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Potential Nutrition Support for Age-Related Muscular Conditions

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Abstract

The world's population is aging and the elderly population is living longer. This demographic change poses a challenge to public health: How can the elderly sustain health and well-being? Retention of muscle health can help older adults to preserve independence and improve their quality of life. However, there are limited data on nutrition improvement as an approach to manage age-associated loss of muscle mass and strength, also known as sarcopenia. It is unclear whether specific nutrients could be beneficial to muscle health in the ageing process. To help answer this question, we reviewed the emerging data from human Randomized Controlled Trials (RCTs) on individual nutrients and muscle health in the past decade. Nineteen RCTs reported benefits of the following nutrients, supplemented alone or in combination, on improving muscle mass or strength in the elderly: Proteins and essential amino acids, vitamin D, bovine colostrum, omega-3 fatty acids, and anti-inflammatory ingredients. Cocktail supplementation of multiple nutrients was reported to be more effective than single nutrient interventions. A systems approach integrating multi-faceted interventions may help us better understand the multifactorial etiology of sarcopenia and find effective solutions towards healthy muscle conditions with age.

Keywords: Nutrients; Sarcopenia; Muscle mass; Muscle function; Aging

Introduction

The world's population is aging. By the year 2050, 21% of the world's population, or 2 billion people, is projected to be ≥ 60 years of age. Individuals aged ≥ 80 years are estimated to triple to 392 million [1]. The elderly population is living longer and this demographic change poses a challenge to public health: How can the elderly sustain good health and the highest quality of life? Mobility is an essential component of life quality, which includes muscle, joint and bone maintenance. Extensive research has been conducted on nutrients that influence age-related joint and bone deteriorations. However, there are limited data on nutritional approaches to manage loss of muscle mass and strength with age, also known as sarcopenia. It is estimated that muscle mass and strength start to decline at an annual rate of 1%-2% after the age of 50 years. After 60 years, losses in muscle mass and strength often accelerate to a higher rate, 3% per year [2, 3]. Retention of muscle mass and/or strength can help older adults to preserve independence and improve the quality of life [1, 4, 5].

Currently there is no consensus definition of sarcopenia. The most commonly used criteria to diagnose sarcopenia are from the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS) and Foundation for the National Institutes of Health Sarcopenia Project (FNIH). These three groups define sarcopenia as the presence of both low muscle mass (whole-body or appendicular) and low muscle function (either strength and/or physical functioning), resulting from an increase in protein catabolism and anabolic resistance [6-8]. However, measures of muscle mass and function are not standardized and arbitrary cut-off values and various interpretations have been applied in clinical trials. Such methodological inconsistencies have led to discrepancies in relevant literature including, but not limited to, prevalence, risk factors and efficacy of interventions.

The etiology of age-related deterioration of muscle mass or strength is yet to be fully understood. Lifestyle factors, such as reduced physical activity and an unbalanced diet, are believed to be one of the main contributors to sarcopenia. Exercise is one known factor that prevents loss of muscle mass and function. A combination of resistance and aerobic exercise with moderate intensity (20 minutes daily, 5 times per week) was reported to increase muscle strength by 38% and lower the serum concentration of a generic inflammation marker, C-Reactive Protein (CRP) ($P<0.01$) [9]. A systematic review of 62 Progressive Resistance Training (PRT) trials (3,674 subjects) reported that PRT was effective in improving muscle strength and some aspects of functional limitations, such as gait speed, among the

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elderly aged 60+ years [10]. A recent review confirmed most exercise interventions improved muscle strength or physical performance, but not always muscle mass among older people [11]. Furthermore, risks associated with exercise could not be evaluated due to lack of data on adverse events [10]. Beneficial effects of exercise training alone may not be enough to improve physical functioning or muscle mass in elderly at risk for, or with sarcopenia [11,12], suggesting a need for multifactorial interventions to achieve clinically relevant results.

The relationship between dietary patterns and sarcopenia has been examined in diverse populations. Cross-sectional data have reported high prevalence of sarcopenia is associated with alcohol intake, low dietary diversity, and insufficient intakes of fruit, vegetables and dairy food [3, 13-15]. In particular, high adherence to a Mediterranean diet is associated with slower decline in muscle and physical functioning and a lower risk of sarcopenia among the elderly [16-18]. Unfortunately, these findings are largely based on observational data and there are limited well-designed Randomized Controlled Trials (RCTs) investigating the efficacy of nutrition interventions on age-related muscular conditions [11]. To help better understand potential nutrition solutions to age-related loss of muscle mass and/or strength, we reviewed the emerging human data from RCTs in the past decade and summarized the evidence supporting nutrition interventions in managing sarcopenic conditions.

Literature Search Methods

We searched PubMed from January 1, 2007 to June 6, 2017, by using a combination of the following keywords: "nutrient" OR "vitamin" OR "mineral" OR "nutraceutical" AND "mobility" OR "muscle" AND "2007/01/01 to current" [Date-Completion] AND "randomized controlled trial" [Publication Type]. Key words were searched in the title/abstract of articles. Once the search was implemented and the publication titles were retrieved, titles of articles were screened, and abstracts of titles determined to be potentially relevant were retrieved for screening. Then full-text articles of abstracts determined to be potentially relevant were retrieved and reviewed for inclusion or exclusion.

The focus of this review is human RCTs on individual nutrients which are published in English and show improvement in muscle mass or function among older adults. Specific dietary patterns, food groups, gene/drug-nutrient interactions, biochemical/molecular mechanism, observational and in-vitro studies are not the focus of the present review.

Table 1 summarizes nineteen human RCTs that were published in English and reported positive effects of individual nutrients on age-related loss of muscle mass or function. In the section of "Literature Summary and Discussion", we cite additional studies, reviews and meta-analyses in order to provide a balanced point of view beyond the RCTs that are listed in Table 1.

Literature Summary and Discussion

Nineteen RCTs reported benefits of the following nutrients, either supplemented alone or with other nutrients, for improving the deterioration of muscle mass or strength due to ageing: Proteins and Essential Amino Acids (EAAs), vitamin D, bovine colostrum, omega-3 fatty acids, and select anti-inflammatory ingredients (curcumin, combination of multiple compounds). In these human trials, study populations were from North America, South America, Europe and Asia with a mean age of ≥ 55-65 years, and the duration of nutrition interventions ranged from 28 days to one year. Table 1 summarizes key characteristics of these RCTs including objectives, nutrition interventions, main outcomes and key findings.

Proteins and EAAs

Protein supplementation has been reported to have beneficial effects on muscle mass and strength among healthy adults, including the elderly. A higher protein intake than the recommended dietary allowance of 0.8 g/kg body weight (BW)/day may help preserve muscle mass and support healthy aging besides physical activity [19, 20]. A meta-analysis of 22 randomized trials reported protein supplementation at a dose of >1.2 g/kg BW/day during resistance exercise training increased Fat-Free Mass (FFM) by an average of 0.69 kg and leg strength among healthy adults aged 12-72 years compared to placebo ($p<0.005$) [20]. Subgroup analysis of six studies conducted in older subjects (>50 years of age) indicated an increase of 38% in FFM and a gain of 33% in muscle strength with protein supplementation [20]. These benefits were observed for protein supplementation either as supplements or through food. However, it remains unknown if such benefits could be generalized to those with sarcopenia. In a recent trial, 210 g of ricotta cheese (18 g protein) was consumed daily along with the habitual diet among Mexican older adults without sarcopenia [21]. Based on local reference intake of dietary protein (0.9 g/kg BW/day) in older people, the addition of ricotta cheese was estimated to increase protein intake in the intervention group from 0.9 g/kg BW/day to 1.2 g/kg BW/day for the 12-week duration of the study [21]. It was likely that increase in protein intake via ricotta cheese contributed to improved muscle mass in the intervention group compared to placebo [21]. In particular, at 12 weeks, the mean value of appendicular muscle mass in the intervention group was significantly increased by 0.6 kg [Standard Deviation (SD): ±3.5g], while the change from baseline values was negative in the control group (mean ± SD: -1±2.6g) [21]. In contrast, the same intervention was implemented among Mexican elderly with sarcopenia but did not improve any of the outcome measures [22]. More research is needed to help understand if responsiveness to protein supplementation among the elderly is influenced by muscle status (i.e. healthy, at risk, or sarcopenic).

Supplementation of EAAs alone has limited or no benefit on muscle mass and function even at a high dose (i.e. 6 g EAAs/day for 3 months) [23]. When supplemented with other nutrients, favorable effects of EAAs have been reported in a number of trials. A systematic review reported EAAs in combination with 2.5-2.8 g leucine were beneficial to muscle mass and function [12]. Favorable effects with a smaller dose of leucine (1.2 g/day)

Table 1: Human randomized controlled trials showing benefits of nutrients on age-related loss of muscle mass or strength

Reference	Design	Objectives	Nutrient Intervention	Main Health Outcomes	Population	Sample Size	Key Findings	Additional Notes
Da Boit 2017 [38]	Randomized, placebo-controlled, double-blind trial (placebo versus intervention)	To evaluate gender differences in the effects of fish oil supplementation together with resistance exercise on muscle mass and function among the elderly.	18 weeks, -Intervention: resistance training (twice per week) + 3 g/day omega-3 (providing 2.1 g EPA + 0.6 g DHA/day) -Placebo: resistance training (twice per week) + identical-looking placebo (3 g/day safflower oil)	Muscle function (knee-extensor isometric and isokinetic torque), physical performance (short-performance physical battery test)	Older adults aged > 60 years UK	N=50 -Placebo: n=23 -Intervention: n=27	At the end of intervention, supplemented women, not men, had greater increases in resistance training-induced muscle isometric torque and muscle quality than the placebo group ($P<0.05$).	No differences in markers of inflammation (TNF-α, IL-6) were observed between intervention and placebo groups.
Abe 2016 [24]	Randomized, controlled, single-blind, parallel group trial (control versus two interventions)	To evaluate a combination of nutrients [L-leucine and D_3- enriched essential amino acids (LD-EAAs) +medium-chain triglycerides (MCT), or , LD-EAAs + long-chain triglycerides (LCT)] in habitual diets for the treatment of sarcopenia in the elderly	3 months (1 time/ day at dinner): -LD-EAAs + MCT group: L-leucine (1.2 g) enriched EAAs (40% leucine in 3g EAAs) + D3 (800 IU) + MCT 6 g). -LD-EAAs + LCT group: L-leucine (1.2 g) enriched EAAs (40% leucine in 3g EAAs) + D3 (800 IU) + LCT (6 g). -Control: no supplement	At baseline and after the 3-month intervention: Muscle strength (right-hand grip strength), function (walking speed, respiratory function), appendicular muscle mass (mid-upper arm muscle area) , cognitive function	Elderly nursing home residents ≥ 65 years (mean age: 86.6 years). Yokohama, Japan	N=36 -Control: n=11 -LD+MCT: n=13 -LD+LCT: n=12	After 3 month, LD-EAAs + MCT significantly improved muscle mass (only mid-upper arm muscle area), strength (right-hand grip strength) and function (peak respiratory flow) compared to controls, and walking speed compared to the LD-EAAs + LCT group ($p<0.05$). No significant improvements in muscle mass, strength, or function were observed in the LD-EAAs+ LCT group compared to controls. Participants in the LD-EAAs + MCT group had a 13.1% increase in right-hand grip strength, a 12.5% increase in walking speed, a 68.2% increase in a 10-s leg open-and-close test performance, and a 28.2% increase in peak expiratory flow ($P < 0.05$).	Data collection: September – December 2014. Two intervention groups received energy-matched supplementation. The control group did not receive an energy-equivalent placebo per the study design. Food records were collected daily; no difference between groups at baseline and the end of intervention was found. Exercise protocols that were conducted in the nursing home remained unchanged through the intervention period. Subjects were not blinded about if they received supplements or not, but they were blinded about which supplements they received. Examiners who oversaw the walking speed test were blinded about the intervention groups, but examiners for other assessment were aware of the group assignment. Compliance with supplementation: 100%. No side effects were reported. Limitations: muscle mass was measured by an anthropometric analysis, not directly measured by CT or MRI. There was not a group receiving MCTs only so the effects of MCTs alone could not be assessed.

Franceschi 2016 [43]	Parallel-group clinical trial (control versus two interventions)	To evaluate effects of curcumin (Meriva®) supplementation as an addition to a standardized diet and exercise on parameters of sarcopenia	3 months: -Standard management group: exercise + balanced diet including proteins - Standard management + Meriva® (1g curcumin/tablet, 1 tablet/day) -Standard management + Meriva® (1 g curcumin/ tablet, 1 tablet/ day) + additional supplementation (D 800 IU/day, C 500 mg/day, isoleucine 3 g/day, carnitine 1 g/day)	At baseline and after the 3-month intervention: Muscle strength (hand grip, weight lifting), physical function (time/distance of feeling tired after cycling, walking and climbing stairs), other measures (i.e. oxidative stress)	Otherwise healthy elderly aged ≥ 65 years (mean age: ~73 years) who complained for strength loss and physical tiredness. Genoa, Italy.	N=86 -Standard management: n=33 -Standard management + Meriva: n=31 -Standard management + Meriva + additional supplementation: n=22	Significant improvements in all parameters were observed in the two supplementation groups ($p<0.05$), but not in the standard management group. Compared to the standard management group, both supplementation groups had significant improvements in all parameters ($p<0.05$).	Meriva has a novel phospholipid delivery system of curcumin (named phytosome®[10]) to overcome the poor systemic bioavailability of curcumin. Good compliance to supplementation (>95%). Observed benefits may be partly due to anti-inflammatory properties of curcumin.
Rondanelli 2016 [12]	Randomized, placebo-controlled, double-blind, parallel-group superiority clinical trial (placebo versus intervention)	To assess the efficacy of nutritional supplementation (whey protein + EAAs + D_3) concurrent with regular physical activity in improving fat-free mass, muscle strength and physical function and quality of life	12 weeks (1 time/ day with meals): Whey protein (22 g), EAAs (10.9 g, including 4 g leucine), vitamin D3 [2.5 µg (100 IU)], Concurrent regular physical activity.	At baseline and after the 12-week intervention: Fat-free mass (FFM), muscle strength, physical function, quality of life.	Elderly sarcopenic patients aged ≥ 65 years (mean age: 80.3 years), Pavia, Italy	N=130 -Placebo: n=69 -Intervention: n=61	Compared with placebo (exercise training only), nutritional supplementation plus exercise training increased FFM by 1.7 kg, relative skeletal muscle mass (RSMM), handgrip strength, physical function, nutritional status and insulin-like growth factor I (IGF-I) ($P<0.01$), and reduced inflammation (C-reactive protein, CRP) "68% of sarcopenic people became nonsarcopenic."	Data collection: Jan 2013-Jun 2014. Sarcopenia definition: RSMM < 7.26 kg/m2 for men, <5.5 kg/m2 for women. Dietary supplements included other nutrients (carbohydrates, fiber, calcium, phosphorus, sodium, magnesium, iron) Participants received a control diet providing a mean of 300 IU of vitamin D daily. All subjects engaged in a controlled physical activity program (moderate intensity, resistance+ aerobic, 20 minutes daily, 5 times/week for 12 weeks). Nutritional assessment included anthropometry, diet, and general (lifestyle, medication, and mobility) Compliance: 100% Supplement was well tolerated. Limitations: blood vitamin D concentrations were not assessed. Effects of vitamin D were not separated from essential amino acids.

Bauer 2015 [25]	Multicenter, randomized, controlled, double-blind, parallel-group trial (control versus intervention)	To test if an oral nutritional supplement (leucine-enriched whey protein + D + multi- vitamins/ minerals) can improve muscle mass, strength and function in sarcopenic elderly without protein-energy malnutrition	13 weeks (twice/ day before breakfast and lunch, 40g powder mixed with 100-150 ml water /time) - Active (40g powder): D (800 IU)+ leucine enriched (3g)-whey protein (20 g)+other nutrients (9 g carbohydrates, 3g fat, a mixture of 12 vitamins besides D, 15 minerals, soluble fiber, carotenoids and choline) - Control: iso-caloric product (150 kcal/serving) that only contain carbohydrate (31g), fat (3g), and three minerals (sodium, potassium, chloride)	At baseline, week 7 and 13 of the intervention: Muscle strength (handgrip strength), physical function (by Short Physical Performance Battery, SPPB), appendicular muscle mass (by Dual energy X-ray Absorptiometry , DXA), individual outcomes of SPPB (chair rise test, gait speed, balance score)	Primarily independent-living (85-88%) older adults ≥ 65 years (mean age at enrollment: 77.7 years) with mild to moderate limitations in physical function and low skeletal muscle mass index 18 study centers in 6 European countries (Belgium, Germany, Ireland, Italy, Sweden, UK)	N=380 -Control: n=196 -Active: n=184	Significantly greater improvement (week 13 versus baseline) in an individual outcome of physical function (chair rise test, p=0.018), not the other two measures (gait speed and balance), was observed in the active group compared with control. The increase in appendicular muscle mass (week 13 versus baseline) was greater in the active group than control (mean difference=0.17 kg, ~1%, p<0.05) No significant difference in SPPB or handgrip strength changes over time between the control and active groups.	Data collection: June 2010 – May 2013. No exercise program in the trial. In the active group, 25(OH) D concentrations improved significantly from a median value of 48 nmol/L at baseline to 73 nmol/L at week 13 (p<0.001). At baseline, habitual protein intake in both groups is >0.8 g/ kg/day. At week 13, the active group achieved a total protein intake of 1.5g/kg/day. Compliance with supplementation: 93% (median). Limitation: Primary measures, handgrip strength and SPPB, are not sensitive measures of sarcopenia. Benefits are applicable to independent-living elderly with mobility limitations, not other groups such as those recovering from hospitalization and immobilization.

Verreijen 2015 [26]	Randomized, placebo-controlled, double-blind, parallel-group trial (placebo versus intervention)	To examine the effects of a supplement (whey protein + leucine + D_3 + other nutrients) on muscle mass and strength during a 13-week weight-loss program (a hypocaloric diet + resistance exercise training) in obese older adults.	13 weeks [10 servings/week, including 1 serving daily before breakfast and 3 servings immediately after exercise training (3 times/wk)] -Intervention (per serving, 150 kcal): whey protein (20.7g), leucine (2.8g), D3 (800 IU), other nutrients (9g carbohydrate, 1.3g soluble fiber, fat, minerals-sodium, potassium, chloride) - Placebo (per serving, 150 kcal): an isocaloric control product (carbohydrates, fats, minerals-sodium, potassium, chloride)	At baseline and week 13 of intervention: Body composition including appendicular muscle mass (by DXA) At baseline, week 7 and 13 of intervention: Body weight/BMI/waist circumference, handgrip strength, physical performance (walking, gait speed, and chair stand tests)	Obese older adults aged ≥ 55 years (mean age at enrollment: 63y; mean BMI: 33 kg/m^2) Amsterdam, Netherlands	N=60 Placebo: n=30 Intervention: n=30	The 13-week changes in appendicular and leg muscle mass were different between two groups (p<0.05): Change in appendicular muscle mass: Intervention vs Placebo: 0.4 ± 1.2 kg vs -0.5±2.1 kg Change in leg muscle mass: Intervention vs Placebo: 0.3±1.2 kg vs -0.6±1.8 kg No difference in improvements of muscle strength and function between groups. Both groups lost body weight and fat mass without differences between groups (p>0.05)	Data collection: March 2011 – June 2012. Obesity definition: BMI >30 or >28 with waist circumference >88cm (women) or >102cm (men) All subjects were on a hypocaloric diet (600 kcal below Dutch estimated energy needs) and participated in a resistance exercise program (3 times/week for 1 h) throughout the 13-wk intervention period. Compliance (consumption of at least 7 products/week): no difference between groups (intervention versus placebo: 91% versus 97%) Limitation: High loss to follow-up for the primary outcome (25%)
Smith 2015 [39]	Randomized, placebo-controlled, double-blind, parallel-group trial (placebo versus intervention)	To test if supplementation of omega-3 fatty acids for 6 months would increase muscle mass and function in older adults	6 months, Intervention: omega 3 supplement (Lovaza, GlaxoSmithKline) providing a daily intake of 1.86 g EPA + 1.50 g DHA Placebo: identical looking pills containing corn oil	At baseline and 6 months of intervention: Thigh muscle volume (by MRI), muscle strength including handgrip strength and 1-RM muscle strength (leg & chest press, knee extension & flexion)	Healthy older adults aged 60-85 years St Louis, MO	N=44 Placebo: n=15 Intervention: n=29	Compared with the placebo group, omega-3 supplementation for 6 months improved thigh muscle volume by 3.6% (p<0.05), average isokinetic muscle power by 5.6% (p<0.10), handgrip strength by 2.3kg (p<0.05), and 1-RM muscle strength by 4.0% (p<0.05).	High loss to follow up rate (27%). Study target subjects were 60 and 44 completed the study. Completer-analysis was employed in this study, not Intention to Treat analysis.

Aleman-Mateo 2014 [21]	Randomized, controlled, single-blind, parallel-group trial (control versus intervention)	To investigate whether adding 210 g of ricotta cheese (18 g protein) daily into the habitual diet would improve appendicular skeletal muscle mass (ASMM), handgrip strength, and physical performance in non-sarcopenic older subjects.	12 weeks, Intervention: habitual diet + Ricotta cheese (210 g/day =18 g protein/day) Control: habitual diet only	ASMM (by DXA), handgrip strength, physical performance (by SPPB) including gait speed, chair rise test, balance	Non-sarcopenic older adults ≥ 60 years (mean age: 70.2 years) Mexico	N=100 Control: n=50 Intervention: n=50	The addition of 210 g of ricotta cheese for 12 weeks improved ASMM by 0.6kg (versus baseline), which was significantly different ($p<0.01$) from controls (week 12 versus baseline: -1 g). No difference in changes in handgrip strength or physical performance between groups $P\geq0.05$).	Sarcopenia definition: a low relative ASMM below two standard deviations from the mean value of the ASMM of a young Mexican adult population. The addition of ricotta cheese was estimated to increase protein intake from 0.9 to 1.2 g/kg BW/day. The same nutritional intervention protocol was implemented among sarcopenic elderly prior to this trial but no improvement in measures of sarcopenia including ASMM was found.
Duff 2014 [35]	Randomized, placebo-controlled, double-blind, parallel-group trial (control versus intervention)	To compare the effects of bovine colostrum vs whey protein supplementation during a resistance training on muscle strength, thickness, body composition and other indicators (i.e. inflammation and bone resorption) among older adults aged 50+ year	8 weeks bovine colostrum or whey protein, Bovine colostrum intervention: 60 g/day Whey protein placebo: 60 g/day (consumed 3 times/day, 20 g/time), overall nutritional composition was matched to bovine colostrum.	At baseline and after the 8-week intervention: Upper (by bench press exercise) and lower (by leg press test) muscle strength, muscle mass (by DXA), bone resorption (by urinary cross-linked N-telopeptides of Type 1 collagen, Ntx), inflammation (C-reactive protein, CRP)	Older adults aged 50+ years (mean age: 59 years) Saskatoon, Canada	N=40 Placebo: n=21 Intervention: n=19	The bovine colostrum group had a higher increase in lower body strength (by leg press test) and a greater decrease in bone resorption (by Ntx) compared to the whey protein placebo ($p<0.05$). Both groups had significant increases in lean tissue mass, muscle thickness (by ultrasound), upper body strength (by bench press exercise) and bone mineral content compared to baseline values ($p<0.05$). No difference in changes of these measures between groups	The mechanism for the greater increase in leg press strength in the bovine colostrum group compared to whey protein is not clear. More research is needed to confirm this benefit. No difference between groups for changes in systemic inflammation (CRP). Long-term effects of bovine colostrum need to be investigated further.

Ceglia 2013 [34]	Randomized, double-blind, placebo-controlled trial (placebo versus intervention)	To determine whether vitamin D_3 (4000 IU/d) alters muscle fiber cross-sectional area (FCSA) and intramyonuclear vitamin D receptor (VDR) concentrations	4 months: Vitamin D3: 4000 IU/day Placebo	At baseline and 4 months: Muscle strength (by knee extension test), muscle fiber size (by FCSA via biopsies of the vastus lateralis muscle)	Mobility-limited community-dwelling women (age ≥65 years) with serum 25(OH)D levels of 22.5–60 nmol/L and moderate risk for disability (SPPB score ≤9) Boston, MA	N=24 Placebo: n=13 Vitamin D3: n=11	Vitamin D_3 supplementation increased total muscle fiber size (type I and II) by 10%. No difference in muscle strength changes between groups.	All subjects took vitamin D_3 or placebo once daily immediately after breakfast. Intramyonuclear concentration of VDR was measured in a subset of 14 subjects and was increased by 30% at 4 months in the supplemented group. Mean serum 25(OH)D at baseline was 45.8±10.8 nmol/L with no difference between groups. At 4 months, the supplemented group had a greater increase in 25(OH) D level than placebo (36.4±13.6 vs 4.2±11.9 nmol/L, p<0.001). Sample size was small, which might not have enough power to detect any difference in muscle strength. The dose of 4000 IU/day was high although it is below the safety limit. It is not clear if such a high dose is needed for daily use.
Sakalli 2012 [28]	Randomized, double-blind placebo-controlled trial (two placebos versus two interventions)	To examine effects of a single mega dose of vitamin D administered orally and intramuscularly on physical function and pain among the elderly	A single mega dose of vitamin D (300,000 IU) orally or intramuscularly: Group 1: intramuscular vitamin D Group 2: intramuscular placebo Group 3: oral vitamin D Group 4: oral placebo	Before and 4 weeks after medication Physical function (Timed Up and Go test, TUG), pain (Visual Analog Scale, VAS), quality of life (SF-36)	Community-dwelling elderly aged 65+ years (mean age: 68.9 years) Ankara, Turkey	N=120 30/group	In vitamin D groups (intramuscularly and orally), physical functioning and pain were improved 4 weeks after a single mega dose of vitamin D. Pain measured by VAS was improved in all groups and certain physical functioning was improved in the intramuscular group, which might be due to the placebo effect.	The study was conducted in winter-spring period. Sun exposure could not be evaluated.

Rodacki 2012 [37]	Randomized, controlled trial (one control versus two interventions)	To investigate the effect of fish oil supplementation and strength training on muscle strength and functioning among elderly women	Daily supplementation of fish oil (2 g/day, providing ~0.4 g EPA +0.3 g DHA/ day): Control: strength training only Intervention 90 days: fish oil + strength training for 90 days Intervention 150 days: fish oil for 60 days prior to strength training, then together with strength training for 90 days	Muscle strength (i.e. peak torque by maximal voluntary isometric contraction), functioning (foot up and go, sit and reach, chair rising, 6-min walk)	Healthy white women aged > 60 years Brazil	N=45 Control: n=15 Intervention 90 days: n=15 Intervention 150 days: n=15	Compared to the control group, supplementation groups had higher peak torque post training for all muscles assessed, and bigger improvement post training in the chair-rising test ($p<0.05$). No difference was observed between two intervention groups (90 versus 150 days).	Fish oil supplementation did not result in any change in body mass. Small sample size.
Dunn-Lewis 2011 [44]	Balanced, randomized, double-blind, placebo-controlled, cross-over trial (at least 1-wk washout break)	To examine the effect of a multi-nutrient supplement (BioCharge®) on inflammatory status, joint health and physical performance during the recovery period of active individuals age 40-70 years.	28 days/ supplementation period, at least 1 week washout between periods: Intervention: BioCharge® containing branched chain amino acids (taurine, L-leucine, isoleucine, valine), anti-inflammatory plant extracts (cat's claw, quercetin, green tea, biovin grape extract), and B vitamins (B12, B6, folic acid, pantothenic acid) -Placebo	Physical performance, muscle function, handgrip strength, biochemical tests (i.e. CRP, IL-6), flow mediated dilation (FMD)	Healthy and recreationally active middle-aged adults (mean age: 56.0 year) Storrs CT	N=31	Men had significantly higher power in the vertical jump test and greater grip strength after supplementation. No significant improvement in these measures was observed in women. A decrease in IL-6 post supplementation was significant both in men and women ($P\leq0.05$). Reduction in general pain and joint pain post supplementation was significant only in men, not women	No improvement in other measures such as CRP and FMD was observed. Anxiety decreased in women after supplementation.

Fuller 2011 [33]	Randomized, double-blind, controlled trial (placebo versus intervention)	To determine if effects of a combination of β-hydroxy-β-methylbutyrate, arginine, and lysine (HMB/ARG/LYS) on muscle strength were modified by vitamin D status [<30 or ≥30 ng/ml serum 25(OH)D]	1 year (taken with breakfast): Intervention: daily supplementation of HMB/ARG/ LYS (2.0g CaHMB, 5.0g arginine, and 1.5 g lysine) Control: a drink consisting of a mixture of nonessential amino acids (5.6g alanine, 0.9g glutamic acid, 3.1g glycine, 2.2g serine)	Total leg muscle strength (by the sum of knee extension and flexion), body composition (by Bioelectrical Impedance Analyzer, BIA)	Elderly (mean age: 76 years) Central Iowa, Iowa	N=77 Control: n=37 -25(OH)D <30 ng/ml: n=29 -25(OH)D ≥30 ng/ml: n=11 HMB/ARG/LYS n=40 -25(OH)D <30 ng/ml: n=25 -25(OH)D ≥30 ng/ml: n=12	HMB/ARG/LYS supplementation increased FFM compared to controls regardless of vitamin D status. The HMB/ARG/LYS group with an average of serum 25OHD ≥30 ng/ml had significant strength gains over the yearlong study compared to the other three groups ($p<0.05$).	It was a post hoc data analysis based on serum 25(OH)D. Serum 25(OH)D was measured at 0, 3, 6, 9, and 12 months and an average value over the yearlong study was used to stratify vitamin D status . Two strata by serum 25(OH) D within each group: <30 or ≥30 ng/ml.
Smith 2011 [2]	Randomized, double-blind placebo-controlled trial (placebo versus intervention)	To examine the effects of omega-3 fatty acids on the rate of muscle protein synthesis using stable-isotope-labeled tracers	8 weeks, Intervention: omega 3 supplement (Lovaza, GlaxoSmithKline) providing a daily intake of 1.86 g EPA + 1.50 g DHA Placebo: identical looking pills containing corn oil	At baseline and 8 weeks of intervention: Basal rate of muscle protein synthesis (plasma phenylalanine and muscle free phenylalanine labeling as precursor pool enrichment), anabolic response to amino acid and insulin infusion	Healthy older adults aged ≥ 65 years St Louis, MO	N=15 Placebo: n=7 Intervention: n=8	Omega-3 fatty acids doubled the muscle anabolic response to amino acids and insulin infusion compared to basal values ($P\leq0.01$). The increased response was significantly different from the placebo group ($P<0.05$). No effect on the basal muscle protein synthesis rate was observed for both groups.	No beneficial effects of omega-3 fatty acids on inflammatory markers were observed probably due to low inflammatory status among these healthy subjects.

Zhu 2010 [29]	Randomized, double-blind placebo-controlled trial (placebo versus intervention)	To examine effects of vitamin D_2 on muscle strength and mobility in elderly women with vitamin D insufficiency [25(OH)D <24 ng/ml]	1 year: Vitamin D2+caclium group: 1000 IU D2 + 1000 mg calcium citrate daily Placebo (calcium only) group: placebo + 1000 mg calcium citrate daily	At baseline and 12 months: Mobility (TUG), muscle strength (ankle dorsiflexion, knee/ hip flexor, extensor and abductor strength), serum 25(OH)D	Community-dwelling elderly women aged 70-90 years with vitamin D insufficiency [25(OH)D <24 ng/ml] Perth, Australia	N= 261 Ca: n=132 D2+Ca: n=129	In both groups, significant improvement in knee flexor strength and all hip muscle strength and mobility (TUG test) was observed. But there was no difference between groups. After stratification by baseline values of functional measures, those in the lowest tertile had significant improvement in hip extensor (22.6%), adductor strength (13.5%) and mobility (17.5% faster on TUG test) at 12 months after vitamin D supplementation compared to placebos (P<0.05).	Mean 25(OH)D at baseline: 17.7±4.2 ng/ml. No difference between groups. At 12 months, vitamin D group had significantly increased vitamin D status compared to placebos (79% of subjects had 25(OH)D>20ng/ml).
Cornish 2009 [36]	Randomized, double-blind placebo-controlled trial (placebo versus intervention)	To assess the effect of α-linolenic acid (ALA) supplementation on muscle mass, strength and inflammation in older adults completing a resistance training program.	12 weeks with a resistance training program (3 days/week): Intervention: 30 ml flax oil/day (~14 g ALA/day) Placebo: 30 ml corn oil/day	At baseline and 12 weeks: Muscle thickness of knee & elbow flexors and extensors (by ultrasound), strength (1 repetition maximum chest and leg press strength), body composition (by DXA), markers of inflammation (TNF-α, IL-6)	Healthy older adults aged >60 years (mean age: 65.4 years). Canada	N=51 Placebo: n=26 ALA: n=25	The addition of ALA only lowered IL-6 levels and increased knee flexor muscle thickness in older men but not women. No other benefits of ALA were observed. Progressive resistance training increased muscle thickness, strength, and lean tissue mass in older adults.	Subjects in two groups were matched for gender. ALA and placebo oil were comparable in terms of color and calories. Compliance rate based on returned portions of oil: 78.2 ± 21.0% for placebos vs 83.6 ± 14.4% for ALA group Typical dietary intake was assessed by a food frequency questionnaire. The Ω-6 to Ω-3 ratio for the combined dietary and supplementation sources was assessed. The ratio decreased from 11.6±0.9 to 2.3±0.8 in the ALA group while the ratio increased in placebos (11.0±0.9 to 15.9±0.7) over time (p<0.0001). Null effects might be due to a small sample size.

Moreira-Pfrimer 2009 [32]	Randomized, double-blind, placebo-controlled trial (placebo versus intervention)	To investigate the effects of a 6-month supplementation with calcium and D_3 on biochemical parameters and muscle strength of institutionalized elderly.	6 month: Intervention: daily calcium (1000 mg) + monthly D_3 drop (150,000 IU once a month during the first 2 months, followed by 90,000 IU once a month for the last 4 Months); Placebo: daily calcium (1000 mg) + monthly placebo	At baseline and the end of the study Muscle strength (by hip flexor and knee extensors), serum 25(OH)D	Brazilian institutionalizing people aged ≥ 60 years. Sao Paulo, Brazil	N=41 Placebo: n=25 Intervention: n=26	Supplementation of vitamin D increased serum 25(OH)D levels by 84% compared to baseline values (vs 33% increase in placebos due to seasonality). Muscle strength of hip flexors and knee extensors was increased by 16.4% and 24.7%, respectively, compared to baseline values ($p<0.01$) (versus no improvement in the placebo group, $p>0.1$). After stratified by baseline vitamin D status, improvement in strength of hip flexors was only significant among subjects with low initial vitamin D status [25(OH) D<50 nmol/L, $p<0.01$]	Low serum 25(OH)D at baseline: Mean (range): 39.5 (20.3-68.8) nmol/l for placebos; 45.9 (20.3-84.8) nmol/l for intervention group. No difference between groups ($p>0.1$). By the end of the intervention, no subjects in the intervention group had serum 25(OH)D levels below 50 nmol/L, while 40% of the placebo group had insufficient vitamin D levels (<50 nmol/l)
Holm 2008 [27]	Randomized, double-blind, placebo-controlled trial (placebo versus intervention)	To evaluate the response of various muscle and bone adaptation parameters within 24 wk of strength training after ingestion of a nutrient supplement or a placebo	Immediately after each resistance training session daily for 24 weeks: Intervention: nutrient supplement (730 KJ) comprised of whey protein (10 g), carbohydrate (31 g), fat (1 g), D (5 µg)), and calcium (250 mg). Placebo: a placebo supplement (102kJ) containing carbohydrate (6 g) and calcium (12 mg)	At baseline, 12 and 24 weeks : Body composition (by DXA), muscle strength (by knee extensor test), bone mineral density, markers of bone turnover (serum osteocalcin and collagen type I cross-linked carboxyl terminal peptide)	Healthy, well-nourished early postmenopausal women (mean age: 55 years)	N=29 Placebo: n=16 Intervention: n=13	The lean body mass in the intervention group increased significantly ($p<0.05$), while the body fat mass remained unchanged in both group. The strength improvement from 6 to 24 weeks was significantly different between two groups ($p<0.05$): 9±3% in the intervention group versus 1±2% in placebos.	All women were on a weight-maintaining diet for the duration of the study. Bone mineral density at the lumbar spine at 24 weeks were significantly improved at both groups.

were reported in a trial when supplemented with EAAs, vitamin D_3 and Medium-Chain Triglycerides (MCTs), indicating a potential synergistic effect with these ingredients [24]. In this trial, elderly people were supplemented with a combination of EAAs (leucine-enriched; 40% leucine in 3 g EAAs) + vitamin D_3 (800 IU) + MCTs (6 gram) or long-chain triglycerides (LCTs, 6 g) daily for 3 months. Participants who received leucine-enriched EAAs+D_3+MCTs had improved mid-upper arm muscle mass, right-hand grip strength (13.1% higher), walking speed (12.5% faster) and peak respiratory flow (28.2% more) compared to baseline values [24]. These changes were significantly different from the control group who did not receive any supplementation [24]. However, no improvements were observed in the EAAs+D_3+LCTs group [24]. As there was no MCTs-only group in this trial, it is not clear if the observed benefit was due to the combination (EAAs+D_3+MCTs) or MCTs [24].

Whey protein and leucine are known to be stimulators of muscle protein synthesis and a combination of both has been reported to help preserve muscle mass and improve muscle strength among older adults with or without exercise. Supplementation on muscle function and mass without exercise was investigated in a multicenter, randomized, controlled, parallel-group trial. In this study, European elderly (≥ 65 years of age) with mobility limitations received vitamin D (800 IU), whey protein (20 g) enriched with leucine (3 g), and a mixture of other micronutrients twice per day for 13 weeks. At the end of week 13, the intervention group had greater improvements in lower-extremity function and appendicular muscle mass as compared to the control group ($P<0.05$) [25]. Specifically, the gain in appendicular muscle mass after supplementation was 0.17 kg (~1 % total appendicular muscle mass), which would offset a couple years of muscle mass loss among the elderly aged 70 years above [25]. Protein intakes were also increased from 0.8g/kg/day at baseline to 1.5g/kg BW/day after supplementation [25]. In a similar trial, whey protein (22 g), EAAs (10.9 g, including leucine 4 g), vitamin D_3 (100 IU/day) and minerals were supplemented daily to elderly patients with sarcopenia for 12 weeks. All subjects also participated in regular exercise and received a controlled diet (providing 300IU vitamin D_3 per day) through the course of the study. At the end of intervention, the supplemented elderly gained 1.7 kg FFM, and had significantly improved Relative Skeletal Muscle Mass (RSMM) and muscle strength compared to placebo [11]. Similar benefits on skeletal muscle mass were observed in obese older adults who were on a hypocaloric diet and a resistance training program [26]. These dieting older adults consumed a control product or a supplement containing whey protein (20.7 g/serving), leucine (2.8 g/serving) and vitamin D_3 (800 IU/serving) in a timely bolus amount (10 servings/week, 3 times immediately after exercise every week) [26]. After the 13-week intervention, both placebo and intervention groups lost weight and fat mass. However, the intervention group preserved 0.9 kg of appendicular and leg muscle mass compared to placebo ($p<0.05$) [26]. These measurable differences in skeletal muscle mass were attributed to higher protein intakes in the supplemented group (mean ± SD: 1.11±0.28 g/kg BW/day) than in placebo (mean ± SD: 0.85±0.24 g/kg BW/day) [26]. Daily supplementation immediately following resistance training was further investigated among healthy, early post-menopausal women [27]. At the end of 24-week intervention, supplemented subjects (10 g whey protein, 31 g carbohydrate, 5 µg vitamin D, and 250 mg calcium) had significant improvements in muscle strength and lean body mass compared to placebo (6 g carbohydrate + 12 mg calcium) ($p<0.05$) [27]. These data suggest temporal additive benefits of nutrient supplementation when given immediately post exercise.

Vitamin D

The efficacy of vitamin D on physical functioning and muscle strength has been reported to vary by baseline status, dosage and dosing frequency. A single mega dose of vitamin D (300,000 IU) administered orally and muscularly was reported to improve physical functioning among the elderly 4 weeks after administration [28]. In another trial, vitamin D_2 (1,000 IU/day) was given to elderly women with serum 25-hydroxy vitamin D [25(OH)D] <24 ng/ml for 12 months [29]. Both the intervention and control (calcium only) groups received 1,000 mg/day of calcium throughout the study [29]. Only among those in the lowest tertile of functional measures at baseline did vitamin D_2 supplementation improve muscle strength and mobility at 12 months compared to the calcium only group [29]. Specifically, supplementation of vitamin D_2 improved Timed Up And Go (TUG) time by 17.5% in subjects with baseline TUG time >12 seconds (the clinical cutoff point for normal mobility), hip extensor strength by 22.6% and adductor strength by 13.5% among those with the lowest tertile of baseline values ($P<0.05$) [29]. A systematic review of 12 trials reported vitamin D supplementation at a daily dose of ≥800 IU without any exercise improved balance and muscle strength among older adults aged 60+ years ($P<0.05$), though the magnitude of benefit was small [30]. Other dose intervals (i.e. a single dose, weekly, monthly) did not consistently improve these outcomes as daily doses, indicating the relevance of dosing frequency to efficacy [30]. Another recent systematic review of 30 RCTs confirmed positive effects of vitamin D_3 daily supplementation (≥400 IU) on muscle strength (17% increase, $p<0.05$) [31]. Supplementation was reported to be more effective in improving muscle strength among high-risk groups such as those aged ≥65 years or with vitamin D insufficiency [31, 32].

Supplementation of vitamin D_3 together with other nutrients (i.e. whey protein, EAAs) has been reported to improve muscle mass, strength and function in a number of trials that were previously described [11, 24-26]. Another trial reported a potential synergy between vitamin D sufficiency and a cocktail supplementation of β-hydroxy- β-methylbutyrate, arginine, and lysine (HMB/ARG/LYS; 2.0g CaHMB, 5.0g arginine, and 1.5 g lysine) on muscle strength. In this trial, supplementation of HMB/ARG/LYS for one year was reported to increase FFM among the elderly compared to the control group regardless of serum 25(OH)D status [33]. However, significant strength gains at the

end of 12 months (21% net gain in total leg muscle strength) were observed among supplemented participants with an average of serum 25(OH)D ≥30 ng/ml (P<0.05), but not among those with serum 25(OH)D<30 ng/ml [33]. Given elderly adults are at a high risk of vitamin D insufficiency, vitamin D status may be a factor that is worth considering when we design trials or interpret data regarding the efficacy of interventions on functional measures of sarcopenia [33].

Reversed vitamin D insufficiencies with supplementation may contribute to the retention of muscle mass and function [26, 32]. A human study explored vitamin D on muscle metabolism by measuring muscle Fiber Cross-Sectional Area (FCSA) in muscle biopsy tissues from mobility-limited postmenopausal women. Vitamin D_3 supplementation (4,000 IU/day) increased total muscle fiber size (type I and II) by 10% over the 4-month intervention [34]. In a subset of subjects (n=14), intramyonuclear concentration of vitamin D receptor (VDR) increased by 30% in the supplemented group [34]. However, the underlying mechanism for which vitamin D improves muscle mass and function remains unclear.

Bovine Colostrum

Bovine colostrum is known for its unique nutritional composition which includes EAAs, peptides and bioactive components (eg: immunoglobulins), and it has been reported to reduce upper respiratory tract infection among athletes and increase muscle mass during exercise training [35]. The effects of bovine colostrum on muscle strength and bone resorption were compared to whey protein in older adults aged ≥50 years. These participants were randomized to take either 60 g of colostrum or whey protein daily during resistance training for 8 weeks [35]. After the 8-week intervention, both groups had increased lean tissue mass, muscle thickness, upper body strength and bone mineral content, with no difference between groups (P>0.05)[35]. However, the colostrum group had a greater increase in lower body strength (leg press test) and reduction in bone resorption than the whey protein group (P<0.05) [35]. Specifically, leg press strength was increased by 21% in the colostrum supplemented group (versus 5% in the whey protein group), which may be clinically relevant to those elderly with mobility limitations due to declines in lower body strength [35]. Further research is needed to investigate long-term benefits of bovine colostrum and the underlying mechanism of action [35].

Omega-3 Fatty Acids

Omega-3 fatty acids have been reported to have mixed results in improving muscle mass and strength in older adults, which may be due to methodological differences such as dosage, duration of intervention, sample size, exercise status, and population characteristics (i.e. gender, muscle status). Alpha-Linolenic Acid (ALA) is a precursor to other omega-3 fatty acids such as DHA and EPA. Its anti-inflammatory effect on muscle mass and strength has been investigated among in an elderly population (aged >60 years) with concomitant resistance training [36]. After 12 weeks of flax oil supplementation (~14 g ALA/day), Interleukin 6 (IL-6) concentrations (a measure of inflammatory status) decreased significantly from baseline to 12 weeks among elderly men but not women [36]. While resistance training improved muscle thickness, strength and lean body mass in both placebo and ALA groups, the addition of ALA did not confer an additional benefit, with the exception of an increase in knee flexor muscle thickness in male subjects [36]. In contrast, supplementation with fish oil (2 g/day, providing ~0.4 g EPA and 0.3 g DHA/day)) along with strength training for 90 days was reported to improve muscle strength and functioning in elderly women compared to the group receiving strength training only [37]. Another trial further investigated gender differences in the effects of 3 g fish oil daily for 18 weeks (2.1 g EPA and 0.6 g DHA/day) on muscle functioning of older adults who participated in resistance training twice per week during the study period [38]. Significant improvement was observed only among older women, but not men [38]. These data indicate gender may be a factor that influences the efficacy of omega-3 fatty acids on muscle strength and functioning, and further exploration is needed to confirm sex-specific effects.

A few trials evaluated the effects of omega-3 fatty acids independently of exercise. A commercial supplement (Lavaza, providing a daily dose of 1.86 g EPA and 1.50 g DHA) was consumed by healthy older adults for 6 months. At the end of the intervention, supplemented elderly had significantly improved thigh muscle mass, handgrip strength and average muscle power compared to the placebo group [39]. The benefit of omega-3 fatty acids observed in this trial was estimated to prevent 2-3 years of losses in muscle mass and function with age [39]. However, null effects of omega-3 fatty acids on muscle mass and/or strength were observed in older adults with decreased muscle mass (ratio of appendicular lean mass to squared height [ALM index]: below -1 Standard Deviation [SD] of the population reference value) or frailty [40,41]. In these trials, the duration of omega-3 supplementation, alone or together with other nutrients (i.e. vitamin E), varied from 3 to 6 months and the daily dosage ranged from 1.2 g (0.72 g EPA and 0.48 g DHA) to 1.3 g (0.66 g EPA, 0.44 DHA, 0.20 g other omega-3) [40, 41]. More research is needed to help better understand potential interactions between omega-3 fatty acids and other factors (i.e. muscle status, gender) in order to deliver relevant muscular benefit to the elderly.

While the exact mechanism remains unclear, in vitro and in vivo data suggest omega-3 fatty acids may modulate muscle protein synthesis, breakdown, mitochondrial function and lipid content [39, 2, 42]. A recent human trial examined the effects of omega-3 fatty acids on the muscle protein synthesis rate using stable-isotope-labeled tracers among older adults aged ≥ 65 years [2]. While there was no observed effect on the basal rate of muscle protein synthesis, supplementation of omega-3 fatty acids for 8 weeks doubled the muscle anabolic response to amino acid and insulin infusion compared to basal values (P<0.001), and this increase was significantly greater than the placebo group (P<0.05) [2]. Furthermore, omega-3 fatty acids were reported to regulate select gene expression profiles of human mitochondrial

function and muscle growth, which may help explain the anabolic resistance-countering effects of omega-3 [42]. Given that the ratio of omega-3 to omega-6 in Western diets is much lower than the ancestral diet, supplementation of omega-3 may help achieve a balanced intake of polyunsaturated fatty acids and combat loss of muscle mass with age via augmenting protein metabolism in human muscle [36, 2, 42].

Anti-Inflammatory Ingredients

The etiology of sarcopenia is not clear, but one contributing factor is believed to be chronic systemic inflammation [36]. Curcumin is known for its anti-inflammatory properties. However, a limitation for the application of curcumin is its low bioavailability. A commercial supplement, Meriva®, adopted a novel phospholipid delivery form of curcumin (Phytosome®10) [29]. This supplement, Meriva®, has been investigated for the efficacy on sarcopenia parameters in healthy elderly aged 65+ years. During the 3-month intervention, all subjects received standard care including a balanced diet and exercise [43]. Subjects who took 1 g curcumin/day (Meriva®), alone or in combination with vitamin C, D, isoleucine, and carnitine, had significant improvements in muscle strength (hand grip and weight lifting) and physical performance compared to baseline measures and the control group who received standard care only ($P<0.05$) [43] . Furthermore, the Meriva® group reported reduced oxidative stress [43]. Given the multi-faceted impact of inflammation and aging on physical function, a combination of anti-inflammatory ingredients has been investigated. Bio Charge® is a multi-nutrient supplement containing branched chain amino acids (taurine, L-leucine, isoleucine, valine), anti-inflammatory plant extracts (cat's claw, quercetin, green tea, biovin grape extract), and B vitamins (B_{12}, B_6, folic acid, pantothenic acid)[44]. It was taken orally by healthy and recreationally active individuals aged 40-70 years for 28 days. After supplementation, physical performance, hand grip strength, general and joint pain were improved in men, and IL-6 was reduced both in men and women compared to pre-supplementation values [44]. These data indicate anti-inflammatory ingredients may help manage age-related physical limitations.

Conclusion

This review provides a summary of the current evidence from human RCTs supporting a beneficial role of select nutrients, supplemented alone or in combination with other ingredients, in improving muscle mass and/or function among the elderly. These nutrients include proteins and EAAs, vitamin D, bovine colostrum, omega-3 fatty acids, and select anti-inflammatory ingredients (curcumin, combination of multiple compounds). A higher protein intake (> 0.8 g/kg BW/day) may help preserve muscle mass but more research is needed to examine the responsiveness to protein supplementation by muscle status. EAAs may be beneficial to muscle health when supplemented with other nutrients, but not alone. Favorable effects of vitamin D on muscle strength and physical functioning may be influenced by factors including, but not limited to, baseline status, dosage and dosing frequency. The improvement on body strength by bovine colostrum may be clinically relevant to mobility limitations among older people but its long-term benefit needs to be further investigated. Omega-3 fatty acids appear to be promising in combating losses of muscle mass and strength with age especially when supplemented with concurrent resistance training. Anti-inflammatory ingredients have been reported to improve physical performance among older adults. In summary, cocktail supplementation of multiple nutrients was reported to be more effective than single nutrient interventions. The underlying mechanisms are not fully understood, but may include stimulation of muscle protein synthesis, modulation of muscle protein metabolism, mitochondrial function and lipid content, and/or reduction of chronic inflammation and oxidative stress.

These trials applied various outcome measures, some of which may not be sensitive indicators of sarcopenia. As an example, the Short Physical Performance Battery (SPPB), a measure of physical function, is a categorical measure with less sensitivity to changes than numerical measures [25]. This highlights a methodological challenge we are facing in nutrition research: How can we identify and choose appropriate indicators that are sensitive to changes in functional outcomes? Additionally, the efficacy of nutritional interventions on the retention of muscle mass and function can be influenced by numerous factors including, but not limited to, dosage, dosage frequency, timing, baseline status, host conditions (i.e. vitamin D sufficiency versus insufficiency, healthy versus sarcopenic), and other concomitant nutrients (i.e. synergy between nutrients). A systems approach integrating multi-faceted interventions may help us better understand the multifactorial etiology of sarcopenia and find effective solutions for muscular conditions that occur with age.

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Author Contributions

All authors contributed to the concept of the work. HK performed the literature search, reviewed and summarized the data, and drafted the manuscript. SP performed the literature search and reviewed the manuscript. ME and SHM reviewed the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

Dr. Hua Kern is an employee of the Nature's Bounty Co.Drs. Szabolcs Péter and Manfred Eggersdorfer are employees of DSM Nutritional Products. Dr. Susan Hazels Mitmesser was an employee of the Nature's Bounty Co. when the work was performed.

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