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Diet for the prevention and management of sarcopenia

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ABSTRACT

Sarcopenia is a geriatric condition characterized by a progressive loss of skeletal muscle mass and strength, with an increased risk of adverse health outcomes (e.g., falls, disability, institutionalization, reduced quality of life, mortality). Pharmacological remedies are currently unavailable for preventing the development of sarcopenia, halting its progression, or impeding its negative health outcomes. The most effective strategies to contrast sarcopenia rely on the adoption of healthier lifestyle behaviors, including adherence to high-quality diets and regular physical activity. In this review, the role of nutrition in the prevention and management of sarcopenia is summarized. Special attention is given to current "blockbuster" dietary regimes and agents used to counteract age-related muscle wasting, together with their putative mechanisms of action. Issues related to the design and implementation of effective nutritional strategies are discussed, with a focus on unanswered questions on the most appropriate timing of nutritional interventions to preserve muscle health and function into old age. A brief description is also provided on new technologies that can facilitate the development and implementation of personalized nutrition plans to contrast sarcopenia.

1. Introduction

Sarcopenia is the term coined to define an age-related condition characterized by a supraphysiologic loss of muscle mass and strength [1]. Sarcopenia increases the risk of negative health outcomes, such as falls, hospitalization, institutionalization, disability, and death [2,3]. Sarcopenia may also impact the prognosis of other chronic conditions, such as cancer [4,5], diabetes [6], and heart failure [7]. Due to its clinical relevance, sarcopenia was recognized in 2016 as an independent nosological entity with an International Classification of Diseases-10 code [8].

Several operational definitions of sarcopenia have been proposed over the years, with diagnostic algorithms varying according to the relevance attributed to strength/function parameters [1,9,10]. Regardless of each definition's peculiarities, all identify muscle failure as the biological substratum of sarcopenia. According to the latest diagnostic criteria by the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) [11], low muscle strength is the cardinal element of sarcopenia, low muscle quantity or quality is necessary to confirm the diagnosis, and poor physical performance serves as an indicator of

Abbreviations: AMPK, AMP-activated protein kinase; BMAL1, Brain and Muscle ARNT-like protein 1; BMI, Body Mass Index; BW, Body Weight; CRP, C-Reactive Protein; CASTOR1, Cytosolic Arginine Sensor for mTORC1 subunit 1; DIAAS, Digestible Indispensable Amino Acid Score; DHA, Docosahexaenoic Acid; EPA, Eicosapentaenoic Acid; eIF4, Eukaryotic Initiation Ractor 4; EWGSOP2, European Working Group on Sarcopenia in Older People 2; ECW, Extracellular Water; FAO/WHO/UN, Food and Agriculture Organization/World Health Organization/United Nations; GH, Growth Hormone; HMB, β-Hydroxy-β-Methyl Butyrate; IAAO, Indicator Amino Acid Oxidation; IGF-1, Insulin Growth Factor-1; IL-6, Interleukin-6; ICW, Intracellular Water; KHANES, Korea National Health and Nutrition Examination Survey; mTORC1, Mechanistic Target of Rapamycin (mTOR) Complex 1; MPD, Muscle Protein Degradation; MPS, Muscle Protein Synthesis; Murf1, Muscle RING-finger protein-1; NHANES, National Health and Nutrition Examination Survey; NAD, Nicotinamide Adenine Dinucleotide; NO, Nitric Oxide; PUFA, Poly-Unsaturated Fatty Acid; ROS/NRS, Reactive Oxygen and Nitrogen Species; RDA, Recommended Dietary Allowance; S6K, Ribosomal Protein S6 Kinase; SPPB, Short Physical Performance Battery; VDR, Vitamin D Receptor.

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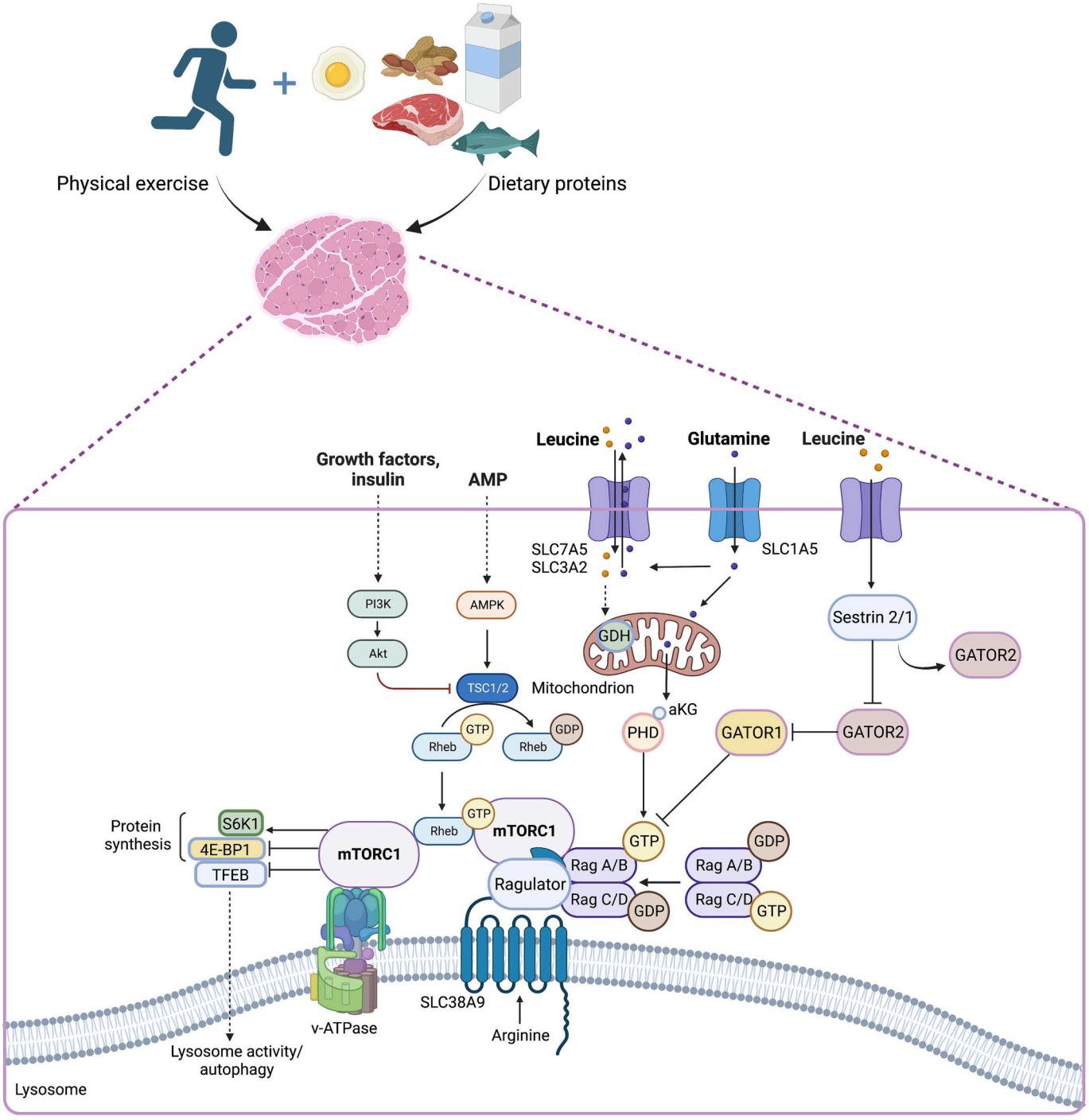

Fig. 1. Main pathways that regulate the mammalian target of rapamycin complex 1 (mTORC1) pathway. mTORC1 can be activated by growth factors (e.g., insulin-like growth factor 1, insulin), nutrients (e.g., amino acids), and exercise. Growth factors engage mTORC1 through a PI3K-Akt-dependent pathway, that involves TSC complex inhibition. Amino acids activate RAG proteins and the Ragulator complex, that in turn facilitates mTORC1 recruitment to the lysosome. Sestrins 1 and 2 function as cytosolic sensors of leucine. The binding of leucine to Sestrins induces their dissociation from GATOR2, leading to RAG/Ragulator activation. Arginine binds CASTOR1, a cytosolic arginine sensor, and enables the release of GATOR2 to activate mTORC1 via Ragulator. Arginine can also activate mTORC1 through its lysosomal transporter SLC38A9 which interacts with the Ragulator complex. Exercise, in particular resistance training, activates mTORC1 via mechanical and non-mechanical stimuli transduced by TSC2 and Rheb. Upon activation, mTORC1 phosphorylates ribosomal proteins S6K and 4E-BP1, and the lysosomal transcription factor TFEB to stimulate anabolism and inhibit autophagy. Low cellular energy (high AMP/ATP ratio) activates AMPK leading to TSC-mediated mTORC1 inhibition. Abbreviations. Akt, protein kinase B; AMPK, AMP-activated protein kinase; CASTOR1, cytosolic arginine sensor for mTORC1 subunit 1; 4E-BP1, eIF4E-binding protein 1; GATOR, GAP activity toward Rags; PI3K, phosphoinositide 3 kinase; RAG, Ras-related GTPase; Rheb, RAS homologue enriched in brain; S6K, S6 kinase; TFEB, transcription factor EB; TSC, tuberous sclerosis protein; SLC, solute carrier.

disease severity. The prevalence of sarcopenia and severe sarcopenia varies between 10% and 27% and between 2% and 9%, respectively, with different sex distributions depending on the definition used [12].

From a pathophysiological point of view, sarcopenia may be considered a prototypical geriatric condition characterized by perturbations at multiple levels, from subcellular processes within skeletal myocytes to social and environmental factors [13–15]. During aging, the homeostasis of the skeletal muscle tissue is altered due to an imbalance between anabolic and catabolic processes, which results in loss of myofibers and their partial replacement by fat and fibrous tissue [16,17].

The reduction in size and number mainly affects type II fibers. This occurs through synergistic effects of different processes, such as progressive loss of motor neurons, fast-to-slow myosin isoform transition (type II to type I fiber switch), and satellite cell depletion [16,18,19]. Alterations in most biological "hallmarks of aging", including chronic inflammation, mitochondrial dysfunction, dysbiosis, cellular senescence, and defective macroautophagy, have been described in older adults with sarcopenia [20–22]. In this context, a deregulated nutrient-sensing network plays a relevant role. This entails a disrupted somatotrophic axis, insulin resistance, and perturbations in the network of receptor tyrosine kinases and intracellular signaling cascades through which growth hormone (GH) and insulin growth factor-1 (IGF-1) regulate muscle anabolic pathways and overall cellular metabolism [23,24].

The regulation of muscle plasticity and trophism is attributed to antagonistic actions of mechanistic target of rapamycin (mTOR), which stimulates protein synthesis, and AMP-activated protein kinase (AMPK), which inhibits mTOR and promotes catabolism (Fig. 1). The role of the mTOR-AMPK dyad in skeletal muscle aging is complex and multifaceted. During aging, mTOR hyperactivation may impair muscle protein synthesis (MPS) and trigger muscle protein degradation (MPD) [24]. This is corroborated by preclinical evidence showing that mTOR inhibitors, such as rapamycin, prevent age-related muscle loss [25]. Moreover, well recognized anti-aging interventions, such as calorie restriction, activate AMPK to induce several cellular processes, including autophagy and mitochondrial biogenesis, which are critical for the preservation of muscle into old age [26].

Preclinical and clinical evidence suggests that an altered crosstalk between muscle and other tissues and organs (e.g., fat, bone, liver) has a significant role in the development and progression of sarcopenia [27–29]. Muscle-organ crosstalk is mediated by tissue-specific molecules (e.g., myokines, adipokines, osteokines, hepatokines) that act in an autocrine, paracrine, and endocrine manner to influence various processes associated with muscle wasting [30]. However, the role of individual biomolecules in the pathogenesis of sarcopenia has yet to be elucidated.

A comprehensive review of the biological factors underlying sarcopenia is beyond the scope of this manuscript and exhaustive reviews are available that explore this topic in detail [16,30,31].

Polypharmacy, the use of multiple concurrent medications, is highly prevalent in older adults and is associated with multiple negative health outcomes [32]. A bidirectional relationship exists between polypharmacy and sarcopenia, whereby specific drugs, including glucocorticoids, chemotherapeutics, and beta-blockers, may induce muscle weakness and atrophy, while reduced muscle mass and quality may influence drug distribution and metabolism [33,34].

Lastly, other non-biological factors, such as depression, social isolation (e.g., living alone, lack of social activities), and environmental factors (e.g., neighborhood safety, access to public transportation), are associated with an increased risk of sarcopenia [14,15].

The intricate relationships between those putative causal factors and the incomplete understanding of the individual contribution of each cellular mechanism to the pathogenesis of sarcopenia have hindered the identification of effective pharmacological interventions to prevent or manage the condition. Changes in muscle mass and strength/function show similar, though not overlapping, trajectories over time, with a sharp increase and a peak in young adulthood, a slow decline from 40 to 45 years, and a steep drop later in life [35,36]. It follows that strategies to counteract sarcopenia should be started early and continued throughout life. Not surprisingly, the most effective interventions to contrast sarcopenia rely on the adoption of healthy lifestyles, including the consumption of high-quality diets and engagement in physical activity routines [37]. In this review, the current knowledge on the role of nutrition in the prevention and management of sarcopenia is summarized. The focus is placed on current nutritional recommendations to counteract age-related muscle wasting, together with the mechanisms of action of the main dietary agents. Issues related to the design and implementation of effective nutritional strategies are discussed, including the definition of their best timing to preserve muscle homeostasis and function into old age. Finally, we briefly elaborate on emerging technologies and how they might be used to build and implement individualized dietary strategies to combat sarcopenia in older persons.

2. Nutritional recommendations to counteract sarcopenia

Older adults are at increased risk of malnutrition [38]. A substantial decline in food intake occurs with age [39], which is paralleled by a reduction in resting energy expenditure [40], mainly due to decreases in muscle mass. The average food consumption is estimated to drop by approximately 25% between the ages of 40 and 70 [41]. Daily energy intake can be reduced by as much as 1300 kcal in men and 600 kcal in women [42], which often leads to energy supplies below the recommended reference values [43].

Anorexia of aging is the term used to describe the reduction in appetite and food intake that frequently occurs in older adults [44]. About 20% of those older than 65 suffer from this condition, although figures may vary depending on sex, setting, and comorbidities [44]. Central and peripheral processes contribute to development of anorexia aging [44]. Impaired sensory perception, including declines in sight, smell, and taste, poor oral health (e.g., oral cavity inflammation, ill-fitting dentures, low number of functional teeth), and swallowing problems adversely affect eating behaviors and limit food choices, which may eventually increase the risk of malnutrition [44]. Physiological changes associated with aging of the gastrointestinal system, such as delayed gastric emptying, altered appetite-regulating hormonal signals (e.g., high levels of satiety-inducing cholecystokinin and low circulating ghrelin), and inflammaging (i.e., age-related chronic, low-grade inflammation), have also been associated with anorexia of aging [45,46]. Neurological disorders, acute and chronic diseases, and inflammatory conditions as well as polypharmacy may further favor malnutrition [47,48].

Malnutrition in older adults is mostly referred to as a failure to meet either energy or individual nutrient requirements, which predisposes to sarcopenia [49]. However, the malnutrition spectrum also entails overnutrition, which may lead to metabolic disturbances and obesity. The latter is becoming a public health concern also in older people [50]. Data from the National Health and Nutrition Examination Survey (NHANES) showed that the prevalence of obesity (i.e., body mass index [BMI] $\geq$30 kg/m^2) in US citizens 70 years and older increased from 26.2% in 2003/2004 to 40.3% in 2017/2018 [51]. Similar trends were observed in Europe and developing countries, though with lower prevalence figures. [52–54].

The co-existence of excess adiposity and sarcopenia is referred to as sarcopenic obesity, which combines the health-damaging effects of the two conditions and is associated with an increased risk of frailty, reduced quality of life, and mortality [55]. However, current nutritional guidelines recommend careful and individual weighing of risks and benefits before prescribing weight-reducing diets in obese older adults, due to the risk of lean mass loss and further functional decline [43]. If weight reduction is considered, energy restriction should be moderate (~500 kcal/d less than estimated needs) to reach a weight loss target of

Table 1
Recommendations by national and international organizations and experts' panels for daily protein intake in older adults.

Organizations	Daily protein intake (g/kg body weight)	
World Health Organization (WHO)[65]	0.83	
Australian National Health and Medical Research Council (NHMRC)/New Zealand Ministry of Health (MoH) [66]	Women 0.94	Men 1.07
Chinese Nutrition Society [67]	1.0	
European Food Safety Authority (EFSA) [68]	0.83	
European Society for Clinical Nutrition and Metabolism (ESPEN) [43]	1.0	
PROT-AGE Study Group [69]	1.0-1.2	
USA [70]	0.80	

about 5-10% of initial body weight (BW) after six months or more. Protein intake of at least 1 g/kg BW/d as well as an adequate intake of micronutrients should be assured and combined with exercise training (whenever possible) to preserve muscle mass [43,56].

Besides malnutrition, dehydration is a critical, but often overlooked phenomenon, associated with negative health outcomes in older adults [57]. Dehydration may be caused by various age-related processes, such as reduced thirst sensation [58], changes in renal function [59], and use of diuretics or other medications affecting body water [60]. Hydration status influences cognitive [61] and physical function [62], especially in more frail and vulnerable people.

Most national and international societies of clinical nutrition and experts' groups issued guidelines and recommendations to promote healthy diet and prevent malnutrition and dehydration in older adults [43,63,64]. Nutritional guidelines include basic general principles, such as simplified targets for daily energy intake (i.e., 30 kcal/kg/BW), protein intake (at least 1.0 g/kg BW) (Table 1), and hydration (at least 1.6 L and 2.0 L of water).

Guidelines and recommendations also emphasize that nutritional interventions should be individualized and use a multidimensional approach, ad hoc screening/assessment cycles, and targets to be monitored over time. The definition of nutritional targets should be based on individual parameters (e.g., total energy requirements, calculated from resting energy expenditure multiplied by physical activity levels), and requires a close monitoring of BW to adapt both energy and protein intakes [43].

Yet, recent evidence pointed out that achieving optimal nutritional goals is particularly challenging for older adults. For instance, a meta-analysis using data of 8107 community-dwelling older adults from the PRevention Of Malnutrition In Senior Subjects in the EU (PROMISS) project showed that the prevalence of protein intake below 0.8, 1.0, and 1.2 g/kg BW/d was 29.1%, 54.3%, and 75.7%, respectively [71]. A lower adherence to nutrition recommendations is especially frequent in institutionalized older adults [72].

In the following sections, nutritional recommendations to maintain muscle mass, strength, and function in older adults are discussed, with a focus on diet quality, protein and fluid intake, and a glance on novel nutritional agents.

2.1. Dietary quality and dietary patterns

Dietary prescription to counteract sarcopenia should provide sufficient calories, ensure the right intake of nutrients according to individual characteristics (e.g., age, sex, comorbidities, concomitant therapies, physical activity levels), be administered at the right time, and for a sufficient time to affect muscle health [73]. Most studies testing nutritional interventions against sarcopenia have focused on the use of individual nutrients or food groups, such as protein or vitamin D, or supplements containing multiple substances [74]. However, diets are not simply the sum of individual nutritional agents; rather, each dietary pattern implies complex interactions between its constituents, which may have synergistic or antagonistic effects on health parameters [75]. Indeed, diet quality and dietary patterns are increasingly considered in nutritional studies on sarcopenia [76,77]. Various indices have been developed to assess dietary quality in older adults, which are based on the consumption of "healthier" food groups (e.g., whole grains, fruits, vegetables), the content of nutrients particularly relevant to aging individuals (e.g., protein, vitamin D, calcium, vitamin B12, folate, fluids), and macronutrients and fatty acid ratio intake [78,79]. Older adults on higher-quality diets show reduced levels of inflammatory and cardiometabolic risk markers, and have a lower risk of negative health outcomes, including limitations in activities of daily living, depression, and mortality, compared with those with poor quality diet scores [79–82]. High-quality diets are also associated with better physical function and reduced risk of sarcopenia [83–85]. In addition, high-quality diets, such as Mediterranean and Nordic diets, are frequently linked to adherence to health-promoting lifestyle patterns [86].

Healthy dietary patterns are prevalently "plant-based" and imply the ingestion of protein from plant sources, high intake of fruits and vegetables, nuts and seeds, daily use of olive or vegetable oil (e.g., canola oil) as the primary fat source, and limited consumption of red meat and processed foods [86]. Their high content in bioactive substances, such as phytosterols, polyphenols, pigments, polyunsaturated fatty acids (PUFAs), confer anti-inflammatory and antioxidant properties, which protect against chronic degenerative diseases (e.g., cardiovascular disease [87], diabetes [88], dementia [89], cancer [90]). Recent evidence suggests that a high Mediterranean diet adherence is associated with greater muscle strength and function, and reduced risk of sarcopenia [91,92]. The muscle-protective properties of the Mediterranean diet are thought to be linked to its balanced content of vitamins (e.g., vitamin E and C, carotenoids) and phytochemicals with antioxidants properties [93]. These nutrients reduce the damage inflicted by reactive oxygen and nitrogen species (ROS/NRS), while preserving hormetic responses to physiological, low doses of ROS and RNS [94]. Inflammation, either acute or chronic, induces muscle protein breakdown [95], interferes with anabolic signals and protein synthesis [96], impairs quality control (e.g., autophagy) [97] and regeneration processes [98], and is associated with reduced muscle strength [99]. Polyphenols, dietary fibers, and mono- and PUFAs attenuate systemic inflammation by reducing the synthesis of pro-inflammatory mediators, such as C-reactive protein (CRP), interleukin-6 (IL-6) and fibrinogen, and by modulating gut microbiota [100].

Most available evidence is based on observational studies using dietary information collected late in life and heterogeneous diet quality indices and definitions of sarcopenia. Hence, substantial knowledge gaps are still to be addressed [76]. As previously mentioned, adherence to high-quality diet and health-promoting dietary patterns is often associated with other healthy lifestyle habits (e.g., engagement in physical and social activities). Therefore, teasing out the effects of diet from those of other factors is challenging and needs to be considered in the design and result interpretation of clinical trials on the subject [76].

2.2. Protein and amino acids

Dietary protein supplies amino acids to support MPS and maintain muscle mass across all life stages [101].

Current recommendations for daily protein intake in healthy adults range from 0.8 to 0.9 g protein/kg BW, with slight variations between national and international organizations (Table 1). For instance, in USA and Canada the Recommended Dietary Allowance (RDA) for protein is 0.8 g/kg BW/d [70], while the European Food Safety Authority and FAO/WHO/UN recommend an intake of 0.83 g/kg BW/d [65,68].

Recommendations, which are the same for all individuals 18+ year-old irrespective of age and sex, are based on nitrogen balance studies. Concerns have been raised about the reliability of this method for assessing protein requirements in older adults. Short-term nitrogen

balance studies may not detect changes in muscle protein turnover associated with age-related phenomena, such as a greater splanchnic extraction of amino acids [102] and anabolic resistance [103]. In addition, clinically relevant outcomes, including the preservation of muscle mass and function over time and changes in protein requirements during acute or chronic illnesses, are disregarded [69,102,104]. Other methods for determining protein requirements, such as the indicator amino acid oxidation (IAAO), estimated that the minimal daily protein intake for older adults should be 1.2 g/kg BW [105].

This view is supported by epidemiological and experimental evidence indicating that older adults may require protein intake greater than the RDA to support MPS and maintain muscle mass. Seminal evidence from the Health, Aging, and Body Composition Study showed that older community-dwellers whose diet contained around 1.2 g protein/kg BW/d lost 40% less appendicular lean mass over a three-year follow-up than those ingesting 0.8 g protein/kg BW/d [106]. A protein intake of approximately 1.2 g/kg BW/d was also found to protect against loss of grip strength in two independent cohorts from the Women's Health Initiative and the Framingham Offspring study [107,108]. Finally, recent systematic reviews and meta-analyses showed that protein intakes higher than the RDA were associated with better physical function and reduced risk of sarcopenia [109,110].

Stable isotope tracer studies demonstrated that MPS in the post-absorptive state did not differ between young and older adults. However, MPS in response to the ingestion of 20 g of protein was 16% lower in those 75+ than in healthy young adults [111].

Based on these observations, several expert groups issued nutritional recommendations to maintain and/or improve lean body mass and function in old age, suggesting daily protein intakes of at least 1.0-1.2 g/kg BW in healthy persons, 1.2-1.5 g/kg BW in those with acute or chronic diseases, and up to 2.0 g/kg BW in cases of severe illnesses, injuries, or malnutrition [69,112,113].

Specific recommendations have also been proposed for older adults who are engaged in exercise training [69]. A daily intake of at least 1.2 g protein/kg BW is recommended, with a high-protein meal or 20-g protein supplement to be consumed soon after exercise sessions. This could maximize muscle anabolic responses, since both exercise (in particular resistance training) and specific amino acids (vide infra) synergistically stimulate mTOR and, hence, MPS [24,114] (Fig. 1).

Protein quality is an additional parameter to consider for preserving muscle health in older adults. Protein quality may be expressed using the digestible indispensable amino acid score (DIAAS), which is based on ileal digestibility of protein and provides a metric of systemic bioavailability of indispensable amino acids from specific foods, mixed meals, or supplements [115]. Most animal food sources supply protein with excellent quality (DIAAS $\geq$100), soy and whey fall into the high-quality category (DIAAS = 75–99), while most plant sources have DIAAS scores <75 [116]. However, plant-derived protein combinations (e.g., potato, soy, pea) may reach excellent quality scores [116].

Leucine content is a key “protein quality” factor. Leucine stimulates MPS through the activation of a signaling cascade involving the mechanistic target of rapamycin (mTOR) complex 1 (mTORC1), eukaryotic initiation factor 4 (eIF4), and ribosomal protein S6 kinase (S6K) [114,117] (Fig. 1). The ingestion of leucine-rich foods or milk-based products may be recommended in the setting of lower protein intake (e.g., anorexia, severe renal disease) or marked catabolism (e.g., prolonged bedrest, intensive care) [118].

The feeding pattern is also relevant to adequately stimulate MPS. Debate is ongoing as to whether a skewed or even protein distribution across meals should be preferred to maximize muscle health in advanced age [119]. However, current recommendations encourage older persons to ingest 25– 30 g of high-quality protein with at least 2.5 g leucine at each meal [69,120].

Besides leucine, other amino acids and derivatives stimulate MPS through an mTORC1-dependent signaling cascade [114,117]. β-hydroxy-β-methyl butyrate (HMB) is a metabolite of leucine that stimulates MPS and inhibits proteolysis [121]. Early investigations showed that HMB supplementation preserved muscle mass in healthy older adults after 10 days of bed rest [122] and in institutionalized older patients [123]. However, recent systematic reviews reported only minor effects of HMB supplementation in attenuating losses of lean mass in older adults, while results on physical function and strengths were inconclusive [124,125]. Potential mechanistic redundancy exists between HMB its precursor leucine [126]; thus, it is unclear whether HMB supplementation conveys additional benefits in case of sufficient leucine supply.

Arginine has been reported to activate mTORC1 through binding to cytosolic arginine sensor for mTORC1 subunit 1 (CASTOR1) [114,117]. Arginine supplementation increases MPS in animal models [127], improves aerobic and anaerobic performance in athletes [128], and has positive effects on physical function in chronic disease states, such as chronic lung disease [129] and congestive heart failure [130]. Furthermore, 28-day arginine supplementation increased walking performance, muscle strength, endothelial function, and fatigue in adults with long COVID [131], a condition associated with accelerated biological aging.

Several preclinical investigations suggest that other amino acids, such as lysine [132], glycine [133], glutamine [134], and glutamic acid [135], may positively affect muscle homeostasis. However, the amino acid blend with the most favorable muscle-protective properties is yet to be established.

As a whole, existing evidence suggests that the ingestion of a moderate amount (25-30 g) of high-quality protein (high in leucine and indispensable amino acids) at every meal should be advised to support muscle health in older adults. Protein intake should be part of a multicomponent lifestyle program that includes physical activity, in particular resistance training, which is the main anabolic stimulus for muscle mass accretion and the key intervention to preserve muscle strength and function [136,137]. Older adults should be advised to consume protein-rich meals in close proximity to their exercise routines [138]. During periods of acute catabolism (e.g., bed rest due to an illness) or inability to engage in physical activity, a greater protein intake is instrumental in protecting skeletal muscle [139]. When dietary protein intake is inadequate, protein/amino acid supplementation should be considered.

2.3. Hydration

Water is the main constituent of human body and accounts for approximately 75% of muscle mass [140]. Body water has critical physiological, structural, and mechanical functions [141]. Hydration status depends on the balance between water ingestion and elimination. Food and beverages provide approximately 20% and 70-75% of total body water, respectively, while 5-10% derives from endogenous metabolic reactions. Main body water outputs are urine, fecal, cutaneous, and respiratory excretions [141]. Plasma and urine osmolarities (i.e., the number of solutes per unit volume of water, expressed in mOsm/L units) are commonly used laboratory markers of hydration. The osmolarity of body fluids in physiological conditions is maintained within a very narrow ranges (normal plasma osmolarity is 275-290 mOsm/L) through the combined action of osmoreceptors, baroreceptors, and hormones (e.g., arginine vasopressin and renin-angiotensin-aldosterone systems), which regulate thirst and renal excretion [141].

Older adults are at increased risk of dehydration due to several age-related processes, including diminished sensation of thirst and kidney function as well as the use of medications (e.g., diuretics, antihypertensive, antidepressant drugs) that increase water loss or blunt thirst [142].

The prevalence of dehydration in older adults is estimated at 20-30% [143], and is associated with several negative outcomes, such as delirium, disability, cognitive decline, and mortality [144].

Chronic mild dehydration and hyperosmotic stress induce

Table 2
Sex-specific recommendations by national and international organizations for total daily water and fluid intake.

Organizations	Daily water intake (food + fluids) (L)		Daily drink intake (L)	
	Women	Men	Women	Men
World Health Organization (WHO) [158]	2.2	2.9		
Australian National Health and Medical Research Council (NHMRC)/New Zealand Ministry of Health (MoH) [66]	2.8	3.4	2.1	2.6
Chinese Nutrition Society [67]	2.7	3.0	1.5	1.7
European Food Safety Authority (EFSA) [140]	2.0	2.5	1.6	2.0
Institute of Medicine (IOM) – USA [159]	2.7	3.7	2.0	3.0

intracellular dehydration, disrupt cellular structures and enzyme activities, and alter mitochondrial function [145]. These alterations, in turn, upregulate the synthesis of pro-inflammatory mediators [146], increase oxidative stress [145], and interfere with glucose homeostasis [147]. Studies in animal models of dehydration showed that skin and muscles were the main organs that lost water as a compensatory mechanism to preserve hydration of vital organs, such as brain and liver [148]. Dehydration has relevant effects on mechanical and metabolic functions of muscle [149]. Loss of intracellular water (ICW) is associated with activation of catabolic processes and concomitant inhibition of mTORC1 and insulin-stimulated anabolic pathways [150]. Dehydration, even if mild, also affects muscle contractile capacity and reduces muscle strength [151].

During aging, a relative expansion of extracellular water (ECW) against ICW accompanies the reduction in muscle mass as assessed by bioelectrical impedance methods [152]. In a cohort of community-dwellers aged 65-90, the ECW-to-ICW ratio of the thigh was negatively associated with knee extension strength and gait speed, independent of age, sex, BMI, and muscle mass [153]. Cross-sectional studies in Spanish community-dwellers aged 80+ showed that ICW was positively associated with handgrip strength, gait speed and Barthel score, independently of major covariates, including muscle mass [154,155]. In older adults from the Korea National Health and Nutrition Examination Survey (KHANES), a water intake below national recommendations was associated with a greater likelihood of sarcopenia [156]. However, in a recent study from KHANES VI, water intake did not predict low grip strength after adjusting for age, BMI, and engagement in resistance training [157].

In conclusion, evidence suggests that hydration status influences muscle mass, strength, and function in older adults. Most nutritional societies have highlighted the importance of early detection and correction of dehydration in older adults (Table 2). More research is needed to identify the mechanisms whereby hydration impacts muscle health in old age.

2.4. Creatine, omega-3 fatty acids, and vitamin D

Creatine is a nitrogenous compound that is synthesized by the kidney and liver from arginine, glycine, and methionine, or introduced with foods (e.g., lean red meat, poultry, seafood) [160]. Daily creatine requirements (~1–3 g) are supplied evenly by endogenous synthesis and food ingestion [161]. Around 60% of creatine is stored in muscles as phosphocreatine where it serves as a buffer to resynthesize repleted ATP [162]. The putative effects of creatine supplementation on the aged muscle have traditionally been attributed to its ergogenic property. Creatine may also increase cell hydration/osmolarity [163], enhance exercise-induced expression of myogenic transcription factors and IGF-1 signaling [164], and attenuate MPD and inflammation [165].

A recent meta-analysis showed that creatine supplementation induced greater increases in fat-free mass, upper and lower-body strength, and physical function compared with placebo in older adults engaged in resistance training [166]. Studies investigating the effect of creatine supplementation on muscle-related parameters in non-exercising older adults yielded mixed results [167–170]. While safety concerns have been raised regarding creatine and renal function, no evidence indicates an increased risk of renal damage after creatine supplementation [171].

Long-chain PUFAs, such as the "marine omega-3" eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) contained in fatty fish and fish oil preparations, have long been studied as components of healthy dietary patterns due to their anti-inflammatory properties [86]. Observational studies support a positive effect of diets rich in PUFAs on muscle strength, physical function, and lean mass in community-dwelling older adults [172,173]. Seminal findings by Smith et al. [174] showed that EPA and DHA supplementation for eight weeks increased MPS during hyperaminoacidemic-hyperinsulinemic clamping in healthy older adults. This effect was accompanied by increased myofiber size and was mediated by activation of the mTORC1-S6K signaling pathway, suggesting that omega-3 fatty acids may have anabolic properties. This hypothesis is supported by intervention studies in older women, in whom fish oil supplementation improved walking speed [175] and enhanced strength gains from resistance training [176]. A 6-month intervention with a combination of DHA and EPA induced greater increase in muscle mass (3.6%), handgrip strength (2.3 kg), and one-repetition maximum lower- and upper-body strength (4%), compared with corn oil in adults aged 60-85 [177]. While some intervention studies did not report improvements in muscle-related parameters following fish oil supplementations [178], recent systematic reviews and meta-analyses consistently showed positive effects of omega-3 PUFA supplementation on muscle strength, especially when combined with resistance exercise [179,180].

Serum levels of vitamin D (commonly evaluated in the form of 25-hydroxy vitamin D_3, 25(OH)D or calcifediol) decline progressively with aging, due to insufficient sun exposure, reduced ability to synthesize vitamin D precursor following UV stimulation, impaired renal-liver axis, and reduced food intake [181]. The prevalence of severe deficiency/deficiency of vitamin D (25(OH)D below 30/50 nmol/L) is in the range of 3–17% and 30–70% in older adults across US, China, and Europe [182,183]. Vitamin D deficiency often co-occurs with negative health outcomes, including frailty and sarcopenia [184]. The mechanisms whereby vitamin D might influence the aging muscle are unclear. Vitamin D receptor (VDR) and the mitochondrial enzyme 25(OH)D-1-alpha hydroxylase, which are expressed in muscle tissue, may play a role [185,186]. VDR knockout mice show reduced size and number of muscle fibers [187]. In human muscle, VDR expression declines with age [186]. In a small sample of older women with reduced physical function, 4-month daily supplementation with 4000 IU vitamin D_3 induced a greater increase in intramyonuclear VDR protein concentration compared with placebo, with a more evident effect in type II fibers [188].

Several observational studies linked vitamin D status to muscle strength and function in older adults. In the Longitudinal Aging Study Amsterdam, older participants with severe vitamin D deficiency (25[OH]D_3 < 25 nmol/L) showed lower physical performance and a twofold greater risk of sarcopenia compared with those with no deficiency [189]. In both active and inactive adults older than 60 from NHANES III, 25(OH)D_3 levels between 40 and 94 nmol/L were associated with faster walking speed and sit-to-stand test compared with those with vitamin D concentrations <40 nmol/L [190]. In middle-aged and older adults from the West China Health and Aging Trend study, vitamin D deficiency was an independent risk factor for sarcopenia [191].

Systematic reviews and meta-analyses of trials of vitamin D supplementation to improve sarcopenia-related parameters in older adults reported mixed results [192–194]. Earlier meta-analyses showed beneficial effects of vitamin D supplementation on muscle strength and function in older adults with vitamin D deficiency [192,193]. However,

a recent meta-analysis of 10 randomized clinical trials reported no improvements from vitamin D monotherapy in any sarcopenia indices in community-dwelling older adults [194]. The PROVIDE study showed that 13-week administration of a supplement containing vitamin D and leucine-enriched whey protein improved muscle mass and lower-extremity function in community-dwelling older adults with sarcopenia [195]. The additive benefit of vitamin D supplementation on sarcopenia is supported by a recent meta-analysis of intervention studies testing vitamin D combined with protein supplementation [196].

Collectively, intervention trials suggest that creatine, long-chain PUFAs, and vitamin D supplementation may positively affect muscle mass, strength, and function, especially in older adults engaged in resistance training. Further studies are needed to assess the optimal dose and length of interventions, the duration of the beneficial effects, and the combination of supplement ingredients with better muscle outcomes in older adults.

2.5. Probiotics, nitrate-rich foods, and nutraceuticals

Emerging evidence suggests that changes in the structure and function of gut microbiota influence muscle homeostasis and overall physical function [197]. Experimental models of microbiota depletion, such as germ-free and antibiotic-treated mice, showed reduced muscle mass and function relative to controls [198]. An altered gut microbiota composition, encompassing lower bacterial diversity and declines in the relative abundance of "beneficial" Lactobacilli, Bifidobacteria, and butyrate-producing bacteria (e.g., *Faecalibacterium prausnitzii*), has been described in older adults with frailty and sarcopenia [199,200]. Gut microbiota may impact muscle physiology through several mechanisms, including modulation of the intestinal digestion of dietary amino acids [201,202], regulation of host glycemic control [203], and the fine-tuning of inflammatory and redox status [204,205]. Therefore, the "gut-muscle axis" has been proposed as a possible target for the development of interventions against physical frailty and sarcopenia [197,206]. Preclinical data showed that the supplementation of different Lactobacillus strains attenuated the age-related decline in muscle mass and strength in mice, through a reduction of circulating pro-inflammatory signals, inhibition of muscle atrophy programs, and stimulation of muscle mitochondrial biogenesis [207–210]. Moreover, fecal microbial transplantation from high-functioning older adults to germ-free mice induced greater increase in muscle strength than colonization with fecal samples from low-functioning individuals [211]. A recent systematic review and meta-analysis of randomized clinical trials showed that probiotic supplementation induced positive effects on muscle mass in younger adults and improved global muscle strength parameters in those 50 years or older, only when interventions lasted for at least 12 weeks [212].

Changes in the bacterial ecosystem of the gastrointestinal tract may also modulate (and be modulated by) the availability and activity of most nutritional factors proposed as remedies for sarcopenia. For instance, nitrate-rich foods, including beetroot juice, exert some of their potential beneficial effects via a two-way relationship with host microbes. Beetroot juice increases nitric oxide (NO) bioavailability through non-canonical nitrate-nitrite-NO pathway, involving the conversion of nitrate to nitrite in the oral cavity by commensal bacteria [213]. Through increasing systemic NO levels, beetroot juice regulates mitochondrial respiration, lowers oxygen cost of exercise [214], enhances skeletal muscle contractile properties [215], and improves blood perfusion and nutrient delivery to muscle and brain [216], thereby positively impacting physical performance [217]. In older adults, beetroot juice supplementation improves endothelial function [218], reduces blood pressure, and ameliorates exercise tolerance [219]. However, in a recent intervention trial beetroot juice supplementation did not substantially impact physical performance in older adults engaged in a six-week aerobic exercise program [220].

Gut microbiota influence the metabolic fate of a wide range of food-derived bioactive substances that could stimulate specific cellular pathways involved in the health-promoting effects of high-quality diets and physical activity [221]. Several nutraceuticals, including resveratrol (found in the skin of grapes) [222], quercetin (from capers and red onion) [223], ursolic acid (from apple peel and herbs) [224], urolithins (derived from bacterial transformation of ellagitannins from pomegranate) [225], fisetin (found in strawberries) [226], and nicotinamide riboside (a trace element in milk and precursor of nicotinamide adenine dinucleotide [NAD]) [227], are increasingly studied in the context of sarcopenia for their potential effects on multiple pathogenic pathways. Although studies in vitro and rodent models have shown promising results, evidence in human muscle aging is inconclusive [228–230].

3. Novel technologies to develop individualized nutritional plans

The growing availability of biological and clinical data gathered from electronic health records, wearable and ambient sensors, and multi-omics platforms has paved the way for the definition of a person's unique physiology and early detection of incident medical conditions [231]. Precision medicine approaches have also been applied in the field of nutrition to predict individualized metabolic response to specific foods or test meals, based on individual genetic, clinical, gut microbiome, and lifestyle characteristics [232–234]. For instance, in the Personalized REsponses to Dietary Composition clinical Trial, a combination of standard clinical parameters, lifestyle characteristics (e.g., meal composition and timing, sleep, exercise), and multi-omics data has shown to predict glycemic and triglyceride responses to food intake in a cohort of about 1000 adults [233]. A large inter-individual variability was found in blood glucose, insulin, and triglycerides following the consumption of identical meals, which was at least partly explained by modifiable factors, such as temporal sequence and composition of meals, physical activity, and sleep patterns [233].

In this context, it was recently shown that alterations in sleep and circadian clocks may play a role in muscle aging [235]. A U-shaped relationship was found between sleep duration and sarcopenia in older adults, with a higher prevalence of sarcopenia in those who slept <6 h or >8 h on a regular basis, independent of several confounding variables (e.g., age, BMI, physical activity, energy intake) [236,237]. Moreover, older adults with an evening chronotype (i.e., those who are more active in the evening, go to sleep and wake up late) may be at increased risk of sarcopenia, independent of sleep length [238]. A recent study from KHANES showed that disruption of circadian rhythm in shift workers with irregular schedule was associated with higher odds of sarcopenia [239].

Preclinical data suggest that the circadian clock influences several aspects of muscle physiology, including MPS and MPD, and may be entrained by physical activity and the feeding/fasting cycle [235]. Atrophy-related genes, such as Atrogin1 (F-box protein 32) and Muscle RING-finger protein-1 (Murf1) show circadian rhythmicity and are modulated by master clock regulators, i.e., Brain and Muscle ARNT-like protein 1 (BMAL1) and REV-ERBα [240]. Disruption of BMAL1 activity impairs lipid and glucose metabolism, and induces protein catabolism [240]. Phosphorylation of BMAL1 via the mTORC1-S6K signaling regulates the diurnal variation in protein translation across different tissues, including liver and muscle [241]. Based on these observations, chrono-nutrition approaches have been suggested to preserve muscle mass in older adults, which focus on the administration of key nutrients during the active phase (e.g., high-protein intake at breakfast) to support muscle growth and ameliorate age-related disruption of circadian clocks [235].

The implementation of precision medicine approaches could help unveil the role of sleep and circadian rhythm in muscle homeostasis, and devise interventions that fine tune the timing of both nutrition and physical activity to prevent aging-related muscle loss and dysfunction.

A recent study evaluated the link between self-reported dietary

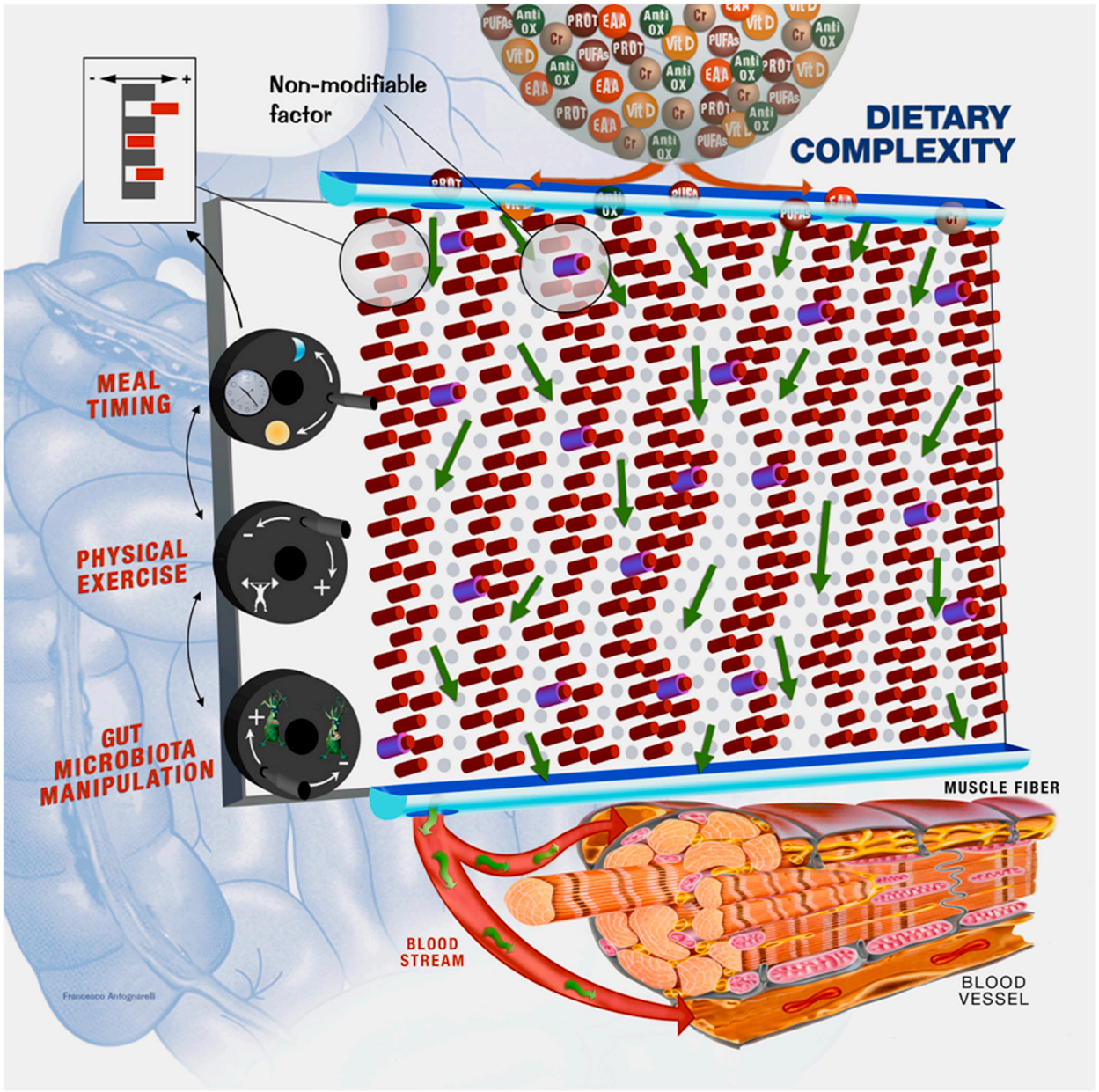

Fig. 2. Precision nutrition approach for sarcopenia: The dynamic "Pachinko model". The mechanism of operation of a Pachinko machine (Japanese pinball) may be used as a metaphor to depict the intricate ways whereby nutrition and other lifestyle factors interact to influence muscle physiology. This model was originally proposed by Nicholson and Wilson in 2003 [244] to represent the metabolism of xenobiotics. Nutrition may be viewed as a flow of balls (dietary ingredients) through the "human pinball". The metabolic destiny of nutrients and their influence on muscle physiology are probabilistic and controlled by numerous variables (shown by pins). Pins can be classified into two categories. One group refers to immutable factors, such as age, sex, genetic background, etc. The other pins include dynamic parameters, such as epigenetic modifications, enzyme activity, body temperature, biofluid pH, hemodynamic variables, etc., that can be controlled (figure inset) via hypothetical "control knobs". Knobs are external factors and stimuli (e.g., meal timing, exercise, gut microbial activities) that may be modulated to maximize the effects of nutrition on muscle parameters. According to the Pachinko model of nutrition, muscle health can be impacted through changing the content of a person's diet and/or acting on "control knobs". This dynamic model exemplifies the multiple sources of complexity to be disentangled to develop a truly personalized intervention against sarcopenia. Abbreviations: Anti-Ox: antioxidants; Cr: creatine; EAA: essential amino acids; Prot: proteins; PUFAs: PolyUnsaturated Fatty Acids; Vit D: vitamin D. Reproduced with permission from [68].

patterns, metabolic profiles, and long-term incidence of diabetes and cardiovascular disease in a large cohort of young adults from the Coronary Artery Risk Development in Young Adults study [242]. A set of metabolites associated with specific dietary food groups and patterns, and/or derived by gut microbiota activity were identified, which were more strongly linked to cardiometabolic outcomes than data obtained through traditional dietary survey methods.

To overcome limitations of self-reported dietary assessment, novel electronic tools have been developed to assess food intake in older adults, including web- or computer-based applications with user-friendly interfaces [243].

The adoption of precision nutrition approaches could assist in characterizing metabolic response to foods and supplements in older adults at risk of sarcopenia at the individual level (Fig. 2), devising tailored nutritional interventions, and monitoring their effects over time.

Before such innovative strategies can be implemented in the sarcopenia context, some limitations should be overcome, including costs

Table 3
Ongoing registered clinical studies testing nutritional interventions against sarcopenia in older adults.

Study title	Sarcopenia definition/criteria	Study Population	Intervention(s)	Primary outcome measure(s)	Sponsor	CT Identifier
Multidisciplinary Combined Exercise and Nutrition Intervention for Sarcopenia (MENTORS)	Asian Working Group for Sarcopenia (AWGS) 2019	168 community-dwellers 65-90 yrs. with metabolic syndrome	Experimental: individualized diet + high-protein drink + multimodal exercise Comparator: usual care Intervention duration: 12 weeks	Performance on the chair stand test	Seoul National University Bundang Hospital (South Korea)	NCT04948736
Exercise and Nutrition for Healthy AgeiNg (ENHANce)	European Working Group on Sarcopenia in Older People (EWGSOP2)	180 older adults (65+ yrs) residing in community or assisted living	1) Resistance exercise + protein placebo + omega-3 fatty acids placebo 2) Protein + omega-3 fatty acids placebo 3) Resistance exercise + protein + omega-3 fatty acids placebo 4) Resistance exercise +protein + omega-3 fatty acids 5) protein placebo + omega-3 fatty acids placebo Intervention duration: 12 weeks	Physical performance measured by SPPB	Universitaire Ziekenhuizen KU Leuven (Belgium)	NCT03649698
Protein Supplement and Exercise Training for the Treatment of Malnutrition and Sarcopenia Risk in Older Adults (POWER)	European Working Group on Sarcopenia in Older People (EWGSOP2)	40 older adults (70+ yrs) requiring supportive homecare	Experimental: Whey protein ONS enriched with leucine and vitamin D + resistance exercise Comparator: Resistance exercise Intervention duration: 12 weeks	Nutritional status assessed by MNA-FF	University College Dublin (Ireland)	NCT05688956
Culinary Medicine to Enhance Protein Intake on Muscle Quality in Older Adults		62 community-dwellers >65 yrs	Experimental: Coaching on high-protein diet from lean ground beef via cooking and educational videos Comparator: control recipes via electronic links Intervention duration: 16 weeks	Lean body and fat mass measured by DXA	Texas Tech University (USA)	NCT05593978
Impact of Protein and Alkali Supplementation on Skeletal Muscle in Older Adults		120 community-dwellers >65 yrs	1) Whey protein isolate (1.5 g/kg/d) + potassium bicarbonate (81 mmol/d) 2) Whey protein isolate (1.5 g/kg/d) + cellulose capsules 3) Isocaloric placebo maltodextrin powder + potassium bicarbonate (81 mmol/d) 4) Maltodextrin powder + cellulose capsules Intervention duration: 24 weeks	Muscle power of lower extremities measure by leg press	Tufts University (USA)	NCT04048616
Effect of Fermented Milk Containing *Lactobacillus Casei* Strain Shirota in Sarcopenia Elderly	Asian Working Group for Sarcopenia (AWGS) 2019	120 community-dwellers 65-85 yrs	Experimental: 2 bottles of fermented milk containing *Lactobacillus Casei* strain Shirota per day Control group: no intervention Intervention duration: 12 weeks	Gut microbiota composition, lean body mass measured by BIA, nutritional parameters	Taipei Medical University (Taiwan)	NCT04985877
The Effect of a Combined Personalized Nutritional Intervention and a Personalized Graded Activity Functional Training Program on Physical Performance in Hospitalized Patients at Risk for Sarcopenia, Compared to Usual Care (FITFOOD)		136 hospitalized patients ≥50 yrs	Experimental: FITFOOD lifestyle intervention (lifestyle intervention with nutritional + exercise) Control: standard care	Performance on the timed up & go test	Radboud University Medical Center (The Netherlands)	NCT05413616
Impact of Diet on the Gut-Muscle Axis in Older Adults	Not specified	24 community-dwellers >65 yrs	Experimental: low-soluble fiber diet Active comparator: high-soluble fiber diet Intervention duration: 12 weeks	Lean body mass measured by DXA, handgrip strength, chair stand test	Tufts University (USA)	NCT05549622
Impacts of Nicotinamide Riboside on Functional Capacity and Muscle Physiology in Older Veterans (NR-VET)	Not specified	144 community-dwellers 65-85 YRS	Experimental: Nicotinamide riboside 1000 mg per day Placebo comparator: Microcellulose pills Intervention duration: 12 weeks	Maximal oxygen uptake, handgrip and leg strength, gait speed	VA Office of Research and Development (USA)	NCT04691986
Dietary Strategy to Tackle Sarcopenia in Early Elderly Subjects (FOOP-Sarc) (FOOP-Sarc)	Low handgrip strength (men <27 kg; women <16 kg) or low gait speed (≤0.8 m/s)	135 community-dwellers 60-74 yrs	Experimental: 1) Virgin olive oil (30 mL/d) rich in phenolic compounds (500 ppm), maltodextrin (7.5 g/d), and nutritional and physical activity recommendations 2) Virgin olive oil (30 mL/d) rich	Muscle mass measured by MRI at the third lumbar vertebra	University Rovira i Virgili (Spain)	NCT05485402

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Table 3 (*continued*)

Study title	Sarcopenia definition/criteria	Study Population	Intervention(s)	Primary outcome measure(s)	Sponsor	CT Identifier
			in phenolic compounds (500 ppm), prebiotic supplementation (FOS and inulin, 7.5 g/d), and nutritional and physical activity recommendations Placebo comparator: Virgin olive oil (30 mL/d; phenolic compound contents, 80 ppm), maltodextrin (7.5 g/d), and nutritional and physical activity recommendations Intervention duration: 12 weeks			
Fish Protein Supplementation and Sarcopenia Outcomes in the Community (SARCO_COMM)		150 community-dwellers 50–70 yrs	Experimental: Blue whiting protein hydrolysates (12.5 g twice daily) Placebo comparator: Isocalorific maltodextrin citrus flavored powder Intervention duration: 8 weeks	Lean body mass measured by BIA	University of Ulster (United Kingdom)	NCT05356559
The Effect of a 12-week Self-composed Vegan Diet With or Without Concurrent Resistance Exercise on Thigh Muscle Volume in Older Adults (Vold)		72 community-dwellers≥65 yrs	Experimental: 1) Vegan diet (self-composed, fully plant-based diet) 2) Vegan diet + biweekly resistance exercise Active comparator: Omnivorous diet Intervention duration: 12 weeks	Thigh muscle volume by MRI	Wageningen University (United Kingdom)	NCT05809466

Abbreviations: BIA, bioelectrical impedance analysis; DXA, dual energy X-ray absorptiometry; FOS, fructooligosaccharides; MNA-FF, mini nutritional assessment – full form; MRI, magnetic resonance imaging; ONS, oral nutritional supplement; SPPB, short physical performance battery.

associated with multi-omics analyses and the low acceptability of mobile health applications by older adults, due to negative attitudes toward technologies and difficulties in handling sophisticated devices [245].

4. Summary and conclusions

Sarcopenia is a challenging geriatric condition. Its complex pathophysiology and heterogeneous clinical expression have hindered the development of effective preventive measures as well as the definition of therapeutic interventions. The combination of high-quality diets (rich in fruits and vegetables), adequate protein intake (high in leucine), and hydration is the cornerstone of nutritional plans to contrast sarcopenia. Novel nutrient candidates and technologies are entering the scene (Table 3).

The advent of precision nutrition approaches will likely set the stage for the definition of truly personalized diets tailored to the older person's needs (Fig. 2). Before this can be implemented in the clinical realm, some practical issues should be addressed. The efficacy, feasibility, and sustainability of precision nutrition approaches should be demonstrated in older adults with sarcopenia through well-designed clinical trials. The availability of digital health and omics technologies at reasonable costs is a critical element to address. Another crucial point is the definition of the optimal combination of nutritional and exercise interventions to contrast sarcopenia.

Both aerobic and resistance training elicit beneficial adaptions in the aging muscle [246]. To simplify, aerobic exercise mainly induces improvements in aerobic fitness (i.e., increase in maximal oxygen uptake) and/or exercise performance (e.g., time-to-exhaustion), while resistance training leads to gains in muscle size (hypertrophy), strength, and power [246]. However, responses to exercise vary substantially depending on the characteristics of the training performed (e.g., frequency, intensity, load, duration of sessions) [246].

Physical activity guidelines by the WHO recommend older adults engaging in 150 min of moderate-intensity or 75 min of vigorous-intensity aerobic activity plus at least two sessions of resistance training weekly [247]. However, this broad advice may not be the optimal exercise prescription for older adults with or at risk of sarcopenia. A recent international experts' consensus advocates high-intensity resistance training to prevent or manage sarcopenia, and suggests a personalized approach based on the intended outcome (e.g., primary prevention, improvement in functional status) [248].

While physical activity is the key element of lifestyle interventions against sarcopenia, the additive effects of most nutritional ingredients is controversial [125]. The identification of the best timing for nutritional intervention is another major point to be explored. The EWGSOP2 diagnostic algorithm suggests prescription of nutritional and physical activity interventions as soon as low muscle strength is ascertained. Knowledge of lifetime trajectories of muscle parameters could allow individuals at risk of sarcopenia to be identified and treated well before the condition reaches its clinical expression (Fig. 3). Like other major chronic conditions, diet (together with physical activity) should therefore be viewed as a key intervention for the primordial prevention of sarcopenia. A lifelong approach should also be envisaged. In this regard, a developmental origin of sarcopenia has been hypothesized, which suggests that birth weight, early childhood, and pubertal growth may influence muscle parameters and physical function in late life [249]. There is no clear evidence on the minimum duration of nutritional interventions to achieve clinically meaningful changes in muscle mass and function. It is also unknown whether nutritional supplementation induces a linear improvement in muscle parameters over time or a ceiling effect occurs before substantial gains in muscle health are achieved. Finally, it needs to be established whether specific nutritional factors differentially impact clinical features of sarcopenia (and overall health) at different stages of life. In this context, further research is needed to unravel the controversial role of mTOR in muscle aging. While stimulation of mTOR pathway is critical for MPS, calorie/protein restriction and, in some cases, resistance exercise may exert their protective actions against sarcopenia through the inhibition of mTOR and the induction of autophagy [24]. These seemingly conflicting findings may be explained, at least partly, by the existence of mTOR-independent signaling pathways that influence MPS and MPD [24] and/or by the differential role of mTOR/AMPK pathways across life stages [250].

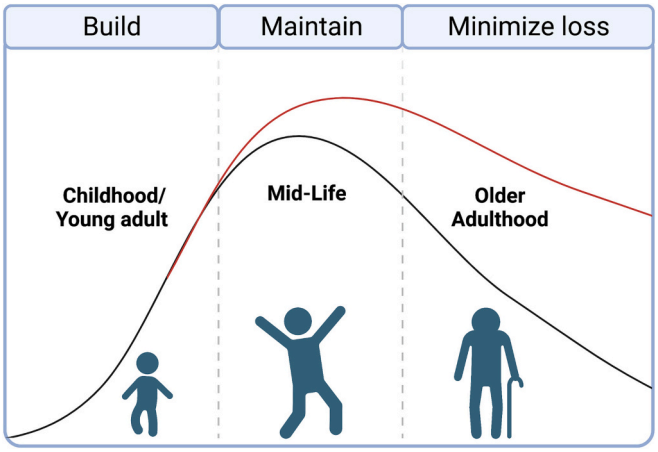

Fig. 3. Lifelong approach to prevent and manage sarcopenia. Muscle mass (red line) and strength/function (black line) follow similar trajectories over the course of life. A sharp increase in muscle mass and strength/function occurs during childhood and young adulthood phase, at the end of which all muscle parameters peak. Around the age of 40-45, a slow decline begins, which is more evident for muscle strength/function than for muscle mass. Later in life, a steeper decline in muscle strength/function ensues. It follows that strategies to contrast the development and progression of sarcopenia should be started early in life and continued throughout. In childhood/young adulthood, nutrition and exercise should be focused on building muscle mass and strength/function. This is a critical phase, as the peak reached at this stage will affect muscle parameters later in life. In middle age, interventions should aim at maintaining peak levels reached in young adulthood. Middle age is the life stage during which the prevalence of "unhealthy" behaviors (e.g., reduced physical activity) increases. Interventions in late adulthood should focus on minimizing losses in muscle mass and strength/function. Nutritional recommendations at all life stages include the consumption of high-quality diets, adequate (age-specific) intake of high quality (high in leucine) protein, and hydration. Diet serves as a support to physical activity, that represents the main intervention to build and preserve muscle mass, strength, and function. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

In conclusion, early identification and correction of malnutrition are key elements to prevent and manage sarcopenia. In the near future, the use of precision nutrition strategies and the widespread of digital health technologies will allow moving from population-based, "one size fits all" dietary recommendations to targeted dietary approach to slow muscle mass decline, preserve independence, and foster quality of life in old age.

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CRediT authorship contribution statement

Riccardo Calvani: Conceptualization, Investigation, Writing – original draft. **Anna Picca:** Conceptualization, Writing – review & editing, Visualization. **Hélio José Coelho-Júnior:** Investigation, Writing – review & editing. **Matteo Tosato:** Investigation, Writing – review & editing. **Emanuele Marzetti:** Conceptualization, Writing – review & editing, Supervision. **Francesco Landi:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

Declarations of interest: E.M. has received personal fees from Abbott, Difass International, Nestlé, and Pfizer.

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