Valenzuela, J.A. Ponce, G.G. Morales-Figueroa, K.A. Muro, V.R. Carreon, H. Aleman-Mateo, Insufficient amounts and inadequate distribution of dietary protein intake in apparently healthy older adults in a developing country: implications for dietary strategies to prevent sarcopenia, Clin. Interv. Aging 8 (2013) 1143–1148.
[42] D. Paddon-Jones, B.B. Rasmussen, Dietary protein recommendations and the prevention of sarcopenia, Curr. Opin. Clin. Nutr. Metab. Care 12 (2009) 86–90.
[43] H.A. Bischoff-Ferrari, B. Dawson-Hughes, H.B. Staehelin, J.E. Orav, A.E. Stuck, R. Theiler, J.B. Wong, A. Egli, D.P. Kiel, J. Henschkowski, Fall prevention with supplemental and active forms of vitamin D: a meta-analysis of randomised controlled trials, BMJ 339 (2009) b3692.
[44] T. Lang, T. Streeper, P. Cawthon, K. Baldwin, D.R. Taaffe, T.B. Harris, Sarcopenia Etiology, clinical consequences, intervention, and assessment, Osteoporos. Int. 21 (2010) 543–559.
[45] E. Gaffney-Stomberg, K.L. Insogna, N.R. Rodriguez, J.E. Kerstetter, Increasing dietary protein requirements in elderly people for optimal muscle and bone health, J. Am. Geriatr. Soc. 57 (2009) 1073–1079.
[46] A. Mithal, J.P. Bonjour, S. Boonen, P. Burckhardt, H. Degens, G. El Hajj Fuleihan, R. Josse, P. Lips, J. Morales Torres, R. Rizzoli, N. Yoshimura, D.A. Wahl, C. Cooper, B. Dawson-Hughes, IOF CSA nutrition working group, impact of nutrition on muscle mass, strength, and performance in older adults, Osteoporos. Int. 24 (2013) 1555–1566.
[47] D.K. Houston, B.J. Nicklas, J. Ding, T.B. Harris, F.A. Tylavsky, A.B. Newman, J.S. Lee, N.R. Sahyoun, M. Visser, S.B. Kritchevsky, Health ABC study, dietary protein intake is associated with lean mass change in older, community-dwelling adults: the health, aging, and body composition (health ABC) study, Am. J. Clin. Nutr. 87 (2008) 150–155.
[48] S. Kobayashi, K. Asakura, H. Suga, S. Sasaki, Three-generation study of women on diets and health study group, high protein intake is associated with low prevalence of frailty among old japanese women: a multicenter cross-sectional study, Nutr. J. 12 (2013), 164-2891-112-164.
[49] J.M. Beasley, A.Z. LaCroix, M.L. Neuhouser, Y. Huang, L. Tinker, N. Woods, Y. Michael, J.D. Curb, R.L. Prentice, Protein intake and incident frailty in the women's health initiative observational study, J. Am. Geriatr. Soc. 58 (2010) 1063–1071.
[50] E. Volpi, W.W. Campbell, J.T. Dwyer, M.A. Johnson, G.L. Jensen, J.E. Morley, R.R. Wolfe, Is the optimal level of protein intake for older adults greater than the recommended dietary allowance, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 68 (2013) 677–681.
[51] J. Bauer, G. Biolo, T. Cederholm, M. Cesari, A.J. Cruz-Jentoft, J.E. Morley, S. Phillips, C. Sieber, P. Stehle, D. Teta, R. Visvanathan, E. Volpi, Y. Boirie, Evidence-based recommendations for optimal dietary protein intake in older people: a position paper from the PROT-AGE study group, J. Am. Med. Dir. Assoc. 14 (2013) 542–559.

[52] S. Chevalier, R. Gougeon, K. Nayar, J.A. Morais, Frailty amplifies the effects of aging on protein metabolism: role of protein intake, Am. J. Clin. Nutr. 78 (2003) 422–429.
[53] Y.C. Luiking, N.E. Deutz, R.G. Memelink, S. Verlaan, R.R. Wolfe, Postprandial muscle protein synthesis is higher after a high whey protein, leucine-enriched supplement than after a dairy-like product in healthy older people: a randomized controlled trial, Nutr. J. 13 (2014) 9.
[54] C. Fortes, S. Mastroeni, A. Sperati, R. Pacifici, P. Zuccaro, F. Francesco, N. Agabiti, G. Piras, D. Amleto, S. Ebrahim, Walking four times weekly for at least 15 min is associated with longevity in a cohort of very elderly people, Maturitas 74 (2013) 246–251.
[55] C.R. Straight, A.O. Brady, E.M. Evans, Muscle quality and relative adiposity are the strongest predictors of lower-extremity physical function in older women, Maturitas 80 (2015) 95–99.
[56] V. Kumar, P. Atherton, K. Smith, M.J. Rennie, Human muscle protein synthesis and breakdown during and after exercise, J. Appl. Physiol. (1985) 106 (2009) 2026–2039.
[57] K.E. Bell, C. Seguin, G. Parise, S.K. Baker, S.M. Phillips, Day-to-day changes in muscle protein synthesis in recovery from resistance, aerobic, and high-intensity interval exercise in older men, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 70 (2015) 1024–1029.
[58] Y. Yang, L. Breen, N.A. Burd, A.J. Hector, T.A. Churchward-Venne, A.R. Josse, M.A. Tarnopolsky, S.M. Phillips, Resistance exercise enhances myofibrillar protein synthesis with graded intakes of whey protein in older men, Br. J. Nutr. 108 (2012) 1780–1788.
[59] N.A. Burd, Y. Yang, D.R. Moore, J.E. Tang, M.A. Tarnopolsky, S.M. Phillips, Greater stimulation of myofibrillar protein synthesis with ingestion of whey protein isolate v. micellar casein at rest and after resistance exercise in elderly men, Br. J. Nutr. 108 (2012) 958–962.
[60] M.J. Drummond, H.C. Dreyer, B. Pennings, C.S. Fry, S. Dhanani, E.L. Dillon, M. Sheffield-Moore, E. Volpi, B.B. Rasmussen, Skeletal muscle protein anabolic response to resistance exercise and essential amino acids is delayed with aging, J. Appl. Physiol. (1985) 104 (2008) 1452–1461.
[61] B. Esmarck, J.L. Andersen, S. Olsen, E.A. Richter, M. Mizuno, M. Kjaer, Timing of postexercise protein intake is important for muscle hypertrophy with resistance training in elderly humans, J. Physiol. 535 (2001) 301–311.
[62] M.F. Holick, Vitamin D deficiency, N. Engl. J. Med. 357 (2007) 266–281.
[63] A. Hossein-nezhad, M.F. Holick, Vitamin D for health: a global perspective, Mayo Clin. Proc. 88 (2013) 720–755.
[64] P. Lips, Vitamin D physiology, Prog. Biophys. Mol. Biol. 92 (2006) 4–8.
[65] M. Visser, D.J. Deeg, M.T. Puts, J.C. Seidell, P. Lips, Low serum concentrations of 25-hydroxyvitamin D in older persons and the risk of nursing home admission, Am. J. Clin. Nutr. 84 (2006) 616–622, quiz 671-2.
[66] M. Zamboni, E. Zoico, P. Tosoni, A. Zivelonghi, A. Bortolani, S. Maggi, V. Di Francesco, O. Bosello, Relation between vitamin D, physical performance, and disability in elderly persons, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 57 (2002) M7–M11.
[67] M.B. Snijder, N.M. van Schoor, S.M. Pluijm, R.M. van Dam, M. Visser, P. Lips, Vitamin D status in relation to one-year risk of recurrent falling in older men and women, J. Clin. Endocrinol. Metab. 91 (2006) 2980–2985.
[68] P. Lips, Vitamin D deficiency and secondary hyperparathyroidism in the elderly: consequences for bone loss and fractures and therapeutic implications, Endocr. Rev. 22 (2001) 477–501.
[69] R. Mascarenhas, S. Mobarhan, Hypovitaminosis D-induced pain, Nutr. Rev. 62 (2004) 354–359.
[70] M.T. Puts, M. Visser, J.W. Twisk, D.J. Deeg, P. Lips, Endocrine and inflammatory markers as predictors of frailty, Clin.Endocrinol. (Oxf.) 63 (2005) 403–411.
[71] F.I. Mahoney, D.W. Barthel, Functional evaluation: the Barthel index, Md. State Med. J. 14 (1965) 61–65.
[72] R.U. Simpson, G.A. Thomas, A.J. Arnold, Identification of 1,25-dihydroxyvitamin D3 receptors and activities in muscle, J. Biol. Chem. 260 (1985) 8882–8891.
[73] A.I. Alvarez-Rios, J.M. Guerrero, F.J. Garcia-Garcia, L. Rodriguez-Manas, P. Medrano-Campillo, M.A. de la Torre Lanza, N. Alvarez-Sanchez, A. Carrillo-Vico, Associations between frailty and serum N-terminal propeptide of type I procollagen and 25-hydroxyvitamin D in older spanish women: the toledo study for healthy aging, Exp. Gerontol. 69 (2015) 79–84.
[74] K.E. Ensrud, S.K. Ewing, L. Fredman, M.C. Hochberg, J.A. Cauley, T.A. Hillier, S.R. Cummings, K. Yaffe, P.M. Cawthon, Study of osteoporotic fractures research group, circulating 25-hydroxyvitamin D levels and frailty status in older women, J. Clin. Endocrinol. Metab. 95 (2010) 5266–5273.
[75] M. Bird, K.D. Hill, I.K. Robertson, M.J. Ball, J. Pittaway, A.D. Williams, Serum [25(OH)D] status, ankle strength and activity show seasonal variation in older adults: relevance for winter falls in higher latitudes, Age Ageing 42 (2013) 181–185.
[76] D.K. Houston, R.H. Neiberg, J.A. Tooze, D.B. Hausman, M.A. Johnson, J.A. Cauley, D.C. Bauer, M.K. Shea, G.G. Schwartz, J.D. Williamson, T.B. Harris, S.B. Kritchevsky, Health ABC Study, Low 25-hydroxyvitamin D predicts the onset of mobility limitation and disability in community-dwelling older adults: the health ABC study, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 68 (2013) 181–187.
[77] K. Zhu, N. Austin, A. Devine, D. Bruce, R.L. Prince, A randomized controlled trial of the effects of vitamin D on muscle strength and mobility in older women with vitamin D insufficiency, J. Am. Geriatr. Soc. 58 (2010) 2063–2068.
[78] S.M. Roth, J.M. Zmuda, J.A. Cauley, P.R. Shea, R.E. Ferrell, Vitamin D receptor genotype is associated with fat-free mass and sarcopenia in elderly men, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 59 (2004) 10–15.
[79] H.A. Bischoff-Ferrari, M. Borchers, F. Gudat, U. Durmuller, H.B. Stahelin, W. Dick, Vitamin D receptor expression in human muscle tissue decreases with age, J. Bone Miner. Res. 19 (2004) 265–269.
[80] A. Tajar, D.M. Lee, S.R. Pye, M.D. O'Connell, R. Ravindrarajah, E. Gielen, S. Boonen, D. Vanderschueren, N. Pendleton, J.D. Finn, G. Bartfai, F.F. Casanueva, G. Forti, A. Giwercman, T.S. Han, I.T. Huhtaniemi, K. Kula, M.E. Lean, M. Punab, F.C. Wu, T.W. O'Neill, The association of frailty with serum 25-hydroxyvitamin D and parathyroid hormone levels in older european men, Age Ageing 42 (2013) 352–359.
[81] K.E. Ensrud, T.L. Blackwell, J.A. Cauley, S.R. Cummings, E. Barrett-Connor, T.T. Dam, A.R. Hoffman, J.M. Shikany, N.E. Lane, M.L. Stefanick, E.S. Orwoll, P.M. Cawthon, Osteoporotic fractures in men study group, circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study, J. Am. Geriatr. Soc. 59 (2011) 101–106.
[82] C.I. Chang, D.C. Chan, K.N. Kuo, C.A. Hsiung, C.Y. Chen, Vitamin D insufficiency and frailty syndrome in older adults living in a northern taiwan community, Arch. Gerontol. Geriatr. 50 (Suppl. 1) (2010) S17–21.
[83] J.E. Morley, J.M. Argiles, W.J. Evans, S. Bhasin, D. Cella, N.E.P. Deutz, W. Doehner, K.C.H. Fearon, L. Ferrucci, M.K. Hellerstein, K. Kalantar-Zadeh, H. Lochs, N. MacDonald, K. Mulligan, M. Muscaritoli, P. Ponikowski, M.E. Posthauer, F.R. Fanelli, M. Schambelan, A.M.W.J. Schols, M.W. Schuster, S.D. Anker, Nutritional recommendations for the management of sarcopenia, J. Am. Med. Dir. Assoc. 11 (2010) 391–396.
[84] M. Shardell, G.E. Hicks, R.R. Miller, S. Kritchevsky, D. Andersen, S. Bandinelli, A. Cherubini, L. Ferrucci, Association of low vitamin D levels with the frailty syndrome in men and women, J. Gerontol. Ser. A: Biol. Sci. Med. Sci. 64 (2009) 69–75.
[85] M. Di Monaco, C. Castiglioni, F. Vallero, R. Di Monaco, R. Tappero, Appendicular lean mass does not mediate the significant association between vitamin D status and functional outcome in hip-fracture women, Arch. Phys. Med. Rehabil. 92 (2011) 271–276.
[86] J. Bollwein, R. Diekmann, M.J. Kaiser, J.M. Bauer, W. Uter, C.C. Sieber, D. Volkert, Distribution but not amount of protein intake is associated with frailty: a cross-sectional investigation in the region of nurnberg, Nutr. J. 12 (2013) 109.