Sarcopenia

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Sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with increased adverse outcomes including falls, functional decline, frailty, and mortality. It occurs commonly as an age-related process in older people, influenced not only by contemporaneous risk factors, but also by genetic and lifestyle factors operating across the life course. It can also occur in mid-life in association with a range of conditions. Sarcopenia has become the focus of intense research aiming to translate current knowledge about its pathophysiology into improved diagnosis and treatment, with particular interest in the development of biomarkers, nutritional interventions, and drugs to augment the beneficial effects of resistance exercise. Designing effective preventive strategies that people can apply during their lifetime is of primary concern. Diagnosis, treatment, and prevention of sarcopenia is likely to become part of routine clinical practice.

Introduction

Sarcopenia is a term derived from the Greek phrase poverty of flesh. It was first described in the 1980s as an age-related decline in lean body mass affecting mobility, nutritional status, and independence.[1] The definition has since evolved, marked by two recent milestones. The first was the introduction of muscle function into the concept in six consensus definitions since 2010.[2–7] This new focus on muscle function, usually defined by muscle strength, muscle power, or physical performance, occurred because function was consistently shown to be a more powerful predictor of clinically relevant outcomes than muscle mass alone.[8–11] The second milestone was recognition of sarcopenia as an independent condition with an International Classification of Diseases-10 code in 2016.[12] Yet, most clinicians remain unaware of the condition and the diagnostic tools needed to identify it.[13,14] This Seminar describes current progress and debate about the need for a consensus definition, desribes the approach to diagnosis and case finding, gives an overview of disease burden and pathophysiology, and outlines current treatment options, and future potential for prevention of the disease.

Search strategy and selection criteria

We developed a structured search strategy in PubMed for publications in English using the search term "sarcopenia" in combination with one of the following keywords: "definition", "screening", "diagnosis", "muscle mass", "strength", "frailty", "malnutrition", "cachexia", "outcomes", "disability", "mortality", "pathophysiology", "life course", "treatment", and "exercise". We focused on clinical trials, meta-analyses, and review articles. The search was completed on Dec 11, 2018. Only articles published after 2010 (when most definitions of sarcopenia were published) were included, but we did not exclude major contributions published before. We referenced articles judged to be relevant to this Seminar. When many similar articles were available, the most recent were used. Additional papers were identified from personal libraries and the reference lists of retrieved articles. Review articles are used to provide useful details and references on specific areas that cannot be covered in depth in this Seminar.

Definition

Sarcopenia has been defined as a progressive and generalised skeletal muscle disorder that involves the accelerated loss of muscle mass and function. Sarcopenia is associated with increased adverse outcomes including falls, functional decline, frailty, and mortality.[15] When first used, the term sarcopenia referred to an age-related loss of muscle mass and function.[1] However, for decades the term was used to describe muscle wasting (low muscle mass) alone without reference to function, and this concept is still used nowadays in some cancer and other disease-related sarcopenia research studies. Nevertheless, progress and updates have been made regarding the definition of sarcopenia, and published consensus definitions by a range of expert groups from around the world now include muscle function in the concept of sarcopenia. Full agreement on the variables to be included and cutoff points have yet to be reached (panel 1). The most widely cited definition nowadays is that proposed by the European Working Group on Sarcopenia in Older People (EWGSOP),[3] supported by the Asian Working Group on Sarcopenia,[6] and updated as EWGSOP2 in January, 2019.[15] This is the only definition endorsed by a range of international scientific societies (European Geriatric Medicine Society; The European Society for Clinical Nutrition and Metabolism; The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases; International Osteoporosis Foundation; and International Association of Gerontology and Geriatrics European Region) for clinical practice and research.

In clinical practice, the EWGSOP2 states that a person with low muscle strength and low muscle mass or quality will be diagnosed with sarcopenia. The condition can be best understood as skeletal muscle failure or insufficiency.[16] As such, sarcopenia might appear acutely (usually in the setting of an acute disease or sudden immobility, as during hospital admission) or have a more protracted (chronic) course. Muscle mass and strength (in parallel with bone mineral density) peak in young adulthood and, after a plateau, start decreasing gradually with a faster decline in strength (figure 1).[17,18] WHO has shifted the focus of the provision of integrated care for older people

from a disease-centered model to a function-centered model, in which intrinsic capacity (defined as a composite of all physical and mental capacities of an individual) interacts with the environment to determine functional ability. Muscle strength is included in the construct of intrinsic capacity that could merit lifelong monitoring.[19,20]

Clinicians can associate sarcopenia with leanness and not be aware that sarcopenia can also be present in obesity, leading to increased disability and mortality.[21] Sarcopenic obesity is usually identified when both low muscle mass and increased adiposity are present in an individual, but it could remain unnoticed when the focus of care is obesity, leading to adverse outcomes.[22] Sarcopenia and obesity share some underlying pathophysiological pathways.[23] Muscle loss can also increase the risks of death and disability during weight loss in individuals with obesity.[24,25] However, a consensus regarding the definition of sarcopenic obesity has not yet been reached, and how muscle strength should be used to make a diagnosis in these patients remains unclear.[21,22,26] Additionally, an association has been identified between sarcopenia and dysphagia[27] (sarcopenic dysphagia) that merits a specific approach in clinical practice.[28]

Case finding

Most cases of sarcopenia go undiagnosed. However, the condition cannot be universally screened for because screening tools are not accurate[29–32] and the effect of such screening on relevant outcomes is far from proven.[33] Therefore, a case finding approach is recommended practice.[15] This approach involves looking for sarcopenia when relevant symptoms are reported. These symptoms could include falling, weakness, slowness, self-reported muscle wasting, or difficulties carrying out daily life activities.[5,15] Case finding is particularly relevant in care settings where a higher prevalence of sarcopenia might be expected, such as temporary admission to hospital, rehabilitation settings, or nursing homes.[34,35] The SARC-F is a commonly recommended case finding instrument with evidence to support its use.[33,36] It can be self-administered and has a low sensitivity but high specificity, so can be a good way to initiate identifying cases of sarcopenia in clinical practice.[31,37] This screening instrument has five questions addressing strength, assistance in walking, rising from a chair, climbing stairs, and falls.

Diagnosis

The diagnosis of sarcopenia, by use of any definition of sarcopenia, is relatively straightforward. Diagnosis requires measurement of a combination of muscle mass, muscle strength, and physical performance (panel 1). All definitions use at least two parameters but different cutoff points lead to lack of standardisation and poor application of these definitions in clinical practice.[14] The updated EWGSOP2 proposed a stepwise approach to diagnosis (figure 2). Diagnosis starts with a measure of muscle strength, usually grip strength, which has a well validated protocol.[38] If grip strength is below the reference values for gender (table) or those proposed by the society definitions (panel 1), then sarcopenia should be suspected. However, the differential diagnosis is wide and other potential causes for low muscle strength should be considered—for example, hand osteoarthritis and neurological disorders. Identifying low grip strength in the first instance is important because it is highly predictive of a range of adverse outcomes.[39–42]

The second step in the diagnosis procedure is measurement of muscle mass. Several techniques have been used to estimate muscle mass, but all have major limitations, including variability in the results, inconsistent use of cutoff points, and the weak association between muscle mass and adverse health outcomes.[39] The most effective procedure to date is the use of dual energy X-ray absorptiometry (DXA), which estimates lean mass. Bioelectrical impedance analysis (BIA), CT, and

***Panel 1:* International definitions of sarcopenia**

- The European Working Group on Sarcopenia in Older People (EWGSOP) in 2010 defined sarcopenia using muscle mass, muscle strength, and physical performance (cutoffs not defined).[3]
- The International Working Group on Sarcopenia[4] and Society of Sarcopenia, Cachexia and Wasting Disorders (SSCWD)[5] in 2011 defined the disease using muscle mass and physical performance (cutoffs defined); SSCWD used the phrase sarcopenia with limited mobility.
- The Asian Working Group on Sarcopenia in 2014 gave the same definition as the EWGSOP and also defined cutoffs for Asia.[6]
- The Foundation for the National Institutes of Health in 2014 defined the disease using muscle mass and muscle strength, and also defined cutoffs; physical performance was used as an outcome.[7]
- EWGSOP updated their definition in 2019 (EWGSOP2) with cutoffs defined; physical performance was used to assess severity of the condition.[15]

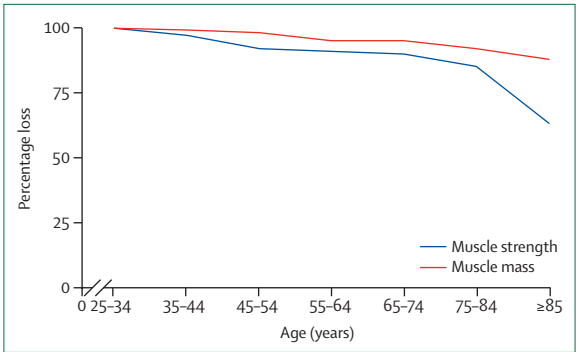

Figure 1: **Percentage loss of muscle mass and muscle strength with age in men**
Data from Ferrucci et al.[17]

MRI can also have a role in some settings.[43] BIA is useful as a bedside test, but as BIA equations and cutoff points are population-specific and device-specific, a lack of standardisation limits its accuracy.[44] CT and MRI are mostly used in research and when needed for the follow-up of another condition—for example, in patients with cancer.[45] From 2018, ultrasound has been proposed as a simple alternative to measure muscle mass in clinical practice, but it is not standardised and does not yet have validated cutoff points.[46,47] Typically, appendicular lean mass (skeletal muscle in the extremities) is estimated, and in most cases adjustment for height is used to define cutoff values. Research focused on identifying cutoff points to define sarcopenia has led to a range of different values that are difficult to reconcile and introduce systematically.[48,49] For this reason, EWGSOP have taken a pragmatic approach in the updated definition, and opted for simple, easy to remember cutoff points exploiting the best available data where possible, although this has sometimes been at the expense of consistency in how the cutoff points have been selected (table).[15] The primary aim is to encourage uptake of the EWGSOP recommendations using a standardised approach to identify sarcopenia in clinical practice, in much the same way that cardiovascular risk factors have been introduced.

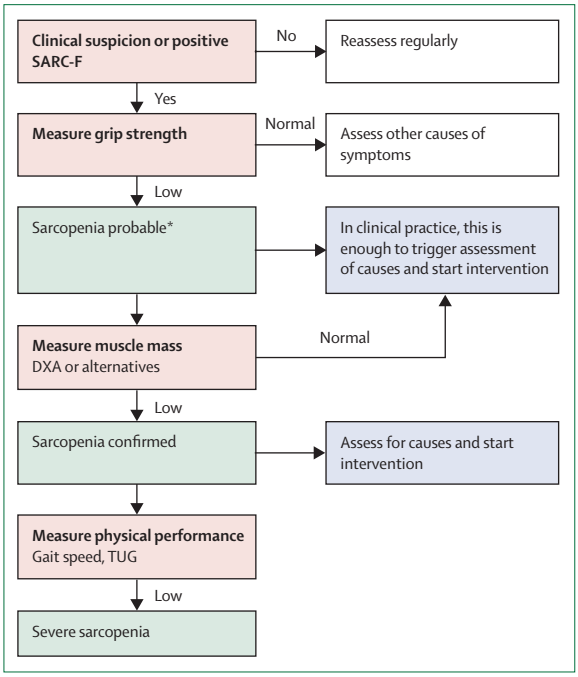

Figure 2: **A simple algorithm to diagnose sarcopenia in clinical practice**
Adapted from Cruz-Jentoft et al,[15] by permission of Oxford University Press. DXA=dual-energy X-ray absorptiometry. TUG=Timed Up and Go test. *Other reasons for low muscle strength should always be considered (eg, depression, stroke, balance disorders, or peripheral vascular disorders).

	Men	Women
Grip strength (kg)	<27	<16
Appendicular skeletal muscle mass divided by height^2 (kg/m^2)	<7	<5·5
Gait speed (m/sec)	≤0·8	≤0·8
Timed Up and Go test (sec)	≥20	≥20

Values shown are those recommended by the European Working Group on Sarcopenia in Older People (EWGSOP2).[15]

Table: **Reference values used to diagnose sarcopenia**

Muscle quality is a term that is now used worldwide, and in many different scientific disciplines. However, the term can refer to two different concepts: the association between strength and mass, and observable characteristics of muscle such as intermuscular or intramuscular adiposity. Muscle quality might prove to be a more relevant concept to health than muscle mass, but as yet is not sufficiently defined for use in clinical practice.[50]

Physical performance is defined as the ability to carry out physical tasks in order to function independently in daily life. It involves function of the whole body as opposed to function of a single organ and depends not only on skeletal muscle but also on an intact musculoskeletal system integrated with the central and peripheral nervous systems and involvement of a range of other body systems. It can be characterised using subjective or objective assessment of mobility, strength, and balance, and commonly used single objective measures include gait speed and the 400m timed walk. More complex composite measures such as the Short Physical Performance Battery and the Timed Up and Go test are also used to measure physical performance.[51,52] Discussions have taken place between the different expert groups trying to advance the definition of sarcopenia about whether physical performance should be part of the definition of sarcopenia[3,5] or be used as an outcome measure.[7] The latest EWGSOP2 definition suggests that physical performance should be considered a measure of the severity of sarcopenia.[15] Grading the severity of sarcopenia is important to predict outcomes and to choose the intensity of interventions. Emerging evidence on the importance of considering severity comes from some clinical trials that have shown that interventions can have different effects in severe and non-severe sarcopenia. For example, an intensive, multi-dimensional intervention that always includes exercise is needed for severe sarcopenia.[53,54]

Blood biomarkers of sarcopenia are not yet available in clinical practice. Research in this area has proved complex for a number of reasons, including different views on the definition of sarcopenia, increasing recognition of acute and chronic sarcopenia, the existence of many interacting pathways involved in the pathophysiology, and the effect of related conditions (including those that might mimic the symptoms of sarcopenia, and other conditions present in the patient that affect sarcopenia).[55]

Nowadays, the most promising approach to measuring skeletal muscle mass is one based on the dilution of oral d3 creatine A. This is a non-invasive isotope dilution test that determines the concentration of methyl-d3 creatine in fasting morning urine, after an oral dose of d3 creatine

A, to calculate total skeletal mass. Methyl-d3 creatine was more strongly linked to outcomes such as physical performance and mobility in men than DXA lean mass.[56–58] By contrast, DXA is useful for quantifying body fat (which can effect muscle function), and in the future, multiple approaches rather than individual measures will probably be needed for diagnostic accuracy.[59–61]

Once sarcopenia has been confirmed, a systematic approach is recommended to ascertain the underlying causes.[3] We summarise the most frequent underlying causes of sarcopenia (panel 2). Sarcopenia can occur in association with a range of long-term conditions in mid-life, hence the growing interest from a range of medical and surgical specialties. However, most older patients will have more than one associated condition. When no evident cause of a gradual onset sarcopenia is present in an older person, age-associated (primary) sarcopenia is diagnosed.

Differential diagnosis

The three main conditions in the differential diagnosis of sarcopenia are malnutrition, cachexia, and frailty.[62–64] Malnutrition has been the focus of a global effort to reach a consensus definition, and this effort is changing understanding of both malnutrition and sarcopenia. The Global Leadership Initiative on Malnutrition has included reduced muscle mass as one of the three phenotypic criteria of malnutrition,[65] and the new EWGSOP2 definition of sarcopenia has put a focus on muscle function.[15] Therefore, a finding of reduced muscle mass with normal muscle strength would be more suggestive of malnutrition than sarcopenia, whereas reduced muscle mass with impaired muscle function would lead to a diagnosis of sarcopenia. Hence, clinicians are moving away from the original approach of defining sarcopenia purely in terms of low muscle mass. Studies of sarcopenia in the context of other conditions (such as cancer) that only consider muscle mass might be referring to malnutrition or cachexia rather than sarcopenia, as muscle function is usually not investigated.[66–68]

Cachexia is a term that has been used for decades to describe severe weight loss and muscle wasting associated with cancer, HIV and AIDS, or end-stage organ failure. Cachexia and sarcopenia can coexist, and some aspects of the definition of sarcopenia, in particular low muscle mass, are included in modern definitions of cachexia.[2,69] Cachexia has a complex pathophysiology including excess catabolism and inflammation, endocrine changes, and neurological changes, all of which are different to those described in sarcopenia.[70] The role of inflammation and cytokines seems to be more relevant in cachexia than in sarcopenia.[71] International consensus definitions of cachexia can guide clinical judgment.[2,69]

Frailty has been defined as a state of vulnerability to poor resolution of homoeostasis after a stressor event, as a consequence of cumulative decline in many physiological systems.[72] Physical frailty is a subset of frailty characterised by the frailty phenotype involving unintentional weight loss, self-reported exhaustion, weakness (low grip strength), slow walking speed, and low physical activity.[73] Therefore, physical frailty and sarcopenia are closely related and sarcopenia has been described as the biological substrate of physical frailty (figure 3).[74–79]

Epidemiology

The disease burden from sarcopenia arises because it is a relatively common condition and is associated with short-term and long-term adverse effects. Estimates of disease frequency are becoming more precise with evolution of the definition. A systematic review explored the effect of definition on the prevalence of sarcopenia in populations of the older community. The review emphasised that the original 2010 EWGSOP definition resulted in one of the lowest pooled prevalence estimates (12·9% [95% CI 9·9–15·5]), whereas the highest estimates (40·4% [19·5–61·2]) came from older definitions that only used assessment of muscle mass.[35] Muscle mass cutoff points have a stronger influence on prevalence estimates than muscle function cutoff points.[80] Prevalence also depends on the setting, with the condition appearing more frequently in patients who are admitted to hospital, in post-acute care settings, or in care homes, than in the community.[34,81]

Studies determining the incidence of sarcopenia are relatively sparse, although emerging evidence suggests that incidence increases with age. A study showed an incidence of 1·6% in European men and women aged 40–79 years using the EWGSOP definition;[82] 3·4% in a

***Panel 2:* Frequent underlying causes of sarcopenia**

Nutritional
- Low protein intake
- Low energy intake
- Micronutrient deficiency
- Malabsorption and other gastrointestinal conditions
- Anorexia (ageing, oral problems)

Associated with inactivity
- Bed rest, immobility, deconditioning
- Low activity, sedentary lifestyle

Disease
- Bone and joint diseases
- Cardiorespiratory disorders including chronic heart failure and chronic obstructive pulmonary disease
- Metabolic disorders (particularly diabetes)
- Endocrine diseases (particularly androgen deprivation)
- Neurological disorders
- Cancer
- Liver and kidney disorders

Iatrogenic
- Hospital admission
- Drug-related

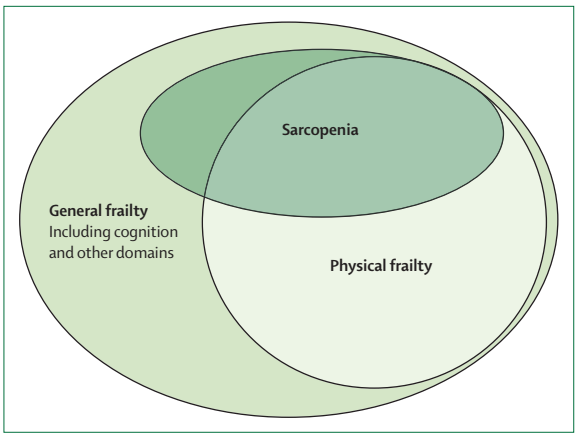

Figure 3: **Schematic diagram showing the diagnostic overlap between sarcopenia and physical or general frailty**

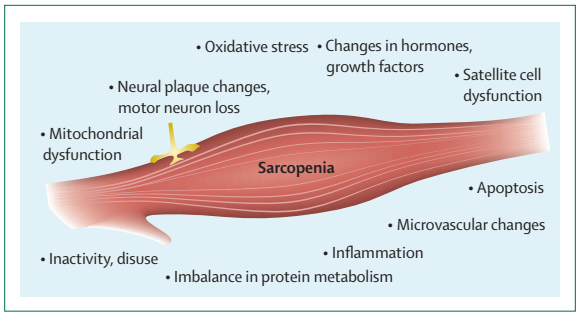

Figure 4: **The multifactorial causes of sarcopenia**

group of Chinese men and women, mean age 72 years, using the similar Asian Working Group definition;[83] and 3·6% in English men and women aged 85 years using the EWGSOP definition.[84]

The link between low muscle strength and adverse health outcomes is long established. A study dating back to the 1980s showed a link between low grip strength before hip fracture surgery, and poor postoperative outcomes.[85] Two more linked systematic reviews have identified an association between low grip strength and increased mortality, as well as some evidence for links between low grip strength and increased morbidity across the four domains of fracture, cognitive decline, cardiovascular disease, and admission to hospitals or institutions.[86,87] Reduced grip strength has also been linked to frailty.[88]

Literature regarding sarcopenia now includes an increasing number of studies that show an association between newer consensus definitions of sarcopenia and adverse health consequences including falls, functional decline, frailty, impaired quality of life, increased health-care costs, and mortality. A systematic review and meta-analysis showed a consistent association between sarcopenia (defined by EWGSOP) and mortality, with a pooled odds ratio of 3·59 (95% CI 2·96–4·27) and a larger effect size in men and women aged 79 years and older.[89] The review also showed that sarcopenia was associated with functional decline and a higher rate of falls and admission to hospital, although the evidence for a link to fractures and length of stay was less consistent.[89] Findings from another systematic review confirm that overall quality of life is impaired in sarcopenia, whether measured using generic self-reported tools or disease-specific questionnaires.[90] In view of the link between sarcopenia and a range of adverse health outcomes, the condition has also been associated with increased health-care costs;[91] however, the full extent of this has yet to be elucidated.[92]

Pathophysiology

Ageing disturbs the homoeostasis of skeletal muscle, which requires balance between hypertrophy and regeneration through complex and not yet fully understood mechanisms and pathways (figure 4). Ageing appears to result in an imbalance between muscle protein anabolic and catabolic pathways, leading to overall loss of skeletal muscle. Cellular changes in sarcopenic muscle include a reduction in the size and number of myofibres, which particularly affects type II fibres. This is partly due to transition of muscle fibres from type II to type I with age, together with intramuscular and intermuscular fat infiltration (myosteatosis), and a decreased number of type II fibre satellite cells.[50,93–95] Pathogenic interrelationships between adipose tissue and muscle are also important in sarcopenia.[26] Additionally, mitochondrial integrity in myocytes is altered.[96] Molecular changes in sarcopenic muscle involve alterations to the complex signalling pathway that includes insulin-like growth factor 1, mammalian target of rapamycin, and forkhead box protein transcription factors, as well as other interlinked pathways.[97] Neurological signalling and control mechanisms also have an important role in muscle function.[8,98] A study showed deregulation in skeletal muscle gene expression, probably mediated through epigenetic changes and modulated via microRNAs.[99]

Research suggests that cross-talk between muscle and bone is mediated through endocrine factors such as myostatin, irisin, osteocalcin, and many others, although the relevance of this communication in the pathogenesis of sarcopenia has not been fully elucidated.[100] Preliminary evidence has shown an association between the age-related decline in production of apelin—an endogenous peptide induced by muscle contraction—and decreased muscle function, through different pathways.[101] A detailed review of the pathophysiology of sarcopenia is beyond the scope of this Seminar, but a number of comprehensive reviews that discuss this rapidly developing area are available.[102,103]

Treatment: non-pharmacological approaches

Understanding the pathophysiology of sarcopenia is key to developing effective new interventions, and translational research in this area is rapidly increasing. Evidence-based clinical practice guidelines were

published in 2018 and provide strong recommendations for physical activity as the primary treatment of sarcopenia.[33] Evidence for the benefits of resistance exercise in improving skeletal muscle strength[104] and mass[105] individually is compelling, and evidence for its benefit in sarcopenia (defined as a combination of both strength and mass) is growing. Two systematic reviews of exercise interventions in older adults with sarcopenia showed evidence of significantly improved strength, mass, and balance, although the number of trials specifically recruiting participants with sarcopenia was small, and the training effect was inconsistent because of heterogeneity in the mode, duration, and intensity of exercise employed.[106,107] Another systematic review confirmed the effect of exercise in sarcopenic obesity.[108] An important gap exists in the evidence needed to recommend a specific exercise programme for sarcopenia, and nowadays wide variation in clinical practice is normal.

The evidence for nutrition interventions is less consistent.[33] A number of studies have investigated the effects of exercise combined with nutrition to treat sarcopenia and a systematic review of non-pharmacological interventions for well characterised sarcopenia in older patients with physical frailty confirmed the effectiveness of exercise with or without nutritional supplementation to improve physical performance, although the overall quality of the evidence was low.[107] Other reviews report variable findings, although did not only include participants with sarcopenia.[109,110] Large scale trials are now underway to specifically address exercise and nutritional interventions for patients with sarcopenia such as the European SPRINTT trial (NCT02582138).[111,112]

The role of a nutritional intervention without exercise for the treatment of sarcopenia is much less clear, although some evidence shows the benefit of healthier dietary patterns such as adequate intake of protein, vitamin D, antioxidant nutrients, and long-chain polyunsaturated fatty acids.[113] However, many of the studies are observational in nature and high quality trials are less common. A debate remains about what constitutes an adequate intake of key nutrients such as protein, and how these nutrients should be taken in terms of timing and distribution throughout the day.[114] The most recent consensus recommends increasing protein intake in the older population.[115,116] However, the only intervention trial comparing the effects of normal versus increased protein intake on mobility was done in non-sarcopenic reduced mobility patients and showed no differences between these interventions.[117]

High protein oral nutritional supplements might be more effective for certain outcomes in the specific context of sarcopenia with malnutrition.[54,118] The value of individual nutrients is of research interest, such as the essential amino acid leucine and its metabolite β-hydroxy β-methylbutyric acid, which have shown some effects in improving muscle mass and function,[119,120] as has fish oil-derived n-3 (omega-3) polyunsaturated fatty acid therapy, which increased muscle mass and function in healthy older adults.[121]

Treatment: pharmacological approaches

No specific drugs have been approved for the treatment of sarcopenia. An umbrella review has brought together systematic reviews and meta-analyses focusing on pharmacological interventions to improve muscle mass, strength, and physical performance in older people.[122] Very few studies have identified baseline sarcopenia status, so the findings could only be generalised to older people rather than to people with sarcopenia. The umbrella review identified ten pharmacological interventions: vitamin D, combined oestrogen-progesterone, dehydroepiandrosterone, growth hormone, growth hormone-releasing hormone, combined testosterone-growth hormone, insulin-like growth factor-1, pioglitazone, testosterone, and angiotensin-converting enzyme inhibitors. A beneficial effect of vitamin D was shown in strength and physical performance in women with low baseline levels (<25 nmol/l). An effect of testosterone on muscle mass (more than strength or function) was shown in men with low serum levels (<200–300 ng/dl), although findings from the high profile Testosterone Trials[123] suggest limited benefit of testosterone for physical function, particularly in those with a slow walking speed, and caution should be taken regarding the cardiovascular side-effect profile.

Research activity is focused on developing new drugs for sarcopenia, although progress has not been straightforward. Initial interest in selective androgen receptor modulators from mainly small phase I and II trials [124,125] has not been followed by convincing results from larger studies. Early evidence suggests that myostatin inhibition could prove beneficial, consistent with recognition that myostatin acts as a brake on muscle differentiation, hypertrophy, and protein synthesis. Results to date have not always been consistent, but positive findings include those from a phase II proof of concept trial that reported that a myostatin antibody was associated with increased muscle mass and improvement in some measures of physical performance in older patients with low muscle strength (defined by low hand grip strength or reduced performance in chair rise tests) who have had falls (but not diagnosed with sarcopenia).[126] Another phase II randomised controlled proof of concept study of bimagrumab for sarcopenia found an increase in thigh muscle volume and increased gait speed in those with reduced gait baseline.[127]

Assessing the effect of interventions in research and clinical practice

Assessment of the effect of interventions in research and clinical practice is required to enable them to be targeted appropriately. Unfortunately, no clear consensus has yet been reached regarding which intermediate measures should be used in research settings[128] or in clinical guidelines.[33] In the absence of an established regulatory

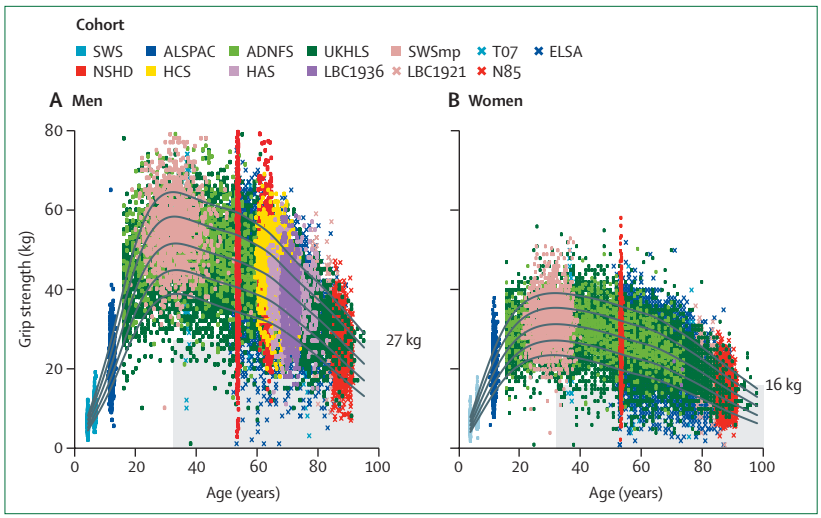

Figure 5: **UK normative data for grip strength across the life course**
Adapted from Dodds et al,[18] by permission of Dodds and colleagues. Centiles shown are 10th, 25th, 50th, 75th, and 90th. Cutoff points based on a T-score of less than −2·5 are shown for men and women (≤27 kg for men and ≤16 kg for women). ADNFS=Allied Dunbar National Fitness Survey. ALSPAC=Avon Longitudinal Study of Parents and Children. ELSA=English Longitudinal Study of Ageing. HAS=Hertfordshire Ageing Study. HCS=Hertfordshire Cohort Study. LBC1921=Lothian Birth Cohort of 1921. LBC1936=Lothian Birth Cohort of 1936. N85=Newcastle 85+ Study. NSHD=Medical Research Council National Survey of Health and Development. SWS=Southampton Women's Survey. SWSmp=mothers and their partners from the SWS. T07=West of Scotland Twenty-07 Study. UKHLS=Understanding Society: the UK Household Panel Study.

pathway for the development of interventions, the European Medicines Agency is using the SPRINTT trial[111] to identify standard outcome measures that could be used in future drug research.

At present, the same muscle strength and physical performance measures can be used during intervention and initial assessments. Improvements in the short physical performance battery of 1 point, or gait speed over 0·1 m/s, are recognised to be of clinical relevance.[129] By contrast, a minimum change has not been well defined for grip strength. Improvement in activities of daily living or in the number of falls might be more relevant for patients than muscle strength, but not so straightforward to determine. However, developing Patient Reported Outcome Measures for sarcopenia is of increasing research interest.[130] Additionally, the SarQoL questionnaire, a sarcopenia-specific quality of life measure, can be used to understand the effect of the intervention on the quality of life of the patient.[131]

Future directions

The prevention of sarcopenia is a major area of research activity and observational epidemiological studies have identified important risk factors such as older age and low socioeconomic status, as well as modifiable influences including low physical activity and poor diet,[132] although the direct effects of alcohol consumption and cigarette smoking are not clear.[133] The focus of preventive strategies to date has been to modify these risk factors in later life (in particular to increase levels of physical activity),[134,135] but these influences might have a role in development of the disease much earlier in life than previously thought.

Birth cohort study findings such as those from the Hertfordshire Ageing Study[136] and Hertfordshire Cohort Study[137] provided initial evidence that small size at birth is linked to lower grip strength at age 60 or 70 years, with confirmation in a subsequent systematic review.[138] These findings have been explained by a life course approach to sarcopenia, which suggests that muscle mass and function in older people depends not only on the rate of functional decline in later life and the factors that influence this (diseases, risk factors, personal conditions, lifestyle) but also on the functional peak reached in young adulthood, which is in turn determined by factors such as low birthweight and prepubertal and pubertal growth, which have an effect earlier in life.[139]

Normative data for grip strength across the life course from UK studies (figure 5)[18] and from global grip strength data[140] are now available. Not only do they confirm the underlying concept of a life course approach to sarcopenia—that skeletal muscle strength peaks in early adulthood, then plateaus, before starting to decline—but have also provided a data driven approach to deriving cutoff points for low grip strength. For example, a grip strength of 2·5 SD or more below the young (age 20–40 years) normal mean indicates low grip strength. This approach is analogous to that used to define osteoporosis in terms of low bone mineral density.

The importance of mid-life influences is also becoming increasingly apparent for the development of sarcopenia. For example, a study using data from the British National Survey of Health and Development (the 1946 birth cohort) has shown evidence of cumulative benefits of increased lifetime physical activity on grip strength at age 60–64 years in men and women. These data showed that those in the upper third of lifetime physical activity score had a mean grip strength 2·11 kg (95% CI 0·88–3·35) greater than those in the lower third after adjustment.[141]

The life course approach to prevention is important and provides opportunity for intervention at a younger age (mid-life and before), when lifestyle changes such as regular physical activity and optimising diet might be easier to implement.[142] This also has the potential to enable public health messages to reach young people encouraging healthy lifestyle changes such as increasing physical activity with immediate to lifelong benefits for skeletal muscle health. However, the evidence to date supporting this approach is largely observational and trials of life course interventions are needed, with use of efficient methodologies such as trials within birth cohorts.[143] Linking a life course approach to understanding the underlying cellular and molecular mechanisms of sarcopenia has the potential to become an effective way to develop targeted treatments and preventive strategies.[144]

Conclusions

Sarcopenia is a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function that is associated with adverse health outcomes. Sarcopenia is increasingly recognised not only as an age-related problem, but also one associated with a range of long-term conditions. Several new consensus definitions have advanced the field over the past decade. Experimental medicine is focusing on translating our understanding of the pathophysiology of sarcopenia into diagnostic, therapeutic, and preventive advances. Additionally, a life course approach could provide a useful framework for the prevention and management of sarcopenia. Important research areas to be addressed include increasing our understanding of underlying cellular and molecular mechanisms, development of biomarkers, improved accuracy of diagnostic tests, and the design of effective strategies to prevent and treat sarcopenia across the life course.

Contributors

AJC-J and AAS both planned the manuscript, did the literature search, contributed to the tables and figures, and wrote, edited, and approved the manuscript.

Declaration of interests

AJC-J has received speaker fees from Abbott Nutrition, Fresenius, Nestlé, Nutricia, and Sanofi-Aventis; is a member of advisory boards for Abbott Nutrition, Nestlé, and Pfizer; and has worked on research projects with Abbott Nutrition and Nutricia. AAS has received speaker fees from Abbott Nutrition in 2011 and 2012.

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