Impact of nutrition on muscle strength and performance in older adults

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Abstract
Summary. With a rapid increase in the aging population across the globe, the prevalence of sarcopenia is likely to increase progressively. This review paper describes the role of nutritional factors in the causation of sarcopenia and suggests potential strategies to attenuate and treat this condition.

Introduction. Muscle strength plays an important role in determining risk for falls, which result in fractures and other injuries. While bone loss has long been recognised as an inevitable consequence of aging, sarcopenia - the gradual loss of skeletal muscle mass and strength that occurs with advancing age - has recently received increased attention. The purpose of this review is to describe the risk factors and etiology of muscle loss, and suggest measures that may help to preserve muscle mass during aging.

Methods. A review of the literature was undertaken to identify nutritional (and other) factors that contribute to loss of muscle mass. Techniques of muscle mass evaluation, and the role of protein, acid-base balance, vitamin D/calcium, and other minor nutrients like B vitamins were reviewed.

Results. Muscle wasting is a multifactorial process involving changes in extrinsic determinants, such as altered nutrition and reduced physical activity, and alterations in intrinsic factors, like an increased expression of the protein myostatin, and reductions in complex auto-paracrine systems involving insulin-like growth factor 1 (IGF-1). An increased proportion of slow muscle fibres, glycation of proteins and insulin resistance may play an important role in the loss of muscle strength and development of sarcopenia. Magnetic resonance imaging (MRI), computed tomography (CT) scanning, dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance are used for muscle mass assessment. Functional evaluation of muscle strength and estimation of physical performance are important clinical tools. Protein intake plays an integral part in muscle health and an intake of 1.0-1.2 g/kg of body weight per day is probably optimum for older adults. In vitamin D deficient elderly, there is a moderate relationship between vitamin D status and muscle strength. Chronic ingestion of dietary acid appears to have a role in development of sarcopenia and a decrease in vitamin B12 and folic acid may also contribute through its action on homocysteine.

Conclusion. While protein intake plays a central role in maintaining muscle mass and strength, multiple nutritional factors including vitamin D/calcium intake, B12 and folic acid may also be important in this regard. Adequate intake of these nutrients and optimal acid-base balance of the diet are important elements of any strategy to preserve muscle mass and strength during aging.
Introduction

The phenomenon of age-related loss of muscle mass was given the name ‘sarcopenia’ by Rosenberg in 1989 [1]. The term is derived from Greek and can be translated to ‘deficiency of muscle’, which quite clearly describes the nature of this condition. Aging has various consequences for the human body and is a process which affects both physical abilities and appearance. Aging is associated with and responsible for bone loss resulting in osteoporosis as well as sarcopenia. Both of these conditions have a negative impact on physical performance and the quality of life. Sarcopenia has been studied in longitudinal population studies and correlated with loss of strength and functional impairment (Fig. 1) [2].

Fig. 1 Life course changes in muscle mass. Taken from [3].

There have been several definitions of sarcopenia, however the term generally describes age-related muscle loss. In 1995, Baumgartner defined sarcopenia as “the gradual loss of skeletal muscle mass and strength that occurs with advancing age” [4]. Baumgartner proposed an operational definition of sarcopenia as appendicular skeletal muscle mass (kg)/height² (m²) of less than 2.0 standard deviations (SDs) or more below the gender-specific mean of a young adult reference group provided by Pichard et al [5, 6]. The comparison to a healthy adult reference group is similar to the definition used to diagnose osteoporosis. Use of Baumgartner’s definition of sarcopenia requires assessment of muscle mass. In a more general sense, sarcopenia is often defined as the loss of muscle mass and muscle function which accompanies advancing age [7]. A recent European Working Group on Sarcopenia recommended that sarcopenia be defined based on the documentation of low muscle mass and either low muscle strength or low physical performance (Table 1) [8].

Table 1 EU working group definition of sarcopenia for clinical and epidemiological studies

<table>
<thead>
<tr>
<th>Diagnosis is based on documentation of criterion 1 plus criterion 2 and/or 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low muscle mass</td>
</tr>
<tr>
<td>2. Low muscle strength</td>
</tr>
<tr>
<td>3. Low physical performance</td>
</tr>
</tbody>
</table>
Sarcopenia increases with age as demonstrated in The Rancho Bernardo Study where prevalence was examined in 1700 community-dwelling men and women aged 55 to 98 years (mean age = 73). In this cohort, the prevalence of sarcopenia (2 SD below a young reference group) increased dramatically from 4% of men and 3% of women aged 70-75 to 16% of men and 13% of women aged 85 or older [9]. This clearly demonstrates the association between age and loss of muscle mass. The prevalence of sarcopenia in the elderly was summarized in a recent review. It varied widely between studies, from 7% to 60% depending on age, gender, and method used to define sarcopenia [see Table 2, 10].

Table 2 Epidemiological studies documenting the prevalence of sarcopenia. Taken from [10]

<table>
<thead>
<tr>
<th>Cohort</th>
<th>n (% female)</th>
<th>Age</th>
<th>Sarcompenia definition (assessment method)</th>
<th>Sarcompenia prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHS (USA)</td>
<td>5036 (56.4%)</td>
<td>&gt;65 years</td>
<td>Categories of skeletal mass index, defined as muscle mass normalized for height (BIA)</td>
<td>Moderate sarcopenia, m: 70.7%, f: 41.9%; severe sarcopenia, m: 17.1%, f: 10.7%</td>
<td>[11]</td>
</tr>
<tr>
<td>EPIDOS (France)</td>
<td>1458 (100%)</td>
<td>All &gt;70 years; Mean 80.3 ± 3.8 years</td>
<td>Appendicular skeletal muscle mass &lt;2 SD below the mean of a young female reference group (DXA)</td>
<td>9.5%</td>
<td>[12]</td>
</tr>
<tr>
<td>InCHIANTI (Italy)</td>
<td>1030 (54.5%)</td>
<td>Range 20–102 years</td>
<td>Calf muscle cross-sectional area more than 2 SD below population mean (CT scan)</td>
<td>m: 20% at 65 years, 70% at 85 years; f: 5% at 65 years, 15% at 85 years</td>
<td>[13]</td>
</tr>
<tr>
<td>NHANES III (USA)</td>
<td>14818</td>
<td>&gt;18 years; 30% &gt;60 years</td>
<td>Skeletal mass index was defined as muscle mass/body mass x 100; sarcopenia class I defined as skeletal muscle mass 1–2 SD, sarcopenia class II defined as skeletal muscle mass &gt;2 SD from the mean of young subjects (BIA)</td>
<td>In subjects aged &gt;60 years: sarcopenia class I, m: 45%, f: 59%; sarcopenia class II: m: 7%, f: 10%</td>
<td>[14]</td>
</tr>
<tr>
<td>NMEHS (USA)</td>
<td>808 (47.3%)</td>
<td>m: 73.6 ± 5.8 years; f: 73.7 ± 6.1 years</td>
<td>Appendicular skeletal muscle mass &lt;2 SD below the mean of a young reference population (substudy of DXA)</td>
<td>&lt;70 years, m: 13.5–16.9%, f: 23.1–24.1%; 70–74 years, m: 18.3–19.8%, f: 33.3–35.1%; 75–80 years, m: 26.7–36.4%, f: 35.3–35.9%; &gt;80 years, m: 52.6–57.6%, f: 43.2–60.0%</td>
<td>[5]</td>
</tr>
</tbody>
</table>

BIA bioelectrical impedance assessment, CHS Cardiovascular Health Study, CT computed tomography, DXA dual-energy X-ray absorptiometry, EPIDOS European Patient Information and Documentation Systems, NHANES National Health and Nutrition Examination Survey, NMEHS New Mexico Elder Health Study, SD standard deviation

Comment: It may be best to Place Tables at end? I do not see reference to Table 2 in the text, so added a small sentence introducing Table would be helpful.
There are different potential causes of sarcopenia but generally the risk factors are poorly understood. Muscle loss occurs during the normal aging process, and is accelerated by physical inactivity or various diseases [15]. Other potential causes can be immobility/disuse due to disability, reduced levels or reduced responsiveness to trophic hormones, poor nutritional status, genetic factors, neuromuscular dysfunction or trauma [16].

As a consequence of demographic changes leading to an increased elderly population, the prevalence of sarcopenia is expected to increase in the future [17]. To reduce sarcopenia, the most obvious and basic intervention is exercise. Resistance training has been demonstrated to be beneficial to rebuild muscle mass and strength in the elderly, however it requires optimal nutritional status to derive optimal benefit of the training [18]. No pharmacological approach is yet available to prevent or treat sarcopenia. Several approaches like hormone replacement have been tested but showed only modest effects [18]. It is therefore appropriate that future clinical research focuses on the development of effective interventions to improve muscle mass and strength in older adults with sarcopenia.

The aim of this manuscript is to discuss the role of dietary factors including intake of vitamin D/calcium, protein and other nutrients, and the acid-base balance of the diet in preserving muscle mass and strength in older adults.

Skeletal muscle in health and disease

The ability of skeletal muscle to shorten and to generate force at the same time is the essential characteristic of this tissue that makes locomotion possible. Skeletal muscle, however, is not only involved in locomotion but is also crucial for respiration, where respiratory failure due to respiratory muscle weakness can be a cause of death in patients with chronic obstructive pulmonary disease and muscle disorders such as Duchenne muscular dystrophy. A substantial loss of appendicular muscle mass can cause such severe weakness that people become unable to perform daily life activities, thus significantly reducing their quality of life. Most studies on sarcopenia are focused on reductions in force generating capacity during an isometric contraction [19-23], but in real life isometric contractions are rarely performed, but rather shortening contractions during which power is generated. Indeed, reductions in the shortening velocity may be as, or even more, important in the prevention of falls in the elderly [24] than the force generating capacity of a muscle. Though the force generating capacity of fibres of the different types is similar [25-28], the shortening velocity of a muscle fibre is largely dependent upon its myosin heavy chain composition, where it is noticeable that fast fibres can generate up to 7-fold more power than slow fibres [26, 29]. With that in mind, the preferential loss and/or atrophy of fast fibres [19, 30, 31], though not always observed [32, 33], is expected to result in a larger reduction in the power than the force generating capacity during aging. In addition to changes in fibre type composition, slowing of the muscle may also occur as a consequence of glycation of myosin molecules [34] that has been observed during aging [35]. Besides slowing of the muscle, an increased tendon compliance may further contribute to the age-related slowing [36].

Skeletal muscle functions not only as a motor, but also as an important metabolic tissue. This is particularly evident in the role of skeletal muscle to store glycogen. During aging, insulin resistance and type 2 diabetes often develop at least partly as a consequence of a
decrease in muscle mass [37]. Neuromuscular junction is likely to be affected as well by aging and be part of age-dependent muscle weakness.

Endurance training enhances the capacity of fatty acid oxidation of skeletal muscle [38], which may help to reduce the development of insulin resistance [39].

Muscle mass is the net result of the balance between protein synthesis and breakdown, which during aging appears to shift to a net increase in protein breakdown. Insulin resistance may be caused by loss of muscle mass, but it in turn also contributes to muscle wasting via impaired insulin signalling, aggravated by low grade systemic inflammation [40, 41]. The systemic inflammation and the accumulation of mini hits over time may cause oxidative stress that would cause further muscle wasting and dysfunction. This process is compounded by a reduced expression of anabolic factors, like the leucine sensitive mammalian target of Rapamycin (mTOR), in old age [40, 42]. Several of these age-related changes that negatively impact on the maintenance of muscle mass and function may be reversed to some extent by adequate nutrition and caloric intake [42].

**Determination of muscle mass and function**

Besides the measurement of muscle mass, functional evaluation of muscle strength and performance, assessment of the subjective components of muscle performance may also be important in both research and clinical settings. The following section will describe some of the techniques available to obtain information of muscle mass and function, respectively. These are summarized in Table 3.

**Muscle mass measurements**

**Magnetic resonance imaging (MRI) and computed tomography (CT)**
MRI and CT provide precise and reliable measurements of the composition of body tissue by visually depicting muscle, fat, and organs. In several studies with cadavers, mid-thigh skeletal muscle areas assessed by MRI or CT were found to exhibit excellent accuracy, with values corresponding to those determined in vivo [43-46]. Data from MRI or CT scans is considered the gold standard; however, these techniques have several limitations including high cost, limited accessibility, and, for CT, significant radiation exposure.

**Dual-energy X-ray absorptiometry (DXA)**
DXA body composition analysis provides total body and regional proportions of fat, bone, and non-fat, non-bone tissue. The latter compartment includes mainly, but not exclusively, muscle. However, since most of the non-fat, non-bone tissue in the lower extremities is skeletal muscle, measurement of this region provides a reasonable estimate of lower extremity muscle mass. Previous studies have shown strong correlations in body composition parameters between DXA and CT or MRI data in adults and adolescents [47-49]. Since DXA is readily available, relatively inexpensive and poses minimal radiation exposure, it is a useful alternative to MRI or CT if these are unavailable.

**Total or partial body potassium scanning**
Total body potassium (TBK) measurement is a classical method to determine the body composition. This technique requires the use of the rare and costly total body gamma counter. Muscle mass is assessed by counting ⁴⁰K, a naturally occurring potassium isotope, which is abundant in skeletal muscle but not in bone or fat tissue. Recently, partial body potassium (PBK) of the arm has been proposed as a somewhat simpler alternative [50].
None of these imaging and scanning instruments is portable.

**Bioelectrical impedance analysis (BIA)**

BIA is a non-invasive, inexpensive method that can be performed with a portable device. With this method one gets an estimate of the proportion of lean and fat body mass. BIA is based on the relation between the volume of a skeletal muscle, a dominant conductor in the body, and its electrical resistance. Under standard conditions, BIA findings correlate well \( r = 0.90 \to 0.98 \) with MRI predictions [51, 52]. Thus, when the above-mentioned devices are unavailable for large-scale epidemiological studies, BIA is a reasonable alternative to predict and to rank muscle mass in field studies. However, caution needs to be exercised as the equation used for calculation may vary with body composition [53].

**Anthropometric measurements**

Measurement of muscle and fat areas in the upper arm is a relatively simple and qualitative measure of nutritional status. The arm muscle mass reflects the reserves of muscle tissue. Anthropometric measurements include the total circumference of the thigh, and the mid-arm circumference minus the thickness of the triceps skinfold [54, 55]. It requires specific training to use skinfold calipers appropriately. Ideally, results in an individual should be compared with the local or regional standards.

**Creatinine excretion**

Creatinine excretion in the urine correlates with total lean body mass \( r = 0.93 \) as assessed by total body \(^{40}\)K counting and with cross-sectional areas of muscle, determined by MRI (upper arm \( r = 0.85 \), thigh \( r = 0.88 \)) in both young and old subjects [56]. This simple biochemical measure was thought to be a useful adjunct in the evaluation of body composition of elderly persons. However, difficulty in collecting 24-hour urine samples in the elderly may make this technique unreliable.

**Functional evaluation of muscle strength**

**Handgrip strength**

Handgrip strength is a convenient, safe and reliable measure of overall muscle strength [57]. It correlates with other measures of strength [58] and with muscle mass [59]. It is measured with a hand-held dynamometer, a simple and accessible device [57] and can be applied in both research and clinical environments. However, conditions of testing have to be well defined and standardised.

**Isokinetic muscle strength**

Isokinetic muscle strength is a measure of maximal muscle tension throughout the full range of motion at constant speed [60]. Slow speed in the range of 30° to 60°/sec is used to assess muscle strength, while fast speeds in the range of 180° to 300°/sec is employed to measure muscle endurance [61]. Muscular tension at slow speeds of motion correlates with muscle mass [62], mimics everyday activities and can be used to evaluate the time-course of changes in muscle function. Muscle strength of knee extensors and flexors is assessed using a standard protocol [60] with a Cybex II isokinetic dynamometer. A familiarisation session is highly advisable as data can be influenced by a learning effect [62].

**Isotonic muscle strength (one repetition maximum [1-RM])**
Muscle strength is assessed by one repetition maximum (1-RM) test conducted using Cybex selectorized weight stack machines for leg press, leg extension, knee flexion and chest press muscles. 1-RM is defined as the maximum load that can be lifted only once using a proper lifting technique. It has been used to monitor changes in muscle strength in diverse populations [63]. Caution should, however, be exercised as increases in 1RM are usually significantly larger than those observed in terms of maximal voluntary isometric force and may well be related to neurological changes rather than changes within the muscle [64].

**Leg power**
Muscle power is defined as the product of muscle force and velocity. With aging, muscle power declines earlier and more dramatically than muscle strength [65]. Muscle power can be assessed in leg extensors. Following measurement of the baseline 1-RM, the percentage of 1-RM at 40 % and 70 % is established. The subjects are asked to perform 5 lifts at each established percentage of 1-RM as fast as possible by using their full range of motion. The highest power output achieved at each % of 1-RM is the peak power and is a reliable measurement in elderly subjects [66].

**Evaluation of physical performance**

**Usual gait speed**
There is a correlation between leg strength and usual gait speed [67]. Some studies have also suggested that timed usual gait is a predictor for the onset of disability [68] and adverse health events (severe mobility limitation, mortality, etc) [69].

**Timed get-up-and-go test**
The subject is instructed to rise from a chair, walk a short distance (3 meters), turn around, return, and sit down again. It thus serves as an assessment of dynamic balance. The balance function is observed and scored on a five-point scale [70].

**One-leg stand test**
This test measures the duration for which one is able to stand on one leg with eyes open and without any support [71]. A review on this test applied in epidemiological research suggests that it is a good indicator of frailty in community-dwelling elderly populations [72].

**Stair-climb power test**
Stair climbing ability is a good indicator of functional capacity in the elderly and is significantly correlated with lower extremity strength and power [73]. Subjects are asked to climb a standard set of stairs as quickly and safely as possible. They may use the handrail if necessary. The test administrator records the time to the nearest 0.01 second when both of the subject’s feet have landed on the top step. Use of handrail is also recorded.

**Short physical performance battery (SPPB)**
This battery of tests evaluates balance, gait, strength and endurance by examining an individual's ability to stand with the feet joined together in semi-tandem and tandem positions, time taken to walk an 8-foot distance and the time taken to rise from a chair and return to the seated position five times back to back (the test ends when the individual stands for the fifth time) [74]. Each of the tests of the SPPB can also be used individually. Recently, SPPB has been recommended by an international working group for use as a functional outcome measure in clinical trials with frail elderly persons [75]. Useful changes in
the SPPB have been previously defined [76, 77]. It is a standard measure for both research and clinical practice.

### Table 3 Evaluation of muscle in research and clinical practice

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Advantages</th>
<th>Limitations</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Muscle mass measurements</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnetic resonance imaging</td>
<td>Precise, reliable, optimal as gold standard, no radiation hazards</td>
<td>Expensive, limited access to equipments, time-consuming</td>
<td>[43-45]</td>
</tr>
<tr>
<td>Computed tomography</td>
<td>Precise, reliable, optimal as gold standard</td>
<td>Expensive, limited access to equipments, X-ray exposure</td>
<td>[45, 46]</td>
</tr>
<tr>
<td>Dual-energy X-ray absorptiometry</td>
<td>Good correlation with CT and MRI data, low radiation exposure</td>
<td>Not portable</td>
<td>[47-49]</td>
</tr>
<tr>
<td>Bioelectric impedance</td>
<td>Non-invasive, inexpensive, portable, reasonable correlation with MRI data</td>
<td>Reference values required for studied population</td>
<td>[51, 52]</td>
</tr>
<tr>
<td>Anthropometry</td>
<td>Simple, non-invasive, inexpensive</td>
<td>Accuracy influenced by confounders</td>
<td>[54, 55]</td>
</tr>
<tr>
<td>Total or partial body potassium</td>
<td>Classical method</td>
<td>Not used routinely</td>
<td>[50]</td>
</tr>
<tr>
<td>Creatinine excretion</td>
<td>Correlates with muscle mass</td>
<td>Lower precision; errors from metabolic factors</td>
<td>[56]</td>
</tr>
<tr>
<td><strong>Functional evaluation of muscle strength</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Handgrip strength</td>
<td>Correlates with muscle mass and other measures of strength</td>
<td>Requires a handheld dynamometer</td>
<td>[57-59]</td>
</tr>
<tr>
<td>Knee extension and flexion strength</td>
<td>Correlates with muscle mass and mimics daily activities</td>
<td>Requires the use of an isokinetic dynamometer</td>
<td>[60-62]</td>
</tr>
<tr>
<td>Isometric muscle strength (One repetition maximum 1-RM)</td>
<td>Monitors changes in muscle strength</td>
<td>Requires weight stack machines for each area to be tested</td>
<td>[63]</td>
</tr>
<tr>
<td>Leg power</td>
<td>Measures peak power reliably in elderly subjects</td>
<td>Requires knowledge of baseline 1-RM</td>
<td>[66]</td>
</tr>
<tr>
<td>Peak expiratory flow</td>
<td>Determines strength of respiratory muscles in a cheap and accessible manner</td>
<td>Limited data available as a measure of muscle strength</td>
<td>[78]</td>
</tr>
<tr>
<td><strong>Physical performance</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Usual gait speed</td>
<td>Predictive value for disability and adverse health events</td>
<td>Proper standardisation required</td>
<td>[67-69]</td>
</tr>
<tr>
<td>Timed “get-up-and-go” Test</td>
<td>Assessment of dynamic balance</td>
<td>Proper standardisation required</td>
<td>[70]</td>
</tr>
<tr>
<td>One-leg standing test</td>
<td>Predictive value for frailty in elderly populations</td>
<td>Proper standardisation required</td>
<td>[71, 72]</td>
</tr>
<tr>
<td>Stair climb power test</td>
<td>Relevant measure of leg power impairment</td>
<td>Proper standardisation required</td>
<td>[73]</td>
</tr>
<tr>
<td>Short physical performance battery</td>
<td>Evaluates balance, gait, strength and endurance. Used as functional outcome measure</td>
<td>Proper standardisation required</td>
<td>[74-77]</td>
</tr>
</tbody>
</table>
The effect of vitamin D and calcium on muscle strength and performance

The relationship between vitamin D status and physical performance was investigated in the National Health and Nutrition Examination Survey (NHANES). Serum 25-hydroxyvitamin D (25(OH)D) showed a significant relationship with time to perform a 8-foot walk and five chair stands tests [79]. These were performed faster when serum 25(OH)D was higher. In the Longitudinal Aging Study Amsterdam (LASA) physical performance, scored over a range of 0 to 12, was assessed by a walking test, five chair stands and a tandem stand test [80]. Physical performance increased significantly by on average two points with increasing serum 25(OH)D up to 50 nmol/l even after adjustment for potential confounders. In the Rancho Bernardo study, a cohort study in Southern California, lower serum 25(OH)D was associated with a lower performance on the timed get-up-and-go test and timed chair stand test [81]. The OPRA study in Malmö in 986 women aged 25 years or older showed positive correlations between serum 25(OH)D and gait speed, the Romberg balance test and thigh muscle strength [82]. An Australian study in Chinese adolescent girls showed a positive association between vitamin D status and handgrip strength [83]. Adolescent girls between 12 and 14 years old were also studied in Manchester, UK. A positive relationship between serum 25(OH)D and jumping velocity, jumping height, power, fitness index and force was observed [84]. In contrast, a German study did not find a significant association between serum 25(OH)D and gait speed, the Romberg balance test and thigh muscle strength [85]. In general, the associations between serum 25(OH)D and muscle strength or performance are significant in the lower range of serum 25(OH)D and may not apply in the “normal” or higher range. In the LASA study, a threshold for this association was observed for serum 25(OH)D between 50 and 60 nmol/l [86].

Several controlled intervention studies were done to investigate the effect of vitamin D on muscle strength. Not all studies were double-blind placebo-controlled. Arab patients with osteomalacia living in Denmark were treated with alfacalcidol 0.5 µg/day, ergocalciferol 400 IU/day and calcium 1 g/day. Serum 25(OH)D increased from 7 to 48.3 nmol/l. Shoulder, hip, and lower extremity muscles all showed an increase in muscle power, the most in knee extensors and flexors, ankle flexors and hip extensors. In the same study, Arab women with a mean serum 25(OH)D of 6.7 nmol/l were treated with ergocalciferol 100,000 IU/week for one month by injection followed by 100,000 IU/month by injection. The patients also received a supplement of calcium carbonate 800-1,200 mg per day and ergocalciferol 400-600 IU/day [87]. Muscle strength increased significantly after three months and further improvement occurred after six months. Treatment with calcium 1200 mg/day and vitamin D 800 IU/day was compared with calcium alone in a 8-weeks double-blind controlled trial in older women with a serum 25(OH)D below 15 nmol/l. The vitamin D-treated group showed a significant 9 % decrease in body sway [88]. The Frailty Interventions Trial in Elderly Subjects compared vitamin D 300,000 IU with placebo in 243 frail older people. Vitamin D supplementation did not improve physical performance in this study [89]. Cholecalciferol 1000 IU/day and calcium 500 mg/day were compared with placebo and calcium in 65 healthy older men. There was no significant difference in muscle strength, power, physical performance and health perception between the groups [90]. In Beirut, a double-blind placebo-controlled study was done in 179 girls between 10 and 17 years. They were randomised to vitamin D 1,400 IU/week or 14.000 IU/week. There was a significant increase
in lean body mass in both vitamin D groups but there was no significant change in grip strength [91]. Another study in 242 community-dwelling older persons compared calcium 1,000 mg/day with calcium 1,000 mg/day and vitamin D 200 IU/day in community-dwelling older persons. In the calcium and vitamin D group, there was a significant improvement in quadriceps strength, a decrease in body sway and a decrease of the timed get-up-and-go test [92]. Mean serum 25(OH)D at the onset of the study was 54 nmol/l. The fall risk also decreased in this study. In Manchester, girls between 12 and 14 years were treated with 150,000 IU vitamin D2 every 3 months or placebo. The vitamin D-treated group showed an improvement in movement efficiency. There were trends to increasing jumping velocity and jumping height [93]. A study in older men and women with vitamin D3 1200 IU/day or placebo did not show a significant decrease in sway, but a post-hoc analysis showed that the decrease in sway was significant in the subgroup with high baseline sway [94].

In summary, cross-sectional and prospective observational studies generally show moderate positive associations of vitamin D status with muscle strength and performance. Intervention studies demonstrate, for most, small to moderate favourable effects of vitamin D supplementation on muscle strength, physical performance and sway in comparison with placebo.

Proteins

Protein content in skeletal muscles

Skeletal muscle mass corresponds to about 40 % of body mass [95]. The total mass of proteins contained in skeletal muscle for a man of 70 kg is around 5.0 kg [96], i.e. 38 % of whole body protein pool.

Skeletal muscle protein turnover

The whole body protein pool is constantly renewed at a mean rate of about 2 %/day [97-100]. This rate can be very slow for structural proteins like collagen, or very rapid for regulatory proteins such as enzymes. The quantity of proteins synthesized in skeletal muscles corresponds to about 30 % of the total body production. In adult human, the main factors enabling the maintenance of skeletal mass are the availability of amino acids, particularly leucine, and physical activity, both enhancing muscle protein synthesis [101, 102]. Furthermore, the stimulation of insulin secretion in response to food intake decreases muscle protein breakdown (MPB) [101, 102]. Whether this effect of insulin on MPB might be enhanced by the supply in amino acids is still debated [103, 104]. It is not known how the balance between protein synthesis and degradation is achieved, taking into account that the two processes appear to be controlled by distinct, independent mechanisms [105].

Skeletal muscle protein synthesis is under the control of the mammalian target of rapamycin (mTOR) pathway. mTOR, a very large protein of 289 kDa, is a key regulator in the formation of the translation initiation complex that leads to the synthesis of proteins [106]. Many hormonal, nutrient and contractile stimuli converge at mTOR. For instance, in humans, several weeks of resistance exercise positively influence the mTOR pathway [106].

Relation between IGF-I and skeletal muscle protein metabolism
Insulin-like growth factor 1 (IGF-1) has been implicated in the control of growth, differentiation, survival and regeneration of skeletal muscle cells. IGF-1 stimulates the development of muscle mass by increasing protein synthesis and myogenesis while decreasing proteolysis and apoptosis [107]. The IGF-1-induced increase in protein synthesis appears to be specific to muscle, including the heart, but it is not observed in various visceral organs such as the kidney, liver, spleen, lung, intestine or brain [108].

IGF-1 is produced and released into the circulation by the liver where it is under the control of growth hormone and nutrition, particularly amino acids, but it can also be produced by the muscle cells themselves [109]. Plasma concentration of IGF-1 declines by 35 to 60 % between early and late adulthood [110]. It is not known whether, within human skeletal muscle, IGF-1 gene expression and synthesis is reduced in parallel to the decline in the plasma concentration of IGF-1 with aging. Nevertheless, IGF-1 mRNA and peptide content are consistently decreased in a wide range of catabolic conditions [108]. Furthermore, in diseases associated with increased catabolism, the decrease in skeletal muscle IGF-1 is proportional to the reduction in protein synthesis [108].

Mechanisms of skeletal muscle protein loss

Muscle wasting is a multifactorial process involving extrinsic determinants, such as nutrition and physical activity, and intrinsic factors [109, 111, 112]. Among intrinsic factors, several proteolytic systems (calpain, ubiquitin, caspase) may enhance protein breakdown, leading to myofibre degeneration and impaired muscle regeneration [109, 111, 112]. Additionally, other factors including stress, oxidative damage and alteration in satellite cell (i.e. quiescent myogenic progenitor) activity and/or number may over time contribute to muscle wasting [109, 111, 112]. Indeed, with aging the number of satellite cells decreased in fast type II, but not in slow type I fibres [113]. Conversely, in elderly men, skeletal muscle hypertrophy following resistance training is accompanied by an increase in the number of satellite cells in type II, but not in type I fibres [114]. Satellite cells play an important role in muscle regeneration after damage, development of hypertrophy and maintenance of skeletal muscle. Thereto these cells undergo proliferation and differentiation to fuse with existing fibres or even form new muscle fibres; a process regulated by several myogenic regulatory factors (MRFs) [112]. In relation with aging, myostatin, a member of TGF-β super family, is a potent inhibitor of muscle growth by inhibiting the proliferation and differentiation of myogenic progenitors [112]. An increase in myostatin mRNA expression was found in skeletal muscle of older (80-89 years) compared to young (18-30 years) women [115]. It is thus possible that various inhibitors that target myostatin could prevent protein catabolism and they are in development to treat disorders accompanied with skeletal muscle-wasting including age-related sarcopenia [116].

Insufficient protein intake and skeletal muscle inactivity are two important factors that cause skeletal muscle depletion [111]. The mechanisms underlying the loss of protein muscle mass and, thereby, the depletion of skeletal muscle tissue, appear to operate mainly by reducing the synthesis rather than increasing the degradation process involved in muscle protein turnover. Nevertheless, the presence of an inflammatory component, in addition to reduced protein intake and physical activity, can stimulate proteolysis. Pro-inflammatory cytokines are also implicated in the progressive sarcopenia [40, 117]. TNF-α, IL-1-β and IL-6 promote muscle wasting by increasing myofibrillar protein degradation [118]. Moreover, they can also reduce muscle protein anabolism and directly impact on skeletal muscle contractility, independent of muscle protein content [40, 118]. TNF-α and-or IL-1-β can also
induce resistance to IGF-1 action [119], presumably by impairing its anabolic effect on SM protein synthesis. In fact, in the presence of TNF-α, IGF-1 may even become apoptotic rather than anabolic [120-122]. Sustaining the key role of IGF-I, its specific skeletal muscle expression was shown experimentally to prevent age-related decline of skeletal muscle mass [123]. Apart from alterations in IGF-1, insulin and glucocorticoids, aging is also associated with modifications in production and sensitivity of estrogens, androgens, and could thereby, influence skeletal muscle protein metabolism [111, 112].

**Relation between protein intake and skeletal muscle mass and strength**

**Observational studies**

A significant number of elderly people do not meet the daily intake of the estimated average protein requirements [124, 125]. An American survey indicates that in the age category of 50 years and older, 32 to 41 % of women, and 22 to 38 % of men consume less than the recommended dietary allowance of 0.8 g/kg of body weight [124]. A prospective epidemiological study over three years showed that protein intake was positively associated with preservation of lean mass in women and men aged 70 to 79 years [126]. Individuals with the highest quintile of daily protein intake (1.1g/kg b.w.) lost 40 % less total body and appendicular lean mass than those in the lowest quintile (0.7g/kg b.w.) [126]. This prospective observational study strongly suggested that increasing the daily protein intake above 0.8 g/kg (about 46 and 56 g/day when using the reference weight of 57 and 70 kg for women and men, respectively) would reduce the risk of sarcopenia in older adults [126]. It has therefore been proposed to increase dietary protein requirements from 0.8 to 1.0-1.2 g/kg per day for optimal skeletal muscle and bone health in elderly people [127].

**Interventional studies**

The regular performance of resistance exercise and the habitual ingestion of adequate amounts of dietary proteins from high quality sources are two important ways for older people to slow down the progression of the age-related loss of skeletal muscle mass and function and eventually, to treat sarcopenia [128]. Resistance training can help older people gain muscle strength and improve balance and physical functioning capabilities [128].

Most studies on the anabolic response of skeletal muscle to various protein supplementations in the elderly have been carried out over a relatively short period. As compared to the bone response, the impact of protein supplementation and/or resistance exercise on skeletal muscle mass and strength can be expected to occur much more rapidly, because of the difference in protein metabolism between the two tissues.

In a 6-month randomised double-blind placebo-controlled trial in patients with recent hip fracture, a casein supplement of 20 g/d increased serum IGF-1 and isometric muscle strength of the biceps by 15.7 % [129]. Over the last 5 years several protein supplementation studies varied in duration from 10 to 72 weeks, and involved women and men in the age range of 48 to 84 years. The supplementation was given as whole proteins such as casein or whey [130-134] or as a mixture of amino acids [135-138] and creatine [131, 133] or carbohydrates [134, 137] were added to the protein or amino acids. The supplementation was given either before or after resistance training program [131, 133, 137] and different techniques were used to assess various endpoints (see Table 4). The magnitude of the responses to protein or amino acid cocktail supplementation in terms of increased skeletal muscle mass, protein metabolism and strength was variable. Factors which may account for at least some of this variability include: participants age range and health condition; initial degree of sarcopenia; baseline protein consumption; degree of oxidative stress; concomitant
intake of creatine, carbohydrate or antioxidant; quality of protein (hydrolysate versus intact) and/or amino acid cocktail (essential, or branched-chain including leucine, an insulin secretion stimulator) supplementation and its daily distribution; and last, but not least, whether or not supplementation was accompanied by resistance exercise training [42, 104, 132, 139-146].

Table 4 Intervention studies (10 weeks+) with protein supplementation

<table>
<thead>
<tr>
<th>Ref</th>
<th>Sex</th>
<th>Age (year)</th>
<th>Baseline protein intake g/d</th>
<th>Supplement type</th>
<th>Protein dose</th>
<th>Duration weeks</th>
<th>Endpoints (methods)</th>
</tr>
</thead>
<tbody>
<tr>
<td>[130]</td>
<td>M/W</td>
<td>60-69</td>
<td>1.0</td>
<td>Protein drink</td>
<td>3x0.4g/LM protein/week</td>
<td>12</td>
<td>Whole BLM (by DXA)</td>
</tr>
<tr>
<td>[131]</td>
<td>M</td>
<td>48-72</td>
<td>0.95-1.03*</td>
<td>Whey±creatine</td>
<td>3x35g/week</td>
<td>14</td>
<td>- BLM - Strength test quadriceps, triceps, biceps, deltois, latissimus dorsi (by isotonic resistance equipment)</td>
</tr>
<tr>
<td>[132]</td>
<td>M</td>
<td>59-76</td>
<td>1.3-1.4</td>
<td>Protein before or after RET</td>
<td>3x0.3g/kg/b.w./week</td>
<td>12</td>
<td>- Lean tissue mass - Muscle thickness of elbow, knee, ankle flexor and extensors - Muscle strength (by leg and bench press)</td>
</tr>
<tr>
<td>[135]</td>
<td>W</td>
<td>68±5</td>
<td>NA</td>
<td>EAA</td>
<td>15g/day</td>
<td>12</td>
<td>-Muscle protein FSR (by biopsy) - LBM (by DXA) - Muscle strength of arms and legs (by isotonic resistance equipment) - Muscle IGF-I expression (by biopsy)</td>
</tr>
<tr>
<td>[133]</td>
<td>M</td>
<td>48-72</td>
<td>0.95-1.03*</td>
<td>Whey±creatine</td>
<td>3x35g/week</td>
<td>14</td>
<td>- Bone free-fat free mass (by DXA and multifrequency BIA)</td>
</tr>
<tr>
<td>[134]</td>
<td>W</td>
<td>55±4 (PM)</td>
<td>1.0</td>
<td>Whey+CH+Ca+VitD</td>
<td>3x10g/week</td>
<td>24 / 72</td>
<td>- Muscle hypertrophy (by biopsies, MRI and DXA) - Concentric and isotonic strength (by dynamometer)</td>
</tr>
<tr>
<td>[137]</td>
<td>M/F</td>
<td>M: 72±4 F: 73±6</td>
<td>AA mixture+CH</td>
<td>Yes</td>
<td>3x22g/week</td>
<td>12</td>
<td>- Body composition (by BIA) - Muscle thickness (by US) - Muscle strength (by isotonic resistance equipment) Functional ability tests (by &quot;go up and go&quot;, &quot;standing from lying&quot;, &quot;six-minute walk&quot;)</td>
</tr>
<tr>
<td>[138]</td>
<td>NA</td>
<td>66-84</td>
<td>NA*</td>
<td>AA mixture</td>
<td>No</td>
<td>2x 8g/day</td>
<td>24</td>
</tr>
</tbody>
</table>

NA Not Available M Men W Women PM Postmenopausal +RET coupled to resistance exercise training L(B)M Lean (Body) Mass AA amino acid CH Carbohydrate BIA Bioelectric impedance analysis FSR Fractional synthesis rate US Ultrasonography 1RM 1 repetition maximum DXA dual-energy X-ray absorptiometry

Dietary protein requirements for optimal muscle mass and strength in the elderly

The current recommended dietary allowances (RDA) for adults aged 19 years and older is 0.8 g/kg of body weight per day. This level was determined from short-term, i.e. 10 to 14 days nitrogen balance studies [147]. It is an estimation of the minimal protein intake needed to
maintain nitrogen balance in healthy young adults [148], based on the concept of preventing deficiency as opposed to promoting optimal health [149]. However, nitrogen balance is not directly related to functional outcomes including maintenance of skeletal muscle and bone health [148, 149]. There is a consensus that optimal daily intake is higher than 0.8 g/kg [148]. However, there is some concern that consuming dietary protein in excess of the RDA may promote renal damage [150]. Protein restriction may be appropriate for existing chronic kidney disease (CKD), although severe restriction can lead to protein-energy wasting in non-dialysis-dependent CKD [151]. However, there is no evidence for a detrimental effect of high protein intakes much above RDA in healthy persons with normal renal function [148, 150]. In older adults, taking into account the attenuated anabolic response to dietary proteins, a moderate increase from 0.8 to 1.0-1.2 g/kg per day [127] would be optimal for skeletal muscle health without affecting renal function. Long term intervention studies are needed to determine the optimal protein intake for older adults.

**Influence of the acid-base system on the muscle**

Acid-base balance affects muscle in both exercise and non-exercise settings. This review focuses on the role of acid-producing diets on muscle in the non-exercise setting. In the presence of extracellular acidosis, hydrogen ion efflux from muscle is inhibited in dogs [152], while alkalosis is thought to promote the efflux by the increased buffering capacity in the extracellular fluid [153]. More importantly, metabolic acidosis promotes protein degradation and nitrogen excretion and inhibits protein synthesis [154-156]. This leads to muscle wasting and to the loss of muscle power. Muscle wasting can also be considered an adaptive response to acidosis, especially in elderly persons [157, 158]. Amino acids released from muscle provide substrate for the hepatic synthesis of glutamine, which in turn allows the synthesis of ammonia in the kidneys [159]. Ammonia spontaneously accepts a hydrogen ion and is excreted as ammonium, mitigating the acidosis. The effect of acidosis on muscle may also be mediated through the suppression of IGF-1 [160]. IGF-1 increases lean tissue mass in adults and enhances protein anabolism [161]. Although a dietary acid load does not change the intracellular pH of the muscle cells [162], chronic intake of excess acid-producing nutrients such as meat and cereal grains in combination with a low intake of the alkalisising fruits and vegetables [163] leads to a chronic acid challenge and to negative effects on bone [164] and muscle. Alkali-producing diets favoured lean tissue mass in older adults [165]. Administration of bicarbonate improved lower-extremity peak muscle power and endurance over a 3-month period in non-exercising healthy older women [166]. This went along with a lowering of nitrogen excretion, confirming a previous observation in postmenopausal women that ingestion of a neutralising dose of potassium bicarbonate reduced nitrogen excretion [167].

There is some evidence that acid-base balance and vitamin D may be interdependent in their effects on muscle. For instance, acidosis may influence the action of vitamin D on muscle indirectly.

The hydroxylation of vitamin D into active and inactive metabolites is pH-dependent. The enzymes involved require an optimal pH of around 7.4. A higher or lower pH tends to result in a lower activity of the enzymes regulating 25(OH)D metabolism [168]. But the variation of medium pH from 7.2 to 7.4 did not increase 1,25(OH)2D3 production [169]. On the other hand, chronic metabolic acidosis increased serum concentration of 1,25-dihydroxyvitamin D.
in humans [170]. There is probably a difference between the effect of acute versus chronic pH changes. The functionality of the vitamin D receptors also requires optimal pH, at least in vitro [171]. In addition, pH variations could modify vitamin D binding proteins as well as vitamin D receptor interactions within target tissues. Alternatively, acidosis may be one mechanism by which vitamin D insufficiency adversely affects muscle. Animal studies suggest that vitamin D deficiency results in a metabolic acidosis whereas repletion with vitamin D results in a metabolic alkalosis [172, 173]. Clinical evidence for interaction of acid-base with vitamin D in their effects on muscle is lacking at this time. In summary, chronic ingestion of a dietary acid load appears to contribute to age-related declines in muscle function, and also possibly in muscle mass in older adults. Large numbers of elders chronically consume acid-producing diets. Diet modification to reduce the acid load is likely to benefit muscle as well as bone.

B vitamins and muscle function

A high serum level of homocysteine (hyperhomocystinemia) is a risk factor for cardiovascular disease. Hyperhomocysteinemia is also associated with fractures in three large prospective cohort studies, the Rotterdam Study, LASA and the Framingham Study [174, 175]. The latter association was independent of bone mineral density in the LASA and Rotterdam studies. Fractures might occur through a change in bone quality (change in collagen cross-links) or a higher fall incidence. Higher homocysteine levels were associated with greater decline in physical function in the MacArthur Studies of Successful Aging [176]. In the NHANES survey, elevated homocysteine levels were associated with lower quadriceps strength and gait speed and more disability in older persons [177]. In patients with peripheral arterial disease, elevated homocysteine levels were associated with lower calf muscle density [178]. The OPRA Study in 996 women of 75 years old showed a relationship between high homocysteine levels and poor physical performance [179]. Hyperhomocystinemia can be corrected by folic acid and vitamin B12. A prospective intervention study in Japan in patients who sustained a stroke showed that vitamin B12 and folic acid decreased fracture incidence compared with placebo [180]. Vitamin B12 and/or folic acid might improve postural stability and/or muscle function and strength, but this has yet to be demonstrated in randomised clinical trials.

Conclusion

Sarcopenia or muscle loss with aging is a widely prevalent clinical condition. Estimation of muscle mass can be performed accurately with techniques such as MRI, CT, DXA and bioelectrical impedance. Among nutritional factors, protein, vitamin D/calcium, and the acid-base balance of the diet play an important role in maintaining muscle mass. Intrinsic autocrine and paracrine factors are also important and proteins like myostatin may be potential targets for drug development. Given the present state of knowledge in this area, adequate dietary protein, vitamin D/calcium, and acid-base balance (along with resistance training) are the key factors for the attenuation and treatment of sarcopenia.

Acknowledgments

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possible suggested added ref for androgens and SARMs