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FRAILTY AND NUTRITION: SEARCHING FOR EVIDENCE

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Abstract: Frailty is a geriatric syndrome that predicts disability, morbidity and mortality in the elderly. Poor nutritional status is one of the main risk factors for frailty. Macronutrients and micronutrients deficiencies are associated with frailty. Recent studies suggest that improving nutritional status for macronutrients and micronutrients may reduce the risk of frailty. Specific diets such as the Mediterranean diet rich in anti-oxidants, is currently investigated in the prevention of frailty. The aim of this paper is to summarize the current body of knowledge on the relations between nutrition and frailty, and provide recommendations for future nutritional research on the field of frailty.

Key words: Nutrition, frailty, elderly.

Introduction

Frail elderly are at increased risk for physical or functional decline, disability and death (1–3). Several operational and objective approaches, scales or indexes have been proposed to diagnose frailty (4). The scale developed by Linda Fried from the Cardiovascular Health Study (CHS) has been repeatedly reported to identify frail persons at high risk of adverse health-related outcomes (1). This operational definition was validated by demonstrating its ability to predict physical disability and mortality in a sample of community-dwelling elderly. The presence of three or more of the following five criteria characterise frailty: low muscle strength, unintentional weight loss, feeling of exhaustion, poor physical performance, and reduced physical activity. All theses factors may be more or less influenced by poor nutrition. Unintentional weight loss may be due to inadequate energy and protein intake. Weight loss is associated with a lean mass decline especially for skeletal muscle mass, and with energy production decrease both for aerobic and anaerobic metabolism. Weight loss leads to lower muscle strength, poor physical performances, feeling of exhaustion and therefore to reduced physical activity. Frailty is considered as a geriatric syndrome associated with alterations in multiple physiological systems and reduced functional reserve (brain, endocrine, immune, renal, cardiovascular, skeletal muscle…). Such changes are responsible for reduced ability to maintain physiological homeostasis after an acute or stressful event (1–5). However, at the individual level, the relationship between the five domains of frailty and nutrition is certainly much more complex, as many factors interact with each other (e.g. diseases that increase catabolism and decrease anabolism, psychological factors that impact performances, genetics that influence muscle quality, or medications that result in fatigue...).

The aim of this manuscript is to summarize the current body of knowledge on nutrition and frailty and provide recommendations for future nutritional research on the field of frailty.

Methods

For this review, Medline, and Google databases were searched with the six following keywords: frailty, elderly or older adults, sarcopenia, protein synthesis, intakes. The main author prepared an initial list of publications from English peer-reviewed journals providing relevant data about the relations between frailty and nutrition .The most informative papers (interventional, observational studies, reviews about various specific nutrients…) were selected by the listed authors on behalf of the French expert group on elderly nutrition.

Energy intake and frailty

Recent studies have shown an association between frailty and nutritional status. showing a close relation between nutritional status assessed by mini nutritional assessment (MNA) and frailty (6, 7). Nutritional risk assessed by MNA was also associated with incident disability in elderlies (8). Anorexia of aging is generally defined as a loss of appetite or reduced food intake and considered as a modifiable risk factor for frailty (9). Epidemiological studies have shown that reduced caloric intake is associated with changes in body composition and decline of physical function in the elderly (10). Low energy intake is a frequent condition in the older population. It may

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affect 11.3 % of men living in the community and up to 34.1% in long term care facilities (11). Food intake decreases by nearly 25% between the fourth and seventh decades of life (12). The decline of energy intake can result in a dramatic decline in muscle mass and strength, leading to weight loss and disability (12). In the Chianti study (802 persons aged 65 years or more), a daily energy intake of less than 21 kcal/kg/day was associated with frailty (2). A minimum of 25 Kcal/Kg/day is required to meet the energy requirements of the elderly. Measured resting energy expenditure (REE) has been calculated between 20 and 28 kcal/kg/day in elderly (13). Taking account of those data, the total energy expenditure to REE ratio (counting for physical activity level) should be at a minimal level of 1.3. Persons with intakes lower than such levels may not cover their energy requirements and then lose weight and fat free mass. Vellas et al. have shown, in a ten year longitudinal study among 304 free-living elderly, that women with energy intake below 25 kcal/kg/day were more likely to become frail or to die (OR 3.3 CI 1.2-8.6) (14). In older patients with low socio-economic status living in the community and with low energy intake, a protein and energy supplementation of 400 kcal/day and 25 g of proteins resulted in reducing the progression of functional decline (15).

Protein intake and frailty

Sarcopenia, the age-related loss of skeletal muscle mass and strength, is considered as a key component of frailty (4). Among various factors, adequate dietary protein intake is required to maintain muscle mass and function, and delay sarcopenia (16). Most current evidence rely on longitudinal observational studies such as the Health, Aging and Body Composition Study (Health ABC). In this study, over a three years period, healthy older volunteers in the highest quintile of protein intake lost nearly 40% less total lean mass than those in the lowest quintile (17). However, this study also highlighted that even the subjects in the highest quintile lost muscle mass during the follow-up, suggesting that the process can only be slowed down but not completely prevented.

Amino acids can stimulate muscle protein synthesis (MPS). Most of the enhancing effects on MPS after a meal are attributed to amino acids (18). Dietary protein intake can stimulate MPS and inhibit protein breakdown both in young and elderly people inducing a positive protein balance (19). Furthermore, many studies suggest that protein or amino-acid may be useful for increasing fractional synthesis rate (FSR) of muscle protein (20). Within the perspective of increasing muscle mass with optimal levels of proteins or amino acids intake, it is of crucial importance to determine the response to graded intake. Brodsky et al. have shown that consumption of an iso-energetic diet with 0.71g proteins/kg of fat free mass (FFM) resulted, after a period of 4 weeks, in inhibition for myosin synthesis (21). This notably highlighted a lower fractional synthesis rate of nearly 20% for myosin heavy chain compared to the results recorded in volunteers given a protein intake of 1.67g/kg FFM .However, such results may not be obtained when dose of proteins increases at higher levels. No difference in MPS was observed following 10 days of iso-caloric diets containing 1.5 or 3 g/kg FFM/day both in younger and older men (22). Similarly, results of several studies indicate that high protein diets increase MPS until a plateau is reached at nearly 20g of protein supplementation (23). A recent meta-analysis has examined the effects of high-protein or amino-acids supplementation from 0.12 to 1.13 g/kg of body weight(BW) on MPS rate in the elderly (24). Short term protein intake increased muscle protein synthesis continuously when the protein dose was under 0.8 g/kg/day only. When initial protein dose was above 0.8 g/kg BW /day, the level of fractional synthesis rate was lowered (19). In consequences, beneficial effects of protein supplementation appear dose-dependent only when protein dose is low (less than 0.8 g/kg BW/day. However, results may differ depending on the protein source.

Determining the adequate protein intake is of utmost importance since excessive amino acids intake could result in increased oxidation, enhanced urea genesis and gluconeogenesis, and may also be a detrimental load for the kidneys (25). On the other hand, higher dose of proteins may be required because of different muscle protein metabolism in the elderly. Several hypotheses have been developed to explain the relative anabolic resistance to amino acids. A higher splanchnic extraction of dietary amino acids has been observed and may be responsible for a decreased delivery to the skeletal muscles (16). A resistance to the effect of leucine on muscle protein synthesis has been suggested since higher leucine concentration is required to stimulate protein synthesis in the older animal compared to the younger (26). Basic research suggests that the observed anabolic resistance may be mediated through impairments in mammalian target of rapamycin (mTOR) (27). mTOR concentrations are 50% lower in the skeletal muscle of the old (28). Concentrations of kinases are also diminished and their phosphorylative status is blunted in the elderly while concentrations of NF kappa beta (NF kb) signalling for wasting are a fourfold greater in the older muscle (28).

The daily requirement for dietary protein is defined as the minimum amount resulting in a whole body net nitrogen balance of zero (23, 29, 30). The current Recommended Dietary Allowance (RDA) for protein is established at 0.8g/kg-BW / day for all adults (31) However, several limitations have been discussed for nitrogen balance studies. Precisely measuring nitrogen intake is very difficult as well as detecting short term changes in muscle mass. Therefore measures may result in underestimation of protein requirements (32). Furthermore, around 15% of people older than 60 years have a protein consumption below than RDA (33).

Short-term nitrogen balance results do not suggest that requirements for total dietary proteins are different in younger and older healthy adults (34). Although conflicting data are reported in the literature, most nutritionists agree that protein needs in the elderly should be higher than the RDA (35). Morse et al. have studied nitrogen balance in healthy elderly women fed with 0.5; 0.75 or 1g protein/kg/day during 18 days trial (36). The adequate protein allowance was estimated to be greater than the RDA at week 2 (0.9g/kg/day) but not different with the RDA at week 3 (0.76g/kg/day). Short-term nitrogen balance studies results appear insufficient to clearly establish the RDA in the elderly. In another study with eucaloric diet that contained 0.8g proteins/kg/day during 14 weeks, Campbell et al. have found a decline in mid-thigh muscle cross sectional area and a decrement in nitrogen urea (37). These results suggests that current RDA may not be adequate for older adults, and the existence of a metabolic accommodation in the elderly (38).

Insufficient protein intake also influences the decline of physical function and co-morbidities. These factors must be taken into account when determining protein requirements in older people. Higher amounts of protein intake seem to reduce the risk of adverse events and to prevent frailty. In a 10 year longitudinal study, Vellas et al. have reported that women with protein intake higher than 1.2 g/kg/day had fewer health problems than those with protein intake less than 0.8 g/kg/day (14). In the Women's Health Initiative (WHI) observational study, over a three years period, 13.5% of the 24,417 eligible women developed frailty. After adjustment for confounders, a 20% increase in protein intake was associated with a 32% lower risk of frailty (39). Protein-Energy supplementation for 12 weeks (400Kcal/day and 25 g of protein) increased physical functioning in frail older adults in a controlled study (15).

These observational studies support the idea that protein supplementation can prevent or reverse sarcopenia and frailty. A recent meta-analysis concluded that protein supplementation could increase not only muscle mass but also strength gains, in addition to strength training both in younger and older subjects (40). However, longer-term trials are scarce and are needed to define optimal protein intake in the elderly (41). Finally, according to literature data and previous recommendations, specific recommendations from the PROT-AGE Study Group for healthy older people have been published recently (42). They indicate that to maintain muscle, elderly should have a higher average protein daily intake than younger people, in the range of 1.0 to 1.2 g/kg BW/day. It should be considered that nearly 10% of frail elderly and 35% of institutionalised elderly have an average protein intake below these estimates, making them major targets for interventions (43). However, there is no clear evidence till date for benefits of higher protein consumption in frail elderly, and several studies with protein supplementation alone have failed to show improvement on muscle mass or function (44, 45). Taken account all this , an excessively sedentary lifestyle -a hallmark of frailty – or the presence of inflammatory cytokines in frail skeletal muscle (4) may induce a blunted response of muscle protein synthesis to protein ingestion (46, 47) New strategies clearly need to be developed.

Micronutrients and frailty

Presence of reactive oxygen species (ROS) in excess in cells may be deleterious, causing damage to DNA, lipids or proteins, and inducing mitochondrial dysfunction and apoptosis. ROS are normally counterbalanced by antioxidant defence mechanisms. However, an accumulation of ROS may induce oxidative damage and also be a contributing factor to muscle fibres atrophy, muscle fibres loss and sarcopenia (48). Beside enzymatic anti-oxidants, many vitamins or trace elements like selenium have anti oxidative capacity and may play a preventive role in reducing consequences of oxidative stress.

In the Women's health and aging study (WHAS), studying 545 older women living in the community, high oxidative stress and protein oxidative damage, indicated by serum protein carbonyls, were predictive of the decline in walking speed and of the progression to severe walking disability (49). In addition, protein carbonylation was found independently associated with poor grip strength in a cross sectional study from the WHAS (50).

Micronutrient deficiencies are commonly observed among elderly with inadequate intake of various nutrients. Such deficits were observed for many vitamins (A, B6, B12, folate, E) and also for antioxidant trace elements (Zinc and Selenium) (51–56).

Frail elderly women are more likely to have multiple micronutrient deficiencies. In a cross sectional study of 754 women of the WHAS, Michelon et al. have observed lower serum concentrations especially for carotenoids, and also for vitamin B6 and folates (50). Furthermore, frail women were more likely to have at least two or more micronutrient deficiencies (57).

Carotenoid levels are generally considered as an indicator of fruit and vegetable intake, and may thus be considered as a biomarker of fruit and vegetable consumption (58–60). Semba et al. have shown in the WHAS that women in the lowest quartile for carotenoids were 57% more likely to develop severe walking disability (CI 1.24-2.00 p=0.0002) (49). Lauretani et al. have examined the association between total plasma carotenoids and changes in muscle strength over a six years follow up in 628 participants of the in Chianti study (61). After adjustment for confounders, volunteers with plasma carotenoids in the lowest quartile were at higher risk to develop lower hip or knee muscle strength (OR were 3.01 CI 1.43-6.31 and 2.89 CI 1.38-6.02 respectively). Mean serum carotenoids levels were also associated with mean walking speed in the WHAS (62).

These observations from epidemiological studies also suggest a positive effect of carotenoids on reactive oxygen species damage. Carotenoids may modulate redox–sensitive transcriptional factors such as NF-kB. As NF-kB up-regulates pro-inflammatory cytokines (63), carotenoids may thus be protective against pro-inflammatory mechanisms that lead to sarcopenia. A diet rich in fruits and vegetables may then reduce frailty factors (62). However randomized clinical trials are required to validate such hypothesis.

Vitamin E and C supplementation have been shown to improve antioxidant enzymes and muscle function in aged animals (64). In the In Chianti study, Ble et al. found an association between low circulating levels of vitamin E and frailty (65). From the WHAS, Bartali et al. showed that lower vitamin C intake is independently related to frailty (66). In this cohort a lower decline of physical performances assessed by Short Physical Performance Battery Score (SPPB) was related only to higher vitamin E blood level and not to any other antioxidant parameters. However, data from the WHAS study suggest inter-relationships between vitamin B6, B12, selenium and frailty (57). Indeed, women in the lowest quartile of serum concentrations of vitamin B6, B12, and selenium ,in the WHAS study, had significantly higher risk of disability in activities of daily living (66). In another cross sectional study involving 655 subjects, plasma vitamin C concentration was correlated with handgrip strength and walking speed after adjusting for confounding factors (67). In the WHAS, women in the lowest quartile for alpha tocopherol had an increased risk of becoming frail (68).

Selenium may also play an important role in muscle function (69) and seleno-enzymes such as glutathione peroxidase may protect myocytes from reactive oxygen species (70). Low serum selenium concentrations have been found associated with poor hip, knee and grip strength in older adults (71, 72). Other dietary nutrients such as iron, magnesium, phosphorus and zinc intake have been found to be negative predictors of change in appendicular lean mass, after adjustment for protein intake in a longitudinal study of 740 elderly over a 2-6 years follow up (73). However all these data are observational and more clinical studies including randomized controlled trials are needed before robust conclusions. At this stage, the current knowledge cannot be translated into nutritional recommendations.

Mediterranean Diet

Mediterranean diet is known to be the best diet for healthiness. Even though they are many reports of the composition of such diet, most of them agree that the main components are each day several vegetables (especially raw vegetables), fruits (including nuts), which provide many vitamins, raw cereals (bringing antioxidant trace elements) and olive oil. In addition, this diet is poor in red meat and rich in fish, bringing n-3 fatty acids. Many spices with antioxidant properties and garlic with antihypertensive properties are largely used (74). Mediterranean diet may also be considered as a key component for healthy aging and preventing strategies for age related disability (75, 76). It has been shown that adherence to a Mediterranean diet had positive effects on mobility after a 9-years follow-up of 935 men and women aged 65 years and more (77). High adherence to Mediterranean diet was associated with fewer declines in SPPB score at 3, 6, and 9 years and a lower risk of developing mobility disability. In a recent study, nutritional characteristics of Mediterranean diet were associated with frailty criteria with significant lower dietary scores in frail elderly (78).

Vitamin D and frailty

Vitamin D deficiency is generally associated with poorer physical performances and is predictive of incident mobility disability in community elderly people (79). In a cross-sectional study using data from the Third National Health and Nutrition survey (NHANES III), 25 hydroxy-vitamin D (25(OH)D deficiency defined as serum concentration below 15 ng/ml was associated with a 3.7–fold increase of frailty according to modified Fried's criteria (80). Similar results were also reported by Ensrud et al. (81) in a cohort study of 6307 women older than 69 years. They have shown that frailty was associated with lower vitamin D levels at baseline (less than 20 ng/ml), and that vitamin D level below 15 ng/ml predicted death (OR 1.4 CI 1.04-1.88) and frailty (OR 1.47 CI 1.19-1.82) after a 4.5-years follow-up. Interestingly, this study has also shown an association between frailty and a high level of vitamin D (higher than 30 ng/ml), suggesting a U-shape pattern. In the In-Chianti prospective cohort study, pre-frail participants with 25(OH) D levels lower than 20 ng /ml were 8.9% more likely to die or to become frail than pre-frail participants with 25(OH) D levels higher than 20 ng /ml (82). In the CHS study participants with a 25(OH)D deficiency (less than 20 ng/ml) were at greater risk of incident mobility disability over the three years follow-up (hazard ratio 1.56) (83).

Nevertheless, conflicting results can also be found. In a Chinese elderly men cohort, serum 25(OH)D level was not associated with 4 years change in physical performances (84). In another large prospective cohort study of 1606 men aged more than 65 years 25(OH)D, deficiency did not predict greater risk of frailty at 4.6 years (85). Moreover, results from vitamin D supplementation studies are still less convincing. In a double-blind placebo-controlled trial performed in 2256 community-dwelling elderly women aged 70 years and over, Sanders et al. have found that annual high-dose of vitamin D during 3 to 5 years resulted paradoxically in an increased risk of falls and fractures (86). Therefore, an acute very high dose of vitamin D may be deleterious. A meta-analysis involving 5072 participants from 17 randomized controlled trials has investigated the effect of vitamin D supplementation on muscle strength (77). No significant effect on muscle strength was demonstrated with vitamin D levels above 25 nmol/l. However two studies with vitamin D deficient participants have shown positive results (87) suggesting that vitamin D may still improve muscle function in patients with vitamin D deficiency. A recent study has examined the effect of 25(OH) D3 versus vitamin D3 on lower extremity function and markers of innate immunity in post-menopausal women with an average level of 13.2 ng/ml for 25(OH)D. Supplementation with 20 µg of 25(OH)D3 per day resulted in a 2.8 fold increase in lower extremity function while improvement was noted on markers of innate immunity (88). Besides improvement of lower extremity function, the influence of vitamin D on immunity may also be an important challenge in frail elderly, since vitamin D supplementation studies have shown beneficial effects on immune function (89).

N-3 long chain polyunsaturated fatty acids (PUFA) and frailty

Diets rich in n-6 and poor in n-3 PUFA may result in a pro-inflammatory environment that may be deleterious for muscle or other tissues. N-6 PUFA are a precursor of arachidonic acid that are a substrate of cyclooxygenase and lipo oxygenase enzymes (90). Low intake of eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) is associated with poor mobility in men according to the results of a cross-sectional study involving 417 Japanese elderly (91).

Fish-oil supplementation enhanced the benefits of strength training for lower limb strength, in a randomised study in elderly women (90). In the same study, a greater improvement for chair-rising performances was observed for the trained group supplemented with fish oil. In another interventional study, fish oil supplementation resulted in an improvement in walking speed in postmenopausal women (92). These results suggest that fish oil supplementation has a favourable effect especially in addition with strength training and may represent a promising preventive therapeutic strategy.

Research perspectives

Abnormal muscle protein synthesis with ageing may result from various factors such as lower response to insulin or impaired response to amino acids (47, 93). Dietary strategies should be developed to compensate such anabolic resistance, and to counteract muscle atrophy caused by periods of immobilisation that are frequently observed in the elderly (94). The muscle's anabolic response also depends on the digestion and absorption kinetics and amino acid composition of proteins. It may be considered that dietary proteins showing a more rapid digestion and absorption generally lead to a greater postprandial muscle protein synthetic response (95). Pennings et al. have shown that whey proteins stimulate postprandial muscle protein accretion more effectively than casein in older men (96). This effect was attributed to both faster digestion and absorption kinetics of whey proteins and higher leucine content.

Branched amino acids and especially leucine may contribute to increased protein anabolism and to decreased protein breakdown (41). Whey proteins from milk are rich in leucine and contain leucine up to: 12% more than 8-9% for meat or ,eggs, and <8% in wheat (97). Many studies suggest that dietary leucine supplementation may maximize the response of skeletal muscle accretion, and graded intake of whey proteins (35g compared with 10 or 20g) results in greater amino acid absorption and stimulation of protein synthesis in elderly men (98). Nevertheless the long-term effects of leucine supplementation remain to be established since a long term study failed to show any increase in muscle mass or strength in healthy elderly men (99). However, a dose response effect has been suggested, since increasing amount of proteins with 1.7g to 2.8 g leucine during meals may represent an effective dietary strategy (20).

The efficacy of leucine metabolite, β-hydroxy-β-methylbutyrate (HMB), has been investigated in several studies with attenuation of muscle loss and increase in muscle strength in the elderly (100). However, results may differ from various studies, indicating that larger long-term studies are required to confirm these preliminary results (100).

Citrulline is another amino acid that may have an effect on muscle mass and function (101). Citrulline bypasses the splanchnic area and directly stimulates muscle synthesis via the mTOR pathway. Citrulline supplementation in malnourished old rats increases protein synthesis, protein content in muscle, muscle mass and mobility (102, 103). Efficacy of citrulline supplementation in healthy and malnourished humans is the object of on-going researches.

To optimize protein utilization,not only quality of proteins but also timing and amount of protein ingestion must be explored further. Adequate postprandial stimulation of muscle protein synthesis is a major contribution for maintaining muscle mass. A higher protein amount seems necessary in the elderly with a threshold of 25-30g protein per meal, suggesting ingestion of proteins at breakfast, lunch and dinner (42). Conversely to this most common approach, benefits on lean mass have also been shown with one meal containing most of the protein daily intake (80% of the 1.5g/kg body weight/day in midday meal in hospitalized patients (ie protein pulse feeding) (104). Further multi-centre studies are needed to confirm the anabolic response over weeks and to better understand the mechanisms involved.

In everyday life, the distribution of protein intake seems very heterogeneous among the different meals with less than 10 g of protein ingested during the breakfast in a population of frail and institutionalized elderly (43). This clearly implies, in nursing homes, a huge period of nearly 18 hours between dinner and lunch without sufficient amounts of protein. Furthermore, this may explain why anabolism could be impaired even though the daily protein intake was found adequate in this population at risk of multiple bad outcomes.

It is generally assumed that digestion and absorption is less efficient during sleep (105). However, a recent study has shown that intra gastric protein administration during overnight sleep results in normal digestion and absorption kinetics in healthy elderly volunteers and stimulates muscle protein synthesis (105). In another study, the same authors have shown that proteins ingested immediately before sleep and after exercise were also effectively digested and absorbed, resulting in muscle protein stimulation in young men (106). Therefore protein ingestion during sleep time could be an interesting strategy in specific clinical situations.

Curcumin (diferuloylmethane), a component of the turmeric spice, may stimulate muscle regeneration after a trauma and may prevent muscle wasting during sepsis, by inhibiting NF-kB (107). Additional studies are however required to confirm these potential benefits.

Creatine may be found in meat or synthesized from several amino acids as arginine, glycine or methionine. In the skeletal muscle, creatine is the precursor of adenosine triphosphate, necessary for muscle contraction. Several studies have found positive results of creatine supplementation in addition with exercise on body composition and muscle function (108, 109). More recently, similar results were observed after a 12 weeks study with an amount of 5g /day (110). However, effects of a longer-term intake remain to be assessed.

It is now well established that dietary proteins, in addition with resistance exercise, increase muscle protein accretion during the post exercise period (111). However, there are conflicting results from literature about intensity and duration of exercise and quantity of protein supplementation itself. A systematic review has involved young and older participants from 22 randomized controlled trials with resistance exercise training more than 6 weeks and a supplementation with proteins or protein diets containing more than 1.2g/kg BW/day. Positive effects on muscle mass and strength gains were observed (40). However, mean age for older people was only 62 years and such results should be confirmed in frail elderly. Tieland et al. have shown an increase in skeletal muscle mass only in the group with protein supplementation (30g/day) after 24 weeks resistance exercise training in frail elderly people (112). Conversely, no efficacy on muscle was observed from whey protein supplementation in addition with resistance exercise for 6 months. Further studies are needed to determine the optimal efficacy of prolonged exercise (intensity, frequency) and dietary proteins or amino acid supplementation (type, source, quantity, and timing) on body composition and physical function in frail elderly.

In order to prevent frailty and decreases in physical performances, the optimal levels of nutrients, i.e. antioxidants, proteins, remain to be determined for the elderly. It is obvious that such optimal levels depend on equilibrium in between nutrients. Such levels exist in routine food as shown in Mediterranean diet for cardiovascular prevention. Future works should search for such equilibrium, depending on food consumptions rather than looking for supplement to prevent or treat frailty. Adherence for meals is far higher than for pills.

Conflict of interest: None

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