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Nutrition and physical activity for the prevention and treatment of age-related sarcopenia

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Sarcopenia, defined as loss of skeletal muscle mass and function, is associated with adverse outcomes such as physical disability, impaired quality of life and increased mortality. Several mechanisms are involved in the development of sarcopenia. Potentially modifiable factors include nutrition and physical activity. Protein metabolism is central to the nutritional issues, along with other potentially modifying nutritional factors as energy balance and vitamin D status. An increasing but still incomplete knowledge base has generated recent recommendations on an increased protein intake in the elderly. Several factors beyond the total amount of protein consumed emerge as potentially important in this context. A recent summit examined three hypotheses: (1) A meal threshold; habitually consuming 25–30 g protein at breakfast, lunch and dinner provides sufficient protein to effectively stimulate muscle protein anabolism; (2) Protein quality; including high-quality protein at each meal improves postprandial muscle protein synthesis; and (3) performing physical activity in close temporal proximity to a high-quality protein meal enhances muscle anabolism. Optimising the potential for muscle protein anabolism by consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, appears as a promising strategy to prevent or delay the onset of sarcopenia. However, results of interventions are inconsistent, and well-designed, standardised studies evaluating exercise or nutrition interventions are needed before guidelines can be developed for the prevention and treatment of age-related sarcopenia.

Sarcopenia: Ageing: Protein: Vitamin D

Life expectancy at birth has increased rapidly in the last century, due to economic growth worldwide manifested by reductions in infant mortality, improved standards of living, better lifestyles and education, as well as increased quality and availability of health care[1,2]. In 2012, the share of the population aged 65 years and above in the European Union was about 18 % of the total population[1] and is expected to increase to one-third of the total population by 2060[3]. The share of the population aged 80 years and older is projected to almost triple between 2011 and 2060. As a result of the demographic transition, the old-age dependency ratio is projected to be more than doubled from 27 % in 2012 to 53 % by 2060[1,3].

Life expectancy in Europe is generally higher than in most other regions of the world, but it varies between countries. For example, a female born in 2012 is expected to live between 77·9 years (Bulgaria) and 85·5 years (Spain), a difference of 7·6 years. A man born in 2012 can be expected to live between 68·4 years (Lithuania) and 79·9 years (Sweden), a variation of 11·5 years[1].

The growing ageing population is a global phenomenon[4]. Between 1970 and 2025 an increase of about 694 million (223 %) of people aged 60 years and older is expected. In 2050, the projection is 2 billion elderly worldwide, 80 % of them living in developing countries,

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and the fastest growing segment of the older population will be that of 80 years and older[4].

In response to the demographic challenges, the European Union has taken several actions to facilitate the creation of an active ageing culture in Europe, based on the principle of 'a society for all ages'. Active ageing aims to create more opportunities for older people to continue working and to stay healthy longer.

Definition and classification of ageing

Definitions of elderly may vary between different countries and different cultures, but generally include individuals from the newly retired to those over 100 years old. Thus, older adults cover an age span of more than a generation and imply a great variation in living conditions and exposure to environmental factors, such as housing, health care and lifestyle. Older adults thereby constitute a heterogeneous group in many different aspects, as cognitive, physiological and functional abilities.

Ageing could be described as a continuous and gradual process characterised by great variability among individuals, and could occur in different ways and at different rates, depending on multiple factors such as environmental, cultural, genetic, as well as the presence or absence of chronic disease. Normal ageing is characterised by diminished capacity in all bodily functions as well as in cognitive function. Ageing is often characterised in four different categories: 1. Chronological ageing: years lived by an individual from birth; 2. Biological ageing: the physiological changes of an organ system as it ages; 3. Psychological ageing: changes in sensory and perceptual processes, cognitive abilities, adaptive capacity and personality; and 4. Social ageing: changing roles and relationships with family, friends and society as one gets old.

An individual could vary in ages depending on which category is used. Chronological age is often poorly related to the other categories. Individuals at the same chronological age could have very different physical, physiological, psychological and mental performance, due to influences of genetic factors, lifestyle, and disease or disability. Of prime importance is the functional capacity.

Physiology of ageing

With increasing age all physiological systems will decline in both capacity and function. However, the pace of decline will be different between different individuals and even between different organ system within the same individual[5]. To distinguish between a state of health and illness becomes more complicated as individuals get older. Symptoms of disease often vary and become less obvious for elderly people.

Frailty, sarcopenia and cachexia

Frailty, sarcopenia and cachexia are three terms mutually related to each other within the frame of pathophysiology of ageing. Frailty is a common global health and social care challenge, meaning a state of impaired reserve capacity and resistance to stressors[6]. Frailty is both a physical and cognitive state. It is a result of cumulative decline across multiple physiological systems, causing vulnerability to different adverse health outcomes related to activity limitations, participation restrictions and co-morbidity. It stands for a dynamic progressive process from healthiness to functional decline, ultimately leading to death. Frail elderly have an increased risk of falls and suffer from limited mobility and cognitive capacity, and a dependency on assistance from community, health care and institutional care. Understanding risk factors of frailty is a prerequisite to implement programmes for early detection and management in order to prevent or delay functional decline and enhance vitality and quality of life. Cachexia has been defined as 'a complex metabolic syndrome associated with underlying illness and characterised by loss of muscle with or without loss of fat mass'[7].

The ageing process is associated with several changes in body composition, including loss of muscle mass, as well as loss of strength and function. Since the first use of the term sarcopenia to describe this age-related decrease of muscle mass by Rosenberg[8], definitions have evolved to describe it as 'a syndrome characterised by progressive loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and increased mortality'[9,10]. The European Working Group on Sarcopenia in Older People definition[9] uses both low muscle mass and low muscle function (strength or performance) for the diagnosis of sarcopenia. European Working Group on Sarcopenia in Older People also defines stages as presarcopenia (low muscle mass only), sarcopenia (low muscle mass and low strength or performance) and severe sarcopenia (low muscle mass, strength and performance). Sarcopenia should be distinguished from undernutrition. The relationship between age-related loss of muscle mass and strength is often independent of body mass. When muscle mass is lost but fat mass is elevated the state is called sarcopenic obesity and a suggested definition is 'deficiency of skeletal muscle relative to fat tissue'[11,12].

Loss of muscle mass and function can be caused by multiple mechanisms. The term primary, or age-related sarcopenia is used when no other cause than ageing is evident, while secondary sarcopenia includes categories as disease-related muscle wasting, muscle loss resulting from inactivity and from malnutrition[9].

Nutritional status

Body composition reflects nutritional status, indicating body energy and protein stores. Age-related changes in body composition include decreases in fat free mass, mainly skeletal muscle mass and an increase in body fat, with a large variability between individuals[13]. A number of

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methods have been utilised to estimate body composition, most of them using a two-compartment model where body mass is sub-divided in body fat mass (reflecting energy stores) and fat-free mass (indicating protein content). The fat-free mass thus not only includes skeletal muscle, but also organs and supportive tissues. Anthropometry based on whole-body measurements such as weight and height, usually expressed as BMI (kg/m^2), has been extensively used as an indicator of body composition and its change, but cannot distinguish between fat and lean tissue, including muscle. For most individuals both body weight and height decrease with age. Both low BMI and weight loss are significant risk factors for all causes of mortality, but elevated BMI and body fat seem not to carry the same risk in elderly as in middle age, and even a protective role on health and survival has been observed[14–17]. BMI is a proxy measure for energy stores and for older adults these stores seem to be protective, and also the cardiovascular risk by overweight appears to diminish with age. It has been shown that BMI in the overweight range (25–30) is associated with greater disability-free life expectancy compared to groups of lower and higher BMI[14]. Ageing is associated with changes in body composition not evident by BMI. During weight stability loss of muscle mass is accompanied by fat gain[18–20]. Fat mass *per se* may play a role in age-related loss of muscle mass and quality through different metabolic pathways[19,21]. An increased fat mass decreases the anabolic action of insulin in stimulating protein synthesis. Obesity may also cause fat infiltration in muscle which, mediated through insulin resistance, lipotoxicity and inflammation, and impairs muscle synthesis and muscle strength[22].

Muscle mass measurements

In the context of sarcopenia, muscle mass estimates become a key issue. As mentioned earlier, fat-free mass, often height-adjusted as fat-free mass index (fat-free mass(kg)/height$(m)^2$), can and has been used as a proxy measure of muscle, but more direct determinations require other methods than those based on two-compartment body composition models.

The reference method for measuring muscle is generally regarded as whole-body imaging by MRI using multiple slices[23]. The imaging information could also be obtained by computed tomography; however, the radiation exposure by whole-body computed tomography imaging is generally regarded as unacceptable for this purpose. The whole-body MRI method is very resource and time demanding, and single-slice determinations are therefore most commonly used, as muscle volume determinations from mid-thigh and abdominal images have been shown to correlate with whole-body determinations[24].

Whole-body dual-X-ray absorptiometry scans have also been shown to give valid estimates of muscle mass[25] and give very low radiation exposure. For the purpose of estimating muscle mass, the lean soft tissue of the arms and legs, i.e. appendicular lean soft tissue, is used.

Muscle determinations by dual-X-ray absorptiometry, computed tomography and MRI require a dedicated laboratory setting. For use outside such settings, anthropometry[26] and bioimpedance methods[27–30] have been developed. Anthropometric measures are regarded by European Working Group on Sarcopenia in Older People as vulnerable to error and not recommended for routine use in the diagnosis of sarcopenia[9]. Bioimpedance methods are conceptually attractive, as wrist-to-ankle bioimpedance predominantly measures water-containing tissue in the arms and legs[31], but validation studies are still somewhat limited, although reference values in elderly populations have been published[29,32].

Functional measurements

A number of methods to estimate muscle strength and performance are in use. The European Working Group on Sarcopenia in Older People Report[9] recommends for strength knee flexion/extension, peak expiratory flow and handgrip strength for research purposes and handgrip strength for clinical practice. For performance, Short Physical Performance Battery, usual gait speed, timed get-up-and-go test and stair climb power test are listed for research, and Short Physical Performance Battery, gait speed and get-up-and-go test for clinical practice[9].

Gait speed is associated with survival in older adults[33], and this association seems to be robust and valid for both males and females, while for muscle mass estimates the relation is less clear and may be different in males and females[32]. It should also be noted that application of different measurement criteria for sarcopenia may yield widely different prevalence estimates in a population[34]. Nevertheless, sarcopenia prevalence was reported by the International Sarcopenia Initiative to be 1–29 % in community-dwelling populations, 14–33 % in long-term care populations and 10 % in the only acute hospital-care population examined[35].

Nutrition and ageing

The progressive loss of function over time that characterises ageing appears to result from accumulation of damage to cellular macromolecules[36]. Nutrition may modulate the ageing process in several ways, as recently reviewed by Mathers[37]. Energy restriction increases lifespan in several animal models, but its effects in primates and human subjects are uncertain. However, translating available data from studies in primates suggests that avoiding obesity may improve healthy ageing[37].

As long as old adults stay healthy, an adequate energy and nutrient intake based on good food habits is generally considered optimal. With ageing, energy needs decrease mainly due to less physical activity. However, micronutrient needs do not necessarily decrease, implying that for elderly with reduced appetite there is a need to increase nutrient density of the food they consume. For most micronutrients the scientific evidence for daily intake recommendations specific for elderly is still scarce. However, several studies have examined protein and vitamin D supplements for old adults.

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Nutrition and sarcopenia

Vitamin D

In the US and Nordic Nutrition Recommendations, for vitamin D, a level of 20 μg/d is recommended for older adults, 5–10 μg more than that for young adult populations[38,39]. Insufficient vitamin D status is common in elderly. Also, the capacity to metabolise vitamin D decreases by age for several reasons: time spent outdoors may be limited; the amount of 7-dehydrocholesterol in the skin epidermis diminishes with age; and the conversion of this precursor into vitamin D becomes less effective[40–42]. A recent literature review concluded that there is a convincing evidence of the protective effect of vitamin D against bone deficiency, total mortality and the risk of falling[43]. The effect was seen in persons with low basal serum 25-OH-vitamin D concentrations (<50 nM/l). In intervention studies, effects were seen for combined supplementation of vitamin D and calcium[43]. Two recent recommendations suggest 50 nM/l as optimal status[38,39], but the question of what is an optimal status is controversial and some researchers are in favour of higher levels than 50 nM/l[44–46]. There is, however, some epidemiological evidence that very high blood levels are associated with increased total mortality[43]. Vitamin D has also important roles in many other physiological systems such as the immune system, the pancreatic β-cells, brain and muscle[46].

One important target tissue is muscle. It has been shown that lower 25-OH-vitamin D and higher parathyroid hormone levels are associated with risk of sarcopenia in older adults[47]. In addition, deficiency has been reported to affect predominantly the weight-bearing muscles of the lower limb, which are necessary for postural balance and walking[48], and a significant correlation between serum levels and the occurrence of falls has been shown[49–51]. Positive effects of supplementation has been shown on hand grip strength, proximal lower limb strength as well as hip muscle strength[43]. Mechanisms are still unclear, but in animal models vitamin D pathways regulate muscle development and in cultured muscle cells vitamin D signalling alters various molecular pathways[52].

n-*3 Fatty acids*

The blunted anabolic response to nutritional stimuli in ageing muscle cells is partly due to an impaired anabolic signalling cascade (i.e. decreased activation of the mammalian target of rapamycin signalling pathway)[53,54], which may be mediated by increased inflammatory activity[22,55]. *n*-3 Fatty acids have been shown to stimulate protein anabolism in animals. If this effect is relevant also for human subjects it is not fully confirmed but a clinical trial has shown promising results[56]. Supplementation with dietary *n*-3 fatty acid increased muscle anabolic signalling activity and the insulin/amino acid-mediated increase in muscle protein synthesis. The exact mechanisms by which *n*-3 fatty acids stimulate muscle protein synthesis during hyperinsulinaemia–hyperaminoacidaemia remain however to be resolved[57].

Protein

Protein is necessary for synthesis of fat-free mass, metabolic processes, and to offset inflammatory and catabolic conditions associated with chronic and acute diseases that occur commonly with ageing[58]. A recent systematic review suggests that the evidence for optimal protein intake relates to functional outcomes such as maintenance of bone mass, muscle mass and strength as well as morbidity, and suggest a safe intake of up to at least 1·2–1·5 g protein/kg body weight/d or approximately 15–20 E %[59].

Maintenance of muscle mass depends on the balance between muscle protein synthesis and breakdown. Feeding induces a postprandial net protein accretion that normally compensates for losses in the postabsorptive period[60]. Major drivers are the availability of amino acids, especially leucine, physical activity and hormonal signals, particularly insulin and insulin-like growth factor-1[61]. In ageing, this anabolic response decreases, though available data suggest that muscle protein anabolism can still be stimulated in the elderly by higher amino acid availability[60–62]. Thus, the prevailing nutritional strategy to overcome this 'anabolic resistance' and maintain muscle mass and function is to increase amino acid (leucine) availability, in combination with physical activity, especially resistance exercise[11].

In addition to the amount of protein ingested in a meal, postprandial amino acid availability depends on factors such as rate of digestion, absorption and splanchnic extraction. The concept of 'slow' *v.* 'fast' proteins has been proposed to describe this[60], and e.g. whey protein is considered to have advantages in this respect[63]. Thus, postprandial muscle protein synthesis response depends on the amount of protein ingested, its digestibility and rate of absorption, and amino acid profile, i.e. content of essential amino acids, especially leucine.

A recent summit examined current understanding of the role of protein in healthy ageing, with the hypothesis that 'throughout adult life, consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, may prevent the onset or slow the progression of sarcopenia'[64]. The conclusion was that skeletal muscle mass and function are influenced by a variety of modifiable behaviours, and that three hypotheses/recommendations represent a promising strategy to prevent or delay the onset of sarcopenia: (1) habitually consume 25–30 g protein at breakfast, lunch and dinner; (2) include a variety of high-quality proteins at each meal; and (3) perform physical activity in close temporal proximity to a protein-rich meal[64].

Physical activity

A contributing factor to the development of sarcopenia is inactivity followed by anabolic resistance[65]. Immobilisation induces resistance of muscle to anabolic stimulation[66]. Age-related muscle loss is primarily due to decreased postprandial muscle protein synthesis rather than increased breakdown[11,65]. Inactivity induces anabolic resistance[65], and a reduction of physical activity for 2 weeks was shown

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to induce anabolic resistance in older adults, with decreased postprandial protein synthesis, decreased insulin sensitivity, and decreases in leg muscle mass[67]. Ageing muscle is still able to respond to increased activity, especially resistance exercise[68]. A meta-analysis in older adults indicated clear effects of progressive resistance training on muscle function[69].

Increased insulin sensitivity, improved glucose utilisation[70] and[71] enhanced myofibrillar protein synthesis[72] are proposed mechanisms behind this effect of resistance exercise,[9] but it has also been suggested that exercise-induced improvement in protein synthesis may be due to nutrient-stimulated vasodilation and nutrient delivery to muscle rather than to improved insulin signalling[73].

The International Sarcopenia Initiative Report[35] also concluded that exercise interventions appear to have a role in increasing muscle strength and improving physical performance, although they do not seem to consistently increase muscle mass, in frail older individuals. It was noted that improved standardisation of exercise interventions is needed, along with common outcome measures, and that future interventions should focus on well-defined populations, with well-defined sarcopenia[35].

Effects of combined physical activity and nutrition

The anabolic response to dietary protein or amino acids and insulin is limited in ageing muscles, but a combination effect of physical activity and nutrition stimulates muscle protein synthesis. Both endurance- and resistance exercises are recommended at individualised levels that are safe and tolerated. Several recent reviews have examined the effects of nutritional and physical activity interventions on sarcopenia[35,74–78], with inconsistent results. Cermak *et al.*[74] included data from twenty-two randomised controlled trials with 680 subjects and concluded that protein supplementation increases muscle mass and strength gains during resistance training in both younger and older subjects. Malafarina *et al.*[78] examined seventeen studies with 1287 patients, and concluded that nutritional supplementation is effective, and that effects increase when associated with physical exercise. Finger *et al.*[76] examined effects of protein supplementation in older adults during resistance training and concluded, from data on nine randomised controlled trials with 462 subjects, that protein supplementation is effective to gain fat-free mass, but does not seem to increase muscle mass or strength. Denison *et al.*[75] examined effects of combined nutrition and exercise interventions in seventeen studies in older adults, and concluded that enhanced benefits of exercise training, when combined with dietary supplementation, have been shown in some studies indicating potential for future interventions, but that existing evidence is inconsistent. Hickson[77], reviewing nutrition intervention trials targeting sarcopenia, also found inconsistent effects and concluded that this could be explained by factors like variations in study design, composition of the supplement and failure to monitor voluntary food intake, adherence and baseline nutritional status. The report of the International Sarcopenia Initiative[35] found that moderate quality evidence suggests that exercise interventions improve muscle strength and performance, but that results of nutrition interventions are equivocal due to the low number of studies and heterogeneous study design. Essential amino acid supplements were found to have some effects in improving muscle mass and function parameters, but protein supplements have not shown consistent benefits on muscle mass and function. It is concluded that well-designed, standardised studies evaluating exercise or nutrition interventions are needed before treatment guidelines can be developed[35].

Muscle function is a prerequisite for independence and thereby quality of life. In a demographic situation globally with an increasing proportion of older adults up in very high ages the challenge is to reach more knowledge of how muscle function changes by age and what are proper actions to prevent or delay the onset of the functional decline and sarcopenia.

Conclusions

Loss of muscle mass and function has debilitating effects in the elderly. Optimising the potential for muscle protein anabolism by consuming an adequate amount of high-quality protein at each meal, in combination with physical activity, appears as a promising strategy to prevent or delay the onset of sarcopenia. Other nutritional targets of interest for maintaining muscle mass and function are *n*-3 fatty acids, avoiding obesity and vitamin D deficiency. However, results of interventions are inconsistent, and well-designed, standardised studies evaluating exercise or nutrition interventions are needed before guidelines can be developed for the prevention and treatment of age-related sarcopenia.

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Conflict of interest

None.

Authorship

The authors contributed equally to all aspects of the preparation of this paper.

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