Published Online March 2, 2010

Sarcopenia: characteristics, mechanisms and functional significance

Marco V. Narici[†*] and **Nicola Maffulli**[‡]

[†]*Faculty of Science and Engineering, Institute for Biomedical Research into Human Movement and Health, Manchester Metropolitan University, John Dalton Building, Chester Street, Manchester, UK, and* [‡]*Centre for Sports and Exercise Medicine, Barts and The London School of Medicine and Dentistry, Mile End Hospital, London, UK*

Sarcopenia reflects a progressive withdrawal of anabolism and an increased catabolism, along with a reduced muscle regeneration capacity. Muscle force and power decline more than muscle dimensions: older muscle is intrinsically weak. Sarcopenic obesity (SO) among the elderly corroborates to the loss of muscle mass increasing the risk of metabolic syndrome development. Recent studies on the musculoskeletal adaptations with ageing and key papers on the mechanisms of muscle wasting, its functional repercussions and on SO are included. Neuropathic, hormonal, immunological, nutritional and physical activity factors contribute to sarcopenia. Selective fast fibre atrophy, loss of motor units and an increase in hybrid fibres are typical findings of ageing. Satellite cell number decreases reducing muscle regeneration capacity. SO promotes further muscle wasting and increases risk of metabolic syndrome development. The proportion of fast to slow fibres seems maintained in old age. In elderly humans, nuclear domain is maintained constant. Basal protein synthesis and breakdown show little changes in old age. Instead, blunting of the anabolic response to feeding and exercise and of the antiproteolytic effect of insulin is observed. Further understanding of the mechanisms of sarcopenia requires disentangling of the effects of ageing alone from those of disuse and disease. The causes of the greater anabolic resistance to feeding and exercise of elderly women need elucidating. The enhancement of muscle regeneration via satellite cell activation via the MAPK/notch molecular pathways seems particularly promising.

Keywords: muscle atrophy/muscle weakness/muscle fibres/satellite cells/protein metabolism/sarcopenia/sarcopenic obesity

Accepted: February 7, 2010

**Correspondence address. Faculty of Science and Engineering, Institute for Biomedical Research into Human Movement and Health Manchester Metropolitan University John Dalton Building, Chester Street, Manchester M1 5GD, UK. E-mail: m.narici@mmu.ac.uk*

Introduction

The loss of flesh and vigour with old age has been a preoccupation of mankind since early Greek and Roman history. Classic Greeks abhorred ageing since it represented corruption of their highly prized youthful vigour and was considered as a chronic, incurable and progressive disease (Aristotle, 384 BC). Instead, the Greek physician Galen of Pergamon (now part of Turkey), who at the age of 37 moved to Rome, viewed ageing not as a disease but as a mid-way stage between health and illness and recognized the benefits of moderate exercise and nutrition for healthy ageing. Cicero (44 BC) also rejected the concept of old age as an irreversible illness and opposed the widespread expectation amongst most members of the society that older men, because physically frail, should refrain from any activities, including those not requiring bodily strength. In his treatise 'Cato Maior de senectute' he states: '... Grant that old age is devoid of strength; none is even expected of it. By law and by custom men of my age are exempt from those public services that cannot be rendered without body strength,... we are not only not required to do what we cannot perform but we are not required to do even as much as we can', but a few passages later argues 'it is our duty... to resist old age, to compensate for its defects, to fight against it as we would fight a disease; to adopt a regimen of health; to practice moderate exercise; and to take just enough food and drink to restore our strength'.

This concern of combating physical frailty in old age while maintaining an active role in life is indeed extremely actual as we have entered the third millennium with a proportion of elderly citizens exceeding that of young people.

If the problem of physical frailty in old age is to be effectively mitigated with the final goal of maintaining mobility and independence till the individual limit of chronological age, a full understanding of the aetiology of the mechanisms responsible for muscle wasting and weakness must be achieved first. Hence the aim of this paper is to review the mechanisms leading to muscle wasting in old age, the anatomical alterations thereof and its functional consequences.

SARCOPENIA, a term, proposed by Rosenberg in 1989,[1] specifically refers to the loss of muscle mass associated with ageing. However, the meaning of this term has often been extended to the age-related loss of muscle strength. Although muscle weakness is indeed an inevitable consequence of sarcopenia, these two terms should not be used interchangeably since this would imply a direct proportionality between the two, which, as will be discussed later in this review, is not the case since skeletal muscle becomes intrinsically weaker in old age. Hence the term sarcopenia will be uniquely used to refer to the age-related loss of muscle mass and its relation to the loss in muscle strength will be discussed in detail.

Definition of sarcopenia

The most commonly used definition of sarcopenia has been proposed by Janssen *et al.*[2] and is based on a skeletal muscle mass index obtained by dividing appendicular skeletal muscle mass (ASM), evaluated by DEXA, by body height squared (ASM/ht^2). According to this definition, individuals presenting an ASM/ht^2 ratio between -1 and -2 standard deviations (SD) of the gender-specific mean value of a young controls, are categorized as having class I sarcopenia. Instead, individuals with an ASM/ht^2 ratio below -2 SD are categorized as having class II sarcopenia. Another definition of sarcopenia uses a percentage of skeletal muscle index (SMI%, total muscle mass/body mass $\times$ 100).[3] Although the use of these indexes to classify sarcopenia may be practical for clinical purposes, they do not seem very accurate. This is because sarcopenia is not a uniform condition as it affects postural muscles more than non-postural ones and are based on DEXA, which has been shown known to underestimate limb body mass by up to 20%.[4]

Epidemiology of sarcopenia

Epidemiological studies show that from the second to the eighth decade of life, total lean body mass (LBM) declines by about 18% in men and by 27% in women (calculated using gender-specific equations from Fig. 2 of Janssen *et al.*[3]) and at any given age of adult life women have a considerably smaller muscle mass than men. From the second to the eighth decade, this difference between the two genders is fairly constant, for women's LBM is about 64% that of men. In both men and women, a decline in LBM seems to become detectable after the age of 45 years. However, since total body mass significantly increases from 18 to 40 years, while skeletal muscle mass remains practically constant, it seems not surprising that the onset of the decline in LBM expressed as percentage of total body mass, is detectable as early as in the third decade.[5]

Regional distribution of sarcopenia

For both men and women, the decrease in LBM is greater in the lower limbs (about 15%) than in the upper limbs (about 10%),[3] which may seem counterintuitive when considering the constant use of the lower limbs for locomotion. The reasons for this difference are presently

unclear, however, given that physical activity is significantly reduced in old age even in fully independent older individuals,[6] the greater loss of muscle mass in the lower limbs may be simply due to a detraining effect. Another possibility is that this difference may arise from of a greater loss of motor units in the legs than in the arms. Although no absolute data on MU count in the upper versus lower limbs are available, indirect estimates of MU number based on electrophysiological methods (the ratio between the compound muscle action potential size and the mean surface-detected motor unit action potential size) suggest a greater decrease in MU number in the distal than in the proximal muscles.[7] Considering regional changes of muscle mass, particularly of those muscles essential for locomotion such as the thigh muscles, men and women lose about 24–27% of muscle mass[3] (or volume since muscle has a density of 1.056 g/cm^3) or 25% of muscle cross-cross sectional area[8] between the second and seventh decade. However, when sarcopenia is accelerated by disuse, disease or anorexia, this loss of muscle mass may place women at greater risk of falling below the level of critical muscle mass essential for mobility and independent living. Also, due to their higher longevity, women are more likely to spend the last years of life under institutional care than men are.

Intramuscular fat accumulation and SO

Several computed tomography,[9–11] MRI[12] and ultrasonography[13] studies have shown that in sarcopenia, the loss of muscle tissue is accompanied by infiltration with fat and connective tissue, a condition known as *myosteatosis*.[11] As a result, the net contractile muscle mass is actually smaller than that measured by a simple muscle cross-sectional area (CSA) and mistakes in the estimation of the contractile muscle mass are likely to be made if this non-contractile mass is not accounted for. In older women and men this averages to ~15% of the total muscle CSA, about 2.5-fold greater than in young controls (~6%).[11] The accumulation of intramuscular fat and connective tissue has been shown to be inversely related to the level of physical activity, doubling the level of physical activity practically halves the amount of intramuscular fat and connective tissue.[12] Myosteatosis is of particular concern in older individuals in which sarcopenia is combined with obesity, a condition known as *sarcopenic obesity*. Baumgartner[14] defined SO as a ratio of ASM to body height squared (ASM/ht^2) less than 2 standard deviations below the sex-specific mean of a younger reference group and as a percentage of body fat greater than 27% in men and 38% in women. Using this definition, the prevalence of SO rises from 2% in men and women aged 60–69 years to about 10% in those aged 80 and above.

Fat infiltration of skeletal muscle not only represents a burden for locomotion because of the added inert mass to be carried by the individual, but is also believed to sustain sarcopenia through a macrophage infiltration mediated-release of pro-inflammatory cytokines (such as TNF-α, IL-6, IL-1) and adipokines (leptin, adiponectin and resistin) from adipocytes.[15] Increasing evidence exists that chronic inflammation may be a mechanism for insulin resistance[16,17] and for its widespread abnormalities generally described as the 'metabolic syndrome'.[18] Epidemiological evidence shows that SO is associated with an accelerated functional decline and high risk of diseases and mortality.[19] Because the loss of muscle mass associated with sarcopenia promotes insulin resistance, the association between SO and sarcopenia, likely sets up a vicious circle, resulting in further loss of muscle mass and mobility, insulin resistance and risk of metabolic syndrome development.[20]

Muscle fibre size, number and composition

The decrease in muscle mass that gives rise to sarcopenia involves both a decrease in muscle fibre size (atrophy) and number (hypoplasia). In this respect, sarcopenia shows a fundamental difference from disuse atrophy that involves only a decrease in fibre size but not in number. There is firm evidence that with ageing type II fibres are more vulnerable to atrophy than type I fibres.[21–23] In one of the earliest studies on this topic, Larsson[24,25] reported that in older individuals aged 60–55 years, the areas respectively occupied by Type I and Type II fibres were respectively 23% and 42% smaller than those found in 20–29 year subjects. Consistent with this earlier report, Lexell[24–26] found Type II fibre CSA of 80-year-old subjects to be 26% smaller than that of 20-year-old controls, whereas no difference existed in Type I fibre CSA. More recently, Andersen[27] found Type II fibre CSA of 85+ year-old individuals to be 57% smaller than that of 25 year-old controls but also found Type I fibres to be 25% smaller in the older group. Considering the subtypes of Type II fibres, greater atrophy of Type II B fibres (Type X using the myosin heavy chain-based classification) than of Type IIA fibres has been found in older men (22%, versus 13%) and women (30% and 24%);[26,28] instead, Klitgaard[23] found both fibre subtypes to be similarly reduced (27% for Type II A and a 31% for Type IIX fibres). Consistent with the notion that fibre atrophy mainly affects the postural muscles, Klitgaard *et al.*[28] did not find significant differences between Type I, Type IIA and IIx fibres of the biceps brachii of young and older individuals.

However, what has become clear over the last 20 years is that the net distinction between fibre types becomes obfuscated in old age since at

least one-third of the fibres are neither type I, nor type II as they co-express both type MHC-I and MHC-II.[27,29,30] An explanation for this increased heterogeneity in MHC isoforms in old age has been given by D'Antona.[30,31] With ageing, due to neuropathic processes leading to motor unit denervation, a preferential loss of fast motor units (containing Type IIA and IIX fibres) occurs[32,33] and this is expected to cause a shift towards the slower phenotype. However, the final MHC expression is also affected by the level of neuromuscular activity: whereas disuse favours the expression of fast MHC isoforms, training (regardless of whether it is of endurance or strength type) leads to a shift towards the slower population of fast fibres, that is to say a shift from the MHC-2X to MHC-2A.[34,35] Hence, a profile in MHC distribution characteristic of ageing does not quite exist since it is the result of the interaction between age-related neuro-degenerative changes and physical activity status, which varies across different individuals.

In terms of changes in fibre number with ageing, evidence of a decrease comes from cross-sectional morphological studies on human muscle samples[22,25] and from electrophysiological studies. These studies showed that MU number remained fairly constant up to the sixth decade of age but form 60 to 80 years of age it declined by 50%.[22]

Similarly, using electrophysiologic methods, Campbell[32] reported that the number of motor units was almost constant up to the age of 60 years but rapidly declined thereafter at a rate of 3%/year, which at the age of 80 years represents a 60% loss of MUs. Although early cross-sectional studies comparing young and older individuals, reported a selective loss of type II fibres with a concomitant increase in the ratio of type I/II fibre ratio,[24] consistent with a slowing down of muscle contractile properties,[36,37] recent evidence suggests that this is not the case. In meticulously conducted autopsy studies using whole muscle cross-sectional slices rather than bioptic samples, Lexell[22,25,38] found a similar decline in the number of types I and II fibres of the vastus lateralis muscle. This finding seems also confirmed by one of the few longitudinal investigations performed in the same older individuals over the course of 12 years.[39] No evidence of type I fibre sparing was found, since at the age of 65 years the proportion of type I fibres was 60% whereas at the age of 77 years it was 40%. The current view is that with ageing a loss of both type of fibres occurs but with a different time course; whereas greater loss of type II fibres may occur up to the late 70s, past 80 years also type I fibres are lost and a new 'balance' between the two types of fibres is reached, as seems suggested by the finding of a similar type I/II fibre ratio in individuals aged 85–97 years.[27]

Satellite cells and myonuclear number

Muscle fibres are notoriously large multinucleated cells. Each myonucleus controls a certain volume of cytoplasm known as *nuclear domain* and it has long been sustained that changes in fibre size should occur with a proportionate change in myonuclei number in order to maintain the nuclear domain constant.[40] Previous studies, mainly in rodents, based on conventional histology of muscle cross sections observed under the light microscope (with which distinction of myonuclei from other nuclei proves often difficult), reported that with muscle hypertrophy the number of myonuclei increases through donation of nuclei from satellite cells whereas in atrophy the number of myonuclei decreases through apoptosis (see[41] for review). However, the reported reduction in myonuclei number with muscle atrophy has only been found in rodent and not in human models and is actually challenged by recent fundings in murine as well as human muscle. Using *in vivo* time lapse imaging of single fibres in which the nuclei are labelled with GFP, no loss of myonuclei was found in denervated murine muscle, despite a 50% reduction in fibre volume.[41] Similar observations were made on muscle fibres of denervated mouse plantaris muscle.[42] The scanty data on humans seem in line with the findings of no loss in myonuclei number with ageing. Indeed, in older frail humans aged 70–83 years in which satellite cells and myonuclei were visualized using a monoclonal antibody and counterstained with Mayer's haematoxylin, Kadi *et al.*[43] observed that despite a lower number (25%–37%) of satellite cells, myonuclei number was not lower, as reported for aged animal muscle,[44] but actually higher (12%–19%) than of young controls. The consequence of an increase in myonuclear number (through satellite cells recruitment) in the presence a decreased fibre size suggests a decrease in myonuclear efficiency in old age[43] and does not lend support to the concept of a constant nuclear domain with ageing since each myonucleus would have less cytoplasm to control, which would predict a decrease in nuclear domain.

Changes in muscle architecture

The morphological changes of skeletal muscle associated with sarcopenia not only involve a sheer reduction in muscle cross-sectional area and volume but also a remodelling of muscle architecture. Muscle architecture describes the spatial arrangement of muscle fibres within a muscle and is a main determinant of muscle mechanical characteristics, namely the length–force (L-F) and the force–velocity (F-V)

relationships.[45] This is because muscle force depends on the number of sarcomeres placed in parallel, thus on muscle CSA, while maximum shortening velocity depends on the number of sarcomeres placed in series, thus on fibre length. Over the last 20 years, an increasing number of investigations into human muscle architecture have been performed *in vivo* using ultrasound imaging. Using this technique in the gastrocnemius muscle of young and older adults, Narici *et al.*[46] reported for the fist time that both the length of muscle fibre fascicles and their angle of insertion into the tendon aponeurosis (angle of pennation) decreased with ageing. The decrease in fascicle length (Lf) implies a loss of sarcomeres in series and predicts a loss of muscle shortening velocity, whereas a decrease in pennation angle reflects a loss of sarcomeres in parallel, hence in muscle CSA, and thus in muscle force generating potential.[47] Since muscle power is the product of force and velocity, changes in muscle architecture with ageing play a role in the loss of muscle force and power in old age.[47] Comparing the force–velocity properties of the human gastrocnemius muscle of young and older men, Thom *et al.*[47] found that, after normalization of shortening velocity to Lf, the shorter Lf accounted for about 16% of the difference on maximum shortening velocity while, after normalization of torque to muscle physiological CSA (PCSA), the smaller PCSA accounted for about 10% of the difference in maximum isometric force.

The actual causes of these changes in muscle architecture are to be reconducted to the remodelling of skeletal muscle that occurs with atrophy. A decrease in the angle of pennation is explained by the evolutional phenomenon that led to the development of pennate muscle. This is because the pennate arrangement of muscle fibres is a response to the requirement of packing as much contractile tissue as possible along the tendon aponeuroses to generate large forces, in fact with muscle hypertrophy pennation angle increases[48]. Thus with atrophy, as muscle tissue is lost, the packing of contractile tissue along the tendon aponeuroses decreases. Eventually, this removal of sarcomeres in parallel (leading to the decrease in pennation angle and in muscle CSA) and in series (leading to the decrease in Lf) is consequential to the decrease in protein synthesis that occurs with ageing and disuse (see following section). Several factors can cause a depression of the protein signalling pathway[49,50], and it has been recently shown that one of the molecular modulators of this process is the mechanosensitive protein focal adhesion kinase (FAK) located in the costamere region of skeletal muscle fibres and known to be sensitive to changes in mechanical loading. After just 10 days of unloading of the human knee extensors, FAK content and activity were found to decrease by 20 and 30%, respectively[51], leading to a 50% fall in protein synthesis and to a 6% decrease in fibre Lf, equivalent to a loss of 2700 sarcomeres[50].

Aetiology of sarcopenia

The aetiology of sarcopenia is rather complex since it involves central and peripheral nervous system alterations, hormonal, nutritional, immunological and physical activity changes (Fig. 1). Amongst these factors, neuropathic processes are probably one of the most important causes, as they are responsible for α-motoneuron degeneration and muscle fibre denervation, resulting in a loss of motor units.[52] Throughout the lifespan, skeletal muscle undergoes a continuous cycle of denervation and reinnervation[53] but in old age it seems that the process of reinnervation cannot keep pace with that of denervation, contributing to the loss of motor units. Although no longitudinal studies have been performed to define the time course of these events, cross-sectional studies suggest that motoneuron or motor unit numbers are well maintained until the seventh decade but then decline at a fast rate.[32] The precise causes of this age-associated loss of motoneurons are yet to be fully elucidated but recent findings in rodents have shown that an age-related decline in the synthesis of ciliary neurotrophic factor (CNTF), a protein that promotes the differentiation and survival of motoneurons, is associated with motoneuron degeneration.[54] Some of the denervated muscle fibres, mostly of type II, are reinnervated through axonal sprouting from type I fibres,[33,55,56] giving rise to giant motor units characterized by very large motor unit action potential. Although this affords a small compensation against the loss of force, it

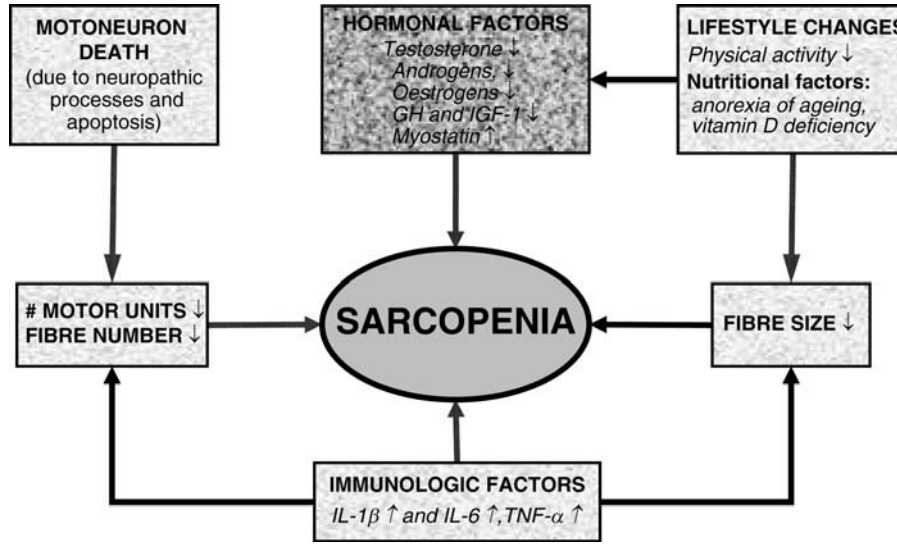

Fig. 1 Scheme summarizing the factors contributing to sarcopenia.

increases the innervation ratio of the affected motor units thereby reducing fine control of force during motor unit recruitment.

The degenerative changes of the nervous system also concern the neuromuscular junction, which undergoes considerable remodelling and fragmentation with ageing. Degenerative changes in these structures include fragmentation in the distribution of acetylcholine receptors and an increase in the incidence of branches or boutons that are spatially separate or only connected by fine nerve filaments, suggesting fragmentation of the terminal (for reviews see refs (53,57)). Recent experiments on transgenic mice lacking the antioxidant enzyme superoxide dismutase have shown an acceleration of sarcopenia due to neuromuscular degeneration following mitochondrial dysfunction. This finding indicates that a decline in the ability to cope with an increase in oxidative stress may be, at least in rodents, an important cause of sarcopenia.[58]

The degenerative changes of the neuromuscular system may also affect directly the muscle cell itself independently of the neuropathic processes since there is increasing evidence that apoptosis of skeletal myocytes contributes to sarcopenia.[59] Mitochondrial dysfunction and sarcoplasmic reticulum stress seem to play a key role in inducing skeletal muscle cell apoptosis and reactive oxygen species (ROS), as superoxide anion and hydrogen peroxide, are believed to play a key role in triggering these events.[60,61] Mitochondrial ROS production is believed to increase with ageing due to altered respiratory chain function and decreased cell defence against free radicals[62] causing mitochondrial DNA (mtDNA) damage.[59] Until recently, there was little evidence of a causative relationship between mtDNA damage and muscle tissue dysfunction, but in 2004 Trifunovic *et al.*[63] showed that somatic mtDNA mutation were associated with premature onset of ageing-related phenotypes such as osteoporosis, myocardial hypertrophy and sarcopenia.

Muscle cell apoptosis seems to be caused through the activation of specific signalling pathways, initiated by ligand binding of tumour necrosis factor alpha (TNF-α) to a cell membrane receptor, involving a cascade of caspases (endoproteases) responsible for the proteolytic events resulting in cell breakdown and death. In addition, the mitochondrion, commonly regarded as the 'main regulator' of apoptosis,[59] may provoke apoptosis via several different pathways, by releasing cytochrome *c* into the cytosol leading to the activation of effector caspases, but also through the release of pro-apoptotic proteins leading to DNA fragmentation. Stress to the endoplasmic reticulum may also lead to apoptosis following the release of calcium into the cytosol eventually leading to the activation of effector caspases. Although the precise contribution of apotosis to sarcopenia is difficult to establish, muscle weight has been found to be inversely proportional to the incidence of

apoptosis when expressed as apoptotic index,[59] suggesting a causative relationship.

As a result of the loss of motoneurons, due to neuropathic processes, and of muscle cell apoptosis, the number of muscle fibres considerably decreases with ageing.[25]

Fibre size also decreases with age (atrophy) and this is probably due to both a decrease satellite cell proliferation due to an age-related decrease in the level of growth factors such as IGFs,[64] and a reduction in mechanical stimuli due to decreased physical activity. In fact, recent evidence suggests that, even 'physically active' septuagenarians (individuals aged 70–79 years) are about 20% less active than their vicenarian (individuals aged 20–29 years) counterparts.[6] Besides, reduced physical activity may also lead to muscle fibre apoptosis since it has been found after hindlimb suspension in rats.[65] However, age-related muscle loss seems blunted in life-long trained athletes (master athletes) who display greater Type I, IIA and IIB fibre areas than age-matched untrained controls.[66] The protective effect of high level physical activity against muscle loss in master athletes, slows down but does not prevent the decline in muscle performance which, between 20 and 80 years of age, falls by about 40% in endurance runners and by 60% in weight lifters.[67] In fact, comparing young to older sprinters Korhonen *et al.*[66] found that the older athletes showed the typical ageing-associated reduction in the size of fast fibres, shift toward a slower MHC isoform profile and lower Vo of type I MHC fibres. Instead, specific tension of both type I and type II fibres did not differ between the young and older sprinters.[66] They concluded that these changes likely played a role in the decline in explosive force-production capacity observed in older sprinters. Hence these data suggests that, while regular, intense physical activity prevents or even reverses the age-related muscle mass by leading to hypertrophy of the surviving muscle fibres, it is unlikely to reverse the loss in fibre number due to the neuropathic processes and to the slowing down of the myosin molecule. The latter does not appear to be due to a reduction in the level of physical activity since it occurs both in sedentary and in highly active older sprinters and seems more likely due to posttranslational modifications of the contractile proteins. Among these, an ageing-related increase in non-enzymatic glycation of the myosin molecule, associated with a slowing down of its intrinsic speed of shortening, observed in *in vitro* motility assays, could contribute to this phenomenon.[68]

In addition to these neuropathic and physical activity-related changes, nutritional, hormonal and immunological factors are also known to contribute to sarcopenia. Malnutrition in ageing is quite common, and this is due to a progressive a loss of appetite, a reduction in food intake and also to vitamin D deficiency, largely due to skin

atrophy.[69] Furthermore, low vitamin D, in association with high parathyroid hormone levels, has been found to increase the risk of muscle wasting in old age.[70,71]

The hormonal and immunological alterations contributing to sarcopenia are represented by the withdrawal, or resistance, to those factors responsible for anabolism (decreased levels of GH, IGF-1, testosterone) and by an increased catabolic activity (increased levels of IL-1, IL-6, TNF-α, myostatin).[72]

Protein turnover

Although the individual contribution of each of the above factors is very difficult to establish, it may be generally stated that sarcopenia is the result of a mismatch between protein synthesis and degradation. In humans, basal protein breakdown has been found to be either unaffected[73–75] or slightly elevated in old age[76] and surprisingly, also basal protein synthesis does not appear to differ between young and older individuals.[76–78] However, differences in protein synthesis between young and older individuals do exist in the response to feeding and exercise, with older people showing a blunted response to anabolic stimuli. Compared to young controls, older people show a lower increase in muscle protein synthesis in response to amino acid feeding under insulin clamping conditions ($\sim -40\%$) and also in response to an acute bout of exercise ($\sim -30\%$).[79]

Likewise, despite the absence of differences in breakdown in the basal state, important differences have been recently discovered in response to feeding. Wilkes *et al.*[80] have indeed reported that the inhibition of proteolysis by insulin in response to feeding and activation of the Akt-protein kinase B signalling pathway are blunted in older individuals compared with young adults. These effects were found by feeding young and older individuals with a low glycaemic-index meal and by measuring whole leg protein turnover (using an arteriovenous tracer dilution method) and muscle protein synthesis after infusion of stable amino acid isotopes. Protein breakdown was estimated as leg protein flux from arterial and venous amino acid tracers concentrations multiplied by plasma flow. Whereas no differences in basal leg protein breakdown (LPB) existed between the young and older groups, in response to feeding, only a 12% reduction in LBP in response to insulin was found in the older group compared with a 47% decrease in the younger group. Taken together, these results suggest that sarcopenia in humans is not only due to a blunted anabolic response (reduced sensitivity and responsiveness) to amino acid feeding but also to a reduced sensitivity to the inhibitory effect of insulin on protein

breakdown. Although increased protein breakdown through activation of the ubiquitin-proteasome system (UPS) has been reported for old rats[81] it seems hazardous to extrapolate these findings to humans since distinct differences in protein turnover exist between the two species.[82] The role of the UPS in human muscle wasting has been recently thoroughly reviewed by Murton *et al*.[83] Essentially, the available data show that activation of the ubiquitin ligases MAFbx/atrogin-1 and MuRF1 mainly occurs in muscle wasting caused by inflammation (such as in cancer, COPD, critical illness, severe trauma, amytrophic lateral sclerosis, AIDS). Instead, the data on changes in MAFbx/atrogin-1 and MuRF1 mRNAs and protein expression in non-inflammatory muscle atrophy are inconsistent,[83] questioning the role of the UPS in muscle wasting in medically stable individuals. The role of the UPS in non-inflammatory muscle wasting is also put into question by the observation of no change in muscle protein breakdown in the presence of insulin-mediated alterations in protein expression of atrogin-1 and MuRF1.[84]

Even assuming that the UPS plays a role in sarcopenia, the available evidence only shows a slight elevation in basal protein breakdown in human beings.[76]

Capacity for muscle regeneration

Satellite cells are quiescent myogenic precursors that play a fundamental role in muscle repair and growth.[85] Following injury, satellite cells become activated and proliferate and differentiate into myoblasts. Provided the basal lamina remains intact, the myoblasts fuse with each other to form myotubes, which then mature into a new fibre or fuse with an existing one, resulting in myofibre repair. Recent investigations show that the breaking of satellite cells quiescence and the initiation of proliferation are mediated by Notch, a trans-membrane receptor.[86] With ageing, Notch activation declines due to a fall in mitogen-activated protein kinase (MAPK) activity, thereby reducing satellite cell activation. This process is compounded by an increase in the levels of transforming growth factor beta (TGF-β) causing accumulation of cyclin-dependent kinase, which inhibits satellite cells and prevents their regenerative response to injury.[86]

Functional consequences of sarcopenia

There is a wealth of studies reporting a decline in muscle strength and power in old age (for review see[87]). The rate of loss of muscle power

(3–4%/year) is however about 2-fold greater than that of isometric force (1–2%/year).[88] Hence when comparing values of isometric force and peak power of older individuals (mean age 74 years) to those of young controls (mean age 26 yr), a 40% difference in isometric force against a 60% difference in peak power, are found.[47] From a functional point of view, a greater decline in muscle power than in force is of considerable consequences for the quality of life of older people since most daily actions, such as raising from a chair or climbing a flight of stairs require the development of muscle power. This problem is exacerbated in sarcopenic-obese people since not only they have a lower muscle mass available for delivering the power necessary for daily activities but they have to generate extra-power, and thus use more energy, to displace the excess body fat due their condition.

Despite the fact that sarcopenia is a major determinant of muscle weakness in old age, the loss of muscle strength and power exceeds that of muscle size and volume and, as a consequence, there is a decline in force per unit of muscle cross-sectional area and in peak power per unit volume.[6,8,9,28,89] (Force depends on muscle CSA, that is to say, on the number of force-generating sarcomeres arranged in-parallel, while power, being the product of force and velocity, which in turn depends on the number of sarcomeres arranged in-series, depends on muscle volume, which is the product of cross-sectional area and muscle length.) Several factors contribute to this phenomenon, frequently referred to as a deterioration in 'muscle quality'. These factors can be grouped under two main categories: neuromuscular and tendinous. Each of these factors is discussed separately in the following sections.

Loss of force per cross-sectional area

Among the muscular changes, a reduction in single fibre force per cross-sectional area (specific tension) is one of the major factors contributing to the decline in intrinsic muscle force and recent evidence suggests that this is tightly associated with a decrease in the number of actomyosin cross-bridges rather than in the force exerted by each cross-bridge.[30] A reduction in excitation–contraction coupling may also contribute to the decrease in specific tension, as there is increasing evidence of E:C uncoupling in old age[90,91] as a decline in the function of the dehydropyridine receptors leading to reduced Ca^{2+} release by the sarcoplasmic reticulum has been found in ageing skeletal muscle.[57] Another cause of the decrease in single fibre specific tension with ageing is protein glycation. Several studies have shown an accumulation of advanced glycation end products (AGEs) with ageing. These have

been shown to alter the structural and functional properties of the contractile protein myosin, leading to a decrease in maximum shortening speed and specific tension[92] as well as to an increase in intramuscular collagen cross-linking[93] which is thought to be associated with an increased muscle stiffness and impaired muscle function in the elderly. The accumulation of AGEs is particularly frequent in diabetes and in individuals with low physical activity levels.[93]

Loss of specific power

Muscle power is affected by changes in both force and velocity of shortening. In addition to the above-listed causes of the loss in muscle force (together with changes in neural drive in the case of voluntary contractions, see below), factors contributing to the loss in shortening velocity in old age are a selective loss of fast twitch fibres (whose power is about 10 times higher than that of slow fibres)[94] and a decrease in the intrinsic speed of shortening of the myosin molecule.[68]

Changes in neural drive

Other contributors include a reduction in neural drive to the agonist muscles and an increase in neural drive to the antagonist muscles. Several investigators have found a reduced activation capacity in older individuals,[10,95,96] while others reported no differences,[97–99] although it is generally agreed that a considerable heterogeneity in activation capacity exists among muscles.[100] Both motor unit recruitment and firing frequency have been found to be reduced in older adults,[101] though a lower firing frequency may not necessarily lead to a decrease in activation capacity since motor unit fusion frequency is reduced with ageing because of prolongation of twitch contraction time.[37] An increased co-activation of antagonist muscles, probably necessary for joint stabilization, has also been suggested as a possible mechanism for the loss of force with ageing.[102]

Tendinous changes

Ageing not only involves qualitative and quantitative changes of skeletal muscles but also of tendons. Tendon mechanical properties studied *in vivo* with ultrasonography have been found to be significantly deteriorated in old age.[103] These alterations are represented by a decrease in tendon stiffness (−36%) and in Young's modulus (−48%) suggesting that a deterioration in tendon material properties accounts for most of

the decline in stiffness. These alterations in tendon properties with old age are expected to have a direct impact on muscle mechanical behaviour by affecting the degree of shortening of muscle fibres and the rate of force development upon contraction.[103] This is because a decrease in tendon stiffness would cause muscle fibres to shorten more upon contraction in order to take up the greater tendon slack. This greater shortening upon contraction may place fascicles in a non-favourable portion of the length–tension relationship and may thus contribute to the loss of intrinsic muscle force with ageing.[103] Despite these earlier findings of age-related decreases in tendon stiffness and Young's modulus, no differences in tendon material properties or in tendon size have been recently observed between young and older individuals.[104]

Conclusions

Sarcopenia has a complex aetiology involving neuronal, hormonal, immunological, nutritional and physical activity mechanisms. Although this process affects both genders, women are more at risk of losing functional independence than men are since they live longer and at any given age have a lower muscle mass than men also because they display greater blunting of the anabolic response to exercise and feeding in addition to blunting of the antiproteolytic effect of insulin. However, muscle mass in old age is not only lost due to reduced anabolism and increased catabolism, but also due to a reduced capacity of muscle regeneration as satellite cell activation and proliferation becomes impaired in old age. Lastly, the increased prevalence of obesity in the older population is a recognized compounding factor of sarcopenia, giving rise to SO, a condition that likely contributes to the loss of muscle mass, mobility and independence in old age.

Perspective

Although considerable knowledge has been gained on the prevalence, aetiology and functional consequences of sarcopenia, much remains to be elucidated. For instance, efforts should be made to dissociate the effects of ageing *per se* from those of disuse and disease. Most of the available knowledge in this field is based on cross-sectional studies comparing young and older people with diverse genetic and phenotypic characteristics, thus unconsciously assuming that the same determinants drive the ageing process of different individuals. More longitudinal studies are needed, playing specific attention to the choice of a representative phenotype, or a minimal battery of phenotypes affecting

different characteristics (strength, fatigability, power, balance, coordination). Future workers should also attempt to clarify the role of muscle protein breakdown in medically stable older people, as many current views of the immediate causes of atrophy place what may be unwarranted emphasis on its role. In fact there is no published evidence deriving from modern methods of measurement of muscle protein breakdown in older people showing that it is elevated; furthermore none of the so-called proteolytic markers have not been validated against such methods. Also, evidence of activation of the ATP dependent ubiquitin-proteasome pathway (and of the other pathways involving caspase and autophagy) comes mainly from increased expression of mRNA (not protein or even measured enzyme activity) and derives from studies of rodents with a distinctly different lifetime pattern of protein turnover than is seen in people. In human beings, evidence of activation of the UPS comes from studies performed on cachectic patients, who may show both a faster and different mode of wasting characterized by activation of catabolic hormones and inflammation.

Although strong evidence exists that regular resistive exercise slows down the ageing-associated decrease in muscle mass, its possible role in protecting against the loss of motor units should be further explored. Other possible treatments deserving attention include selective androgen receptor molecules and anti-myostatin antibodies, both of which are currently in phase II trials in the USA. Whether muscle regenerative capacity through activation of notch-mediated satellite cells proliferation can be modulated by targeted pharmacological interventions seems an approach also worth investigating. Finally, more understanding on the exact causes of the blunted anabolic response of older women to feeding and resistive exercise needs to be gained.

Funding

Original work in Prof. M.V. Narici's Laboratory described in this review was supported by UK BBSRC, EU Framework 5 (Better Ageing project, No QLRT-2001-00323) EU Framework 7 MYOAGE Project (No: 223576) and ESA MAP program funding.

References

1 Rosenberg IH. Sarcopenia: origins and clinical relevance. *J Nutr* 1997;**127**:990S–1.
2 Janssen I, Heymsfield SB, Ross R. Low relative skeletal muscle mass (sarcopenia) in older persons is associated with functional impairment and physical disability. *J Am Geriatr Soc* 2002;**50**:889–96.
3 Janssen I, Heymsfield SB, Wang ZM *et al*. Skeletal muscle mass and distribution in 468 men and women aged 18–88 yr. *J Appl Physiol* 2000;**89**:81–8.

4 Ryan AS, Dobrovolny CL, Smith GV *et al*. Hemiparetic muscle atrophy and increased intramuscular fat in stroke patients. *Arch Phys Med Rehabil* 2002;**83**:1703–7.
5 Gallagher D, Visser M, De Meersman RE *et al*. Appendicular skeletal muscle mass: effects of age, gender, and ethnicity. *J Appl Physiol* 1997;**83**:229–39.
6 Morse CI, Thom JM, Davis MG *et al*. Reduced plantarflexor specific torque in the elderly is associated with a lower activation capacity. *Eur J Appl Physiol* 2004;**92**:219–26.
7 Galea V. Changes in motor unit estimates with aging. *J Clin Neurophysiol* 1996;**13**:253–60.
8 Young A, Stokes M, Crowe M. The size and strength of the quadriceps muscles of old and young men. *Clin Physiol* 1985;**5**:145–54.
9 Jubrias SA, Odderson IR, Esselman PC *et al*. Decline in isokinetic force with age: muscle cross-sectional area and specific force. *Pflugers Arch* 1997;**434**:246–53.
10 Harridge SD, Kryger A, Stensgaard A. Knee extensor strength, activation, and size in very elderly people following strength training. *Muscle Nerve* 1999;**22**:831–9.
11 Taaffe DR, Henwood TR, Nalls MA *et al*. Alterations in muscle attenuation following detraining and retraining in resistance-trained older adults. *Gerontology* 2009;**55**:217–23.
12 Kent-Braun JA, Ng AV, Young K. Skeletal muscle contractile and noncontractile components in young and older women and men. *J Appl Physiol* 2000;**88**:662–8.
13 Sipila S, Suominen H. Knee extension strength and walking speed in relation to quadriceps muscle composition and training in elderly women. *Clin Physiol* 1994;**14**:433–42.
14 Baumgartner RN. Body composition in healthy aging. *Ann N Y Acad Sci* 2000;**904**: 437–48.
15 Neels JG, Olefsky JM. Inflamed fat: what starts the fire? *J Clin Invest* 2006;**116**:33–5.
16 Goodpaster BH, Krishnaswami S, Resnick H *et al*. Association between regional adipose tissue distribution and both type 2 diabetes and impaired glucose tolerance in elderly men and women. *Diabetes Care* 2003;**26**:372–9.
17 Goodpaster BH, Thaete FL, Kelley DE. Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. *Am J Clin Nutr* 2000;**71**: 885–92.
18 Reaven GM, Chen YD. Role of insulin in regulation of lipoprotein metabolism in diabetes. *Diabetes Metab Rev* 1988;**4**:639–52.
19 Stenholm S, Harris TB, Rantanen T *et al*. Sarcopenic obesity: definition, cause and consequences. *Curr Opin Clin Nutr Metab Care* 2008;**11**:693–700.
20 Roubenoff R. Sarcopenic obesity: the confluence of two epidemics. *Obes Res* 2004;**12**:887–8.
21 Larsson L, Sjodin B, Karlsson J. Histochemical and biochemical changes in human skeletal muscle with age in sedentary males, age 22–65 years. *Acta Physiol Scand* 1978; **103**:31–9.
22 Lexell J, Henriksson-Larsen K, Winblad B *et al*. Distribution of different fiber types in human skeletal muscles: effects of aging studied in whole muscle cross sections. *Muscle Nerve* 1983;**6**:588–95.
23 Klitgaard H, Zhou M, Schiaffino S *et al*. Ageing alters the myosin heavy chain composition of single fibres from human skeletal muscle. *Acta Physiol Scand* 1990;**140**:55–62.
24 Larsson L. Morphological and functional characteristics of the ageing skeletal muscle in man. A cross-sectional study. *Acta Physiol Scand Suppl* 1978;**457**:1–36.
25 Lexell J, Taylor CC, Sjostrom M. What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci* 1988;**84**:275–94.
26 Coggan AR, Spina RJ, King DS *et al*. Histochemical and enzymatic comparison of the gastrocnemius muscle of young and elderly men and women. *J Gerontol* 1992;**47**:B71–6.
27 Andersen JL. Muscle fibre type adaptation in the elderly human muscle. *Scand J Med Sci Sports* 2003;**13**:40–7.
28 Klitgaard H, Mantoni M, Schiaffino S *et al*. Function, morphology and protein expression of ageing skeletal muscle: a cross-sectional study of elderly men with different training backgrounds. *Acta Physiol Scand* 1990;**140**:41–54.
29 Klitgaard H, Bergman O, Betto R *et al*. Co-existence of myosin heavy chain I and IIa isoforms in human skeletal muscle fibres with endurance training. *Pflugers Arch* 1990;**416**: 470–2.

30 D'Antona G, Pellegrino MA, Adami R *et al*. The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J Physiol* 2003;**552**:499–511.
31 D'Antona G, Pellegrino MA, Carlizzi CN *et al*. Deterioration of contractile properties of muscle fibres in elderly subjects is modulated by the level of physical activity. *Eur J Appl Physiol* 2007;**100**:603–11.
32 Campbell MJ, McComas AJ, Petito F. Physiological changes in ageing muscles. *J Neurol Neurosurg Psychiatry* 1973;**36**:174–82.
33 Lexell J. Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci* 1995;**50**:11–6.
34 Fluck M, Hoppeler H. Molecular basis of skeletal muscle plasticity–from gene to form and function. *Rev Physiol Biochem Pharmacol* 2003;**146**:159–216.
35 Liu Y, Schlumberger A, Wirth K *et al*. Different effects on human skeletal myosin heavy chain isoform expression: strength vs. combination training. *J Appl Physiol* 2003;**94**:2282–8.
36 Brooks SV, Faulkner JA. Contractile properties of skeletal muscles from young, adult and aged mice. *J Physiol* 1988;**404**:71–82.
37 Narici MV, Bordini M, Cerretelli P. Effect of aging on human adductor pollicis muscle function. *J Appl Physiol* 1991;**71**:1277–81.
38 Lexell J, Downham D, Sjostrom M. Distribution of different fibre types in human skeletal muscles. Fibre type arrangement in m. vastus lateralis from three groups of healthy men between 15 and 83 years. *J Neurol Sci* 1986;**72**:211–22.
39 Frontera WR, Hughes VA, Fielding RA *et al*. Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* 2000;**88**:1321–6.
40 Hall ZW, Ralston E. Nuclear domains in muscle cells. *Cell* 1989;**59**:771–2.
41 Gundersen K, Bruusgaard JC. Nuclear domains during muscle atrophy: nuclei lost or paradigm lost? *J Physiol* 2008;**586**:2675–81.
42 Wada KI, Takahashi H, Katsuta S *et al*. No decrease in myonuclear number after long-term denervation in mature mice. *Am J Physiol Cell Physiol* 2002;**283**:C484–8.
43 Kadi F, Charifi N, Denis C *et al*. Satellite cells and myonuclei in young and elderly women and men. *Muscle Nerve* 2004;**29**:120–7.
44 Brack AS, Bildsoe H, Hughes SM. Evidence that satellite cell decrement contributes to preferential decline in nuclear number from large fibres during murine age-related muscle atrophy. *J Cell Sci* 2005;**118**:4813–21.
45 Lieber RL, Friden J. Functional and clinical significance of skeletal muscle architecture. *Muscle Nerve* 2000;**23**:1647–66.
46 Narici MV, Maganaris CN, Reeves ND *et al*. Effect of aging on human muscle architecture. *J Appl Physiol* 2003;**95**:2229–34.
47 Thom JM, Morse CI, Birch KM *et al*. Influence of muscle architecture on the torque and power-velocity characteristics of young and elderly men. *Eur J Appl Physiol* 2007;**100**:613–9.
48 Kawakami Y, Abe T, Fukunaga T. Muscle-fiber pennation angles are greater in hypertrophied than in normal muscles. *J Appl Physiol* 1993;**74**:2740–4.
49 Rennie MJ, Wackerhage H, Spangenburg EE *et al*. Control of the size of the human muscle mass. *Annu Rev Physiol* 2004;**66**:799–828.
50 de Boer MD, Maganaris CN, Seynnes OR *et al*. Time course of muscular neural tendinous adaptations to 23 day unilateral lower-limb suspension in young men. *J Physiol* 2007;**583**:1079–91.
51 de Boer MD, Selby A, Atherton P *et al*. The temporal responses of protein synthesis, gene expression and cell signalling in human quadriceps muscle and patellar tendon to disuse. *J Physiol* 2007;**585**:241–51.
52 Brown WF. A method for estimating the number of motor units in thenar muscles and the changes in motor unit count with ageing. *J Neurol Neurosurg Psychiatry* 1972;**35**: 845–52.
53 Luff AR. Age-associated changes in the innervation of muscle fibers and changes in the mechanical properties of motor units. *Ann N Y Acad Sci* 1998;**854**:92–101.
54 Guillet C, Auguste P, Mayo W *et al*. Ciliary neurotrophic factor is a regulator of muscular strength in aging. *J Neurosci* 1999;**19**:1257–62.

55 Larsson L, Ansved T. Effects of ageing on the motor unit. *Prog Neurobiol* 1995;**45**:397–458.
56 Frey D, Schneider C, Xu L *et al*. Early and selective loss of neuromuscular synapse subtypes with low sprouting competence in motoneuron diseases. *J Neurosci* 2000;**20**:2534–42.
57 Delbono O. Neural control of aging skeletal muscle. *Aging Cell* 2003;**2**:21–9.
58 Jang YC, Lustgarten MS, Liu Y *et al*. Increased superoxide in vivo accelerates age-associated muscle atrophy through mitochondrial dysfunction and neuromuscular junction degeneration. *FASEB J* 2009.
59 Dirks AJ, Leeuwenburgh C. The role of apoptosis in age-related skeletal muscle atrophy. *Sports Med* 2005;**35**:473–83.
60 Drew B, Phaneuf S, Dirks A *et al*. Effects of aging and caloric restriction on mitochondrial energy production in gastrocnemius muscle and heart. *Am J Physiol Regul Integr Comp Physiol* 2003;**284**:R474–80.
61 Short KR, Bigelow ML, Kahl J *et al*. Decline in skeletal muscle mitochondrial function with aging in humans. *Proc Natl Acad Sci USA* 2005;**102**:5618–23.
62 Harman D. Aging: a theory based on free radical and radiation chemistry. *J Gerontol* 1956;**11**:298–300.
63 Trifunovic A, Wredenberg A, Falkenberg M *et al*. Premature ageing in mice expressing defective mitochondrial DNA polymerase. *Nature* 2004;**429**:417–23.
64 Barton-Davis ER, Shoturma DI, Sweeney HL. Contribution of satellite cells to IGF-I induced hypertrophy of skeletal muscle. *Acta Physiol Scand* 1999;**167**:301–5.
65 Allen DL, Linderman JK, Roy RR *et al*. Apoptosis: a mechanism contributing to remodeling of skeletal muscle in response to hindlimb unweighting. *Am J Physiol* 1997;**273**:C579–87.
66 Korhonen MT, Cristea A, Alen M *et al*. Aging, muscle fiber type, and contractile function in sprint-trained athletes. *J Appl Physiol* 2006;**101**:906–17.
67 Faulkner JA, Larkin LM, Claflin DR *et al*. Age-related changes in the structure and function of skeletal muscles. *Clin Exp Pharmacol Physiol* 2007;**34**:1091–6.
68 Hook P, Sriramoju V, Larsson L. Effects of aging on actin sliding speed on myosin from single skeletal muscle cells of mice, rats, and humans. *Am J Physiol Cell Physiol* 2001;**280**:C782–8.
69 Tawa NE, Goldberg AL. Protein and amino acid metabolism in muscle. In Engel A, GaF AG (eds). *Myology*, Vol. 1, 2nd edn. New York: McGraw Hill, 1994,683–707.
70 Visser M, Deeg DJ, Lips P. Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam. *J Clin Endocrinol Metab* 2003;**88**:5766–72.
71 Schacht E. Rationale for treatment of involutional osteoporosis in women and for prevention and treatment of corticosteroid-induced osteoporosis with alfacalcidol. *Calcif Tissue Int* 1999;**65**:317–27.
72 Doherty TJ. Invited review: aging and sarcopenia. *J Appl Physiol* 2003;**95**:1717–27.
73 Volpi E, Rasmussen BB. Nutrition and muscle protein metabolism in the elderly. *Diabetes Nutr Metab* 2000;**13**:99–107.
74 Welle S, Thornton C, Statt M. Myofibrillar protein synthesis in young and old human subjects after three months of resistance training. *Am J Physiol* 1995;**268**:E422–7.
75 Balagopal P, Rooyackers OE, Adey DB *et al*. Effects of aging on in vivo synthesis of skeletal muscle myosin heavy-chain and sarcoplasmic protein in humans. *Am J Physiol* 1997;**273**:E790–800.
76 Volpi E, Sheffield-Moore M, Rasmussen BB *et al*. Basal muscle amino acid kinetics and protein synthesis in healthy young and older men. *JAMA* 2001;**286**:1206–12.
77 Volpi E, Mittendorfer B, Rasmussen BB *et al*. The response of muscle protein anabolism to combined hyperaminoacidemia and glucose-induced hyperinsulinemia is impaired in the elderly. *J Clin Endocrinol Metab* 2000;**85**:4481–90.
78 Cuthbertson D, Smith K, Babraj J *et al*. Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. *FASEB J* 2005;**19**:422–4.
79 Cuthbertson DJ, Babraj J, Smith K *et al*. Anabolic signaling and protein synthesis in human skeletal muscle after dynamic shortening or lengthening exercise. *Am J Physiol Endocrinol Metab* 2006;**290**:E731–8.

80 Wilkes EA, Selby AL, Atherton PJ *et al*. Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. *Am J Clin Nutr* 2009;**90**:1343–50.

81 Combaret L, Dardevet D, Rieu I *et al*. A leucine-supplemented diet restores the defective postprandial inhibition of proteasome-dependent proteolysis in aged rat skeletal muscle. *J Physiol* 2005;**569**:489–99.

82 Rennie MJ, Selby A, Atherton P *et al*. Facts, noise and wishful thinking: muscle protein turnover in aging and human disuse atrophy. *Scand J Med Sci Sports* 2009.

83 Murton AJ, Constantin D, Greenhaff PL. The involvement of the ubiquitin proteasome system in human skeletal muscle remodelling and atrophy. *Biochim Biophys Acta* 2008;**1782**:730–43.

84 Greenhaff PL, Karagounis LG, Peirce N *et al*. Disassociation between the effects of amino acids and insulin on signaling, ubiquitin ligases, and protein turnover in human muscle. *Am J Physiol Endocrinol Metab* 2008;**295**:E595–604.

85 Grounds MD. Muscle regeneration: molecular aspects and therapeutic implications. *Curr Opin Neurol* 1999;**12**:535–43.

86 Carlson ME, Suetta C, Conboy MJ *et al*. Molecular aging and rejuvenation of human muscle stem cells. *Embo Mol Med* 2009;**1**:1–11.

87 Macaluso A, De Vito G. Muscle strength, power and adaptations to resistance training in older people. *Eur J Appl Physiol* 2004;**91**:450–72.

88 Skelton DA, Greig CA, Davies JM *et al*. Strength, power and related functional ability of healthy people aged 65–89 years. *Age Ageing* 1994;**23**:371–7.

89 Macaluso A, Nimmo MA, Foster JE *et al*. Contractile muscle volume and agonist-antagonist coactivation account for differences in torque between young and older women. *Muscle Nerve* 2002;**25**:858–63.

90 Delbono O, O'Rourke KS, Ettinger WH. Excitation-calcium release uncoupling in aged single human skeletal muscle fibers. *J Membr Biol* 1995;**148**:211–22.

91 Payne AM, Delbono O. Neurogenesis of excitation-contraction uncoupling in aging skeletal muscle. *Exerc Sport Sci Rev* 2004;**32**:36–40.

92 Ramamurthy B, Hook P, Jones AD *et al*. Changes in myosin structure and function in response to glycation. *FASEB J* 2001;**15**:2415–22.

93 Haus JM, Carrithers JA, Trappe SW *et al*. Collagen, cross-linking, and advanced glycation end products in aging human skeletal muscle. *J Appl Physiol* 2007;**103**:2068–76.

94 Bottinelli R, Reggiani C. Human skeletal muscle fibres: molecular and functional diversity. *Prog Biophys Mol Biol* 2000;**73**:195–262.

95 Yue GH, Ranganathan VK, Siemionow V *et al*. Older adults exhibit a reduced ability to fully activate their biceps brachii muscle. *J Gerontol A Biol Sci Med Sci* 1999;**54**:M249–53.

96 Scaglioni G, Ferri A, Minetti AE *et al*. Plantar flexor activation capacity and H reflex in older adults: adaptations to strength training. *J Appl Physiol* 2002;**92**:2292–302.

97 Phillips SK, Bruce SA, Newton D *et al*. The weakness of old age is not due to failure of muscle activation. *J Gerontol* 1992;**47**:M45–9.

98 De Serres SJ, Enoka RM. Older adults can maximally activate the biceps brachii muscle by voluntary command. *J Appl Physiol* 1998;**84**:284–91.

99 Kent-Braun JA, Ng AV. Specific strength and voluntary muscle activation in young and elderly women and men. *J Appl Physiol* 1999;**87**:22–9.

100 Dowling JJ, Konert E, Ljucovic P *et al*. Are humans able to voluntarily elicit maximum muscle force? *Neurosci Lett* 1994;**179**:25–8.

101 Kamen G, Sison SV, Du CC *et al*. Motor unit discharge behavior in older adults during maximal-effort contractions. *J Appl Physiol* 1995;**79**:1908–13.

102 de Boer MD, Morse CI, Thom JM *et al*. Changes in antagonist muscles' coactivation in response to strength training in older women. *J Gerontol A Biol Sci Med Sci* 2007;**62**:1022–7.

103 Narici MV, Maganaris CN. Plasticity of the muscle-tendon complex with disuse and aging. *Exerc Sport Sci Rev* 2007;**35**:126–34.

104 Couppe C, Hansen P, Kongsgaard M *et al*. Mechanical properties and collagen cross-linking of the patellar tendon in old and young men. *J Appl Physiol* 2009;**107**:880–6.