European Journal of Nutrition (2019) 58:2983–3008
https://doi.org/10.1007/s00394-018-1882-z

REVIEW

Supplements with purported effects on muscle mass and strength

Pedro L. Valenzuela[1,2] · Javier S. Morales[3] · Enzo Emanuele[4] · Helios Pareja-Galeano[3,5] · Alejandro Lucia[3,5]

Received: 17 July 2018 / Accepted: 13 December 2018 / Published online: 2 January 2019

Abstract

Purpose Several supplements are purported to promote muscle hypertrophy and strength gains in healthy subjects, or to prevent muscle wasting in atrophying situations (e.g., ageing or disuse periods). However, their effectiveness remains unclear.

Methods This review summarizes the available evidence on the beneficial impacts of several popular supplements on muscle mass or strength.

Results Among the supplements tested, nitrate and caffeine returned sufficient evidence supporting their acute beneficial effects on muscle strength, whereas the long-term consumption of creatine, protein and polyunsaturated fatty acids seems to consistently increase or preserve muscle mass and strength (evidence level A). On the other hand, mixed or unclear evidence was found for several popular supplements including branched-chain amino acids, adenosine triphosphate, citrulline, β-Hydroxy-β-methylbutyrate, minerals, most vitamins, phosphatidic acid or arginine (evidence level B), weak or scarce evidence was found for conjugated linoleic acid, glutamine, resveratrol, *tribulus terrestris* or ursolic acid (evidence level C), and no evidence was found for other supplements such as ornithine or α-ketoglutarate (evidence D). Of note, although most supplements appear to be safe when consumed at typical doses, some adverse events have been reported for some of them (e.g., caffeine, vitamins, α-ketoglutarate, *tribulus terrestris*, arginine) after large intakes, and there is insufficient evidence to determine the safety of many frequently used supplements (e.g., ornithine, conjugated linoleic acid, ursolic acid).

Conclusion In summary, despite their popularity, there is little evidence supporting the use of most supplements, and some of them have been even proven ineffective or potentially associated with adverse effects.

Keywords Hypertrophy · Ergogenic aid · Skeletal muscle · Protein supplementation · Prevention of atrophy · Sarcopenia

Introduction

Muscle mass and strength have been linked to athletic performance [1] and to overall health and mortality [2, 3]. Thus, the improvement of these two skeletal muscle properties (or at least preventing muscle wasting in disuse/atrophying situations) is essential in all subjects, from elite athletes to older untrained individuals [4].

Skeletal muscle is a dynamic, plastic tissue whose mass is regulated by the balance between the rate of muscle protein synthesis (MPS) and breakdown (MPB) (for a review, see [5]). Anabolic stimuli such as resistance training (RT) are capable of driving MPS, though RT can also have the opposite effect of MPB especially if performed in a fasted state [6]. To facilitate an anabolic response to RT [7] or prevent muscle wasting in atrophying situations, an appropriate dietary strategy (e.g., inducing hyperaminoacidemia) will play a key role by suppressing MPB. Thus, appropriate

Pedro L. Valenzuela, Javier S. Morales have contributed equally to this work.

Helios Pareja-Galeano, Alejandro Lucia share senior authorship.

✉ Helios Pareja-Galeano
helios.pareja@universidadeuropea.es

[1] Department of Sport and Health, Spanish Agency for Health Protection in Sport (AEPSAD), Madrid, Spain

[2] Physiology Unit. Systems Biology Department, University of Alcalá, Madrid, Spain

[3] Faculty of Sport Sciences, Universidad Europea De Madrid, Villaviciosa De Odón, 28670 Madrid, Spain

[4] 2E Science, Robbio, Pavia, Italy

[5] Research Institute of the Hospital 12 De Octubre (i+12), Madrid, Spain

nutrient intake is essential to maintain and improve muscle properties.

Under this paradigm, several supplements have been proposed to offer benefits for muscle mass or strength. Owing to their purported effects, the use of supplements has rapidly grown at an estimated annual rate of 9% during 2013–2019 [8]. It has been recently estimated that more than half of the adults in the United States take some form of dietary supplement (especially vitamins, minerals, protein-sport supplements and botanical/herbal ones) to improve health or well-being [9]. Supplements are also widely consumed in the sporting context, with 60–90% of the athletes taking vitamin/minerals, proteins/amino acids, creatine, herbal supplements, caffeine, energy drinks or fatty acids [10, 11]. However, the effectiveness of many of these supplements has not been scientifically proven, and their use has been linked to serious adverse effects in some cases [9]. For instance, a meta-analysis and systematic review of the effects of several supplements found that only protein, creatine and β-hydroxy-β-methylbutyrate (HMB) had beneficial impacts on muscle mass and strength [12, 13]. A recent review also concluded that, although the aforementioned compounds could have muscle building effects, there is little to no evidence supporting the efficacy or safety of many popular supplements (notably, glutamine or arginine, herbs extracts such as Fenugreek or *tribulus terrestris*, and minerals such as baron, chromium or zinc) [14]. Moreover, despite their widely spread use for the promotion of muscle anabolism, some supplements such as prohormones are included in the World Anti-Doping Agency list of banned substances, and have been associated with several adverse effects on multiple organ systems [15].

Given the widespread use of multiple nutritional supplements for the improvement of muscle mass/strength and the controversy surrounding their real effectiveness, the objective of this review was to summarize the effects of some of the most popular nutritional supplements when administered alone or in combination with exercise. For this purpose, we performed a non-systematic review in PubMed using the name of the supplement (e.g., creatine) and terms such as muscle mass, strength, body composition, hypertrophy or muscle atrophy. Reference lists of relevant articles and reviews were also examined to find additional publications on the topic. First, we mention the potential mechanisms by which each of the supplements might provide benefits on muscle mass or strength based on mechanistic studies (performed in humans when available, or animals/in vitro studies if there were no human studies). We then summarize the results of relevant studies assessing the effectiveness of each supplement in humans (if available), with a priority focus on randomized controlled trials (RCTs) and meta-analyses, when available. Finally, the main weaknesses of each supplement (e.g., side effects, lack of evidence in humans) are presented. Based on this information, the evidence supporting the beneficial effects of each supplement on muscle mass/strength was categorized as outlined by the National Heart, Lung and Blood Institute [16]:

- Evidence level A: Overwhelming data from RCTs and, if possible, meta-analyses supporting their effectiveness and safety. These supplements could be thus recommended for the promotion of muscle mass or strength (Table 1).
- Evidence level B: Supplements with mixed evidence and/or few RCTs supporting their effectiveness and safety in humans. There is not enough evidence that these supplements could provide benefits on muscle mass or strength, and caution should, therefore, be taken regarding recommendation (Table 2).
- Evidence level C: Supplements with little evidence or uncontrolled, non-randomized or observational studies supporting their effectiveness and safety in humans. Accordingly, there is not enough evidence that these supplements could provide benefits on muscle mass or strength, and at present they should not be recommended for the promotion of muscle mass or strength (Table 3).
- Evidence level D: Supplements with insufficient evidence to be categorized in levels A to C. These supplements should not be recommended for the promotion of muscle mass or strength (Table 3).

Supplements with evidence A

Caffeine

Caffeine supplementation is a commonly used strategy in endurance and high-intensity sports [17, 18], as it could have ergogenic effects on strength performance through different mechanisms [17]. Caffeine stimulates the central nervous system (CNS), increasing catecholamines and endorphins, and antagonizing the receptors of adenosine, a molecule involved in pain perception and somnolence. It can also enhance Na^+/K^+ ATPase activity, reducing intracellular K^+ accumulation and consequently postponing fatigue. Moreover, it has been suggested that caffeine could augment the glycolytic flux (as reflected by an increased lactate concentration). However, this could be the result of a greater exercise tolerance due to CNS activation. In addition, some evidence has demonstrated that caffeine ingestion might lead to greater increases in the production of testosterone and cortisol following resistance exercise (for a review, see [19–21]).

Meta-analytical evidence has shown that caffeine supplementation improves muscular endurance and maximal voluntary contraction [22] and is safe at doses recommended

Table 1 Supplements with strong evidence (level A) supporting their purported effects on muscle mass or strength in humans

Supplement	Typical forms and doses	Proposed biological mechanism	Safety issues	Comments
Caffeine	Coffee, energy drinks or tablets 3–6 mg/kg	Stimulates central nervous system Reduces pain perception and somnolence	Large doses of caffeine (≥ 9 mg/kg) can lead to nausea, anxiety, accelerated heart rate, and insomnia [319] The intake of excessive doses (≥ 500 mg/day) can reduce physical performance	Most evidence supports effectiveness in force resistance, but mixed results for effects on maximal force or power production Benefits seem to depend on variables such as training experience, quantity of muscle mass exercised and habitual use or not
Creatine	Powder or tablets. Loading phase of 20–25 g/day for 5–7 days and maintenance phase of 3–5 g/day	Increases energy availability Confers a greater training volume Increases cell osmolarity Induces anabolic signaling pathways Induces myogenic regulatory factors	Short and long-term supplementation (up to 30 g/day for 5 years) is safe and well-tolerated [38]	Mechanisms for increased muscle mass not fully elucidated
Nitrate	Leafy green and root vegetables, tablets, powder or ready to drink solution 5–13 mmol/day	Increases $NO^{\cdot}$ levels Increases blood flow	Nitrate supplementation seems to be safe [320]	Increases fatigue resistance, but does not seem to improve maximal force production
Protein	Powder, bars or food 0.8–2.0 g/kg/day depending on population	Improves muscle protein balance	There is no evidence of adverse effects of long-term, high-protein diets on kidney or liver function in healthy subjects [100]	Increases muscle strength especially when combined with RT
PUFAs n-3	Tablets 800–1200 mg/day	Anti-inflammatory effect Improves muscle protein balance	No known adverse effects [321]	Greater benefits when combined with RT

Levels of evidence assigned attending to the categories proposed by the National Heart, Lung and Blood Institute [16]. Level A indicates that overwhelming data from randomized controlled trials and, if possible, meta-analyses, support the effectiveness and safety of these supplements

NO nitric oxide, *PUF* As n-3, polyunsaturated fatty acids (e.g., omega-3), *RT* resistance training

Table 2 Supplements with mixed or unclear evidence (level B) supporting their purported effects on muscle mass or strength

Supplement	Typical forms and doses	Proposed biological mechanism	Safety issues	Comments
BCAA	Powder 10–20 g/day	Improves muscle protein balance	The intake of up to 20 g of BCAA is safe[a] Leucine intake > 550 mg/kg/day or ~ 39 g/day may be a risk to health [322]	Leucine seems to be the most beneficial amino acid
ATP	Powder or tablets 200–400 mg/day	Influences neurotransmission and neuromodulation Increases blood flow	ATP supplementation may be safe [152]	Some evidence supporting its use during repetitive fatiguing actions, but more research is still needed
Citrulline	Powder or tablets 6–8 g/day	Arginine precursor	Some cases of gastrointestinal discomfort have been reported [166]	Some benefits found for citrulline malate, but not L-citruline
HMB	Powder 2–4 g/day	Improves muscle protein balance Improves exercise recovery allowing a higher training volume	None of the few studies that tested HMB in humans has reported negative health consequences of HMB supplementation [182]	Most benefits observed in untrained individuals
Minerals	Tablets Magnesium: 300 mg/day Zinc: 10–40 mg/day Chromium: 600–100 µg/day	Promotes hormone function, including insulin and testosterone	Most mineral supplements are safe in recommended dosages. Excess zinc may decrease HDL-cholesterol levels and increase cardiovascular disease risk [217]	Benefits seem to depend on basal mineral status
Vitamins	Tablets Vitamin D: 1000–5000 IU/day Vitamin C: 500–2000 mg/day Vitamin E: 400–600 IU/day	Role in regulating mitochondrial function in skeletal muscle (vitamin D) Role in muscle repair and remodeling (vitamin D) Antioxidant effects (vitamins C and E)	No known adverse effects with vitamin supplementation with the doses typically used [a]. However, high-dose vitamin intakes, especially of vitamin E and C, might be harmful [240]	Could be beneficial in individuals with vitamin deficiency Vitamin D provides no additional benefits over RT Vitamins C and E inhibit anabolic signaling pathways
Phosphatidic acid	Tablets or powder 750 mg/day	Improves muscle protein balance	Not enough evidence to determine its safety	Anabolic properties detected in basic research Scarce mixed evidence in humans
Arginine	Powder 3–9 g/day	Induces GH secretion Promotes creatine synthesis Promotes $NO^{\cdot}$ production	The intake of > 9 g/day can result in gastrointestinal discomfort and reduce arterial blood pressure[a]	Some benefits found for long-term supplementation Evidence supporting its use is insufficient

Levels of evidence assigned attending to the categories proposed by the National Heart, Lung and Blood Institute [16]: Level B indicates that scarce or mixed evidence (both positive and negative results, or unclear findings) supports the effectiveness of these supplements in humans

ATP adenosine triphosphate, *BCAA* branched-chain amino acids, *HDL* high-density lipoprotein, *HMB* β-hydroxy-β-methylbutyrate, *RT* resistance training

[a]Information extracted from the Office of Dietary Supplements-National Institute of Health (https://ods.od.nih.gov/factsheets/ExerciseAndAthleticPerformance-Consumer/)

Table 3 Supplements with weak (level C) or no evidence (level D) supporting their purported effects on muscle mass or strength

Supplement	Typical forms and doses	Proposed biological mechanism	Safety issues	Comments
CLA	Tablets 4–8 g/day	Improves muscle protein balance	Not enough evidence to determine its safety	Mixed evidence of its effects on muscle mass and strength Conflicting evidence of anti-inflammatory effects
Glutamine	Powder 20–40 g/day	Improves muscle protein balance	No known adverse effects with doses up to 45 g/day[a]	Benefits observed for parenteral use during catabolic states Insufficient or negative evidence supporting its oral use
Resveratrol	Tablets 250–500 mg/day	Improves muscle protein balance Anti-inflammatory and antioxidant effects	No known adverse effects [323, 324]	Mixed evidence in basic research Insufficient evidence in humans
Ursolic acid	Tablets 450 mg/day	Improves muscle protein balance Increases serum GH and induces IGF-1 secretion	Not enough evidence to determine its safety	Despite possible anabolic properties, effects have not been consistently confirmed
Tribulus terrestris	Tablets 200–450 mg/day	Stimulates androgens and anabolic hormones	Not enough evidence in humans to determine its safety Cases of injury in heart, liver and kidney have been reported in animals with high doses[a]	Androgen levels seem not increased in healthy subjects, though could be effective in those with androgen deficiency
AKG	Powder or tablets Alone or in combination with ornithine. 1.5–3 g/day	Arginine and glutamine precursor Improves muscle protein balance Induces anabolic signaling pathways	Although this supplement has been reported to be overall safe [311], some important cardiovascular adverse effects have been detected, possibly due to its vasodilatory effects [313]	Some benefits found in basic research No short or long-term studies on the effects of AKG alone on muscle mass or strength
Ornithine	Powder or tablets 4–12 g/day	Activates anabolic signaling pathways Increases GH production	Not enough evidence to determine its safety	Some evidence supporting acute somatotropic effects No short or long-term studies of its effects on muscle mass

Levels of evidence assigned attending to the categories proposed by the National Heart, Lung and Blood Institute [16]: Levels C and D indicate that weak (uncontrolled, non-randomized or observational studies) or no evidence, respectively, supports their effectiveness and safety in humans

AKG arginine alpha-ketoglutarate, *CLA* conjugated linoleic acid, *GH* growth hormone, *IGF-1* insulin-like growth factor-1, *NO* nitric oxide, *RT* resistance training

[a]Information extracted from the Office of Dietary Supplements-National Institute of Health (https://ods.od.nih.gov/factsheets/ExerciseAndAthleticPerformance-Consumer/)

by the International Olympic Committee (IOC, see below). Some studies observed an improved capacity to accomplish RT to failure without modifying or even reducing the rate of perceived exertion [23, 24]. However, some authors have detected no such ergogenic effects [25, 26], while others describe beneficial effects for lower body, but not upper body exercises [27–29]. Acute ingestion of 6 mg/kg increases bench press strength, whether expressed as one repetition maximum (1RM) [29] or number of repetitions to failure [23, 24]. Interestingly, a meta-analysis by Warren et al. [22] concluded that caffeine improves muscular strength exclusively in the knee extensors and not in other muscle groups such as the forearm or the knee flexors. On the other hand, Grgic et al. [30] found that caffeine significantly improves upper but not lower body strength. Consensus regarding evidence of the effects of caffeine supplementation on maximal strength is, nevertheless, greater, and indeed a recent meta-analysis concluded that caffeine ingestion increases maximal muscle strength and power production capacity [30].

The recent consensus statement by the IOC recommends a posology of 3–6 mg/kg of body mass in the form of anhydrous caffeine 60 min prior to exercise or lower doses (< 3 mg/kg) when consumed with a carbohydrate source [31]. Indeed, larger doses (≥ 9 mg/kg) might not enhance muscle performance and in fact increase the risk of negative side effects (nausea, anxiety, accelerated heart rate, insomnia) that outweigh potential performance benefits [31]. Some evidence suggests that coffee and other energy drinks may not be a good source of caffeine for performance enhancement since these products contain other ingredients that might counteract the benefits of caffeine [32]. However, emerging data show that coffee might be at least as ergogenic as caffeine alone when caffeine doses are matched [33]. Moreover, caffeine benefits could depend on variables such as training experience, quantity of muscle mass exercised and how used subjects are to its consumption [17].

In summary, strong evidence based on systematic reviews and meta-analysis supports the ergogenic effect and safety of low to moderate doses of anhydrous caffeine (~ 3–6 mg/kg) consumed 60 min before exercise on muscle power and strength (Table 1).

Creatine

Phosphocreatine is an essential molecule for adenosine triphosphate (ATP) synthesis [34]. Creatine is endogenously synthesized in the liver, pancreas and kidney from the amino acids glycine, arginine and methionine [35], but it can also be exogenously administered through the intake of its main sources (i.e., meat and fish) [36]. Creatine is one of the most popular supplements among professional and recreational athletes, but has also been employed in clinical practice [37, 38]. Although the commonest form of creatine used by athletes as well as in scientific research is creatine monohydrate (CM) [37], other forms of creatine can be found in the market including creatine ethyl ester [39], creatine hydrochloride, buffered creatine, liquid creatine, and creatine magnesium chelate. However, their use as ergogenic supplements might not be recommendable considering the scarcity, absence or negative results of research related to the use of these alternative forms of creatine compared with CM [39–41]. Thus, for the sake of simplicity we will focus on CM.

CM can be effective as adjuvant therapy to treat muscle wasting diseases, CNS disorders and bone and metabolic disturbances [42]. Despite exerting no effects on MPS [43], CM has been reported to enhance muscle strength and performance in response to bouts of exercise shorter than 3 min, independently of supplementary doses or duration [44, 45]. Further, CM supplementation attenuates muscle mass and strength losses during immobilization [46] and promotes hypertrophy, shortening the recovery time from disuse-induced muscle atrophy [47]. When combined with RT, CM was found to increase the type II fiber surface area of the *vastus lateralis* relative to the consumption of placebo [48]. As type II muscle fiber atrophy is an important hallmark of ageing [49], CM combined with RT could be an effective intervention against sarcopenia. However, no beneficial effects on lean body mass (LBM) or muscle function were observed in elderly women [50], which could be attributed to the low doses given (1 g/day). A loading CM dose of 20–25 g/day divided into 4–5 intakes of 5 g each over 4–6 days followed by a maintenance dose of 3–5 g/day seems to be the most effective protocol to saturate skeletal muscle creatine stores [51].

The optimal timing of CM ingestion is a matter of controversy. In recreational bodybuilders, consuming CM immediately post-workout was related to more benefits on LBM, fat mass and muscle strength than taking CM before training [52]. On the contrary, no differences in muscle mass and strength were observed in older adults given CM before versus after exercise [53]. Notwithstanding, it seems clear that, independently of the timing of ingestion, CM combined with RT provides more benefits than training alone [54].

CM supplementation seems to be effective at increasing muscle mass and strength, and as such is a potential tool against muscle wasting [55]. CM promotes strength and LBM gains in patients with different muscular dystrophies [56]. The majority of studies that have analyzed the effect of CM in the muscle wasting associated to ageing have combined this supplement with RT, demonstrating strong benefits on muscle mass and strength [57]. However, CM supplementation without RT has also proven to increase the muscle mass and strength, as well as the functional capacity of the elderly [58]. In this regard, periods as short as 7 days of CM (0.3 g/kg) have proven to improve performance in

the sit–stand test [59] in elderly women as well as muscle strength, functional capacity and LBM in elderly men [60]. Although some cases of kidney dysfunction have been reported [61], CM supplementation does not induce renal damage in healthy subjects [42], and is, therefore, considered a safe and well-tolerated supplement in healthy individuals and in a number of patient populations ranging from infants to the elderly [38] (Table 1).

Nitrate

Nitric oxide ($NO^{\cdot}$) is a signaling molecule that induces smooth muscle relaxation. Although its main function is to induce vasodilatation and consequently improve oxygen delivery, $NO^{\cdot}$ also takes part in other processes that could enhance hypertrophy such as muscle contraction, glucose metabolism and myoblast differentiation [62–64]. Thus, the exogenous administration of $NO^{\cdot}$ could promote hypertrophy and muscle regeneration. Nitrate is a source of $NO^{\cdot}$ that can be obtained through the consumption of green, leafy vegetables, and beetroot especially [65]. In this regard, Jonvik et al. [66] found that highly trained athletes already intake an important quantity of nitrate in their habitual diet (~ 106 mg/day), mainly from vegetables. However, performance benefits have been found after the consumption of greater doses (310–560 mg) [67, 68].

The effects of nitrate supplementation on endurance performance have been widely assessed [69, 70], but its effects on strength or anabolism have received less attention. Supplementation with a nitrate-rich compound (beetroot juice) has been reported to increase muscle efficiency for a given force production, although it does not seem to increase force levels [71]. Nitrate supplements also reduce energy cost and improve the time to exhaustion during low and high intensity muscle contractions [72]. Moreover, they also lead to increases in the number of repetitions that can be performed to failure during RT [73]. Despite null effects on peak force, nitrate intake diminishes muscle fatigue in hypovolemic conditions [74].

Although the anabolic effects of long-term nitrate supplementation remain to be elucidated, this strategy allows for completion of a higher training volume, and therefore, could potentially induce a greater anabolic stimulus and indirectly promote hypertrophy [75]. Although recent evidence indicates that there is no association between estimated intake of nitrite and nitrate in the diet and stomach cancer [76], more research is needed on the safety of long-term nitrate supplementation (Table 1).

Proteins

Protein is a critical nutrient to optimize MPS [77], especially when combined with RT [78]. There is meta-analytic evidence that protein supplementation increases muscle fiber cross sectional area, and muscle mass and strength in young, adult and elderly subjects [7, 79]. However, other meta-analyses have detected no beneficial effects of protein supplementation alone or in combination with RT on muscle mass or strength in elderly subjects [80–82].

Factors such as nutritional state, capacity to digest proteins and absorb amino acids, the sensitivity of muscle anabolic pathways, or the characteristics of the RT program might influence the effects of protein supplementation on muscle mass and strength [80]. The anabolic response to protein ingestion could be also affected by the source, dose and timing of protein intake. In this context, Gillen et al. [83] found in a cohort of 553 well-trained athletes that their habitual protein intake was above the recommended dose of 1.2 g/kg per day. However, these athletes consumed most proteins (38%) during the dinner, and the authors suggested that optimizing protein distribution throughout the day should be considered in order to maximize the skeletal muscle adaptive response to training [83]. Given that postprandial MPS rates are enhanced following the ingestion of a 20–25 g of high-quality protein, a balanced distribution of protein throughout the day (4–5 evenly spaced feedings of 20 g high-quality protein) can maximize the anabolic stimulus [84–86].

Among all proteins, whey proteins (WP) are of greatest biological value as they are rapidly digested and show higher essential amino acids (EAA) content than other proteins [87]. WP induce MPS more than other types of protein both at rest and after RT in young [78] and elderly subjects [88, 89]. They are accordingly considered the "gold standard" of protein supplements [90]. When comparing the effects of different types of protein on muscle mass and strength, results have been mixed. Thus, while reports exist that WP supplementation offers greater benefits for LBM that soy protein [91], and greater benefits for LBM and strength than casein [92], other studies have detected greater beneficial impacts of casein on muscle strength than WP [93] or at least similar gains in LBM and strength after the intake of WP, soy or casein when combined with RT [94, 95].

Controversy also exists over the optimal amount of protein that should be consumed. Although US Dietary Reference Intakes are a daily dietary protein intake of 0.8 g/kg as adequate for almost all persons aged 19 years and older [96], 1.4–2.0 g protein/kg per day is recommended in the more recent International Society of Sports Nutrition position stand aimed at gaining muscle mass [97]. In a recent meta-analysis, no additional benefits were found for LBM when healthy adults consumed over 1.6 g/kg per day of protein [79]. However, elderly subjects showed a reduced muscle protein balance associated with impaired MPS [98]. This effect, known as anabolic resistance, could be one of the main determinants of age-related muscle wasting.

Accordingly, this population may require a greater relative protein intake than young subjects to maximally stimulate MPS [99]. A higher protein intake (1.2–2.0 g/kg per day) is also recommended for athletes to support metabolic adaptation, repair, and remodeling, as well as for protein turnover [16].

In summary, protein supplementation has proven overall effective for increasing muscle mass and strength. Controversy exists regarding its effectiveness in the elderly, but this could be due to the need of higher doses in this and other populations (e.g., athletes, or during calorie restriction periods). In this sense, there is no evidence of adverse effects of long-term, high-protein diets (i.e., > 3 g/kg per day) during 2–4 months on kidney or liver function in healthy young subjects [100], and indeed a recent meta-analysis concluded that high-protein diets (> 1.5 g/kg per day or 100 g/day) do not adversely influence kidney function in healthy individuals [101] (Table 1).

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are those that contain two or more carbon–carbon double bonds. The PUFAs omega 3 (*n*-3) and 6 (*n*-6) have a double bond at their third and sixth carbon atoms, respectively, counting from the methyl end. Humans do not synthesize enough PUFAs to fulfill basic requirements, so these must be supplied in the diet [102]. *N*-6 PUFAs such as linoleic acid, have been linked to the production of pro-inflammatory markers [103]. Conversely, *n*-3 PUFAs have anti-inflammatory properties, and thus a correct *n*-6/*n*-3 balance is beneficial for health [102]. Linoleic acid is the precursor of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which in turn are the precursors of eicosanoids and mediate *n*-3 PUFA-associated anti-inflammatory effects [104].

There is growing evidence to suggest that *n*-3 PUFAs may facilitate anabolic processes. Thus, supplementation with a 4 g/day of a commercial compound containing 1.86 g of EPA and 1.50 g of DHA during 8 weeks has been reported to enhance MPS and promote the phosphorylation of anabolic signaling pathways both in young [105] and older [106] subjects. Similarly, supplementation with this compound for 6 months led to increased muscle volume and strength in elderly subjects in comparison with a control group [107]. Moreover, the combination of *n*-3 PUFA and RT provides more benefits for muscle strength and functional capacity than RT alone [108, 109].

Several mechanisms could be responsible for these beneficial effects, as *n*-3 PUFAs induce protein synthesis through increases in muscle mammalian target of rapamycin (mTOR) and p70s6k phosphorylation [106], but also produce an anti-inflammatory effect that could support anabolic processes [110]. Pro-inflammatory markers such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 are associated with reduced muscle mass and strength in elderly subjects [111]. Therefore, *n*-3 PUFAs could effectively protect against these age-related effects owing to their antioxidant capacity. However, no changes in plasma concentrations of C-reactive protein, TNF-α and IL-6 have been observed after *n*-3 PUFAs supplementation neither in young or elderly subjects [105, 106].

Thus, although the effects of *n*-3 PUFAs supplementation on inflammation remain to be confirmed, this form of supplementation has been noted to facilitate anabolic processes and to increase muscle mass both in the young and elderly. The concentration of EPA or DHA that has demonstrated to enhance MPS (1.86 and 1.50 g, respectively) is approximately equivalent to the *n*–3 PUFA content of 200–400 g freshwater fatty fish (e.g., salmon, herring, and sardines) [112]. According to the World Health Organization, the European Food Safety Authority and the US Department of Health and Human Services a minimum of 250–500 mg combined EPA and DHA each day is recommended for healthy adults [113] (Table 1).

Supplements with evidence B

Branched-chain amino acids

EAA play a key role in promoting the accrual of muscle proteins, activating mTOR anabolic signaling pathways and, consequently, in regulating MPS [114, 115]. In contrast, non-essential amino acids (NEAA) do not seem necessary to induce MPS [116]. So far, studies have shown that EAA supplementation may improve MPS in the young and elderly [117], and that this supplement has the potential to attenuate age- and disuse-induced loss of muscle mass and function [118–120]. Among all EAA, branched chain amino acids (BCAA, i.e., leucine, isoleucine, and valine) may be the most effective to induce protein synthesis [121, 122]. BCAA contribute to protein synthesis and formation of glutamine and alanine in the muscle and have also proven to increase myofibrillar muscle protein synthesis rates in resistance-trained men [123]. Therefore, they play a role in regulating muscle protein metabolism, although it is not clear if they do so just by increasing MPS and/or by reducing MPB [124]. Supplementation with BCAA provides an anabolic stimulus both in resting conditions and during exercise [125, 126]. A meta-analysis of RCTs in humans indicates that the use of BCAAs is more effective in reducing muscle soreness and improving muscle function after various forms of exhaustive and damaging exercise than passive recovery or rest [127]. In addition, BCAA supplementation at high doses (> 200 mg/kg/day) for a long period of time (> 10 days) can be efficacious to attenuate exercise-induced muscle damage,

at least if the extent of muscle damage is low-to-moderate and BCAA are taken prior to the damaging exercise [128].

Particularly, the BCAA leucine is considered a "nutrient signal", as it has the capacity to both induce MPS [129] and reduce MPB [130]. Leucine has proven effective at promoting growth hormone (GH) release [131] and insulin secretion, which could support its anabolic effect [132]. Moreover, its anti-catabolic properties determine that in periods of muscle wasting such as immobilization [133] or ageing [134] a higher leucine intake could be recommendable. A recent meta-analysis found that, although leucine augments MPS in elderly subjects, it does not affect LBM. Nevertheless, the heterogeneity of the studies included could have influenced the results [135]. In fact, another meta-analysis detected a beneficial effect of leucine on LBM, although not on muscle strength [136]. In addition, the combination of leucine plus RT gives rise to greater MPS and myofibrillar muscle hypertrophy than leucine supplementation alone [137], and also leads to additional strength gains in untrained men [138].

As an optimal anabolic stimulus [87], 3–4 g/day of leucine (equivalent to 25–33 g/day of WP) seems appropriate whereas intakes of ~ 35 g/day could be the tolerable safe upper intake level [139]. Supplementation with BCAA is quite safe when the three BCAA leucine, isoleucine and valine are provided in a ratio of ~ 2:1:1, as supplementation of leucine alone could trigger BCAA imbalance [121]. Finally, added leucine is unnecessary for the stimulation of MPS when sufficient EAA are provided [140].

BCAA supplementation could be an effective strategy during catabolic situations. Of all BCAAs, leucine seems to be the most effective at stimulating anabolic processes. However, controversy exists regarding its effects on muscle mass, and it seems to provide no muscle strength benefits. On the other hand, although more research is needed, BCAA supplementation appears safe, even in patients with liver dysfunction due to hepatocellular carcinoma [141] (Table 2).

Adenosine-triphosphate

ATP is the primary intracellular energy source, but also has important functions at the extracellular level that could enhance exercise performance. Increased extracellular ATP levels have been related to improved Ca^{2+} kinetics [142], enhancing muscle contraction. In addition, adenosine increases skeletal muscle glucose uptake [143] and stimulates $NO^{\cdot}$ production and consequently vasodilatation [144, 145]. Indeed, long-term ATP supplementation (400 mg/day) induces vasodilatation and increases blood flow, especially after exercise [146].

A single dose (225 mg/day) of ATP has been reported to increase maximal strength, and benefits have been also observed in the number of repetitions that could be performed to failure when ATP supplements were taken for 2 weeks [147]. However, these benefits were not observed with lower doses (150 mg/day) [147]. One dose of ATP (400 mg) has also been reported to increase the total weight lifted during RT in recreational resistance-trained males [148]. ATP supplementation (400 mg/day during 2 weeks) has also been reported to prevent exercise-induced declines in ATP as well as to enhance peak power and muscle excitability [149]. However, other authors observed no beneficial effects with the same protocol of ATP supplementation on peak torque, power or total work performed during 50 repetitions, although an improved low peak torque (lowest torque recorded during contractions) and a tendency for a greater fatigue resistance were observed [150]. Additional gains in muscle mass, strength and power have also been reported after long-term ATP supplementation (12 weeks) in combination with RT in comparison with a placebo intervention, also reducing loss of performance and protein breakdown during high-load training periods [151].

ATP supplementation seems to be safe, as no adverse effects have been reported, including no alterations of liver or kidney parameters, after its prolonged use (5 g/day) [152]. Although meta-analytic evidence is lacking on the potential ergogenic effects of ATP supplementation and the evidence for its benefits on force production is still not sufficient, it seems to be effective in repetitive and fatiguing actions. These benefits could be the result of increased blood flow owing to the vasodilatory effects of adenosine [144, 153], with the consequent improved oxygen supply and metabolite removal rate. Nevertheless, the evidence on the mechanism/s supporting a biological rationale for the effectiveness of ATP supplementation is still scarce, and the bioavailability after oral intake of this supplement remains unclear [152, 154]. Thus, in future work, the mechanism whereby ATP supplementation might improve performance needs to be established (Table 2).

Citrulline

Citrulline is an arginine precursor that can be exogenously or endogenously obtained from glutamine and from the conversion of arginine to $NO^{\cdot}$ [155]. The consumption of citrulline alone has been reported to increase plasma levels of ornithine, nitrite and arginine [156–158]. It has been proposed that citrulline might increase muscle mass because some in vitro and in vivo studies found an increased anabolic response with arginine supplementation [159, 160]. Citrulline supplementation has also been associated with an increased systemic amino acid availability in malnourished older subjects of both genders and with an increased LBM, although the latter was only observed in women [161]. However, oral L-citrulline supplementation does not acutely increase insulin or GH levels at rest [162] and its intake over

a 7-day period does not modify insulin or insulin growth factor (IGF)-1 levels or affect protein synthesis [156]. Indeed, the ingestion of L-citrulline in isolation has been reported to reduce the insulin response to submaximal exercise to exhaustion [163] and to our knowledge, no study has analyzed the effects of isolated L-citrulline supplementation on RT or strength.

In contrast, the combination of L-citrulline and malate (8 g) seems to offer some performance benefits, such as an improved maximal strength, power and number of repetitions performed to failure while diminishing post-exercise muscular soreness [164–167]. Nevertheless, other authors failed to detect a beneficial effect with lower doses (6 g/day) on the number of repetitions performed to failure [168] or on LMB after its combination with RT during 8 weeks (2 g/day) [169]. Of note, gastrointestinal discomfort has been reported in 15% of citrulline malate users [166] (Table 2).

β-Hydroxy-β-methylbutyrate

The leucine metabolite HMB is naturally produced in humans from α-ketoisocaproate [170]. Endogenous HMB production depends on the content of leucine in the diet, as L-leucine (the HMB precursor) cannot be synthesized in the organism. Only 5% of leucine is transformed into HMB [171].

A meta-analysis of 6 RCTs (of which 5 did not include concomitant RT) indicated that HMB supplementation can prevent LBM loss in elderly subjects, 3 g/day being the most effective dose [172]. HMB has also been reported to produce anti-catabolic effects in older adults during disuse periods [173]. However, HMB supplementation in combination with RT induced no significant strength gains over those observed in an age-matched placebo group [174].

HMB seems to have ergogenic effects in untrained individuals, whereas different meta-analyses have found no benefits on muscle strength or body composition in well-trained subjects [175, 176]. Acute HMB supplementation before RT seems to enhance the GH and IGF-1 response to exercise in resistance-trained men [177]. In contrast, a RCT found that intake of leucine metabolites (HMB or α-hydroxyisocaproic acid) before RT induced no ergogenic effect on muscle mass or strength [178]. Furthermore, long-term supplementation with HMB produced no significant effects on the hormone profiles (GH, IGF-I, testosterone) of elite adolescent volleyball players, although it was found to improve LBM and strength [179].

The intake of 3 g/day of HMB has been reported as more effective than 1.5 g/day, though no additional benefits were observed for 6 g/day [180]. Of note, 3 g of HMB exert the same effect on MPS as 3 g of leucine, and although both supplements activate the mTOR pathway, this effect is more pronounced with the latter [181].

HMB can be taken safely by both young and old populations as it has no adverse effects [180, 182]. Its use as a supplement may serve to prevent catabolic states in the elderly, although it does not help to improve muscle strength. Further, similarly to leucine, HMB can have ergogenic effects in untrained individuals, although this does not seem to be the case in athletes (Table 2).

Minerals

Unlike macronutrients, micronutrients such as magnesium, zinc or chromium are ingested in very small doses though they still have important functions in the organism [183]. For this reason, it has been traditionally proposed that supplementation with these minerals could provide some benefits on well-being and physical performance [183].

There is a wide inter-individual variability in the intakes of magnesium, but it is often deficient [184]. Some differences can be observed for instance between geographical areas. Whereas ~25% of Brazilian adolescent athletes have a lower than adequate intake [185], in European countries such as Spain, Italy, Denmark, France or the Czech Republic the prevalence reaches up to 80% [186, 187]. However, a recent study reported that basal diet (i.e., without dietary supplements) already provided sufficient amount of magnesium in both male and female Dutch athletes, with <4% not meeting the requierements of this mineral [188]. On the other hand, factors such as exercise can increase the requirements of this nutrient [183]. In addition, a meta-analysis found that the dietary intake of magnesium was below the recommended dietary allowance in sarcopenic older adults [189]. Thus, supplementation with magnesium could be recommended in some specific populations.

Magnesium plays a role in metabolism and in physiological functions such as neuromuscular, cardiovascular, immune, and hormone responses [190]. It has been suggested that magnesium might improve muscle mass/strength owing to its influence on MPS and energy metabolism, and also contributes to the process of muscle contraction and relaxation [189, 191]. For instance, magnesium levels have been related to the anabolic response produced in the organism owing to effects on testosterone levels [192]. Serum magnesium and dietary magnesium intake have been related to muscle strength [193], muscle mass [194] and submaximal exercise performance in aged subjects [195], and to greater strength and power in elite athletes [196]. However, there has been disparity in reported effects of magnesium supplementation. Some authors described that magnesium supplementation (until a dose of 8 mg/kg per day in combination with diet) given over 7 weeks led to additional strength gains over a placebo intervention [197]. Similarly, an increased bench press 1RM was observed after 1 week of magnesium

supplementation (300 mg/day), although not when supplementation was maintained for 4 weeks [198]. By contrast, other authors found no such benefits [199, 200]. In conclusion, meta-analytical evidence does not support a beneficial effect of magnesium supplementation on muscle fitness in most athletes or in physically active individuals who have a relatively high magnesium status [201].

Zinc is an intracellular cation involved in several biochemical reactions, including protein synthesis, cell differentiation and hormone function [202]. As opposed to magnesium, there does not appear to exist remarkable intergeographic variability in the intakes of this mineral, with countries of different areas such as Brazil, France, Italy and Denmark not meeting the adequate intake [185–187]. In a study involving 553 Dutch athletes it was concluded that users of nutritional supplements have an adequate intake of zinc [188]. Zinc levels have been related to testosterone production [203]. The intake of this mineral has also been associated with greater muscle mass in adults [194]. Additionally, the antioxidant and anti-inflammatory effects of zinc could be important in the prevention and treatment of sarcopenia [204]. Low zinc levels with impaired muscle performance [205]. In one study, strength was increased after 14 days of zinc supplementation (135 mg/day) in comparison with a placebo intervention [206]. Zinc supplementation for 1 year increased anabolic hormone concentrations and promoted growth in children with growth disorders [207]. Long-term zinc supplementation (6 months, 459 µmol/day) was also found to raise testosterone levels in elderly persons with zinc deficiency [203] and in response to 4 weeks of supplementation, the post-exercise testosterone response was enhanced in healthy young subjects (though not basal testosterone levels) [208]. Further, a systematic review concluded that zinc supplementation was associated with increased LBM among children with growth failure [209].

Chromium has an important insulinogenic function [210], which could facilitate the anabolic response and consequently induce hypertrophy. 12 weeks of chromium picolinate supplementation (200 µg/day) did not improve muscle strength in comparison with a placebo group, although an increased body mass was observed in the female subjects [211]. Similarly, its intake during an 8-week RT program provided no additional muscle mass or strength gains over those provided by a placebo intervention [212]. No beneficial effects of long-term chromium supplementation (12 weeks, 400 µg/day) were observed on body composition in overweight women whose chromium status was normal [213]. Similarly, no strength or body composition benefits were noted in football players in response to 9 weeks of chromium picolinate supplementation plus intense training in comparison with a placebo group [214]. Neither were benefits observed in strength, power or muscle mass of chromium picolinate supplementation in elderly men [215].

Most studies addressing mineral supplementation have reported no benefits for muscle mass or strength. Effectiveness could depend on basal mineral status. Thus, it could be that this form of supplementation may be only useful in individuals with deficient mineral levels [216]. This means that mineral status, intake, and losses, along with physiological function need to be assessed before prescribing supplementation with minerals. Finally, it is important to note that most mineral supplements are safe in recommended dosages, although it has been suggested that excess zinc might decrease high-density lipoprotein-cholesterol levels and consequently increase cardiovascular risk [217] (Table 2).

Vitamins

Vitamin supplements are not necessary if a balanced, vitamin-rich diet is followed. However, when this is not possible, vitamins could help prevent deficiencies that could be detrimental for muscle health [16].

Vitamin D is a fat-soluble vitamin that, despite being traditionally known because of its role in bone metabolism [218], has recently been paid special attention due to its impacts on skeletal muscle [219]. The prevalence of vitamin D deficiency in European countries is worryingly high (93–100%) [186–188]. The use of vitamin D supplements has proven to reduce the prevalence of this condition among some populations such as athletes, although low intakes were still observed in some individuals (43% and 19% of male and female athletes, respectively) [188]. The elderly population is more prone to suffer vitamin D deficiency [220]. Further, older men with 25-hydroxy vitamin D (25(OH)D) concentrations defined as lower than 'adequate' (< 20 ng/ml) by the Institute of Medicine [221] showed reduced muscle mass, strength and function [222]. A longitudinal cohort study reported that elderly women with lower serum concentrations of 25(OH)D (< 10 ng/mL) had a threefold increased risk of developing frailty than those with higher 25(OH)D (≥ 30 ng/mL) levels [223]. In addition, in response to 1 year of supplementation with HMB, arginine, and lysine in elderly subjects, only those with a vitamin D status ≥ 30 ng/mL showed improved muscle strength, suggesting that vitamin D deficiency could also blunt strength gains [224]. Accordingly, it has been hypothesized that vitamin D supplementation could be an effective strategy to avoid sarcopenia and its associated disorders.

There is nonetheless controversy over the effects of vitamin D supplementation on muscle mass and strength. A meta-analysis including individuals older than 60 years given vitamin D supplements confirmed beneficial effects on strength and balance [225]. Likewise, vitamin D supplementation can increase upper and lower limb strength in young subjects [226], and improve handgrip strength in athletes with vitamin D deficiency (< 30 ng/ml) [227].

In contrast, two further meta-analyses observed no significant improvement in muscle strength after vitamin D intake in older (> 65 years) [228] and younger adults [229]. Similarly, another meta-analysis including subjects of all ages detected no significant effects of vitamin D supplementation on muscle mass [230], and vitamin D offered no additional benefits in terms of greater muscle mass or strength in response to RT in young or elderly subjects [231]. However, a recent systematic review and meta-analysis found an improved lower-limb muscle strength in elderly subjects taking vitamin D_3 supplementation (doses ranging from 400 to 1920 IU/day) in combination with RT compared to their peers performing RT but not taking supplements or to those not doing RT but taking supplements [232].

Vitamin supplements containing the antioxidants vitamins C and E are also popular. There is a wide inter-geographic variability in the intake of vitamins C and E. For instance, the prevalence of subjects with inadequate intake ranged between 5–65% for vitamin C and 34–95% for vitamin E in different groups including athletes and general population [185, 186, 188]. On the other hand, although it has been reported that most athletes users of nutritional supplements have an adequate intake of vitamin C and E [188], the use of antioxidants has been questioned, as they seem to interfere with exercise-induced physiological adaptations by attenuating the activation of hypertrophic signaling pathways [233, 234]. For instance, in strength-trained young subjects, supplementation with these vitamins diminished the gains in strength produced after a RT program [234]. In other studies, the increase in LBM and muscle strength was also offset after supplementation with these vitamins [235, 236]. In contrast, a higher LBM has been observed after the combination of RT and supplementation with vitamins E and C in elderly subjects, although no benefits were noted on muscle strength [237, 238].

In summary, there is evidence of the importance of optimal vitamin D levels to maintain muscle health, but results regarding the effects of supplementation with this vitamin on muscle mass and strength have been conflicting. The effectiveness of supplementation could especially depend on the subject's vitamin D status. This has proved to be of special relevance in aged subjects or in those with vitamin D deficiency [230]. Special caution should be taken with antioxidant supplements (e.g., vitamins E and C), as they seem to block anabolic signaling pathways and thus minimize adaptations to RT. Nevertheless, the effects of antioxidants on muscle properties could also depend on the subject's level of oxidative stress and antioxidant status. Further, no adverse effects are associated with vitamin D supplementation as long as the recommended dosage is not exceeded [239]. However, taking high-dose vitamin supplements, especially of vitamin C and E, might be harmful (e.g., by increasing the risk of cardiovascular disease morbidity and mortality and certain types of cancer) [240] (Table 2).

Phosphatidic acid

Phosphatidic acid (PA) is a diacyl-glycerophospholipid that is synthesized endogenously or supplied via the diet [241]. PA supplementation has been suggested to have pro-anabolic and anti-catabolic effects. Exogenous PA promotes mTOR complex 1 (mTORC1) pathway activation and tends to increase MPS levels in vivo [242, 243], and thus its combination with an anabolic stimulus such as RT is likely to induce greater increases in muscle growth [244]. However, exogenous PA may also reduce MPB via attenuation of atrogenes, that is, atrophy-related genes involved in muscle protein catabolism [245]. Recent studies have analyzed the effects of PA supplementation in combination with RT on muscle mass and strength. By adding this supplement (750 mg/day) to an RT program, benefits were detected on muscle strength and mass in comparison with a placebo group in resistance-trained subjects [246, 247]. However, other authors have reported no further gains in muscle mass or strength associated with PA supplementation (250–750 mg/day) [244, 248].

Although PA has demonstrated anabolic properties, its benefits for muscle mass or strength have not been consistently proven in humans (Table 2).

Arginine

Arginine is a widely used amino acid in both a clinical and sports setting [249] that can be synthesized endogenously from glutamine, glutamate, and proline. However, it has been defined as a semi-EAA, as in situations in which its levels are low its synthesis ratio is not increased endogenously, and its uptake needs to be augmented to maintain homeostasis [250]. Arginine supplementation has been purported to show ergogenic potential through its proposed effects on GH secretion, its involvement in creatine synthesis and its role in increasing $NO^{\cdot}$ [249].

Although intravenous perfusion with this amino acid stimulates GH secretion at rest [251] and during exercise [252], the effects of its oral use remain unclear [253]. Thus, whereas some authors have reported increased GH after a single dose (7 g) of arginine in young men [254], others have found no differences in comparison with the ingestion of a placebo [255–257]. Moreover, acute supplementation with arginine (7 g) has been shown to reduce the GH-response to RT [254, 257].

On the contrary, chronic arginine supplementation seems to offer greater benefits. Higher basal GH levels have been observed following arginine supplementation for 10 days (0.1 mg/kg per day) in young trained subjects [256] and

for 30 days (9 g/day) in postmenopausal women [258]. Although no impacts were observed on muscle mass or strength of 10 days of arginine supplementation and RT [256], both variables were increased in comparison with a placebo group when supplementation was extended to 8 weeks [259]. However, no changes on LBM were found after 45 days of arginine supplementation (2 g/day) in soccer players [260].

Evidence of the effects of arginine supplementation on creatine levels has also been scarce and overall not optimistic, showing mild or no benefits at the level of the brain [261, 262] and as yet unknown effects at the muscle level. Extracellular arginine can also be transported to endothelial cells to form $NO^{\cdot}$ [70], yet no clear relationship has been found between arginine supplementation and $NO^{\cdot}$ levels [70, 263]. Indeed, no changes in markers of $NO^{\cdot}$ production nor muscle strength have been observed after acute arginine supplementation [264].

In summary, although arginine supplementation could have ergogenic potential [249], data regarding its benefits have been inconsistent. In those cases in which improvements in performance have been observed, the inherent physiological mechanisms have not been reported [70, 265]. No somatotropic response, increased $NO^{\cdot}$ or creatine levels are produced in response to acute supplementation with arginine. Some studies show that the chronic ingestion of this amino acid might increase GH levels [256] and maximize strength and muscle mass gains after RT [259], but evidence is still scarce and mixed to support its effectiveness (Table 2).

Supplements with evidence c

Conjugated linoleic acid

Naturally found in meat and dairy products, conjugated linoleic acid (CLA) is a mixture of isomers of essential 18-carbon fatty acids such as linoleic acid. CLA supplementation has been purported to provide benefits on body composition (increased LBM and decreased body fat) through the biological activity of two isomers of linoleic acid: *cis*-9,trans-11 and *trans*-10,*cis*-12 [266]. CLA supplementation (5 g/day) for 7 weeks combined with RT has been noted to increase muscle mass and strength and reduce markers of protein catabolism over RT alone in young subjects [267]. Augmented muscle mass and strength have been also reported in elderly subjects, but the supplement was combined with CM so these benefits cannot be solely attributed to CLA alone [268]. Other authors found no additional benefits on body composition, strength, or general markers of catabolism when adding CLA supplementation (6 g/day) to a RT program [269]. The anti-inflammatory effects of CLA are a matter of debate. In healthy young adults, CLA (3 g/day) for 12 weeks decreased and increased levels of pro- and anti-inflammatory cytokines, respectively [270]. However, in older adults, CLA (6 g/day during 6 months in combination with exercise and CM) showed no effect on other indicators of inflammation [268].

In summary, there is yet no evidence supporting a role of CLA supplementation in increasing muscle mass or strength (Table 3).

Glutamine

Glutamine is the most abundant amino acid in the organism, and its content is especially high in skeletal muscle. Among other functions, glutamine plays a role in immunity and anabolic processes [271]. Although glutamine has been traditionally considered a NEAA, it has now been proposed as a semi-essential nutrient because in catabolic situations such as disease, its synthesis rate is insufficient to meet demands [272]. Glutamine has been mainly used in a clinical setting [273]. Parenteral glutamine supplementation has been reported to improve several clinical outcomes in hospitalized and diseased populations [274–276], including counteraction of the fall in muscle protein synthesis and improvement in nitrogen balance after abdominal surgery [276]. However, evidence regarding the benefits of oral supplementation is scarce.

Oral glutamine (0.5 g/kg) taken over 10 days diminished protein breakdown in patients with Duchenne muscle dystrophy, although it did not provide greater benefits than an isocaloric, isonitrogenated mixture of amino acids [277]. No acute benefits of glutamine supplementation (0.3 g/kg) have been observed in weightlifting performance in resistance-trained subjects [278]. Similarly, no acute or long-term benefits of glutamine supplementation (0.9 g/kg/day) during 6 weeks have been reported in weightlifting performance, muscle mass or protein breakdown in comparison with a placebo intervention [279]. In fact, recent meta-analytical evidence concludes that glutamine supplementation has no effect on athletes' performance, body composition or immune system [280].

In summary, parenteral glutamine supplementation could help to protect immune function and maintain protein synthesis in patients in hyper-catabolic states (e.g., post- trauma or surgery, critical illnesses) [281]. However, there is not enough evidence supporting the hypothesis that oral glutamine supplementation increases muscle mass or strength [282] (Table 3).

Resveratrol

Resveratrol (3,5,4′-trihydroxy-*trans*-stilbene), a natural polyphenol present mainly in peanuts, pines, grape skin, red wine

and mulberries, has been associated with a number of health benefits in animal models [283, 284] and humans [285]. Resveratrol has several therapeutic properties, including anti-inflammatory, anti-atherosclerotic, anti-tumor, cardioprotective, anti-diabetic and antioxidant effects [286]. Resveratrol is a sirtuin-1 activator, the latter being related to an increased proliferation of skeletal muscle precursor cells [287]. Moreover, resveratrol has been reported to enhance the recovery of muscle mass after a period of disuse in animal models [288]. However, supplementation with resveratrol did not prevent the loss of muscle mass associated with ageing [289] or with hind limb suspension in mice [288]. Further, old resveratrol-treated male mice showed a blunted hypertrophic response to a 6-week overload stimulus, and this supplement was associated with a lower satellite cell density [290]. Few studies have examined the role of resveratrol in human subjects. It was recently reported that the combination of resveratrol supplementation (500 mg/day) with physical exercise during 12 weeks improved indices of mitochondrial density, mean fiber area and total myonuclei and muscle function in elderly subjects [291]. Yet, although resveratrol supplementation has been described as a potential strategy to improve some of the main hallmarks of sarcopenia, its beneficial effects on muscle mass and strength have not been consistently proven in animal or human models (Table 3).

Ursolic acid

Ursolic acid (3b-hydroxy-12-urs-12-en-28-oic acid, UA) is a natural pentacyclic triterpenoid carboxylic acid found in plants and fruits such as apples. UA has anti-inflammatory, antioxidant, anticarcinogenic, thermogenic and anti-obesity properties [292]. It has also been attributed anabolic effects [293]. A systematic review including animal studies concluded that UA supplementation might enhance physical fitness (strength and aerobic capacity) due to an increase in muscle sirtuin 1 expression and new muscle satellite cell generation, as well as promote muscle mass gains due to an increase in serum GH and IGF-1 secretion and activation of the skeletal muscle mTOR pathway [292]. UA supplementation has been reported to increase skeletal muscle and strength in a mouse model [294]. However, its hypertrophic effects in humans are less clear. For instance, supplementation with UA (50 mg/day provided through the intake of 500 mg of loquat leaf extract) did not improve muscle strength and mass in comparison with the intake of a placebo in healthy adults [295]. Further, in resistance-trained men, UA (3 g) did not modify activation of anabolic signaling pathways following a single bout of RT [296]. The combination of UA supplementation (450 mg/day) and RT during an 8-week period increased muscle strength and IGF-1 levels in comparison with RT alone, although the authors observed no substantial gains in LBM [297].

In summary, although supplementation with UA may have anabolic effects, these effects have not been consistently confirmed in humans (Table 3).

Tribulus terrestris

Tribulus terrestris is a widely used plant in traditional Chinese and Indian medicine. Supplements containing this ingredient have gained popularity among athletes seeking to gain muscle mass due to its purported effects on testosterone [298]. However, the beneficial impacts of this plant on testosterone levels have not been consistently proven [298]. Thus, in response to long-term supplementation with *tribulus terrestris* alone or combined with physical training, no effects were observed on androgens or anabolic hormones (i.e., testosterone, dihydrotestosterone, luteinizing hormone, IGF-1, and androstenedione) in young men [299, 300]. Moreover, *tribulus terrestris* supplementation provided no benefits over a placebo intervention for body composition or strength when combined with RT [300–302]. In contrast, supplementation with 750 mg/day for 3 months increased free and total testosterone levels in subjects with age-related partial androgen deficiency [303]. This supplement in combination with training has been reported to reduce IGF binding protein-3 levels, which could enhance IGF-1 bioactivity, as well as increase muscle power and reduce post-exercise creatine kinase levels [300].

Tribulus terrestris seems not to increase androgen levels in healthy subjects, although it could be effective in those with androgen deficiency. Moreover, there is no evidence about its benefits on muscle mass, and results regarding its effects on strength or power have been scarce and mixed. It has been proposed that the benefits of *tribulus terrestris* supplementation could be affected by saponin levels in the supplement, which depends on the geographical region and on the part of the plant analyzed [300]. Overall, there is currently insufficient evidence to support the effectiveness of *tribulus terrestris* supplementation [298] (Table 3).

Supplements with evidence D

α-Ketoglutarate

Supplementation with α-ketoglutarate (AKG), a precursor of L-arginine and L-glutamine, has been proposed as treatment against sarcopenia [304] and is commonly used to improve body composition in athletes. Theoretically, AKG supplementation could offer similar benefits as those obtained with L-arginine and glutamine supplementation, including augmented protein synthesis. AKG activates the mTOR signaling pathway and induces protein synthesis in cell cultures [305, 306]. Increased muscle mass and fiber mean cross

sectional area have been observed in mice following long-term AKG supplementation [306]. However, the evidence in the clinical setting has been scarce and mixed. Thus, whereas AKG administration reduced plasma urea levels and improved protein metabolism in dialysis patients [307], its addition to enteral nutrition did not improve the nitrogen balance in patients who had undergone abdominal surgery [308].

AKG is also administered in combination with ornithine (OAKG), especially to regulate the nutritional state of malnourished patients [309]. OAKG supplementation has been reported to reduce cancer-related protein breakdown in rats [310]. The combination of AKG with arginine has also been proposed as beneficial, as in response to its intake over 8 weeks in combination with RT, maximized strength and power gains were observed [311]. However, other authors have noted no benefits of OAKG supplementation on muscle performance [312].

In summary, there is no enough evidence that AKG alone or in combination with other supplements acts as an anabolic or ergogenic stimulus in humans. Nevertheless, as with other amino acids, its intake could be potentially beneficial to regulate protein metabolism in malnourished patients or in catabolic states. Although this supplement is safe overall [311], some authors have reported some cardiovascular adverse effects after AKG intake in young subjects (tachycardia, palpitations, headache and even syncope), possibly due to its vasodilatory effects [313]. Nevertheless, a direct, cause-effect relationship between AKG supplementation and the aforementioned adverse effects remain to be elucidated (Table 3).

Ornithine

Ornithine can be synthesized endogenously from other amino acids such as L-arginine, and has been reported to activate anabolic signaling pathways in vitro and in animal models [314, 315]. Similarly to L-arginine, its intravenous perfusion elicits a marked somatotropic response [316]. However, benefits have also been observed for its oral ingestion. Thus, acute oral ornithine supplementation (especially with doses greater than 0.1 g/kg) has been described to increase the GH-response to RT both in untrained subjects [317] and body-builders [318]. Nevertheless, to our knowledge there is no evidence for any long-standing effects on muscle mass or strength (Table 3).

Conclusion

A great variety of supplements have been purported to provide benefits for strength and muscle mass. However, of all the supplements analyzed, only nitrate and caffeine seem to consistently lead to acute muscle strength gains. When taken over longer periods, only creatine, protein and PUFAs have provided strong evidence supporting their capacity to improve or preserve muscle mass or strength. Nevertheless, their effects could depend on doses (e.g., a linear relationship between protein intake and LBM gains has been observed up to a maximum of 1.6 g/kg/day), type (e.g., not all protein or creatine supplements forms [WP versus other forms of protein, or CM versus other forms of creatine] provide the same benefits), and on the individual's physiological status (e.g., higher protein doses are required in elderly people or athletes) (Table 1). Despite their popularity, most of the supplements available on the market lack scientific support for their alleged effects and some have even proved ineffective or have been found to give rise to serious adverse effects. Although some supplements have shown promising results in the basic research field, their effects in humans have not been consistently analyzed in the scientific literature (Tables 2 and 3). These findings could have important economic and practical implications, as the use of supplements should be avoided until there is sufficient scientifically backed evidence of their benefits. There is a clear need for studies designed to examine the effectiveness of supplements in terms of improving muscle mass and strength gains in healthy subjects or attenuating muscle wasting during catabolic states such as those produced in situations of ageing, injury or inactivity.

Acknowledgements PLV is supported by University of Alcalá (FPI2016); JSM is supported by Spanish Ministry of Education, Culture and Sport (FPU14/03435); HPG is supported by Universidad Europea de Madrid (2017/UEM05) and Cátedra Real Madrid–Universidad Europea (2017/RM03); AL is supported by Spanish Ministry of Economy and Competitiveness and Fondos FEDER (PI15/00558).

Author contributions All authors have contributed significantly to the work: HPG and EE conceived the original idea; JSM and PLV wrote the initial draft; HP-G, EE and AL reviewed the draft and contributed to the final version of the manuscript. All authors (PLV, JSM, EE, HP-G and AL) have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

References

1. McGuigan MR, Wright GA, Fleck SJ (2012) Strength training for athletes: does it really help sports performance? Int J Sports Physiol Perform 7(1):2–5. https://doi.org/10.1123/ijspp.7.1.2
2. Spahillari A, Mukamal KJ, DeFilippi C, Kizer JR, Gottdiener JS, Djoussé L, Lyles MF, Bartz TM, Murthy VL, Shah RV (2016) The association of lean and fat mass with all-cause mortality in older adults: the cardiovascular health study.

Nutr Metab Cardiovasc Dis 26(11):1039–1047. https://doi.org/10.1016/j.numecd.2016.06.011
3. Volaklis KA, Halle M, Meisinger C (2015) Muscular strength as a strong predictor of mortality: a narrative review. Eur J Intern Med 26(5):303–310. https://doi.org/10.1016/j.ejim.2015.04.013
4. Egan B, Zierath JR (2013) Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab 17(2):162–184. https://doi.org/10.1016/j.cmet.2012.12.012. (S1550-4131(12)00503-7 [pii])
5. Millward DJ, Garlick PJ, Stewart RJ, Nnanyelugo DO, Waterlow JC (1975) Skeletal-muscle growth and protein turnover. Biochem J 150(2):235–243
6. Phillips SM (2014) A brief review of higher dietary protein diets in weight loss: a focus on athletes. Sports Med 44(Suppl 2):S149–S153. https://doi.org/10.1007/s40279-014-0254-y
7. Cermak NM, Res PT, de Groot LC, Saris WH, van Loon LJ (2012) Protein supplementation augments the adaptive response of skeletal muscle to resistance-type exercise training: a meta-analysis. Am J Clin Nutr 96(6):1454–1464. https://doi.org/10.3945/ajcn.112.037556
8. Naderi A, de Oliveira EP, Ziegenfuss TN, Willems MT (2016) Timing, optimal dose and intake duration of dietary supplements with evidence-based use in sports nutrition. J Exerc Nutr Biochem 20(4):1–12. https://doi.org/10.20463/jenb.2016.0031
9. Ronis MJJ, Pedersen KB, Watt J (2018) Adverse Effects of Nutraceuticals and Dietary Supplements. Annu Rev Pharmacol Toxicol 58:583–601. https://doi.org/10.1146/annurev-pharmtox-010617-052844
10. Knapik JJ, Steelman RA, Hoedebecke SS, Austin KG, Farina EK, Lieberman HR (2016) Prevalence of dietary supplement use by athletes: systematic review and meta-analysis. Sports Med 46(1):103–123. https://doi.org/10.1007/s40279-015-0387-7
11. Wardenaar FC, Ceelen IJ, Van Dijk JW, Hangelbroek RW, Van Roy L, Van der Pouw B, De Vries JH, Mensink M, Witkamp RF (2017) Nutritional supplement use by dutch elite and sub-elite athletes: does receiving dietary counseling make a difference? Int J Sport Nutr Exerc Metab 27(1):32–42. https://doi.org/10.1123/ijsnem.2016-0157
12. Nissen SL, Sharp RL (2003) Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. J Appl Physiol (1985) 94(2):651–659. https://doi.org/10.1152/japplphysiol.00755.2002
13. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, Reginster JY, Chapurlat R, Chan DC, Bruyère O, Rizzoli R, Cooper C, Dennison EM, Group I-ESW (2017) Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int 28 (6):1817–1833. https://doi.org/10.1007/s00198-017-3980-9
14. Kerksick CM, Wilborn CD, Roberts MD, Smith-Ryan A, Kleiner SM, Jäger R, Collins R, Cooke M, Davis JN, Galvan E, Greenwood M, Lowery LM, Wildman R, Antonio J, Kreider RB (2018) ISSN exercise and sports nutrition review update: research & recommendations. J Int Soc Sports Nutr 15(1):38. https://doi.org/10.1186/s12970-018-0242-y
15. Goldman A, Basaria S (2017) Adverse health effects of androgen use. Mol Cell Endocrinol https://doi.org/10.1016/j.mce.2017.06.009
16. Thomas DT, Erdman KA, Burke LM (2016) American College of Sports Medicine Joint Position Statement. Nutrition and athletic performance. Med Sci Sports Exerc 48(3):543–568. https://doi.org/10.1249/MSS.0000000000000852
17. Davis JK, Green JM (2009) Caffeine and anaerobic performance: ergogenic value and mechanisms of action. Sports Med 39(10):813–832. https://doi.org/10.2165/11317770-000000000-00000
18. Ganio MS, Klau JF, Casa DJ, Armstrong LE, Maresh CM (2009) Effect of caffeine on sport-specific endurance performance: a systematic review. J Strength Cond Res 23(1):315–324. https://doi.org/10.1519/JSC.0b013e31818b979a
19. Burke LM (2008) Caffeine and sports performance. Appl Physiol Nutr Metab 33(6):1319–1334. https://doi.org/10.1139/H08-130
20. Spriet LL (2014) Exercise and sport performance with low doses of caffeine. Sports Med 44 (Suppl 2):S175–S184. https://doi.org/10.1007/s40279-014-0257-8
21. Grgic J, Mikulic P, Schoenfeld BJ, Bishop DJ, Pedisic Z (2018) The influence of caffeine supplementation on resistance exercise: a review. Sports Med. https://doi.org/10.1007/s40279-018-0997-y
22. Warren GL, Park ND, Maresca RD, McKibans KI, Millard-Stafford ML (2010) Effect of caffeine ingestion on muscular strength and endurance: a meta-analysis. Med Sci Sports Exerc 42(7):1375–1387. https://doi.org/10.1249/MSS.0b013e3181cabbd8
23. Duncan MJ, Oxford SW (2011) The effect of caffeine ingestion on mood state and bench press performance to failure. J Strength Cond Res 25(1):178–185. https://doi.org/10.1519/JSC.0b013e318201bddb
24. Duncan MJ, Smith M, Cook K, James RS (2012) The acute effect of a caffeine-containing energy drink on mood state, readiness to invest effort, and resistance exercise to failure. J Strength Cond Res 26(10):2858–2865. https://doi.org/10.1519/JSC.0b013e318241e124
25. Jacobs I, Pasternak H, Bell DG (2003) Effects of ephedrine, caffeine, and their combination on muscular endurance. Med Sci Sports Exerc 35(6):987–994. https://doi.org/10.1249/01.MSS.0000069916.49903.70
26. Williams AD, Cribb PJ, Cooke MB, Hayes A (2008) The effect of ephedra and caffeine on maximal strength and power in resistance-trained athletes. J Strength Cond Res 22(2):464–470. https://doi.org/10.1519/JSC.0b013e3181660320
27. Astorino TA, Martin BJ, Schachtsiek L, Wong K, Ng K (2011) Minimal effect of acute caffeine ingestion on intense resistance training performance. J Strength Cond Res 25(6):1752–1758. https://doi.org/10.1519/JSC.0b013e3181ddf6db
28. Green JM, Wickwire PJ, McLester JR, Gendle S, Hudson G, Pritchett RC, Laurent CM (2007) Effects of caffeine on repetitions to failure and ratings of perceived exertion during resistance training. Int J Sports Physiol Perform 2(3):250–259
29. Goldstein E, Jacobs PL, Whitehurst M, Penhollow T, Antonio J (2010) Caffeine enhances upper body strength in resistance-trained women. J Int Soc Sports Nutr 7:18. https://doi.org/10.1186/1550-2783-7-18
30. Grgic J, Trexler ET, Lazinica B, Pedisic Z (2018) Effects of caffeine intake on muscle strength and power: a systematic review and meta-analysis. J Int Soc Sports Nutr 15:11. https://doi.org/10.1186/s12970-018-0216-0
31. Maughan RJ, Burke LM, Dvorak J, Larson-Meyer DE, Peeling P, Phillips SM, Rawson ES, Walsh NP, Garthe I, Geyer H, Meeusen R, van Loon LJC, Shirreffs SM, Spriet LL, Stuart M, Vernec A, Currell K, Ali VM, Budgett RG, Ljungqvist A, Mountjoy M, Pitsiladis YP, Soligard T, Erdener U, Engebretsen L (2018) IOC consensus statement: dietary supplements and the high-performance athlete. Br J Sports Med 52(7):439–455. https://doi.org/10.1136/bjsports-2018-099027
32. Graham TE (2001) Caffeine and exercise: metabolism, endurance and performance. Sports Med 31(11):785–807. https://doi.org/10.2165/00007256-200131110-00002
33. Trexler ET, Smith-Ryan AE, Roelofs EJ, Hirsch KR, Mock MG (2016) Effects of coffee and caffeine anhydrous on strength and sprint performance. Eur J Sport Sci 16(6):702–710. https://doi.org/10.1080/17461391.2015.1085097

34. Wyss M, Kaddurah-Daouk R (2000) Creatine and creatinine metabolism. Physiol Rev 80(3):1107–1213
35. Walker JB (1979) Creatine: biosynthesis, regulation, and function. Adv Enzymol Relat Areas Mol Biol 50:177–242
36. Balsom PD, Söderlund K, Ekblom B (1994) Creatine in humans with special reference to creatine supplementation. Sports Med 18(4):268–280
37. Buford TW, Kreider RB, Stout JR, Greenwood M, Campbell B, Spano M, Ziegenfuss T, Lopez H, Landis J, Antonio J (2007) International Society of sports nutrition position stand: creatine supplementation and exercise. J Int Soc Sports Nutr 4:6. https://doi.org/10.1186/1550-2783-4-6
38. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, Candow DG, Kleiner SM, Almada AL, Lopez HL (2017) International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr 14:18. https://doi.org/10.1186/s12970-017-0173-z
39. Spillane M, Schoch R, Cooke M, Harvey T, Greenwood M, Kreider R, Willoughby DS (2009) The effects of creatine ethyl ester supplementation combined with heavy resistance training on body composition, muscle performance, and serum and muscle creatine levels. J Int Soc Sports Nutr 6:6. https://doi.org/10.1186/1550-2783-6-6
40. Gill ND, Hall RD, Blazevich AJ (2004) Creatine serum is not as effective as creatine powder for improving cycle sprint performance in competitive male team-sport athletes. J Strength Cond Res 18(2):272–275. https://doi.org/10.1519/R-13193.1
41. Jagim AR, Oliver JM, Sanchez A, Galvan E, Fluckey J, Riechman S, Greenwood M, Kelly K, Meininger C, Rasmussen C, Kreider RB (2012) A buffered form of creatine does not promote greater changes in muscle creatine content, body composition, or training adaptations than creatine monohydrate. J Int Soc Sports Nutr 9(1):43. https://doi.org/10.1186/1550-2783-9-43
42. Gualano B, Artioli GG, Poortmans JR, Lancha Junior AH (2010) Exploring the therapeutic role of creatine supplementation. Amino Acids 38(1):31–44. https://doi.org/10.1007/s00726-009-0263-6
43. Deane CS, Wilkinson DJ, Phillips BE, Smith K, Etheridge T, Atherton PJ (2017) "Nutraceuticals" in relation to human skeletal muscle and exercise. Am J Physiol Endocrinol Metab 312(4):E282–E299. https://doi.org/10.1152/ajpendo.00230.2016
44. Lanhers C, Pereira B, Naughton G, Trousselard M, Lesage FX, Dutheil F (2015) Creatine supplementation and lower limb strength performance: a systematic review and meta-analyses. Sports Med 45(9):1285–1294. https://doi.org/10.1007/s40279-015-0337-4
45. Lanhers C, Pereira B, Naughton G, Trousselard M, Lesage FX, Dutheil F (2017) Creatine supplementation and upper limb strength performance: a systematic review and meta-analysis. Sports Med 47(1):163–173. https://doi.org/10.1007/s40279-016-0571-4
46. Johnston AP, Burke DG, MacNeil LG, Candow DG (2009) Effect of creatine supplementation during cast-induced immobilization on the preservation of muscle mass, strength, and endurance. J Strength Cond Res 23(1):116–120
47. Hespel P, Op't Eijnde B, Van Leemputte M, Ursø B, Greenhaff PL, Labarque V, Dymarkowski S, Van Hecke P, Richter EA (2001) Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. J Physiol 536(Pt 2):625–633
48. Burke DG, Candow DG, Chilibeck PD, MacNeil LG, Roy BD, Tarnopolsky MA, Ziegenfuss T (2008) Effect of creatine supplementation and resistance-exercise training on muscle insulin-like growth factor in young adults. Int J Sport Nutr Exerc Metab 18(4):389–398
49. Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, Santos-Lozano A, Fiuza-Luces C, Moran M, Emanuele E, Joyner MJ, Lucia A (2015) Exercise attenuates the major hallmarks of aging. Rejuvenation Res 18(1):57–89. https://doi.org/10.1089/rej.2014.1623
50. Lobo DM, Tritto AC, da Silva LR, de Oliveira PB, Benatti FB, Roschel H, Nieß B, Gualano B, Pereira RM (2015) Effects of long-term low-dose dietary creatine supplementation in older women. Exp Gerontol 70:97–104. https://doi.org/10.1016/j.exger.2015.07.012
51. Cooper R, Naclerio F, Allgrove J, Jimenez A (2012) Creatine supplementation with specific view to exercise/sports performance: an update. J Int Soc Sports Nutr 9(1):33. https://doi.org/10.1186/1550-2783-9-33
52. Antonio J, Ciccone V (2013) The effects of pre versus post workout supplementation of creatine monohydrate on body composition and strength. J Int Soc Sports Nutr 10:36. https://doi.org/10.1186/1550-2783-10-36
53. Candow DG, Zello GA, Ling B, Farthing JP, Chilibeck PD, McLeod K, Harris J, Johnson S (2014) Comparison of creatine supplementation before versus after supervised resistance training in healthy older adults. Res Sports Med 22(1):61–74. https://doi.org/10.1080/15438627.2013.852088
54. Candow DG, Vogt E, Johannsmeyer S, Forbes SC, Farthing JP (2015) Strategic creatine supplementation and resistance training in healthy older adults. Appl Physiol Nutr Metab 40 (7):689–694. https://doi.org/10.1139/apnm-2014-0498
55. Gualano B, Roschel H, Lancha AH, Brightbill CE, Rawson ES (2012) In sickness and in health: the widespread application of creatine supplementation. Amino Acids 43(2):519–529. https://doi.org/10.1007/s00726-011-1132-7
56. Kley RA, Tarnopolsky MA, Vorgerd M (2008) Creatine treatment in muscle disorders: a meta-analysis of randomised controlled trials. J Neurol Neurosurg Psychiatry 79(4):366–367. https://doi.org/10.1136/jnnp.2007.127571
57. Candow DG, Chilibeck PD, Forbes SC (2014) Creatine supplementation and aging musculoskeletal health. Endocrine 45(3):354–361. https://doi.org/10.1007/s12020-013-0070-4
58. Moon A, Heywood L, Rutherford S, Cobbold C (2013) Creatine supplementation: can it improve quality of life in the elderly without associated resistance training? Curr Aging Sci 6(3):251–257
59. Cañete S, San Juan AF, Pérez M, Gómez-Gallego F, López-Mojares LM, Earnest CP, Fleck SJ, Lucia A (2006) Does creatine supplementation improve functional capacity in elderly women? J Strength Cond Res 20(1):22–28. https://doi.org/10.1519/R-17044.1
60. Gotshalk LA, Volek JS, Staron RS, Denegar CR, Hagerman FC, Kraemer WJ (2002) Creatine supplementation improves muscular performance in older men. Med Sci Sports Exerc 34(3):537–543
61. Pritchard NR, Kalra PA (1998) Renal dysfunction accompanying oral creatine supplements. Lancet 351(9111):1252–1253
62. Anderson JE (2000) A role for nitric oxide in muscle repair: nitric oxide-mediated activation of muscle satellite cells. Mol Biol Cell 11(5):1859–1874. https://doi.org/10.1091/mbc.11.5.1859
63. Smith LW, Smith JD, Criswell DS (2002) Involvement of nitric oxide synthase in skeletal muscle adaptation to chronic overload. J Appl Physiol 92(5):2005–2011. https://doi.org/10.1152/japplphysiol.00950.2001
64. Stamler JS, Meissner G (2001) Physiology of nitric oxide in skeletal muscle. Physiol Rev 81(1):209–237
65. Lundberg JO, Govoni M (2004) Inorganic nitrate is a possible source for systemic generation of nitric oxide. Free Radic Biol Med 37(3):395–400. https://doi.org/10.1016/j.freeradbiomed.2004.04.027

66. Jonvik KL, Nyakayiru J, van Dijk JW, Wardenaar FC, van Loon LJ, Verdijk LB (2017) Habitual dietary nitrate intake in highly trained athletes. Int J Sport Nutr Exerc Metab 27(2):148–157. https://doi.org/10.1123/ijsnem.2016-0239
67. Hoon MW, Jones AM, Johnson NA, Blackwell JR, Broad EM, Lundy B, Rice AJ, Burke LM (2014) The effect of variable doses of inorganic nitrate-rich beetroot juice on simulated 2,000-m rowing performance in trained athletes. Int J Sports Physiol Perform 9(4):615–620. https://doi.org/10.1123/ijspp.2013-0207
68. Peeling P, Cox GR, Bullock N, Burke LM (2015) Beetroot juice improves on-water 500 m time-trial performance, and laboratory-based paddling economy in national and international-level kayak athletes. Int J Sport Nutr Exerc Metab 25(3):278–284. https://doi.org/10.1123/ijsnem.2014-0110
69. Clements WT, Lee SR, Bloomer RJ (2014) Nitrate ingestion: a review of the health and physical performance effects. Nutrients 6(11):5224–5264. https://doi.org/10.3390/nu6115224
70. Bescós R, Sureda A, Tur JA, Pons A (2012) The effect of nitric-oxide-related supplements on human performance. Sports Med 42(2):99–117. https://doi.org/10.2165/11596860-000000000-00000
71. Fulford J, Winyard PG, Vanhatalo A, Bailey SJ, Blackwell JR, Jones AM (2013) Influence of dietary nitrate supplementation on human skeletal muscle metabolism and force production during maximum voluntary contractions. Pflugers Archiv Eur J Physiol 465(4):517–528. https://doi.org/10.1007/s00424-013-1220-5
72. Bailey SJ, Fulford J, Vanhatalo A, Winyard PG, Blackwell JR, DiMenna FJ, Wilkerson DP, Benjamin N, Jones AM (2010) Dietary nitrate supplementation enhances muscle contractile efficiency during knee-extensor exercise in humans. J Appl Physiol 109(1):135–148. https://doi.org/10.1152/japplphysiol.00046.2010
73. Mosher SL, Sparks SA, Williams EL, Bentley DJ, Mc Naughton LR (2016) Ingestion of a nitric oxide enhancing supplement improves resistance exercise performance. J Strength Cond Res 30(12):3520–3524. https://doi.org/10.1519/JSC.0000000000001437
74. Hoon MW, Fornusek C, Chapman PG, Johnson NA (2015) The effect of nitrate supplementation on muscle contraction in healthy adults. Eur J Sport Sci 15(8):712–719. https://doi.org/10.1080/17461391.2015.1053418
75. Schoenfeld BJ, Ogborn D, Krieger JW (2017) Dose-response relationship between weekly resistance training volume and increases in muscle mass: a systematic review and meta-analysis. J Sports Sci 35(11):1073–1082. https://doi.org/10.1080/02640414.2016.1210197
76. Bryan NS, Alexander DD, Coughlin JR, Milkowski AL, Boffetta P (2012) Ingested nitrate and nitrite and stomach cancer risk: an updated review. Food Chem Toxicol 50(10):3646–3665. https://doi.org/10.1016/j.fct.2012.07.062
77. Schoenfeld BJ, Aragon AA, Krieger JW (2013) The effect of protein timing on muscle strength and hypertrophy: a meta-analysis. J Int Soc Sports Nutr 10(1):53. https://doi.org/10.1186/1550-2783-10-53
78. Tang JE, Moore DR, Kujbida GW, Tarnopolsky MA, Phillips SM (2009) Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein synthesis at rest and following resistance exercise in young men. J Appl Physiol 107(3):987–992. https://doi.org/10.1152/japplphysiol.00076.2009
79. Morton RW, Murphy KT, McKellar SR, Schoenfeld BJ, Henselmans M, Helms E, Aragon AA, Devries MC, Banfield L, Krieger JW, Phillips SM (2017) A systematic review, meta-analysis and meta-regression of the effect of protein supplementation on resistance training-induced gains in muscle mass and strength in healthy adults. Br J Sports Med. https://doi.org/10.1136/bjsports-2017-097608
80. Xu ZR, Tan ZJ, Zhang Q, Gui QF, Yang YM (2014) Clinical effectiveness of protein and amino acid supplementation on building muscle mass in elderly people: a meta-analysis. PLoS One 9(9):e109141. https://doi.org/10.1371/journal.pone.0109141
81. Finger D, Goltz FR, Umpierre D, Meyer E, Rosa LH, Schneider CD (2015) Effects of protein supplementation in older adults undergoing resistance training: a systematic review and meta-analysis. Sports Med 45(2):245–255. https://doi.org/10.1007/s40279-014-0269-4
82. Thomas DK, Quinn MA, Saunders DH, Greig CA (2016) Protein supplementation does not significantly augment the effects of resistance exercise training in older adults: a systematic review. J Am Med Dir Assoc 17(10):959.e951–959.e959. https://doi.org/10.1016/j.jamda.2016.07.002
83. Gillen JB, Trommelen J, Wardenaar FC, Brinkmans NY, Versteegen JJ, Jonvik KL, Kapp C, de Vries J, van den Borne JJ, Gibala MJ, van Loon LJ (2017) Dietary protein intake and distribution patterns of well-trained dutch athletes. Int J Sport Nutr Exerc Metab 27(2):105–114. https://doi.org/10.1123/ijsnem.2016-0154
84. Phillips SM, Moore DR, Tang JE (2007) A critical examination of dietary protein requirements, benefits, and excesses in athletes. Int J Sport Nutr Exerc Metab 17 Suppl:S58-76
85. Areta JL, Burke LM, Ross ML, Camera DM, West DW, Broad EM, Jeacocke NA, Moore DR, Stellingwerff T, Phillips SM, Hawley JA, Coffey VG (2013) Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. J Physiol 591(9):2319–2331. https://doi.org/10.1113/jphysiol.2012.244897
86. Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, Layman DK, Paddon-Jones D (2014) Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. J Nutr 144(6):876–880. https://doi.org/10.3945/jn.113.185280
87. Stark M, Lukaszuk J, Prawitz A, Salacinski A (2012) Protein timing and its effects on muscular hypertrophy and strength in individuals engaged in weight-training. J Int Soc Sports Nutr 9(1):54. https://doi.org/10.1186/1550-2783-9-54
88. Yang Y, Churchward-Venne TA, Burd NA, Breen L, Tarnopolsky MA, Phillips SM (2012) Myofibrillar protein synthesis following ingestion of soy protein isolate at rest and after resistance exercise in elderly men. Nutr Metab (Lond) 9(1):57. https://doi.org/10.1186/1743-7075-9-57
89. Burd NA, Yang Y, Moore DR, Tang JE, Tarnopolsky MA, Phillips SM (2012) 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(6):958–962. https://doi.org/10.1017/S0007114511006271
90. Galvan E, Arentson-Lantz E, Lamon S, Paddon-Jones D (2016) Protecting skeletal muscle with protein and amino acid during periods of disuse. Nutrients 8 (7). https://doi.org/10.3390/nu8070404
91. Volek JS, Volk BM, Gómez AL, Kunces LJ, Kupchak BR, Freidenreich DJ, Aristizabal JC, Saenz C, Dunn-Lewis C, Ballard KD, Quann EE, Kawiecki DL, Flanagan SD, Comstock BA, Fragala MS, Earp JE, Fernandez ML, Bruno RS, Ptolemy AS, Kellogg MD, Maresh CM, Kraemer WJ (2013) Whey protein supplementation during resistance training augments lean body mass. J Am Coll Nutr 32(2):122–135. https://doi.org/10.1080/07315724.2013.793580
92. Cribb PJ, Williams AD, Carey MF, Hayes A (2006) The effect of whey isolate and resistance training on strength, body composition, and plasma glutamine. Int J Sport Nutr Exerc Metab 16(5):494–509

93. Demling RH, DeSanti L (2000) Effect of a hypocaloric diet, increased protein intake and resistance training on lean mass gains and fat mass loss in overweight police officers. Ann Nutr Metab 44(1):21–29. doi:12817
94. Candow DG, Burke NC, Smith-Palmer T, Burke DG (2006) Effect of whey and soy protein supplementation combined with resistance training in young adults. Int J Sport Nutr Exerc Metab 16(3):233–244
95. Wilborn CD, Taylor LW, Outlaw J, Williams L, Campbell B, Foster CA, Smith-Ryan A, Urbina S, Hayward S (2013) The effects of pre- and post-exercise whey vs. casein protein consumption on body composition and performance measures in collegiate female athletes. J Sports Sci Med 12(1):74–79
96. Institute-of-Medicine (2005) Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids. National Academies Press, Washington
97. Jäger R, Kerksick CM, Campbell BI, Cribb PJ, Wells SD, Skwiat TM, Purpura M, Ziegenfuss TN, Ferrando AA, Arent SM, Smith-Ryan AE, Stout JR, Arciero PJ, Ormsbee MJ, Taylor LW, Wilborn CD, Kalman DS, Kreider RB, Willoughby DS, Hoffman JR, Krzykowski JL, Antonio J (2017) International society of sports nutrition position stand: protein and exercise. J Int Soc Sports Nutr 14:20. https://doi.org/10.1186/s12970-017-0177-8
98. Volpi E, Mittendorfer B, Rasmussen BB, Wolfe RR (2000) The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. J Clin Endocrinol Metab 85(12):4481–4490. https://doi.org/10.1210/jcem.85.12.7021
99. Moore DR, Churchward-Venne TA, Witard O, Breen L, Burd NA, Tipton KD, Phillips SM (2015) Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. J Gerontol A Biol Sci Med Sci 70(1):57–62. https://doi.org/10.1093/gerona/glu103
100. Antonio J, Ellerbroek A, Silver T, Vargas L, Peacock C (2016) The effects of a high protein diet on indices of health and body composition–a crossover trial in resistance-trained men. J Int Soc Sports Nutr 13:3. https://doi.org/10.1186/s12970-016-0114-2
101. Devries MC, Sithamparapillai A, Brimble KS, Banfield L, Morton RW, Phillips SM (2018) Changes in kidney function do not differ between healthy adults consuming higher- compared with lower- or normal-protein diets: a systematic review and meta-analysis. J Nutr 148(11):1760–1775. https://doi.org/10.1093/jn/nxy197
102. Jeromson S, Gallagher IJ, Galloway SD, Hamilton DL (2015) Omega-3 fatty acids and skeletal muscle health. Mar Drugs 13(11):6977–7004. https://doi.org/10.3390/md13116977
103. Fritsche KL (2008) Too much linoleic acid promotes inflammation-doesn't it? Prostaglandins Leukot Essent Fatty Acids 79(3–5):173–175. https://doi.org/10.1016/j.plefa.2008.09.019
104. D'Antona G, Nabavi SM, Micheletti P, Di Lorenzo A, Aquilani R, Nisoli E, Rondanelli M, Daglia M (2014) Creatine, L-carnitine, and ω3 polyunsaturated fatty acid supplementation from healthy to diseased skeletal muscle. Biomed Res Int 2014:613890. https://doi.org/10.1155/2014/613890
105. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, Mittendorfer B (2011) Omega-3 polyunsaturated fatty acids augment the muscle protein anabolic response to hyperinsulinaemia-hyperaminoacidaemia in healthy young and middle-aged men and women. Clin Sci (Lond) 121(6):267–278. https://doi.org/10.1042/CS20100597
106. Smith GI, Atherton P, Reeds DN, Mohammed BS, Rankin D, Rennie MJ, Mittendorfer B (2011) Dietary omega-3 fatty acid supplementation increases the rate of muscle protein synthesis in older adults: a randomized controlled trial. Am J Clin Nutr 93(2):402–412. https://doi.org/10.3945/ajcn.110.005611
107. Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B (2015) Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. Am J Clin Nutr 102(1):115–122. https://doi.org/10.3945/ajcn.114.105833
108. Rodacki CL, Rodacki AL, Pereira G, Naliwaiko K, Coelho I, Pequito D, Fernandes LC (2012) Fish-oil supplementation enhances the effects of strength training in elderly women. Am J Clin Nutr 95(2):428–436. https://doi.org/10.3945/ajcn.111.021915
109. Edholm P, Strandberg E, Kadi F (2017) Lower limb explosive strength capacity in elderly women: effects of resistance training and healthy diet. J Appl Physiol 123(1):190–196. https://doi.org/10.1152/japplphysiol.00924.2016
110. Ryan AM, Reynolds JV, Healy L, Byrne M, Moore J, Brannelly N, McHugh A, McCormack D, Flood P (2009) Enteral nutrition enriched with eicosapentaenoic acid (EPA) preserves lean body mass following esophageal cancer surgery: results of a double-blinded randomized controlled trial. Ann Surg 249(3):355–363. https://doi.org/10.1097/SLA.0b013e31819a4789
111. Visser M, Pahor M, Taaffe DR, Goodpaster BH, Simonsick EM, Newman AB, Nevitt M, Harris TB (2002) Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. J Gerontol A Biol Sci Med Sci 57(5):M326–M332
112. Kris-Etherton PM, Harris WS, Appel LJ, Committee AHAN (2002) Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation 106(21):2747–2757
113. From the Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition (2008) Interim summary of conclusions and dietary recommendations on total fat and fatty acids. Joint FAO/WHO Expert Consultation on Fats and Fatty Acids in Human Nutrition, Geneva
114. Candow DG, Forbes SC, Little JP, Cornish SM, Pinkoski C, Chilibeck PD (2012) Effect of nutritional interventions and resistance exercise on aging muscle mass and strength. Biogerontology 13(4):345–358. https://doi.org/10.1007/s10522-012-9385-4
115. Rundqvist HC, Esbjörnsson M, Rooyackers O, Österlund T, Moberg M, Apro W, Blomstrand E, Jansson E (2017) Influence of nutrient ingestion on amino acid transporters and protein synthesis in human skeletal muscle after sprint exercise. J Appl Physiol 123(6):1501–1515. https://doi.org/10.1152/japplphysiol.00244.2017
116. Børsheim E, Tipton KD, Wolf SE, Wolfe RR (2002) Essential amino acids and muscle protein recovery from resistance exercise. Am J Physiol Endocrinol Metab 283(4):E648–E657. https://doi.org/10.1152/ajpendo.00466.2001
117. Paddon-Jones D, Sheffield-Moore M, Zhang XJ, Volpi E, Wolf SE, Aarsland A, Ferrando AA, Wolfe RR (2004) Amino acid ingestion improves muscle protein synthesis in the young and elderly. Am J Physiol Endocrinol Metab 286(3):E321–E328. https://doi.org/10.1152/ajpendo.00368.2003
118. Dillon EL, Sheffield-Moore M, Paddon-Jones D, Gilkison C, Sanford AP, Casperson SL, Jiang J, Chinkes DL, Urban RJ (2009) Amino acid supplementation increases lean body mass, basal muscle protein synthesis, and insulin-like growth factor-I expression in older women. J Clin Endocrinol Metab 94(5):1630–1637. https://doi.org/10.1210/jc.2008-1564
119. Wall BT, van Loon LJ (2013) Nutritional strategies to attenuate muscle disuse atrophy. Nutr Rev 71(4):195–208. https://doi.org/10.1111/nure.12019
120. Ferrando AA, Paddon-Jones D, Hays NP, Kortebein P, Ronsen O, Williams RH, McComb A, Symons TB, Wolfe RR, Evans W (2010) EAA supplementation to increase nitrogen intake improves muscle function during bed rest in the elderly. Clin Nutr 29(1):18–23. https://doi.org/10.1016/j.clnu.2009.03.009

121. Shimomura Y, Murakami T, Nakai N, Nagasaki M, Harris RA (2004) Exercise promotes BCAA catabolism: effects of BCAA supplementation on skeletal muscle during exercise. J Nutr 134(6 Suppl):1583S–1587S
122. Holeček M (2018) Branched-chain amino acids in health and disease: metabolism, alterations in blood plasma, and as supplements. Nutr Metab (Lond) 15:33. https://doi.org/10.1186/s12986-018-0271-1
123. Jackman SR, Witard OC, Philp A, Wallis GA, Baar K, Tipton KD (2017) Branched-chain amino acid ingestion stimulates muscle myofibrillar protein synthesis following resistance exercise in humans. Front Physiol 8:390. https://doi.org/10.3389/fphys.2017.00390
124. Kobayashi H, Kato H, Hirabayashi Y, Murakami H, Suzuki H (2006) Modulations of muscle protein metabolism by branched-chain amino acids in normal and muscle-atrophying rats. J Nutr 136(1 Suppl):234S–236S
125. Borgenvik M, Apró W, Blomstrand E (2012) Intake of branched-chain amino acids influences the levels of MAFbx mRNA and MuRF-1 total protein in resting and exercising human muscle. Am J Physiol Endocrinol Metab 302(5):E510–E521. https://doi.org/10.1152/ajpendo.00353.2011
126. Apró W, Blomstrand E (2010) Influence of supplementation with branched-chain amino acids in combination with resistance exercise on p70S6 kinase phosphorylation in resting and exercising human skeletal muscle. Acta Physiol (Oxf) 200(3):237–248. https://doi.org/10.1111/j.1748-1708.2010.02151.x
127. Rahimi MH, Shab-Bidar S, Mollahosseini M, Djafarian K (2017) Branched-chain amino acid supplementation and exercise-induced muscle damage in exercise recovery: a meta-analysis of randomized clinical trials. Nutrition 42:30–36. https://doi.org/10.1016/j.nut.2017.05.005
128. Fouré A, Bendahan D (2017) Is branched-chain amino acids supplementation an efficient nutritional strategy to alleviate skeletal muscle damage? A Systematic Review. Nutrients. https://doi.org/10.3390/nu9101047
129. Atherton PJ, Smith K, Etheridge T, Rankin D, Rennie MJ (2010) Distinct anabolic signalling responses to amino acids in C2C12 skeletal muscle cells. Amino Acids 38(5):1533–1539. https://doi.org/10.1007/s00726-009-0377-x
130. Buse MG, Reid SS (1975) Leucine. A possible regulator of protein turnover in muscle. J Clin Invest 56(5):1250–1261. https://doi.org/10.1172/JCI108201
131. Bratusch-Marrain P, Waldhäusl W (1979) The influence of amino acids and somatostatin on prolactin and growth hormone release in man. Acta Endocrinol (Copenh) 90(3):403–408
132. Anthony JC, Lang CH, Crozier SJ, Anthony TG, MacLean DA, Kimball SR, Jefferson LS (2002) Contribution of insulin to the translational control of protein synthesis in skeletal muscle by leucine. Am J Physiol Endocrinol Metab 282(5):E1092–E1101. https://doi.org/10.1152/ajpendo.00208.2001
133. English KL, Mettler JA, Ellison JB, Mamerow MM, Arentson-Lantz E, Pattarini JM, Ploutz-Snyder R, Sheffield-Moore M, Paddon-Jones D (2016) Leucine partially protects muscle mass and function during bed rest in middle-aged adults. Am J Clin Nutr 103(2):465–473. https://doi.org/10.3945/ajcn.115.112359
134. Devries MC, McGlory C, Bolster DR, Kamil A, Rahn M, Harkness L, Baker SK, Phillips SM (2018) Protein leucine content is a determinant of shorter- and longer-term muscle protein synthetic responses at rest and following resistance exercise in healthy older women: a randomized, controlled trial. Am J Clin Nutr 107(2):217–226. https://doi.org/10.1093/ajcn/nqx028
135. Xu ZR, Tan ZJ, Zhang Q, Gui QF, Yang YM (2015) The effectiveness of leucine on muscle protein synthesis, lean body mass and leg lean mass accretion in older people: a systematic review and meta-analysis. Br J Nutr 113(1):25–34. https://doi.org/10.1017/S0007114514002475
136. Komar B, Schwingshackl L, Hoffmann G (2015) Effects of leucine-rich protein supplements on anthropometric parameter and muscle strength in the elderly: a systematic review and meta-analysis. J Nutr Health Aging 19(4):437–446. https://doi.org/10.1007/s12603-014-0559-4
137. Dickinson JM, Gundermann DM, Walker DK, Reidy PT, Borack MS, Drummond MJ, Arora M, Volpi E, Rasmussen BB (2014) Leucine-enriched amino acid ingestion after resistance exercise prolongs myofibrillar protein synthesis and amino acid transporter expression in older men. J Nutr 144(11):1694–1702. https://doi.org/10.3945/jn.114.198671
138. Ispoglou T, King RF, Polman RC, Zanker C (2011) Daily L-leucine supplementation in novice trainees during a 12-week weight training program. Int J Sports Physiol Perform 6(1):38–50
139. Elango R, Chapman K, Rafii M, Ball RO, Pencharz PB (2012) Determination of the tolerable upper intake level of leucine in acute dietary studies in young men. Am J Clin Nutr 96(4):759–767. https://doi.org/10.3945/ajcn.111.024471
140. Pasiakos SM, McClung JP (2011) Supplemental dietary leucine and the skeletal muscle anabolic response to essential amino acids. Nutr Rev 69(9):550–557. https://doi.org/10.1111/j.1753-4887.2011.00420.x
141. Chen L, Chen Y, Wang X, Li H, Zhang H, Gong J, Shen S, Yin W, Hu H (2015) Efficacy and safety of oral branched-chain amino acid supplementation in patients undergoing interventions for hepatocellular carcinoma: a meta-analysis. Nutr J 14:67. https://doi.org/10.1186/s12937-015-0056-6
142. Sandonà D, Danieli-Betto D, Germinario E, Biral D, Martinello T, Lioy A, Tarricone E, Gastaldello S, Betto R (2005) The T-tubule membrane ATP-operated P2×4 receptor influences contractility of skeletal muscle. FASEB J 19(9):1184–1186. https://doi.org/10.1096/fj.04-3333fje
143. Heinonen I, Kemppainen J, Kaskinoro K, Peltonen JE, Sipilä HT, Nuutila P, Knuuti J, Boushel R, Kalliokoski KK (2012) Effects of adenosine, exercise, and moderate acute hypoxia on energy substrate utilization of human skeletal muscle. Am J Physiol Regul Integr Comp Physiol 302(3):R385–R390. https://doi.org/10.1152/ajpregu.00245.2011
144. Rådegran G, Hellsten Y (2000) Adenosine and nitric oxide in exercise-induced human skeletal muscle vasodilatation. Acta Physiol Scand 168(4):575–591. https://doi.org/10.1046/j.1365-201x.2000.00705.x
145. Nyberg M, Mortensen SP, Thaning P, Saltin B, Hellsten Y (2010) Interstitial and plasma adenosine stimulate nitric oxide and prostacyclin formation in human skeletal muscle. Hypertension 56(6):1102–1108. https://doi.org/10.1161/HYPERTENSIONAHA.110.161521
146. Jäger R, Roberts MD, Lowery RP, Joy JM, Cruthirds CL, Lockwood CM, Rathmacher JA, Purpura M, Wilson JM (2014) Oral adenosine-5′-triphosphate (ATP) administration increases blood flow following exercise in animals and humans. J Int Soc Sports Nutr 11:28. https://doi.org/10.1186/1550-2783-11-28
147. Jordan AN, Jurca R, Abraham EH, Salikhova A, Mann JK, Morss GM, Church TS, Lucia A, Earnest CP (2004) Effects of oral ATP supplementation on anaerobic power and muscular strength. Med Sci Sports Exerc 36(6):983–990
148. Freitas MC, Cholewa JM, Gerosa-Neto J, Gonçalves DC, Caperuto EC, Lira FS, Rossi FE (2017) A single dose of oral atp supplementation improves performance and physiological response during lower body resistance exercise in recreational resistance trained males. J Strength Cond Res. https://doi.org/10.1519/JSC.0000000000002198
149. Purpura M, Rathmacher JA, Sharp MH, Lowery RP, Shields KA, Partl JM, Wilson JM, Jäger R (2017) Oral

Adenosine-5′-triphosphate (ATP) administration increases postexercise ATP levels, muscle excitability, and athletic performance following a repeated sprint bout. J Am Coll Nutr 36(3):177–183. https://doi.org/10.1080/07315724.2016.1246989
150. Rathmacher JA, Fuller JC, Baier SM, Abumrad NN, Angus HF, Sharp RL (2012) Adenosine-5′-triphosphate (ATP) supplementation improves low peak muscle torque and torque fatigue during repeated high intensity exercise sets. J Int Soc Sports Nutr 9(1):48. https://doi.org/10.1186/1550-2783-9-48
151. Wilson JM, Joy JM, Lowery RP, Roberts MD, Lockwood CM, Manninen AH, Fuller JC, De Souza EO, Baier SM, Wilson SM, Rathmacher JA (2013) Effects of oral adenosine-5′-triphosphate supplementation on athletic performance, skeletal muscle hypertrophy and recovery in resistance-trained men. Nutr Metab (Lond) 10(1):57. https://doi.org/10.1186/1743-7075-10-57
152. Coolen EJ, Arts IC, Bekers O, Vervaet C, Bast A, Dagnelie PC (2011) Oral bioavailability of ATP after prolonged administration. Br J Nutr 105(3):357–366. https://doi.org/10.1017/S0007114510003570
153. Rådegran G, Calbet JA (2001) Role of adenosine in exercise-induced human skeletal muscle vasodilatation. Acta Physiol Scand 171(2):177–185. https://doi.org/10.1046/j.1365-201x.2001.00796.x
154. Arts IC, Coolen EJ, Bours MJ, Huyghebaert N, Stuart MA, Bast A, Dagnelie PC (2012) Adenosine 5′-triphosphate (ATP) supplements are not orally bioavailable: a randomized, placebo-controlled cross-over trial in healthy humans. J Int Soc Sports Nutr 9(1):16. https://doi.org/10.1186/1550-2783-9-16
155. Curis E, Nicolis I, Moinard C, Osowska S, Zerrouk N, Bénazeth S, Cynober L (2005) Almost all about citrulline in mammals. Amino acids 29(3):177–205. https://doi.org/10.1007/s00726-005-0235-4
156. Thibault R, Flet L, Vavasseur F, Lemerle M, Ferchaud-Roucher V, Picot D, Darmaun D (2011) Oral citrulline does not affect whole body protein metabolism in healthy human volunteers: results of a prospective, randomized, double-blind, cross-over study. Clin Nutr 30(6):807–811. https://doi.org/10.1016/j.clnu.2011.06.005
157. Bailey SJ, Blackwell JR, Lord T, Vanhatalo A, Winyard PG, Jones AM (2015) l-Citrulline supplementation improves O_2 uptake kinetics and high-intensity exercise performance in humans. J Appl Physiol 119(4):385–395. https://doi.org/10.1152/japplphysiol.00192.2014
158. van Wijck K, Wijnands KA, Meesters DM, Boonen B, van Loon LJ, Buurman WA, Dejong CH, Lenaerts K, Poeze M (2014) L-citrulline improves splanchnic perfusion and reduces gut injury during exercise. Med Sci Sports Exerc 46(11):2039–2046. https://doi.org/10.1249/MSS.0000000000000332
159. Moinard C, Cynober L (2007) Citrulline: a new player in the control of nitrogen homeostasis. J Nutr 137(6 Suppl 2):1621S–1625S. https://doi.org/10.1093/jn/137.6.1621S
160. Ham DJ, Caldow MK, Lynch GS, Koopman R (2014) Arginine protects muscle cells from wasting in vitro in an mTORC1-dependent and NO-independent manner. Amino Acids 46(12):2643–2652. https://doi.org/10.1007/s00726-014-1815-y
161. Bouillanne O, Melchior JC, Faure C, Paul M, Canouï-Poitrine F, Boirie Y, Chevenne D, Forasassi C, Guery E, Herbaud S, Le Corvoisier P, Neveux N, Nivet-Antoine V, Astier A, Raynaud-Simon A, Walrand S, Cynober L, Aussel C (2018) Impact of 3-week citrulline supplementation on postprandial protein metabolism in malnourished older patients: the Ciproage randomized controlled trial. Clin Nutr. https://doi.org/10.1016/j.clnu.2018.02.017
162. Moinard C, Nicolis I, Neveux N, Darquy S, Bénazeth S, Cynober L (2008) Dose-ranging effects of citrulline administration on plasma amino acids and hormonal patterns in healthy subjects: the Citrudose pharmacokinetic study. Br J Nutr 99(4):855–862. https://doi.org/10.1017/S0007114507841110
163. Hickner RC, Tanner CJ, Evans CA, Clark PD, Haddock A, Fortune C, Geddis H, Waugh W, McCammon M (2006) L-citrulline reduces time to exhaustion and insulin response to a graded exercise test. Med Sci Sports Exerc 38(4):660–666. https://doi.org/10.1249/01.mss.0000210197.02576.da
164. Glenn JM, Gray M, Jensen A, Stone MS, Vincenzo JL (2016) Acute citrulline-malate supplementation improves maximal strength and anaerobic power in female, masters athletes tennis players. Eur J Sport Sci 16(8):1095–1103. https://doi.org/10.1080/17461391.2016.1158321
165. Glenn JM, Gray M, Wethington LN, Stone MS, Stewart RW, Moyen NE (2017) Acute citrulline malate supplementation improves upper- and lower-body submaximal weightlifting exercise performance in resistance-trained females. Eur J Nutr 56(2):775–784. https://doi.org/10.1007/s00394-015-1124-6
166. Pérez-Guisado J, Jakeman PM (2010) Citrulline malate enhances athletic anaerobic performance and relieves muscle soreness. J Strength Cond Res 24(5):1215–1222. https://doi.org/10.1519/JSC.0b013e3181cb28e0
167. Wax B, Kavazis AN, Weldon K, Sperlak J (2015) Effects of supplemental citrulline malate ingestion during repeated bouts of lower-body exercise in advanced weightlifters. J Strength Cond Res 29(3):786–792. https://doi.org/10.1519/JSC.0000000000000670
168. Cutrufello PT, Gadomski SJ, Zavorsky GS (2015) The effect of L-citrulline and watermelon juice supplementation on anaerobic and aerobic exercise performance. J Sports Sci 33(14):1459–1466. https://doi.org/10.1080/02640414.2014.990495
169. Hwang P, Morales Marroquín FE, Gann J, Andre T, McKinley-Barnard S, Kim C, Morita M, Willoughby DS (2018) Eight weeks of resistance training in conjunction with glutathione and L-Citrulline supplementation increases lean mass and has no adverse effects on blood clinical safety markers in resistance-trained males. J Int Soc Sports Nutr 15(1):30. https://doi.org/10.1186/s12970-018-0235-x
170. Clarkson PM, Rawson ES (1999) Nutritional supplements to increase muscle mass. Crit Rev Food Sci Nutr 39(4):317–328. https://doi.org/10.1080/10408699991279196
171. Van Koevering M, Nissen S (1992) Oxidation of leucine and alpha-ketoisocaproate to beta-hydroxy-beta-methylbutyrate in vivo. Am J Physiol 262(1 Pt 1):E27–E31
172. Wu H, Xia Y, Jiang J, Du H, Guo X, Liu X, Li C, Huang G, Niu K (2015) Effect of beta-hydroxy-beta-methylbutyrate supplementation on muscle loss in older adults: a systematic review and meta-analysis. Arch Gerontol Geriatr 61(2):168–175. https://doi.org/10.1016/j.archger.2015.06.020
173. Deutz NE, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, Wolfe RR (2013) Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr 32(5):704–712. https://doi.org/10.1016/j.clnu.2013.02.011
174. Vukovich MD, Stubbs NB, Bohlken RM (2001) Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. J Nutr 131(7):2049–2052
175. Rowlands DS, Thomson JS (2009) Effects of beta-hydroxy-beta-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: a meta-analysis. J Strength Cond Res 23(3):836–846. https://doi.org/10.1519/JSC.0b013e3181a00c80
176. Sanchez-Martinez J, Santos-Lozano A, Garcia-Hermoso A, Sadarangani KP, Cristi-Montero C (2018) Effects of beta-hydroxy-beta-methylbutyrate supplementation on strength and body composition in trained and competitive athletes: a

meta-analysis of randomized controlled trials. J Sci Med Sport 21(7):727–735. https://doi.org/10.1016/j.jsams.2017.11.003
177. Townsend JR, Hoffman JR, Gonzalez AM, Jajtner AR, Boone CH, Robinson EH, Mangine GT, Wells AJ, Fragala MS, Fukuda DH, Stout JR (2015) Effects of β-Hydroxy-β-methylbutyrate free acid ingestion and resistance exercise on the acute endocrine response. Int J Endocrinol 2015:856708. https://doi.org/10.1155/2015/856708
178. Teixeira FJ, Matias CN, Monteiro CP, Valamatos MJ, Reis J, Tavares F, Batista A, Domingos C, Alves F, Sardinha LB, Phillips SM (2018) Leucine metabolites do not enhance training-induced performance or muscle thickness. Med Sci Sports Exerc. https://doi.org/10.1249/MSS.0000000000001754
179. Portal S, Zadik Z, Rabinowitz J, Pilz-Burstein R, Adler-Portal D, Meckel Y, Cooper DM, Eliakim A, Nemet D (2011) The effect of HMB supplementation on body composition, fitness, hormonal and inflammatory mediators in elite adolescent volleyball players: a prospective randomized, double-blind, placebo-controlled study. Eur J Appl Physiol 111(9):2261–2269. https://doi.org/10.1007/s00421-011-1855-x
180. Wilson JM, Fitschen PJ, Campbell B, Wilson GJ, Zanchi N, Taylor L, Wilborn C, Kalman DS, Stout JR, Hoffman JR, Ziegenfuss TN, Lopez HL, Kreider RB, Smith-Ryan AE, Antonio J (2013) International society of sports nutrition position stand: beta-hydroxy-beta-methylbutyrate (HMB). J Int Soc Sports Nutr 10(1):6. https://doi.org/10.1186/1550-2783-10-6
181. Wilkinson DJ, Hossain T, Hill DS, Phillips BE, Crossland H, Williams J, Loughna P, Churchward-Venne TA, Breen L, Phillips SM, Etheridge T, Rathmacher JA, Smith K, Szewczyk NJ, Atherton PJ (2013) Effects of leucine and its metabolite β-hydroxy-β-methylbutyrate on human skeletal muscle protein metabolism. J Physiol 591(11):2911–2923. https://doi.org/10.1113/jphysiol.2013.253203
182. Borack MS, Volpi E (2016) Efficacy and safety of leucine supplementation in the elderly. J Nutr 146(12):2625S–2629S. https://doi.org/10.3945/jn.116.230771
183. Lukaski HC (2000) Magnesium, zinc, and chromium nutriture and physical activity. Am J Clin Nutr 72(2 Suppl):585S–593S
184. Ford ES, Mokdad AH (2003) Dietary magnesium intake in a national sample of US adults. J Nutr 133(9):2879–2882
185. de Sousa EF, Da Costa TH, Nogueira JA, Vivaldi LJ (2008) Assessment of nutrient and water intake among adolescents from sports federations in the Federal District, Brazil. Br J Nutr 99(6):1275–1283. https://doi.org/10.1017/S0007114507864841
186. Mertens E, Kuijsten A, Dofková M, Mistura L, D'Addezio L, Turrini A, Dubuisson C, Favret S, Havard S, Trolle E, Van't Veer P, Geleijnse JM (2018) Geographic and socioeconomic diversity of food and nutrient intakes: a comparison of four European countries. Eur J Nutr. https://doi.org/10.1007/s00394-018-1673-6
187. Olza J, Aranceta-Bartrina J, González-Gross M, Ortega RM, Serra-Majem L, Varela-Moreiras G, Gil Á (2017) Reported dietary intake, disparity between the reported consumption and the level needed for adequacy and food sources of calcium, phosphorus, magnesium and vitamin d in the spanish population: findings from the ANIBES study. Nutrients 9 (2). https://doi.org/10.3390/nu9020168
188. Wardenaar F, Brinkmans N, Ceelen I, Van Rooij B, Mensink M, Witkamp R, De Vries J (2017) Micronutrient intakes in 553 Dutch elite and sub-elite athletes: prevalence of low and high intakes in users and non-users of nutritional supplements. Nutrients. https://doi.org/10.3390/nu9020142
189. van Dronkelaar C, van Velzen A, Abdelrazek M, van der Steen A, Weijs PJM, Tieland M (2018) Minerals and sarcopenia; the role of calcium, iron, magnesium, phosphorus, potassium, selenium, sodium, and zinc on muscle mass, muscle strength, and physical performance in older adults: a systematic review. J Am Med Dir Assoc 19(1):6–11.e13. https://doi.org/10.1016/j.jamda.2017.05.026
190. Musso CG (2009) Magnesium metabolism in health and disease. Int Urol Nephrol 41(2):357–362. https://doi.org/10.1007/s11255-009-9548-7
191. Zhang Y, Xun P, Wang R, Mao L, He K (2017) Can magnesium enhance exercise performance?. Nutrients. https://doi.org/10.3390/nu9090946
192. Maggio M, De Vita F, Lauretani F, Nouvenne A, Meschi T, Ticinesi A, Dominguez LJ, Barbagallo M, Dall'aglio E, Ceda GP (2014) The interplay between magnesium and testosterone in modulating physical function in men. Int J Endocrinol 2014:525249. https://doi.org/10.1155/2014/525249
193. Dominguez LJ, Barbagallo M, Lauretani F, Bandinelli S, Bos A, Corsi AM, Simonsick EM, Ferrucci L (2006) Magnesium and muscle performance in older persons: the InCHIANTI study. Am J Clin Nutr 84(2):419–426
194. Scott D, Blizzard L, Fell J, Giles G, Jones G (2010) Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study. J Am Geriatr Soc 58(11):2129–2134. https://doi.org/10.1111/j.1532-5415.2010.03147.x
195. Lukaski HC, Nielsen FH (2002) Dietary magnesium depletion affects metabolic responses during submaximal exercise in postmenopausal women. J Nutr 132(5):930–935
196. Santos DA, Matias CN, Monteiro CP, Silva AM, Rocha PM, Minderico CS, Bettencourt Sardinha L, Laires MJ (2011) Magnesium intake is associated with strength performance in elite basketball, handball and volleyball players. Magnes Res 24(4):215–219. https://doi.org/10.1684/mrh.2011.0290
197. Brilla LR, Haley TF (1992) Effect of magnesium supplementation on strength training in humans. J Am Coll Nutr 11(3):326–329
198. Kass LS, Poeira F (2015) The effect of acute vs chronic magnesium supplementation on exercise and recovery on resistance exercise, blood pressure and total peripheral resistance on normotensive adults. J Int Soc Sports Nutr 12:19. https://doi.org/10.1186/s12970-015-0081-z
199. Newhouse IJ, Finstad EW (2000) The effects of magnesium supplementation on exercise performance. Clin J Sport Med 10(3):195–200
200. Moslehi N, Vafa M, Sarrafzadeh J, Rahimi-Foroushani A (2013) Does magnesium supplementation improve body composition and muscle strength in middle-aged overweight women? A double-blind, placebo-controlled, randomized clinical trial. Biol Trace Elem Res 153(1–3):111–118. https://doi.org/10.1007/s12011-013-9672-1
201. Wang R, Chen C, Liu W, Zhou T, Xun P, He K, Chen P (2017) The effect of magnesium supplementation on muscle fitness: a meta-analysis and systematic review. Magnes Res 30(4):120–132. https://doi.org/10.1684/mrh.2018.0430
202. Vallee BL, Falchuk KH (1993) The biochemical basis of zinc physiology. Physiol Rev 73(1):79–118
203. Prasad AS, Mantzoros CS, Beck FW, Hess JW, Brewer GJ (1996) Zinc status and serum testosterone levels of healthy adults. Nutrition 12(5):344–348
204. Prasad AS (2014) Zinc is an antioxidant and anti-inflammatory agent: its role in human health. Front Nutr 1:14. https://doi.org/10.3389/fnut.2014.00014
205. Van Loan MD, Sutherland B, Lowe NM, Turnlund JR, King JC (1999) The effects of zinc depletion on peak force and total work of knee and shoulder extensor and flexor muscles. Int J Sport Nutr 9(2):125–135
206. Krotkiewski M, Gudmundsson M, Backström P, Mandroukas K (1982) Zinc and muscle strength and

endurance. Acta Physiol Scand 116(3):309–311. https://doi.org/10.1111/j.1748-1716.1982.tb07146.x
207. Ghavami-Maibodi SZ, Collipp PJ, Castro-Magana M, Stewart C, Chen SY (1983) Effect of oral zinc supplements on growth, hormonal levels, and zinc in healthy short children. Ann Nutr Metab 27(3):214–219
208. Neek LS, Gaeini AA, Choobineh S (2011) Effect of zinc and selenium supplementation on serum testosterone and plasma lactate in cyclist after an exhaustive exercise bout. Biol Trace Elem Res 144(1–3):454–462
209. Gunanti IR, Al-Mamun A, Schubert L, Long KZ (2016) The effect of zinc supplementation on body composition and hormone levels related to adiposity among children: a systematic review. Public Health Nutr 19(16):2924–2939. https://doi.org/10.1017/S1368980016001154
210. Vincent JB (1999) Mechanisms of chromium action: low-molecular-weight chromium-binding substance. J Am Coll Nutr 18(1):6–12
211. Hasten DL, Rome EP, Franks BD, Hegsted M (1992) Effects of chromium picolinate on beginning weight training students. Int J Sport Nutr 2(4):343–350
212. Lukaski HC, Bolonchuk WW, Siders WA, Milne DB (1996) Chromium supplementation and resistance training: effects on body composition, strength, and trace element status of men. Am J Clin Nutr 63(6):954–965
213. Volpe SL, Huang HW, Larpadisorn K, Lesser II (2001) Effect of chromium supplementation and exercise on body composition, resting metabolic rate and selected biochemical parameters in moderately obese women following an exercise program. J Am Coll Nutr 20(4):293–306
214. Clancy SP, Clarkson PM, DeCheke ME, Nosaka K, Freedson PS, Cunningham JJ, Valentine B (1994) Effects of chromium picolinate supplementation on body composition, strength, and urinary chromium loss in football players. Int J Sport Nutr 4(2):142–153
215. Campbell WW, Joseph LJ, Davey SL, Cyr-Campbell D, Anderson RA, Evans WJ (1999) Effects of resistance training and chromium picolinate on body composition and skeletal muscle in older men. J Appl Physiol 86(1):29–39
216. Lukaski HC (2004) Vitamin and mineral status: effects on physical performance. Nutrition 20(7–8):632–644. https://doi.org/10.1016/j.nut.2004.04.001
217. Williams MH (2005) Dietary supplements and sports performance: minerals. J Int Soc Sports Nutr 2:43–49. https://doi.org/10.1186/1550-2783-2-1-43
218. Reginster JY (2005) The high prevalence of inadequate serum vitamin D levels and implications for bone health. Curr Med Res Opin 21(4):579–586. https://doi.org/10.1185/030079905X41435
219. Montero-Odasso M, Duque G (2005) Vitamin D in the aging musculoskeletal system: an authentic strength preserving hormone. Mol Aspects Med 26(3):203–219. https://doi.org/10.1016/j.mam.2005.01.005
220. Vitale G, Cesari M, Mari D (2016) Aging of the endocrine system and its potential impact on sarcopenia. Eur J Intern Med 35:10–15. https://doi.org/10.1016/j.ejim.2016.07.017
221. Ross AC, Manson JE, Abrams SA, Aloia JF, Brannon PM, Clinton SK, Durazo-Arvizu RA, Gallagher JC, Gallo RL, Jones G, Kovacs CS, Mayne ST, Rosen CJ, Shapses SA (2011) The 2011 dietary reference intakes for calcium and vitamin D: what dietetics practitioners need to know. J Am Diet Assoc 111(4):524–527. https://doi.org/10.1016/j.jada.2011.01.004
222. Verlaan S, Maier AB, Bauer JM, Bautmans I, Brandt K, Donini LM, Maggio M, McMurdo ME, Mets T, Seal C, Wijers SL, Sieber C, Boirie Y, Cederholm T (2017) Sufficient levels of 25-hydroxyvitamin D and protein intake required to increase muscle mass in sarcopenic older adults—the PROVIDE study. Clin Nutr. https://doi.org/10.1016/j.clnu.2017.01.005
223. Buta B, Choudhury PP, Xue QL, Chaves P, Bandeen-Roche K, Shardell M, Semba RD, Walston J, Michos ED, Appel LJ, McAdams-DeMarco M, Gross A, Yasar S, Ferrucci L, Fried LP, Kalyani RR (2016) The association of vitamin D deficiency and incident frailty in older women: the role of cardiometabolic diseases. J Am Geriatr Soc. https://doi.org/10.1111/jgs.14677
224. Fuller JC, Baier S, Flakoll P, Nissen SL, Abumrad NN, Rathmacher JA (2011) Vitamin D status affects strength gains in older adults supplemented with a combination of β-hydroxy-β-methylbutyrate, arginine, and lysine: a cohort study. J Parenter Enteral Nutr 35(6):757–762. https://doi.org/10.1177/0148607111413903
225. Muir SW, Montero-Odasso M (2011) Effect of vitamin D supplementation on muscle strength, gait and balance in older adults: a systematic review and meta-analysis. J Am Geriatr Soc 59(12):2291–2300. https://doi.org/10.1111/j.1532-5415.2011.03733.x
226. Tomlinson PB, Joseph C, Angioi M (2015) Effects of vitamin D supplementation on upper and lower body muscle strength levels in healthy individuals. A systematic review with meta-analysis. J Sci Med Sport 18(5):575–580. https://doi.org/10.1016/j.jsams.2014.07.022
227. Farrokhyar F, Sivakumar G, Savage K, Koziarz A, Jamshidi S, Ayeni OR, Peterson D, Bhandari M (2017) Effects of Vitamin D supplementation on serum 25-hydroxyvitamin D concentrations and physical performance in athletes: a systematic review and meta-analysis of randomized controlled trials. Sports Med. https://doi.org/10.1007/s40279-017-0749-4
228. Rosendahl-Riise H, Spielau U, Ranhoff AH, Gudbrandsen OA, Dierkes J (2017) Vitamin D supplementation and its influence on muscle strength and mobility in community-dwelling older persons: a systematic review and meta-analysis. J Hum Nutr Diet 30(1):3–15. https://doi.org/10.1111/jhn.12394
229. Stockton KA, Mengersen K, Paratz JD, Kandiah D, Bennell KL (2011) Effect of vitamin D supplementation on muscle strength: a systematic review and meta-analysis. Osteoporos Int 22 (3):859–871. https://doi.org/10.1007/s00198-010-1407-y
230. Beaudart C, Buckinx F, Rabenda V, Gillain S, Cavalier E, Slomian J, Petermans J, Reginster JY, Bruyère O (2014) The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 99(11):4336–4345. https://doi.org/10.1210/jc.2014-1742
231. Agergaard J, Trøstrup J, Uth J, Iversen JV, Boesen A, Andersen JL, Schjerling P, Langberg H (2015) Does vitamin-D intake during resistance training improve the skeletal muscle hypertrophic and strength response in young and elderly men?—a randomized controlled trial. Nutr Metab (Lond) 12:32. https://doi.org/10.1186/s12986-015-0029-y
232. Antoniak AE, Greig CA (2017) The effect of combined resistance exercise training and vitamin D. BMJ Open 7(7):e014619. https://doi.org/10.1136/bmjopen-2016-014619
233. Makanae Y, Kawada S, Sasaki K, Nakazato K, Ishii N (2013) Vitamin C administration attenuates overload-induced skeletal muscle hypertrophy in rats. Acta Physiol (Oxf) 208(1):57–65. https://doi.org/10.1111/apha.12042
234. Paulsen G, Hamarsland H, Cumming KT, Johansen RE, Hulmi JJ, Børsheim E, Wiig H, Garthe I, Raastad T (2014) Vitamin C and E supplementation alters protein signalling after a strength training session, but not muscle growth during 10 weeks of training. J Physiol 592(24):5391–5408. https://doi.org/10.1113/jphysiol.2014.279950
235. Bjørnsen T, Salvesen S, Berntsen S, Hetlelid KJ, Stea TH, Lohne-Seiler H, Rohde G, Haraldstad K, Raastad T, Køpp U, Haugeberg G, Mansoor MA, Bastani NE, Blomhoff R, Stølevik SB, Seynnes OR, Paulsen G (2016) Vitamin C and E supplementation blunts

increases in total lean body mass in elderly men after strength training. Scand J Med Sci Sports 26(7):755–763. https://doi.org/10.1111/sms.12506
236. Stunes AK, Syversen U, Berntsen S, Paulsen G, Stea TH, Hetlelid KJ, Lohne-Seiler H, Mosti MP, Bjørnsen T, Raastad T, Haugeberg G (2017) High doses of vitamin C plus E reduce strength training-induced improvements in areal bone mineral density in elderly men. Eur J Appl Physiol 117(6):1073–1084. https://doi.org/10.1007/s00421-017-3588-y
237. Bobeuf F, Labonte M, Dionne IJ, Khalil A (2011) Combined effect of antioxidant supplementation and resistance training on oxidative stress markers, muscle and body composition in an elderly population. J Nutr Health Aging 15(10):883–889
238. Labonté M, Dionne IJ, Bouchard DR, Sénéchal M, Tessier D, Khalil A, Bobeuf F (2008) Effects of antioxidant supplements combined with resistance exercise on gains in fat-free mass in healthy elderly subjects: a pilot study. J Am Geriatr Soc 56(9):1766–1768. https://doi.org/10.1111/j.1532-5415.2008.01810.x
239. Minisola S, Cianferotti L, Biondi P, Cipriani C, Fossi C, Franceschelli F, Giusti F, Leoncini G, Pepe J, Bischoff-Ferrari HA, Brandi ML (2017) Correction of vitamin D status by calcidiol: pharmacokinetic profile, safety, and biochemical effects on bone and mineral metabolism of daily and weekly dosage regimens. Osteoporos Int 28 (11):3239–3249. https://doi.org/10.1007/s00198-017-4180-3
240. Hamishehkar H, Ranjdoost F, Asgharian P, Mahmoodpoor A, Sanaie S (2016) Vitamins, are they safe? Adv Pharm Bull 6(4):467–477. https://doi.org/10.15171/apb.2016.061
241. Bond P (2017) Phosphatidic acid: biosynthesis, pharmacokinetics, mechanisms of action and effect on strength and body composition in resistance-trained individuals. Nutr Metab (Lond) 14:12. https://doi.org/10.1186/s12986-017-0166-6
242. Fang Y, Vilella-Bach M, Bachmann R, Flanigan A, Chen J (2001) Phosphatidic acid-mediated mitogenic activation of mTOR signaling. Science 294(5548):1942–1945. https://doi.org/10.1126/science.1066015
243. Mobley CB, Hornberger TA, Fox CD, Healy JC, Ferguson BS, Lowery RP, McNally RM, Lockwood CM, Stout JR, Kavazis AN, Wilson JM, Roberts MD (2015) Effects of oral phosphatidic acid feeding with or without whey protein on muscle protein synthesis and anabolic signaling in rodent skeletal muscle. J Int Soc Sports Nutr 12:32. https://doi.org/10.1186/s12970-015-0094-7
244. Gonzalez AM, Sell KM, Ghigiarelli JJ, Kelly CF, Shone EW, Accetta MR, Baum JB, Mangine GT (2017) Effects of phosphatidic acid supplementation on muscle thickness and strength in resistance-trained men. Appl Physiol Nutr Metab 42 (4):443–448. https://doi.org/10.1139/apnm-2016-0564
245. Shad BJ, Smeuninx B, Atherton PJ, Breen L (2015) The mechanistic and ergogenic effects of phosphatidic acid in skeletal muscle. Appl Physiol Nutr Metab 40 (12):1233–1241. https://doi.org/10.1139/apnm-2015-0350
246. Hoffman JR, Stout JR, Williams DR, Wells AJ, Fragala MS, Mangine GT, Gonzalez AM, Emerson NS, McCormack WP, Scanlon TC, Purpura M, Jäger R (2012) Efficacy of phosphatidic acid ingestion on lean body mass, muscle thickness and strength gains in resistance-trained men. J Int Soc Sports Nutr 9(1):47. https://doi.org/10.1186/1550-2783-9-47
247. Joy JM, Gundermann DM, Lowery RP, Jäger R, McCleary SA, Purpura M, Roberts MD, Wilson SM, Hornberger TA, Wilson JM (2014) Phosphatidic acid enhances mTOR signaling and resistance exercise induced hypertrophy. Nutr Metab (Lond) 11:29. https://doi.org/10.1186/1743-7075-11-29
248. Andre TL, Gann JJ, McKinley-Barnard SK, Song JJ, Willoughby DS (2016) eight weeks of phosphatidic acid supplementation in conjunction with resistance training does not differentially affect body composition and muscle strength in resistance-trained men. J Sports Sci Med 15(3):532–539
249. Campbell BI, La Bounty PM, Roberts M (2004) The ergogenic potential of arginine. J Int Soc Sports Nutr 1(2):35–38. https://doi.org/10.1186/1550-2783-1-2-35
250. Castillo L, Ajami A, Branch S, Chapman TE, Yu YM, Burke JF, Young VR (1994) Plasma arginine kinetics in adult man: response to an arginine-free diet. Metabolism 43(1):114–122
251. Wideman L, Weltman JY, Patrie JT, Bowers CY, Shah N, Story S, Weltman A, Veldhuis JD (2000) Synergy of L-arginine and growth hormone (GH)-releasing peptide-2 on GH release: influence of gender. Am J Physiol Regul Integr Comp Physiol 279(4):R1455–R1466
252. Wideman L, Weltman JY, Patrie JT, Bowers CY, Shah N, Story S, Veldhuis JD, Weltman A (2000) Synergy of L-arginine and GHRP-2 stimulation of growth hormone in men and women: modulation by exercise. Am J Physiol Regul Integr Comp Physiol 279(4):R1467–R1477
253. Chromiak JA, Antonio J (2002) Use of amino acids as growth hormone-releasing agents by athletes. Nutrition 18(7–8):657–661
254. Collier SR, Collins E, Kanaley JA (2006) Oral arginine attenuates the growth hormone response to resistance exercise. J Appl Physiol (1985) 101(3):848–852. https://doi.org/10.1152/japplphysiol.00285.2006
255. Isidori A, Lo Monaco A, Cappa M (1981) A study of growth hormone release in man after oral administration of amino acids. Curr Med Res Opin 7(7):475–481. https://doi.org/10.1185/03007998109114287
256. Walberg-Rankin J, Hawkins CE, Fild DS, Sebolt DR (1994) The effect of oral arginine during energy restriction in male weight trainers. J Strength Cond Res 8(3):170–177
257. Forbes SC, Bell GJ (2011) The acute effects of a low and high dose of oral L-arginine supplementation in young active males at rest. Appl Physiol Nutr Metab 36 (3):405–411. https://doi.org/10.1139/h11-035
258. Blum A, Cannon RO, Costello R, Schenke WH, Csako G (2000) Endocrine and lipid effects of oral L-arginine treatment in healthy postmenopausal women. J Lab Clin Med 135(3):231–237. https://doi.org/10.1067/mlc.2000.104909
259. Angeli G, Barros TLD, Barros DFLD, Lima M (2007) Investigation of the effects of oral supplementation of arginine in the increase of muscular strength and mass. Revista Brasileira de Medicina do Esporte 13(2):129–132
260. Pahlavani N, Entezari MH, Nasiri M, Miri A, Rezaie M, Bagheri-Bidakhavidi M, Sadeghi O (2017) The effect of L-arginine supplementation on body composition and performance in male athletes: a double-blinded randomized clinical trial. Eur J Clin Nutr 71(4):544–548. https://doi.org/10.1038/ejcn.2016.266
261. Chilosi A, Casarano M, Comparini A, Battaglia FM, Mancardi MM, Schiaffino C, Tosetti M, Leuzzi V, Battini R, Cioni G (2012) Neuropsychological profile and clinical effects of arginine treatment in children with creatine transport deficiency. Orphanet J Rare Dis 7:43. https://doi.org/10.1186/1750-1172-7-43
262. Valayannopoulos V, Boddaert N, Chabli A, Barbier V, Desguerre I, Philippe A, Afenjar A, Mazzuca M, Cheillan D, Munnich A, de Keyzer Y, Jakobs C, Salomons GS, de Lonlay P (2012) Treatment by oral creatine, L-arginine and L-glycine in six severely affected patients with creatine transporter defect. J Inherit Metab Dis 35(1):151–157. https://doi.org/10.1007/s10545-011-9358-9
263. Alvares TS, Conte-Junior CA, Silva JT, Paschoalin VM (2012) Acute L-Arginine supplementation does not increase nitric oxide production in healthy subjects. Nutr Metab (Lond) 9(1):54. https://doi.org/10.1186/1743-7075-9-54
264. Alvares TS, Conte CA, Paschoalin VM, Silva JT, Meirelles CeM, Bhambhani YN, Gomes PS (2012) Acute L-arginine supplementation increases muscle blood volume but not strength

performance. Appl Physiol Nutr Metab 37 (1):115–126. https://doi.org/10.1139/h11-144
265. Álvares TS, Meirelles CM, Bhambhani YN, Paschoalin VM, Gomes PS (2011) L-Arginine as a potential ergogenic aid in healthy subjects. Sports Med 41(3):233–248. https://doi.org/10.2165/11538590-000000000-00000
266. Pariza MW, Park Y, Cook ME (2001) The biologically active isomers of conjugated linoleic acid. Prog Lipid Res 40(4):283–298
267. Pinkoski C, Chilibeck PD, Candow DG, Esliger D, Ewaschuk JB, Facci M, Farthing JP, Zello GA (2006) The effects of conjugated linoleic acid supplementation during resistance training. Med Sci Sports Exerc 38(2):339–348. https://doi.org/10.1249/01.mss.0000183860.42853.15
268. Tarnopolsky M, Zimmer A, Paikin J, Safdar A, Aboud A, Pearce E, Roy B, Doherty T (2007) Creatine monohydrate and conjugated linoleic acid improve strength and body composition following resistance exercise in older adults. PLoS One 2(10):e991. https://doi.org/10.1371/journal.pone.0000991
269. Kreider RB, Ferreira MP, Greenwood M, Wilson M, Almada AL (2002) Effects of conjugated linoleic acid supplementation during resistance training on body composition, bone density, strength, and selected hematological markers. J Strength Cond Res 16(3):325–334
270. Song HJ, Grant I, Rotondo D, Mohede I, Sattar N, Heys SD, Wahle KW (2005) Effect of CLA supplementation on immune function in young healthy volunteers. Eur J Clin Nutr 59(4):508–517. https://doi.org/10.1038/sj.ejcn.1602102
271. Curi R, Newsholme P, Procopio J, Lagranha C, Gorjão R, Pithon-Curi TC (2007) Glutamine, gene expression, and cell function. Front Biosci 12:344–357
272. Wu G, Wu Z, Dai Z, Yang Y, Wang W, Liu C, Wang B, Wang J, Yin Y (2013) Dietary requirements of "nutritionally non-essential amino acids" by animals and humans. Amino acids 44(4):1107–1113. https://doi.org/10.1007/s00726-012-1444-2
273. Wernerman J (2008) Clinical use of glutamine supplementation. J Nutr 138 (10): 2040S–2044S
274. Novak F, Heyland DK, Avenell A, Drover JW, Su X (2002) Glutamine supplementation in serious illness: a systematic review of the evidence. Crit Care Med 30(9):2022–2029. https://doi.org/10.1097/01.CCM.0000026106.58241.95
275. Hammarqvist F, Wernerman J, Ali R, von der Decken A, Vinnars E (1989) Addition of glutamine to total parenteral nutrition after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis, and improves nitrogen balance. Ann Surg 209(4):455–461
276. Stehle P, Zander J, Mertes N, Albers S, Puchstein C, Lawin P, Fürst P (1989) Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. Lancet 1(8632):231–233
277. Mok E, Eléouet-Da Violante C, Daubrosse C, Gottrand F, Rigal O, Fontan JE, Cuisset JM, Guilhot J, Hankard R (2006) Oral glutamine and amino acid supplementation inhibit whole-body protein degradation in children with Duchenne muscular dystrophy. Am J Clin Nutr 83(4):823–828
278. Antonio J, Sanders MS, Kalman D, Woodgate D, Street C (2002) The effects of high-dose glutamine ingestion on weightlifting performance. J Strength Cond Res 16(1):157–160
279. Candow DG, Chilibeck PD, Burke DG, Davison KS, Smith-Palmer T (2001) Effect of glutamine supplementation combined with resistance training in young adults. Eur J Appl Physiol 86(2):142–149. https://doi.org/10.1007/s00421-001-0523-y
280. Ramezani Ahmadi A, Rayyani E, Bahreini M, Mansoori A (2018) The effect of glutamine supplementation on athletic performance, body composition, and immune function: a systematic review and a meta-analysis of clinical trials. Clin Nutr. https://doi.org/10.1016/j.clnu.2018.05.001
281. Cruzat V, Macedo Rogero M, Noel Keane K, Curi R, Newsholme P (2018) Glutamine: metabolism and immune function, supplementation and clinical translation. Nutrients. https://doi.org/10.3390/nu10111564
282. Gleeson M (2008) Dosing and efficacy of glutamine supplementation in human exercise and sport training. J Nutr 138(10):2045S–2049S
283. Lin Y, Chen F, Zhang J, Wang T, Wei X, Wu J, Feng Y, Dai Z, Wu Q (2013) Neuroprotective effect of resveratrol on ischemia/reperfusion injury in rats through TRPC6/CREB pathways. J Mol Neurosci 50(3):504–513. https://doi.org/10.1007/s12031-013-9977-8
284. Mattison JA, Wang M, Bernier M, Zhang J, Park SS, Maudsley S, An SS, Santhanam L, Martin B, Faulkner S, Morrell C, Baur JA, Peshkin L, Sosnowska D, Csiszar A, Herbert RL, Tilmont EM, Ungvari Z, Pearson KJ, Lakatta EG, de Cabo R (2014) Resveratrol prevents high fat/sucrose diet-induced central arterial wall inflammation and stiffening in nonhuman primates. Cell Metab 20(1):183–190. https://doi.org/10.1016/j.cmet.2014.04.018
285. Wong RH, Howe PR, Buckley JD, Coates AM, Kunz I, Berry NM (2011) Acute resveratrol supplementation improves flow-mediated dilatation in overweight/obese individuals with mildly elevated blood pressure. Nutr Metab Cardiovasc Dis 21(11):851–856. https://doi.org/10.1016/j.numecd.2010.03.003
286. Dutt V, Gupta S, Dabur R, Injeti E, Mittal A (2015) Skeletal muscle atrophy: potential therapeutic agents and their mechanisms of action. Pharmacol Res 99:86–100. https://doi.org/10.1016/j.phrs.2015.05.010
287. Rathbone CR, Booth FW, Lees SJ (2009) Sirt1 increases skeletal muscle precursor cell proliferation. Eur J Cell Biol 88(1):35–44. https://doi.org/10.1016/j.ejcb.2008.08.003
288. Bennett BT, Mohamed JS, Alway SE (2013) Effects of resveratrol on the recovery of muscle mass following disuse in the plantaris muscle of aged rats. PLoS One 8(12):e83518. https://doi.org/10.1371/journal.pone.0083518
289. Jackson JR, Ryan MJ, Alway SE (2011) Long-term supplementation with resveratrol alleviates oxidative stress but does not attenuate sarcopenia in aged mice. J Gerontol A Biol Sci Med Sci 66(7):751–764. https://doi.org/10.1093/gerona/glr047
290. Ballak SB, Jaspers RT, Deldicque L, Chalil S, Peters EL, de Haan A, Degens H (2015) Blunted hypertrophic response in old mouse muscle is associated with a lower satellite cell density and is not alleviated by resveratrol. Exp Gerontol 62:23–31. https://doi.org/10.1016/j.exger.2014.12.020
291. Alway SE, McCrory JL, Kearcher K, Vickers A, Frear B, Gilleland DL, Bonner DE, Thomas JM, Donley DA, Lively MW, Mohamed JS (2017) Resveratrol enhances exercise-induced cellular and functional adaptations of skeletal muscle in older men and women. J Gerontol A Biol Sci Med Sci. https://doi.org/10.1093/gerona/glx089
292. Katashima CK, Silva VR, Gomes TL, Pichard C, Pimentel GD (2017) Ursolic acid and mechanisms of actions on adipose and muscle tissue: a systematic review. Obes Rev 18(6):700–711. https://doi.org/10.1111/obr.12523
293. Kunkel SD, Suneja M, Ebert SM, Bongers KS, Fox DK, Malmberg SE, Alipour F, Shields RK, Adams CM (2011) mRNA expression signatures of human skeletal muscle atrophy identify a natural compound that increases muscle mass. Cell Metab 13(6):627–638. https://doi.org/10.1016/j.cmet.2011.03.020
294. Kunkel SD, Elmore CJ, Bongers KS, Ebert SM, Fox DK, Dyle MC, Bullard SA, Adams CM (2012) Ursolic acid increases skeletal muscle and brown fat and decreases diet-induced obesity, glucose intolerance and fatty liver disease. PLoS One 7(6):e39332. https://doi.org/10.1371/journal.pone.0039332
295. Cho YH, Lee SY, Kim CM, Kim ND, Choe S, Lee CH, Shin JH (2016) Effect of loquat leaf extract on muscle strength,

muscle mass, and muscle function in healthy adults: a randomized, double-blinded, and placebo-controlled trial. Evid Based Complement Alternat Med 2016:4301621. https://doi.org/10.1155/2016/4301621
296. Church DD, Schwarz NA, Spillane MB, McKinley-Barnard SK, Andre TL, Ramirez AJ, Willoughby DS (2016) L-Leucine increases skeletal muscle IGF-1 but does not differentially increase Akt/mTORC1 signaling and serum IGF-1 compared to ursolic acid in response to resistance exercise in resistance-trained men. J Am Coll Nutr 35(7):627–638. https://doi.org/10.1080/07315724.2015.1132019
297. Bang HS, Seo DY, Chung YM, Oh KM, Park JJ, Arturo F, Jeong SH, Kim N, Han J (2014) Ursolic Acid-induced elevation of serum irisin augments muscle strength during resistance training in men. Korean J Physiol Pharmacol 18(5):441–446. https://doi.org/10.4196/kjpp.2014.18.5.441
298. Qureshi A, Naughton DP, Petroczi A (2014) A systematic review on the herbal extract *Tribulus terrestris* and the roots of its putative aphrodisiac and performance enhancing effect. J Diet Suppl 11(1):64–79. https://doi.org/10.3109/19390211.2014.887602
299. Neychev VK, Mitev VI (2005) The aphrodisiac herb *Tribulus terrestris* does not influence the androgen production in young men. J Ethnopharmacol 101(1–3):319–323. https://doi.org/10.1016/j.jep.2005.05.017
300. Ma Y, Guo Z, Wang X (2015) Tribulus terrestris extracts alleviate muscle damage and promote anaerobic performance of trained male boxers and its mechanisms: roles of androgen, IGF-1, and IGF binding protein-3. J Sport Health Sci 12:1–8
301. Rogerson S, Riches CJ, Jennings C, Weatherby RP, Meir RA, Marshall-Gradisnik SM (2007) The effect of five weeks of *Tribulus terrestris* supplementation on muscle strength and body composition during preseason training in elite rugby league players. J Strength Cond Res 21(2):348–353. https://doi.org/10.1519/R-18395.1
302. Antonio J, Uelmen J, Rodriguez R, Earnest C (2000) The effects of *Tribulus terrestris* on body composition and exercise performance in resistance-trained males. Int J Sport Nutr Exerc Metab 10(2):208–215
303. Roaiah MF, El Khayat YI, GamalEl Din SF, Abd El Salam MA (2016) Pilot study on the effect of botanical medicine (*Tribulus terrestris*) on serum testosterone level and erectile function in aging males with partial androgen deficiency (PADAM). J Sex Marital Ther 42(4):297–301. https://doi.org/10.1080/009262 3X.2015.1033579
304. Barillaro C, Liperoti R, Martone AM, Onder G, Landi F (2013) The new metabolic treatments for sarcopenia. Aging Clin Exp Res 25(2):119–127. https://doi.org/10.1007/s40520-013-0030-0
305. Yao K, Yin Y, Li X, Xi P, Wang J, Lei J, Hou Y, Wu G (2012) Alpha-ketoglutarate inhibits glutamine degradation and enhances protein synthesis in intestinal porcine epithelial cells. Amino Acids 42(6):2491–2500. https://doi.org/10.1007/s00726-011-1060-6
306. Cai X, Zhu C, Xu Y, Jing Y, Yuan Y, Wang L, Wang S, Zhu X, Gao P, Zhang Y, Jiang Q, Shu G (2016) Alpha-ketoglutarate promotes skeletal muscle hypertrophy and protein synthesis through Akt/mTOR signaling pathways. Sci Rep 6:26802. https://doi.org/10.1038/srep26802
307. Riedel E, Nündel M, Hampl H (1996) Alpha-Ketoglutarate application in hemodialysis patients improves amino acid metabolism. Nephron 74(2):261–265
308. Wirén M, Permert J, Larsson J (2002) Alpha-ketoglutarate-supplemented enteral nutrition: effects on postoperative nitrogen balance and muscle catabolism. Nutrition 18(9):725–728
309. Cynober L (2004) Ornithine alpha-ketoglutarate as a potent precursor of arginine and nitric oxide: a new job for an old friend. J Nutr 134 (10 Suppl):2858S–2862S. (discussion 2895S)
310. Le Bricon T, Coudray-Lucas C, Lioret N, Lim SK, Plassart F, Schlegel L, De Bandt JP, Saizy R, Giboudeau J, Cynober L (1997) Ornithine alpha-ketoglutarate metabolism after enteral administration in burn patients: bolus compared with continuous infusion. Am J Clin Nutr 65(2):512–518
311. Campbell B, Roberts M, Kerksick C, Wilborn C, Marcello B, Taylor L, Nassar E, Leutholtz B, Bowden R, Rasmussen C, Greenwood M, Kreider R (2006) Pharmacokinetics, safety, and effects on exercise performance of L-arginine alpha-ketoglutarate in trained adult men. Nutrition 22(9):872–881. https://doi.org/10.1016/j.nut.2006.06.003
312. Wax B, Kavazis AN, Webb HE, Brown SP (2012) Acute L-arginine alpha ketoglutarate supplementation fails to improve muscular performance in resistance trained and untrained men. J Int Soc Sports Nutr 9(1):17. https://doi.org/10.1186/1550-2783-9-17
313. Prosser JM, Majlesi N, Chan GM, Olsen D, Hoffman RS, Nelson LS (2009) Adverse effects associated with arginine alpha-ketoglutarate containing supplements. Hum Exp Toxicol 28(5):259–262. https://doi.org/10.1177/0960327109104498
314. Kokubo T, Maeda S, Tazumi K, Nozawa H, Miura Y, Kirisako T (2015) The effect of L-Ornithine on the phosphorylation of mTORC1 downstream targets in rat liver. Prev Nutr Food Sci 20(4):238–245. https://doi.org/10.3746/pnf.2015.20.4.238
315. Tujioka K, Yamada T, Aoki M, Morishita K, Hayase K, Yokogoshi H (2012) Dietary ornithine affects the tissue protein synthesis rate in young rats. J Nutr Sci Vitaminol (Tokyo) 58(4):297–302
316. Evain-Brion D, Donnadieu M, Roger M, Job JC (1982) Simultaneous study of somatotrophic and corticotrophic pituitary secretions during ornithine infusion test. Clin Endocrinol (Oxf) 17(2):119–122
317. Demura S, Yamada T, Yamaji S, Komatsu M, Morishita K (2010) The effect of L-ornithine hydrochloride ingestion on human growth hormone secretion after strength training. Adv Biosci Biotechnol 1:7–11
318. Bucci L, Hickson JF, Pivarnik JM, Wolinsky I, McMahon JC, Turner SD (1990) Ornithine ingestion and growth hormone release in bodybuilders. Nutr Res 10(3):239–245
319. Peeling P, Binnie MJ, Goods PSR, Sim M, Burke LM (2018) Evidence-based supplements for the enhancement of athletic performance. Int J Sport Nutr Exerc Metab 28(2):178–187. https://doi.org/10.1123/ijsnem.2017-0343
320. Jones AM (2014) Dietary nitrate supplementation and exercise performance. Sports Med 44 (Suppl 1):S35–S45. https://doi.org/10.1007/s40279-014-0149-y
321. Molfino A, Gioia G, Rossi Fanelli F, Muscaritoli M (2014) The role for dietary omega-3 fatty acids supplementation in older adults. Nutrients 6(10):4058–4073. https://doi.org/10.3390/nu6104058
322. Pencharz PB, Elango R, Ball RO (2012) Determination of the tolerable upper intake level of leucine in adult men. J Nutr 142(12):2220S–2224S. https://doi.org/10.3945/jn.112.160259
323. Kantartzis K, Fritsche L, Bombrich M, Machann J, Schick F, Staiger H, Kunz I, Schoop R, Lehn-Stefan A, Heni M, Peter A, Fritsche A, Häring HU, Stefan N (2018) Effects of resveratrol supplementation on liver fat content in overweight and insulin-resistant subjects: a randomized, double-blind, placebo-controlled clinical trial. Diabetes Obes Metab. https://doi.org/10.1111/dom.13268
324. Anton SD, Embry C, Marsiske M, Lu X, Doss H, Leeuwenburgh C, Manini TM (2014) Safety and metabolic outcomes of resveratrol supplementation in older adults: results of a twelve-week, placebo-controlled pilot study. Exp Gerontol 57:181–187. https://doi.org/10.1016/j.exger.2014.05.015