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REVIEW

Supplements with purported effects on muscle mass and strength

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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

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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.

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Compliance with ethical standards

Conflict of interest Authors declare no conflict of interest.

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