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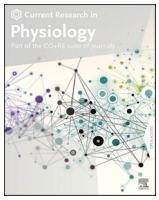

Review Article

From molecular to physical function: The aging trajectory

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ABSTRACT

Aging is accompanied by a decline in muscle mass, strength, and physical function, a condition known as sarcopenia. Muscle disuse attributed to decreased physical activity, hospitalization, or illness (e.g. sarcopenia) results in a rapid decline in muscle mass in aging individuals and effectively accelerates sarcopenia. Consuming protein at levels above (at least 50–100% higher) the current recommended intakes of ~0.8 g protein/kg bodyweight/d, along with participating in both resistance and aerobic exercise, will aid in the preservation of muscle mass. Physiological muscle adaptations often accompany the observable changes in physical independence an older adult undergoes. Muscle fibre adaptations include a reduction in type 2 fibre size and number, a loss of motor units, reduced sensitivity to calcium, reduced elasticity, and weak cross-bridges. Mitochondrial function and structure are impaired in relation to aging and are worsened with inactivity and disease states but could be overcome by engaging in exercise. Intramuscular connective tissue adaptations with age are evident in animal models; however, the adaptations in collagenous tissue within human aging are less clear. We know that the satellite muscle cell pool decreases with age, and there is a reduced capacity for muscle repair/regeneration. Finally, a pro-inflammatory state associated with age has detrimental impacts on the muscle. The purpose of this review is to highlight the physiological adaptations driving muscle aging and their potential mitigation with exercise/physical activity and nutrition.

1. Introduction

The confluence of an aging population and a growing incidence of chronic disease as individuals age places an increasing demand on healthcare systems. By the year 2050, a quarter of the Canadian population will be above the age of 65 (Nauenberg et al., 2023) and similar demographic trends are seen in the US (Zoe Caplan, 2023) and EU (Affairs D-GfEaF, 2024 Ageing Report, 2024). Several factors influence health with age; however, an inactive lifestyle, along with excess energy intake and poor nutrition, can accelerate the natural aging process. Sedentary behaviour and poor nutrition can contribute to a reduction in muscle mass and a gain in fat mass, contributing to numerous metabolic diseases.

Skeletal muscle is a highly plastic tissue in which proteins turnover at a rate of ~1.5% per day, and overall skeletal muscle makes up ~40 ± 10% of our body mass (Koopman and van Loon, 2009). Muscle mass is dictated by the balance between muscle protein synthesis (MPS) and muscle protein breakdown (MPB). When MPS and MPB are in equilibrium (i.e., net protein balance), an individual experiences neither loss nor gain in muscle mass. However, throughout the day, there are times when MPS is greater than MPB and vice versa (McKendry et al., 2021). Exercise, particularly that employing higher loads, and the ingestion of dietary protein can cause rates of MPS to increase resulting in a net positive protein balance (McKendry et al., 2021). In the long term, this constant elevation in MPS may translate to an increase in muscle mass if the stimulus is frequent and triggering enough. However, there are also conditions where MPB is chronically greater than MPS, such as during inactivity, especially when in combination with being in a fasted state. With reduced daily physical activity levels, complete muscle disuse, and inadequate protein and energy intake, muscle protein balance would be in a net negative state, contributing to a loss of muscle. As we age, MPS does not increase as robustly in response to the ingestion of protein and the ensuing hyperaminoacidemia (Moore et al., 2015). The changes affecting the natural sway of protein balance make gaining/maintaining muscle mass when aging more difficult. Besides alterations in the fluctuations in MPS and MPB, many physiological adaptations occur with age that underlie the decline in muscle mass observed. This review focuses on the molecular and physiological changes of the muscle with age and highlights the main reasons why maintaining a healthy amount of

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Abbreviations

MPS	muscle protein synthesis
MPB	muscle protein breakdown
RDA	recommended dietary allowance
1RM	one repetition maximum
CSA	cross-sectional area
COPD	chronic obstructive pulmonary disease
EAA	essential amino acids
RET	resistance exercise training
ROS	reactive oxygen species
AGEs	advanced glycation end-products
ECM	extracellular matrix

Silva et al., 2010) and is dictated by the balance between MPS and MPB, as previously mentioned. Muscle strength and power decline at a faster rate of ~3% per year, indicating that processes other than muscle mass contribute to declines in muscle function (von Haehling et al., 2010). A period of disuse, such as a hospital stay, illness, or a reduction in activity, may result in aging individuals crossing the threshold of physical dependence a lot sooner due to mobility loss (Phillips et al., 2020; Visser et al., 2005). On the contrary, exercise training and increased physical activity in older adults are related to improved mobility and function (Paterson and Warburton, 2010). Activities of daily living become more difficult for aging individuals, and so these individuals will often avoid engaging in these tasks. The result is an increasing cycle of sedentarism that can eventually lead to dependency. This vicious cycle of inactivity and increased risk for physical dependence is shown schematically in Fig. 1 (Oikawa et al., 2019).

The progression of sarcopenia can affect an individual's life due to its

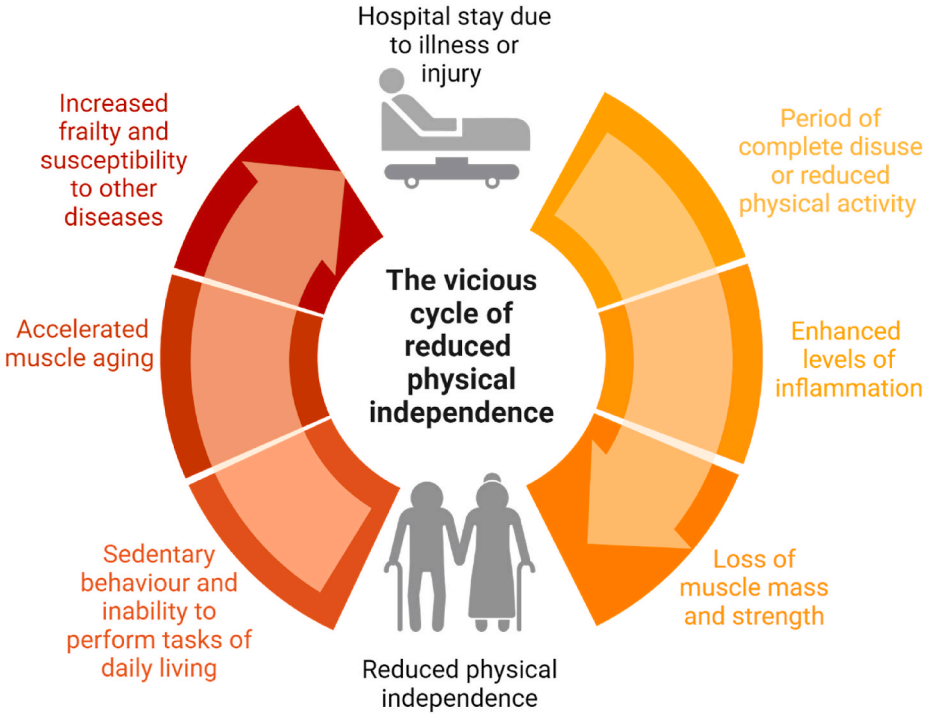

Fig. 1. The vicious cycle of reduced physical independence. Figure created using BioRender.

muscle when aging is so challenging. We do, however, offer some practical strategies to combat age-related sarcopenia.

2. Implications of declining muscle on health and strategies to mitigate muscle loss with age

Muscle loss is a hallmark of aging; in fact, it has been said that no loss of tissue with aging is more remarkable than that of skeletal muscle. As a tissue, its decline is seen by many as inevitable, but there is the ability to change the downward trajectory of muscle mass (and function/strength) with aging.

2.1. Sarcopenia and muscle aging-related diseases

Sarcopenia is characterized by a progressive loss of skeletal muscle mass, strength, and function with age, which is measurable (compared to peak muscle mass at age 20–30) in the fourth-fifth decade of life (i.e. 40-50 years old) (von Haehling et al., 2010). The decline in muscle mass beyond age 30 occurs at a rate of ~0.8% per year (Mitchell et al., 2012;

influence on health span, quality of life, and the interplay between these factors. Firstly, a reduction in muscle mass puts individuals at risk of developing metabolic disorders such as type 2 diabetes mellitus. Muscle mass is inversely related to insulin resistance as muscle is a metabolically active 'sink' for the storage and metabolism (oxidation and conversion to other substrates) of glucose (Srikanthan and Karlamangla, 2011). Secondly, a decline in strength, most frequently assessed as grip strength, is correlated with a reduced health-related quality of life and an increased risk of declines in physical mobility (Sayer et al., 2006). Finally, functional decline and declines in strength and aerobic capacity play roles in the development of cardiovascular disease (Corsi et al., 2018). Interventions that positively affect aging and specifically negate the development of sarcopenia continue to be explored to improve both quality of life and health span.

The loss of muscle mass is common with advancing age; however, several disorders and conditions may be worsened or add to the development of sarcopenia, such as metabolic syndrome, obesity, type 2 diabetes mellitus, cardiovascular disease, and other chronic diseases like dementia (Santilli et al., 2014). It is difficult to determine a

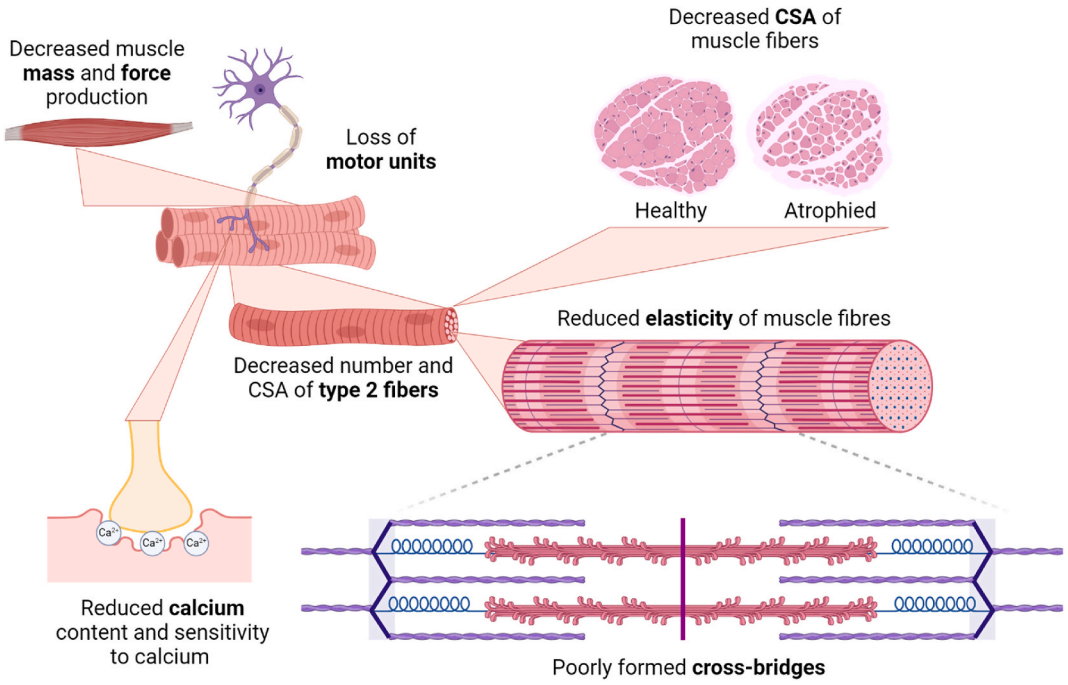

Fig. 2. Myofibrillar changes in skeletal muscle aging. Figure created using BioRender.

cause-and-effect relationship between these conditions as human systems are linked with one another and often display similar underlying molecular changes. Sarcopenic obesity, for example, is characterized by a reduction in muscle mass and accumulation of fat mass that is commonly related to age (Cauley, 2015). Mitochondrial dysfunction, increased inflammation, and unmitigated oxidative stress are all contributors to the worsening of health and are presented as a result of sarcopenic obesity (Polyzos and Margioris, 2018). The natural aging process encompasses a reduction in muscle mass, though chronological age is not the only contributor to muscle atrophy. Molecular adaptations such as mitochondrial dysfunction, increased inflammation, and unmitigated oxidative stress are not only a result of chronic disease states (e.g. sarcopenic obesity) but are also related to the natural aging process, making it difficult to isolate the effect of the illness or aging on the influence of physiological adaptations.

2.2. *Muscle disuse contributes to accelerated aging*

Decreased physical activity (relative sedentarism) or muscle disuse in healthy adults induces muscle atrophy. Full recovery from disuse does not commonly occur in older adults (Suetta et al., 2009, 2013), and those with chronic disease states face a more challenging time with recovery (Della Peruta et al., 2023). Not only do older adults experience increased atrophy in response to muscle disuse (Kortebein et al., 2007, 2008; Coker et al., 2015), but they also have an impaired ability (compared to younger persons) to regain lost muscle and strength (Suetta et al., 2013).

A period of disuse (i.e. bedrest or single-leg immobilization) can have profound implications for an older individual's physical health and function. A two-week-long reduction in daily total steps (a model of abrupt sedentarism but not full disuse) not only reduced postprandial rates of MPS and impaired insulin sensitivity but also significantly reduced leg fat-free mass (Breen et al., 2013). To make matters even worse, older individuals who were immobilized for two weeks not only experienced a reduction in muscle mass but also a decline in muscle strength that was the equivalent of ~2–3 years of normal aging (Rommersbach et al., 2020). Highlighting that disuse in older individuals can lead to muscle atrophy that resembles accelerated aging.

The step-reduction model has shown the profound impact of even short-term periods of reduced activity (Breen et al., 2013; Oikawa et al., 2018; McGlory et al., 2018; Devries et al., 2015; Arentson-Lantz et al., 2019). While a period of reduced steps may seem somewhat benign, our data and those of others have shown that older individuals would be adversely affected after as little as weeks in which they stayed inside of their homes due to inclement weather, were bedridden or convalescing due to illness, or seated for the majority of the day due to an injury (Oikawa et al., 2019). Individuals who are generally healthy may believe that they are at reduced risk of muscle loss during a period of disuse; however, compared to younger individuals, older adults experience greater muscle mass loss in response to bed rest and appear to have a more difficult time returning to pre-inactivity conditions (Pišot et al., 2016).

Healthy older adults experience exacerbated rates of loss of muscle mass in response to muscle disuse and bed rest (Oikawa et al., 2018; Pišot et al., 2016). In real-world settings, individuals are often placed in these conditions due to illness and injury (Quinn et al., 2019). Controlled models of disuse, inactivity, and bed rest tend to utilize healthy older adults, and so the outcome data from these studies likely represents the best-case scenario for health outcomes. We propose that the presence of an underlying chronic condition – type 2 diabetes, peripheral arterial disease, metabolic syndrome – would make older adults much more vulnerable to muscle atrophy and the development of sarcopenia. Older individuals experiencing elective hip surgery experienced substantial leg muscle atrophy after only 6 days of hospitalization (Kouw et al., 2019). The increased muscle loss experienced following hip arthroplasty in the non-operated limb puts an individual at increased risk of delayed recovery from surgery, leading to a cycle of further decreased physical activity. If an individual is in a health-compromised (pre-diabetes, type 2 diabetes, peripheral arterial disease) state prior to hospitalization, this could play an additive role in the drastic reduction in muscle mass (Barreiro and Sieck, 2013; Bruggeman et al., 2016). Current research focuses on strategies to mitigate the reduction in muscle mass seen with disuse through methods of prevention and respective recovery in both disease and non-disease states (Nunes et al., 2022).

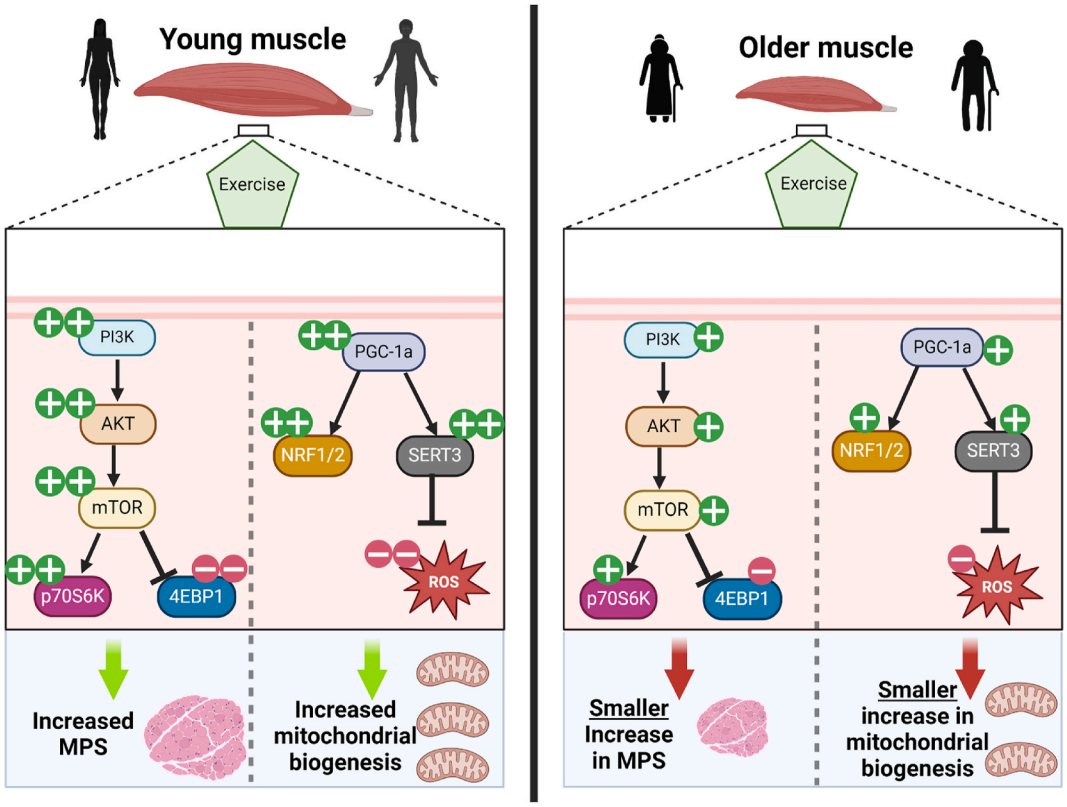

Fig. 3. Phosphorylation/activation of multiple protein signalling pathways changes with aging resulting in decreases in MPS and mitochondrial biogenesis post-exercise when compared to healthy young individuals. The green circles with a white cross in the middle of it indicate an increase in phosphorylation/activation, and the amount of bubbles indicates the amount of proteins that are phosphorylated/activated. The red circles with a white line in the middle of it indicate a decrease in phosphorylation/activation, and the amount of bubbles indicates the amount of proteins that are phosphorylated/activated. Figure created using BioRender.

3. Physiological adaptations that drive muscle aging

We are beginning to uncover several salient changes that occur with aging in skeletal muscle. Most of these age-related changes result in reduced muscle function, and they range from intra to extracellular in location. Here, we outline some of the more prevalent adaptations that occur with age and that are linked to declines in muscle mass and function.

3.1. *Muscle fibre changes with age*

Muscle fibre adaptations with age encompass not only a decrease in muscle fibre size but a loss of muscle fibres, a reduction in motor units, and a disruption of the mechanical properties of myofibrils (Fig. 2). These myofibrillar changes with age can have drastic implications for the physical function, strength, and muscle mass of older adults.

It is well known that type 1 and 2 muscle fibres play distinctive roles in muscle force production and have characteristics that make their role in specific activities predominant (Linssen et al., 1991). With age, there is a reduction in fibre number and size, yet the reduction is most evident in type 2 fibres (Nilwik et al., 2013). Type 2 fibres have a greater capacity for force production, whereas type 1 or slow oxidative fibres are less fatigable (Linssen et al., 1991). Not only are muscle fibres reduced in number and size, but they also have a reduced ability for force production (lower force/fibre CSA) and a lower capacity to trigger contraction, as indicated by a decreased sensitivity to calcium (Lamboley et al., 2015), especially in type 2 fibers. Resistance exercise has been shown to increase type 2 muscle fibre size in older adults and is responsible for most of the increases observed in the quadriceps cross-sectional area in response to exercise (Nilwik et al., 2013). Since most of these changes are fiber type specific, the focus is on the type 2 fibers that show the most change with aging (Verdijk et al., 2007).

With age, there is a decline in number of motor units and decreased stability of neuromuscular junctions (Piasecki et al., 2016). The reduction in motor units may be substantial, and a loss of 40% of motor units can be seen by the age of ~70 (Piasecki et al., 2016). The loss of motor units with age is accompanied by a reduced ability of remaining motor nerves to reinnervate muscle fibres and compensate for this loss (Hepple, 2018). An impaired capacity for reinnervation of denervated muscle fibres, along with the aforementioned anabolic resistance, correlated to increased muscle loss with age (Hepple, 2018). A study by Rowan and colleagues discovered that age-associated muscle fibre atrophy can be largely attributed to muscle denervation (Rowan et al., 2012). Long-term physical activity, at least based on cross-sectional data, has been shown to improve capacity for reinnervation and was related to better relative preservation of muscle strength (Mosole et al., 2014).

Impairments in myofibril mechanical properties can have drastic implications for optimal muscle contraction. Single skeletal muscle fibres from older men experience increased instantaneous stiffness or reduced elasticity in comparison to younger men (Ochala et al., 2007). This reduction in elasticity is also observed in the fascia, which can contribute to reduced flexibility and mobility in older adults (Marcucci and Reggiani, 2020). A reduction in myosin protein content and post-translational modifications may disrupt the mechanism of contraction at the cross-bridge level (Miljkovic et al., 2015). Post-translational modifications of myosin in aging affect its ability to bind to actin, thus reducing the number of strong cross-bridges formed during muscle contraction (Li et al., 2015). Both the reduced elasticity and poorly formed cross-bridges affect force production during muscle

contraction and are deleterious with aging (Fig. 2).

3.2. Mitochondrial changes with age

On top of the myofibrillar changes in our skeletal muscle with aging, changes in the mitochondria of the muscle are also observed (Zhu et al., 2022; Burtscher et al., 2023; Distefano and Goodpaster, 2018). Mitochondrial dysfunction can be associated with age; however, a detailed causal relationship can be difficult to find since there are many variables affecting the muscle's mitochondria other than aging, with relative inactivity being a significant factor(Webb and Sideris, 2020). In addition, in 1996 it was already shown that mitochondrial MPS, oxidative capacity of the skeletal muscle, and mitochondrial function decline with age (Rooyackers et al., 1996). Whether the changes in the mitochondria are caused by or causes of sarcopenia remains unclear. Regardless of the order of events, the function of mitochondria with aging is a target for intervention, as mitochondrial dysfunction has been identified as a key theory in aging (Bratic and Larsson, 2013; Guo et al., 2023).

That age affects the structure of the mitochondria, and the cristae is not new. Miquel et al. (1980) described that changes in mitochondrial structure and cristae in skeletal muscle but also liver, kidney, and the cerebral cortex have been found in mammals (e.g., mice, rats, and human subjects). It has been discovered that with age, there is an increased reactive oxygen species (ROS) production that can have deleterious effects on a number of metabolic pathways, including the phosphorylation of the Akt/mTOR pathway, see Fig. 3. There is an increase in damaged mitochondrial DNA, reduced DNA repair systems, and reduced PGC-1a protein expression thought to be consequences of increased ROS with age (Boengler et al., 2017). PGC-1a plays an important role in the regulation of mitochondrial biogenesis, meaning that when there is a reduced PGC-1a protein expression, mitochondrial biogenesis is also reduced (Liang and Ward, 2006). Additionally, ROS production can hinder the phosphorylation of proteins in anabolic pathways such as the Akt/mTOR pathway and its downstream targets 4E-BP1 and p70S6K can inhibit MPS (Gomez-Cabrera et al., 2020). In addition, the increased amount of damaged mitochondrial DNA, in combination with a reduced DNA repair system, can reduce mitochondrial biogenesis and repair. Damaged mitochondria ultimately negatively affect the mitochondrial structure and function (Joseph et al., 2012). It is also known that the mitochondrial gene (Melov et al., 2007; Phillips et al., 2013) and protein (Murgia et al., 2017; Robinson et al., 2017; Ubaida-Mohien et al., 2019) content are lower in older adults. Some of these downregulated proteins are part of respiratory chain complexes and are consistent with lowering the mitochondrial respiratory function in muscle fibres from older adults (Ubaida-Mohien et al., 2019). The reductions in mitochondrial protein abundance are likely driven by the dysregulation of mitochondrial fusion and fission processes (Murgia et al., 2017).

Short et al. (2005) analyzed muscle from 146 healthy men and women aged 18–89 years old and looked at the functional changes in mitochondria with aging and some of the mechanisms behind the aging process. They found that mtDNA and mtRNA declined with age, which resulted in a reduced mitochondrial protein. In addition, they concluded that the abundance of mtDNA was positively correlated with mitochondrial ATP production which in turn is closely correlated with oxidative capacity and glucose tolerance. Therefore, with aging, the reduced capacity of ATP production by the mitochondria is, at least partly, caused by the reduction in mtDNA and mtRNA. Collectively, the processes mentioned above are suggested to contribute to the lower muscular function and the higher insulin resistance commonly seen in an older population.

It is clear that with aging, the main loss of muscle is found in type 2 muscle fibres (Lexell, 1995), and the distribution of fibre type between different muscles within the same person can be vastly different (Johnson et al., 1973). It is suggested that with aging, differences in function within different muscles can be observed. Conley et al. (2007) showed that with aging, the type 2 muscle fibres are mainly affected, and they suggested that a reduction in oxidative capacity of the mitochondria, specifically in type 2 fibres, is causing the decline in the cross-sectional area (CSA) of type 2 fibres with aging. However, it can also be speculated that the decline in CSA of type 2 muscle fibres is caused by the reduction in engagement in higher-intensity physical activity that would mainly require recruitment of the type 2 muscle fibres. It seems logical that a combination of aging and inactivity would be the cause of the decrease in CSA in type 2 fibres; however, this remains speculative, and more research needs to be done in order to come to a clear consensus.

Some of the age-related changes in the mitochondria of skeletal muscle are partially reversible with different types of exercise, and practically all age-related changes are exacerbated with inactivity (Gram et al., 2014; Hackney and Ploutz-Snyder, 2012; Pillon, 2023), type 2 diabetes mellitus (Jornayvaz and Shulman, 2010), and other diseases such as cancer or Alzheimer's (Jornayvaz and Shulman, 2010; Palmer et al., 2021). Previous research shows that endurance exercise seems to be an effective mode of exercise to stimulate muscle mitochondrial biogenesis and function. Endurance exercise increases the phosphorylation of PGC-1a, which is a marker for mitochondrial biogenesis (Coggan et al., 1990, 1992; Spina et al., 1996). Resistance exercise is found to be very effective in preventing the decline in the CSA of type 2 fibres, mainly by stimulating the mTOR pathway (Moro et al., 2020; Kosek et al., 2006; Verdijk et al., 2009). It is also suggested that a combined exercise protocol could be beneficial for older adults when specifically looking at the decreased oxidative capacity found in an older population. Irving et al. (2015), showed that an 8-week combined training protocol was superior in increasing muscle oxidative capacity when directly compared to an 8-week resistance exercise protocol, an 8-week endurance exercise protocol, and a control group.

To summarize, with aging, there is a decline in mitochondrial volume and a breakdown in structure and function, with differences between muscle fibre types (i.e. greater loss in type 2 fibres). The observed decline in mitochondrial function can, at least partly, be prevented/reversed by different types of exercise and can be exacerbated by inactivity and disease states.

3.3. Connective tissue and extracellular matrix changes

Intramuscular connective tissue is a crucial part of skeletal muscle function and is critical for force translation. The intramuscular connective tissue consists of 3 different extracellular matrix structures (the epimysium, perimysium, and endomysium), serves as protection, and plays an important role as a supportive force-transferring lattice to the contractile portion of the muscle to the tendon to the bone resulting in contraction (Purslow, 2020). It has been suggested that the turnover rate of intramuscular connective tissue protein was lower compared to skeletal muscle turnover (Holm et al., 2010; Trommelen et al., 2020). However, a recent study showed that intramuscular connective tissue showed a relatively greater fractional synthetic rate when compared to the myofibrillar fractional synthetic rate after an acute bout of resistance exercise (Aussieker et al., 2023). Meaning, that even though intramuscular connective tissue turnover might be lower than myofibrillar turnover, intramuscular connective tissue shows characteristics of a highly plastic portion of the skeletal muscle.

Research in murine models has shown that older mice show an increase in collagen crosslinks when compared to younger mice (Wohlgemuth et al., 2023). While enzymatic collagen crosslinks can rapidly change due to external stimuli like exercise, injury, or disease, during aging, there is an increase in non-enzymatic crosslinks, also known as advanced glycation end products (AGEs), as we get older. As a result of the increase in AGEs, the extracellular matrix (ECM) can become stiffer, impair the range of biomechanical properties, and the ECM becomes more resistant to turnover (Wohlgemuth et al., 2023). The increase in difficulty in turning over ECM collagen, most likely due to a

reduced degradation (Nowotny and Grune, 2014), helps to explain the accumulation of collagen, or fibrosis, in older individuals. Interestingly, periods of immobilization worsen ECM stiffness (Järvinen et al., 2002). The intramuscular connective tissue (in this case, the endomysium and perimysium specifically) undergoes both quantitative (i.e. collagen accumulation) and qualitative AGE-induced alteration (Wohlgemuth et al., 2023; Järvinen et al., 2002), further impairing the biomechanical properties of the intramuscular connective tissue with aging.

In mice, it is clear that with aging, the collagen content of the muscle increases (Kragstrup et al., 2011). However, in aging humans, it remains debatable whether the collagen content of the muscle actually increases. Even though some evidence suggests that with human aging, the collagen content of the muscle tends to increase, a clear consensus has not yet been formed (Pavan et al., 2020; Fede et al., 2022). Similarly, collagen synthesis rates, as mice data show, are reduced with aging (Mays et al., 1991; Goldspink et al., 1994), whereas human data shows an increase in collagen synthesis with aging (Babraj et al., 2005). This raises the question if collagen degradation is the main factor at play here and it seems that heavily crosslinked collagen is more difficult to break down (Nowotny and Grune, 2014). However, more research is needed to settle this issue.

It is clear that with resistance exercise, the turnover of muscle connective tissue protein can be increased (Holm et al., 2010; Miller et al., 2005); in addition, whether exercise has a positive effect on the detrimental effects in older persons on intramuscular connective tissue remains to be determined. In addition, it seems to be clear that additional supplementation of protein does not increase intramuscular connective tissue protein synthesis (Holm et al., 2010; Holwerda and van Loon, 2022; Dideriksen et al., 2011; Mikkelsen et al., 2015; Moore et al., 2009; Wilkinson et al., 2008).

More human research is needed to draw firm conclusions about the relationship between age-associated changes in the muscle ECM/intramuscular connective tissue and the decline in force production in older adults. Since the older population is generally less active, it remains difficult to associate changes in the ECM/intramuscular connective tissue with aging specifically and not with other external factors like increased inactivity.

3.4. Changes in the muscle stem cell niche

The muscle stem cell niche in skeletal muscle can be described as the microenvironment that surrounds the muscle stem cells (i.e., satellite cells). The stem cell niche provides structural and biochemical support to regulate satellite cell behaviour, including maintenance, activation, proliferation, differentiation, and self-renewal, which is crucial for muscle growth, repair, and regeneration (Mashinchian et al., 2018).

It has been demonstrated that when a younger mouse is connected to an older mouse through the use of parabiosis the decline of satellite cell activity of the old mice (common with age) can be restored (Conboy et al., 2005). Whereas when combining the vascular systems of two old mice (again through parabiosis) the progenitor cell activity is not restored. To clarify, parabiosis is a surgical procedure in which the skin and blood vessels of two mice are surgically connected, with the goal of creating a shared circulatory system allowing for the blood of both mice to mix. This study (Conboy et al., 2005) suggests that the local vascular environment of these progenitor cells negatively influences the progenitor cell activity with aging.

It is suggested that the ECM of the muscle fibres becomes thicker (i.e., fibrosis) with age and impairs the crosstalk of the muscle stem cell niche. Nederveen et al. showed that the thickness of laminin in type 2 muscle fibres was higher in older participants than in younger participants (Nederveen et al., 2020). In addition, they also showed a greater amount of satellite cells that were surrounded by laminin in the older population (they labelled such cells as incarcerated), which may inhibit the satellite cell activation in older persons following exercise (Nederveen et al., 2020). Based on mouse models, multiple pathways are responsible for this increase in fibrosis with age (Brack et al., 2007; Brack and Rando, 2007; Lukjanenko et al., 2019). However, a very small amount of research has been done on human muscle tissue, and therefore, a lot remains to be confirmed and discovered.

The muscle satellite cell pool decreases with age (Shefer et al., 2006). Interestingly, the impaired regeneration of muscle with aging may be reversible with exercise (Joanisse et al., 2016a). It has been shown that with exercise, mice can increase satellite cell content and improve the systemic environment. The importance of the systemic environment is stressed due to the development of the capillary impact zone theory (Joanisse et al., 2016b). This theory suggests that each capillary within the muscle has a specific area in which it can send blood-borne signals to the muscle satellite cells in order to activate the satellite cell for muscle regeneration, repair, and remodelling. It is good to know that with exercise, the capillary impact zone can be increased. A study in older men has shown that with age, the satellite cells are located further away from capillaries, which would suggest that more satellite cells are outside or on the far end of these capillary impact zones, which could impair/delay regeneration, repair, and remodelling of the muscle (Nederveen et al., 2016). We refer the interested reader to a review by Sousa et al. (Sousa-Victor et al., 2022) and a book by Hwang and Brack (2018) for deeper reading in this area.

3.5. Changes in systemic factors – inflammaging

Inflammaging can be defined as ‘sterile’ immune dysregulation (i.e., inflammation in the absence of a pathogenic vector: bacteria or virus) and, specifically, an increase in systemic concentrations of pro-inflammatory markers with age (Franceschi et al., 2000). The pro-inflammatory state is characterized by an increase in pro-inflammatory markers, including IL-1, IL-1 receptor antagonist protein (IL-1RN), IL-6, IL-8, IL-13, IL-18, C-reactive protein (CRP), IFNα and IFNβ, transforming growth factor-β (TGFβ), tumour necrosis factor (TNF) and its soluble receptors (TNF receptor superfamily members 1A and 1B), and serum amyloid A (Ferrucci and Fabbri, 2018).

A large-scale longitudinal aging study showed that high levels of cytokines, specifically IL-6 and CRP, are associated with an increased risk of muscle loss and reductions in strength (Schaap et al., 2006). The exact mechanism of how the pro-inflammatory state seen in older adults results in the loss of muscle and strength is unknown; however, it is speculated that there could be an increase in the ubiquitin-protease pathway induced via inflammation (Mitch and Goldberg, 1996; Ferrucci et al., 1999). This ubiquitin-proteasome pathway system is mainly responsible for muscle proteolysis but not the myofibrillar lattice. In addition, it is known that the main intramuscular signalling pathways that are influenced by this inflammatory state are the NF-κB, JAK/STAT, and p38MAPK pathways that contribute to the loss of muscle and strength (Huang et al., 2020; Fang et al., 2021; Zanders et al., 2022; Ueno et al., 2021). Finally, inactivity and the development of type 2 diabetes mellitus can lead to an accelerated loss of muscle with age due to increased blood glucose levels and a pro-inflammatory state than in healthy, active older persons (Prattichizzo et al., 2018; Ji et al., 2022).

With the continued developments of (in vivo/vitro in human) measurement techniques, the intricate relationship between inflammaging and the muscle niche with aging will become clearer. Unfortunately, due to the complex nature of these studies, there is a lack of human mechanistic data, and therefore, more studies are required.

4. Mitigating muscle loss in aging

Two main strategies proposed to mitigate sarcopenia include the incorporation of exercise and sufficient dietary protein intake (McKendry et al., 2021). The common issue is that in addition to poor nutrition, or possible malnutrition, and decreased physical activity levels, aging individuals experience anabolic resistance (Burd et al., 2013). Anabolic resistance describes the observation that skeletal

muscle is less sensitive to either (or both) post-absorptive hyperaminoacidemia (Wall et al., 2015) or resistance exercise (Kumar et al., 2009), leading to the reduced response of MPS. Due to this anabolic resistance, aging individuals require additional anabolic stimuli to optimally simulate MPS compared to younger individuals (Burd et al., 2013). Most nutritional and exercise recommendations are based on studies performed using younger individuals, and it has been recognized that the results observed in a younger population do not always translate to older individuals (Volpi et al., 2013).

4.1. Older individuals require specific recommendations for protein consumption

Based on data from previous studies, adults are recommended to consume (with some variability between estimates) ~0.8g protein/kg/day (Traylor et al., 2018) from mixed protein sources. A study by McKendry and colleagues has recently highlighted that the current recommended dietary allowance (RDA) or Recommended Nutrient Intake (RNI) for protein consumption does not optimally simulate MPS rates in older adults (McKendry et al., 2024a). There are several other observations around the requirement of specific essential amino acid needs for optimizing MPS (Szwiega et al., 2021; Rafii et al., 2024), and protein needs to optimize glutathione synthesis (Paoletti et al., 2024; Jackson et al., 2004) that indicate the insufficiency of the RDA or RNI to optimize protein synthesis. In addition, McKendry et al. (2024a) utilized specific strategies to combat anabolic resistance by increasing total protein intake (Traylor et al., 2018), increasing per meal protein dose (Moore et al., 2015), evenly distributing protein throughout the day (Norton et al., 2016; Farsijani et al., 2016), and utilizing high-quality proteins (Pinckaers et al., 2021), which may be important for older persons, based on previous research. By manipulating the previously mentioned strategies of protein intake, rates of MPS were elevated in older adults compared to consuming the current RDA for protein, with more protein being consumed at dinner and less during breakfast and lunch, which are typical of older adult eating patterns.

A study by Moore and colleagues recommended that aging individuals should consume 0.4 g/kg of protein per meal, leading to a total dose (assuming three daily meals) of at least 1.2 g/kg/day in order to maintain muscle mass (Moore et al., 2015). Furthermore, consuming an even distribution of protein in all meals throughout the day ensures that MPS is optimally stimulated during the day and that protein requirements are met (Mamerow et al., 2014). Regarding protein sources, dairy proteins are a high-quality source as they contain a higher relative proportion of leucine (an essential amino acid that is critical for the stimulation of MPS) and is rapidly digested (Szwiega et al., 2021; Tang et al., 2009). Older individuals should consider, in priority order, total protein intake, per meal dose, protein distribution throughout the day, and quality of a protein source when making food selections to take advantage of all available tools to preserve or increase muscle mass (Murphy et al., 2016). Older adults are at risk of inadequate energy intake, which may make it difficult to achieve the aforementioned protein recommendations. By focusing on achieving adequate energy and protein intake older adults can mitigate potential losses of muscle due to poor nutrition (Miller and Wolfe, 2008; Yannakoulia et al., 2018).

4.2. Exercise provides benefits for aging muscle

Increased physical activity and exercise provide a multitude of benefits for not only healthy young adults but also for older individuals (Rebelo-Marques et al., 2018). However, specific recommendations and evidence-based training protocols for older adults are less well-researched.

Resistance exercise is a potent stimulator of MPS leading to muscle hypertrophy and strength. Older individuals should aim to increase, or at least preserve, muscle mass and strength over time. There are various modes of resistance exercise, and there are various training strategies for aging individuals (Izquierdo et al., 2021). Guidance for the development of muscle (or at least to prevent its loss), enhancement of strength, and increased function has been comprehensively summarized (Izquierdo et al., 2021). It is important to note, however, that various resistance exercise training (RET) protocols show benefits for hypertrophy and strength outcomes (Currier et al., 2023; McLeod et al., 2024). Importantly for older persons, the benefits of improving function, as assessed by tests like the short physical performance battery, time-up-and-go, and various walk tests, is that many RET protocols achieve positive outcomes with very little distinction between the different protocols as longs as the intensity is high (i.e. low repetitions with higher weights or higher repetitions with lower weights) (Currier et al., 2023; McLeod et al., 2024). Thus, lower-load (30–50% 1RM, higher volume) RET may be a viable option for RET and may target more of the physiological deficits observed in older adults (e.g., increasing mitochondria content and improving glycemic control) than traditional higher-load RET (80% 1RM) (Burd et al., 2010; Beaudry et al., 2024; Lim et al., 2019). Lower load RET provides an alternate training mode to higher loads and may be a means to combat age- and obesity-related health decrements simultaneously.

4.3. Combined lifestyle strategies are the key to muscle maintenance and preservation

A combination of both resistance and aerobic exercise, along with adequate protein consumption, appears to be a potent strategy to mitigate muscle aging detriments (Churchward-Venne et al., 2012; Burich et al., 2015; Deutz et al., 2014). Performing aerobic exercise combined with a resistance exercise training regimen demonstrated improvements in glycemic control, body composition, strength, and function in older adults with type 2 diabetes mellitus (Tan et al., 2012). Exercise is impactful for the muscles of older adults, but when combined with adequate protein intake may be utilized as a sarcopenia-preventive or at least mitigative strategy. As previously mentioned, a reduction in daily physical activity can exacerbate the muscle aging process, this process is potentially mitigated through the combined use of nutrition and exercise. Consuming a whey supplement (20g) and performing lower-load RET thrice weekly attenuated the decline in rates of MPS and preserved muscle mass during a two-week step reduction protocol (<1500 steps/day) (Devries et al., 2015). Hence, it is evident that the combination of both nutrition and exercise could be an effective target to slow down muscle aging.

4.4. Pre-habilitation: the importance of getting active now

Often in life, there are instances that we cannot prevent that place us at risk for muscle atrophy. For example, some older adults undergo hip surgery, which requires them to be bedridden for a short time. While others may, unfortunately, experience a fall that sends them to the hospital, requiring the immobilization of a limb for recovery. Pre-habilitation is a strategy that has come to light to prevent the risk of poor postoperative outcomes, such as increased length of stay and loss of function, which puts an individual at risk of greater muscle atrophy due to sedentary behaviour (Halloway et al., 2015). Pre-habilitation is a strategy utilized prior to surgery to improve outcomes postoperatively (Baimas-George et al., 2020). A study done by Smeuninx et al. (2023) had older adults perform a unilateral bout of RET prior to 5 days of bed rest (Smeuninx et al., 2023). Although it was not possible to mitigate all reductions in quadriceps CSA due to bed rest, the exercising leg experienced less muscle loss and a less drastic reduction in integrated myofibrillar protein synthesis. Various other strategies have been proposed pre-, during-, and post-disuse to aid in mitigating skeletal muscle atrophy and are discussed in a review by McKendry and colleagues (2024) (McKendry et al., 2024b). Further research is warranted to discover the optimal strategy to preserve muscle mass during disuse. However, it is evident that resistance exercise increases MPS and muscle

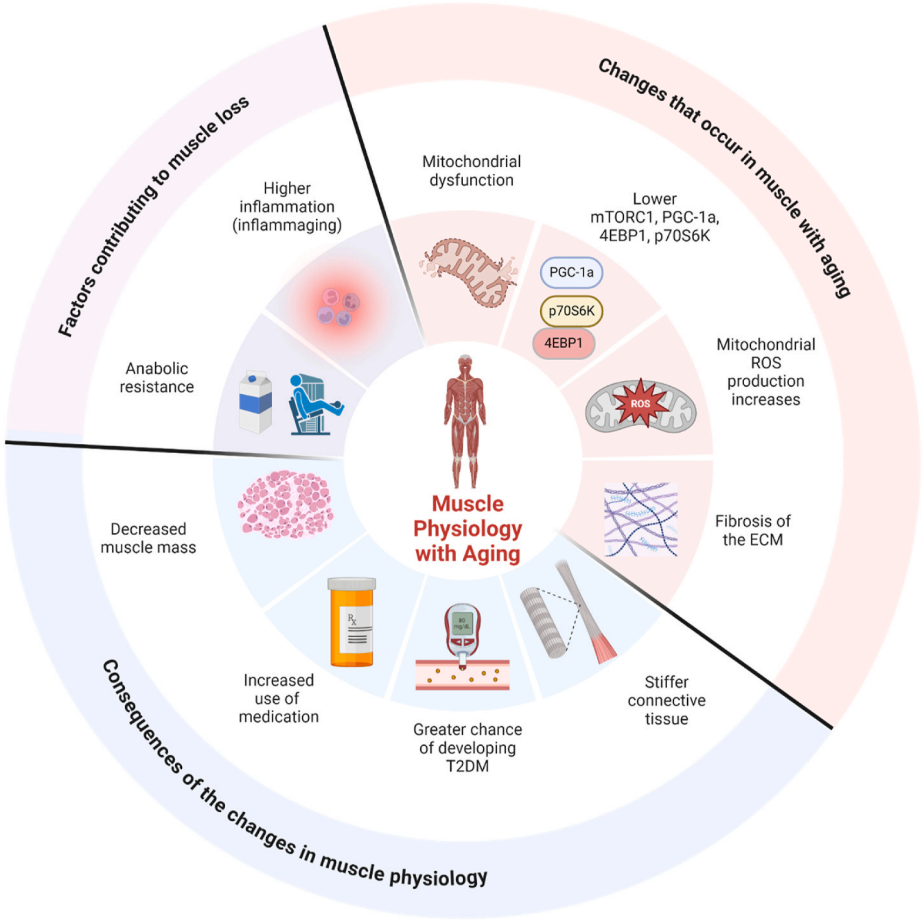

Fig. 4. Several factors influence/change muscle physiology with aging, such as fibrosis, anabolic resistance, mitochondrial structure, decreased muscle mass, lower phosphorylation of several signalling pathways, mitochondrial ROS production increases, higher systemic inflammation, stiffer connective tissue, a greater chance of developing T2D, increased use of medication, and fibrosis of the ECM. The changes/consequences in muscle physiology with aging are divided in 3 subsections. ROS; Reactive oxygen species, T2DM; Type 2 diabetes mellitus, ECM; extracellular matrix. *Figure created using BioRender.*

mass, so getting active now may put you in a better position later in life.

5. Research issues in aging muscle physiology in humans

Working with older persons in muscle physiology research presents several challenges. Researchers face many difficulties when investigating age-related muscular adaptations in older adults. As much as researchers in this field acknowledge the issues with completing clinical trials and studying in this area, here we outline some of the barriers to work in this field.

5.1. Medication use

The exclusion criteria of any given study would ideally include a variety of medications that may affect muscle metabolism or the response to an exercise and/or nutritional intervention; for example, chemotherapy, use of anabolic steroids, use of hormones, etc. Older individuals are, however, prescribed a combination of medications either prophylactically or to control the symptoms of a current condition, such as hypertension, hypercholesterolemia, and various others. In 2015–2016, according to the National Center for Health Statistics, 53.3% of the older population aged 60–79 years old took 1 or more medications, of which 10.4% took 5 or more medications (Hales et al., 2019). It can be assumed that this percentage is even higher in older adults with a BMI higher than 25. The increasing popularity of GLP-1 agonists as a medication for type 2 diabetes mellitus or as a weight loss strategy highlights the difficulties in recruitment in specific older adult populations, such as those with overweight/obesity (Watanabe et al., 2024; Mahase, 2024). However, currently, studies are done on older adults who are not taking these certain medications. Numerous studies have specifically recruited older adults who are not taking any medications. However, this methodology substantially increases the time and resources required to achieve adequate participant enrollment. This raises concerns about the generalizability of such findings to the broader older population, given that it is uncommon to find individuals over the age of 60 who are not on any pharmacological treatment. In summary, it is difficult to isolate conditions within aging when individuals are on medication that affects the muscle; however, finding older adults not on medications is difficult and often limits the generalizability of the results.

5.2. Causal relationships

When looking at the causal relationships of sarcopenia, the effects of the natural aging process, inactivity, and medication use are almost impossible to separate. As mentioned before, older inactive persons usually take one or more medications that can influence the muscle environment or the muscle directly, and therefore, it becomes difficult to discern the effect of the natural aging process in an individual. In addition, since older adults typically have lower muscle mass and reduced ability to build muscle or recover from disuse than healthy adults, bed rest studies to investigate the effect of inactivity are difficult to justify ethically.

6. Future directions

Conducting research in an older population and specifically focusing on the effect of aging can be challenging. However, the outcomes of these studies will provide valuable information to help mitigate declines in muscle with aging, and thus, participation in aging studies should be promoted. Focusing on isolating the causal relationships between normal aging, (in)activity, medication use, and medical complications is crucial, and creating new models in which we can effectively isolate causal relationships of human tissue should be prioritized. Most importantly, methods that focus on getting the message across that mitigation of the decline in muscle mass is better than treating the consequences of having a low muscle mass and attempting to restore muscle loss should be promoted. Therefore, a goal for future research is to translate research to get people active from a young age until the day they physically can no longer be active in an attempt to prolong their health span. In addition, it might be a suggestion to include participants who are on any medicine. This would create a more representable image for your day-to-day 60+-year-old, even though the medication might affect the study outcomes.

There is a "natural" aging process of the muscle. There is a typical reduction in muscle mass, strength, and eventual physical function termed sarcopenia. On top of this "natural" decline in muscle and strength, several factors like disuse, inactivity, disease states, and undernutrition/malnutrition can cause the decline in muscle to be exacerbated. On the other hand, remaining physically active and eating sufficient protein can cause the declines in muscle mass, strength and function to be mitigated. When adopting a muscle-centric view, there are a lot of negative changes with aging in the muscle fibre and mitochondrial pool of the muscle (Fig. 4), the ECM, the muscle stem cell niche, and the microvascular system with age. Although there are challenges when conducting human research in an older population, like the influence of medications, activity levels, and motivation to participate, we strongly encourage researchers to keep developing new techniques and to keep investing in human studies where possible.

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TAHJ, CVL, and SMP conceived and designed the review. TAHJ and CVL wrote the review in an equal and collaborative manner. All authors edited, revised, and approved the final version of the paper.

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Data availability

No data was used for the research described in the article.

References

Affairs D-GfEaF. 2024 Ageing Report, 2024. Economic and Budgetary Projections for the EU Member States (2022-2070).
Arentson-Lantz, E., Galvan, E., Wacher, A., Fry, C.S., Paddon-Jones 2, D., 2019. 000 steps/day does not fully protect skeletal muscle health in older adults during bed rest. J. Aging Phys. Activ 27 (2), 191–197.
Aussieker, T., Hilkens, L., Holwerda, A.M., Fuchs, C.J., Houben, L.H.P., Senden, J.M., et al., 2023. Collagen protein ingestion during recovery from exercise does not increase muscle connective protein synthesis rates. Med. Sci. Sports Exerc. 55 (10), 1792–1802.
Babraj, J.A., Cuthbertson, D.J., Smith, K., Langberg, H., Miller, B., Krogsgaard, M.R., et al., 2005. Collagen synthesis in human musculoskeletal tissues and skin. Am. J. Physiol. Endocrinol. Metab. 289 (5), E864–E869.
Baimas-George, M., Watson, M., Elhage, S., Parala-Metz, A., Vrochides, D., Davis, B.R., 2020. Prehabilitation in frail surgical patients: a systematic review. World J. Surg. 44 (11), 3668–3678.
Barreiro, E., Sieck, G., 2013. Muscle dysfunction in COPD. J. Appl. Physiol. 114 (9), 1220–1221, 1985.
Beaudry, K.M., Surdi, J.C., Pancevski, K., Tremblay, C., Devries, M.C., 2024. Greater glycemic control following low-load, high-repetition resistance exercise compared with moderate-intensity continuous exercise in males and females: a randomized control trial. Appl. Physiol. Nutr. Metabol. 49 (7), 943–955.
Boengler, K., Kosiol, M., Mayr, M., Schulz, R., Rohrbach, S., 2017. Mitochondria and ageing: role in heart, skeletal muscle and adipose tissue. J Cachexia Sarcopenia Muscle 8 (3), 349–369.
Brack, A.S., Rando, T.A., 2007. Intrinsic changes and extrinsic influences of myogenic stem cell function during aging. Stem Cell Rev. 3, 226–237.
Brack, A.S., Conboy, M.J., Roy, S., Lee, M., Kuo, C.J., Keller, C., et al., 2007. Increased Wnt signaling during aging alters muscle stem cell fate and increases fibrosis. Science 317 (5839), 807–810.
Bratic, A., Larsson, N.G., 2013. The role of mitochondria in aging. J. Clin. Invest. 123 (3), 951–957.
Breen, L., Stokes, K.A., Churchward-Venne, T.A., Moore, D.R., Baker, S.K., Smith, K., et al., 2013. Two weeks of reduced activity decreases leg lean mass and induces "anabolic resistance" of myofibrillar protein synthesis in healthy elderly. J. Clin. Endocrinol. Metab. 98 (6), 2604–2612.
Bruggeman, A.R., Kamal, A.H., LeBlanc, T.W., Ma, J.D., Baracos, V.E., Roeland, E.J., 2016. Cancer cachexia: beyond weight loss. J Oncol Pract 12 (11), 1163–1171.
Burd, N.A., West, D.W., Staples, A.W., Atherton, P.J., Baker, J.M., Moore, D.R., et al., 2010. Low-load high volume resistance exercise stimulates muscle protein synthesis more than high-load low volume resistance exercise in young men. PLoS One 5 (8), e12033.
Burd, N.A., Gorissen, S.H., van Loon, L.J., 2013. Anabolic resistance of muscle protein synthesis with aging. Exerc. Sport Sci. Rev. 41 (3), 169–173.
Burich, R., Teljigović, S., Boyle, E., Sjøgaard, G., 2015. Aerobic training alone or combined with strength training affects fitness in elderly: randomized trial. Eur. J. Sport Sci. 15 (8), 773–783.
Burtscher, J., Soltany, A., Visavadiya, N.P., Burtscher, M., Millet, G.P., Khoramipour, K., et al., 2023. Mitochondrial stress and mitokines in aging. Aging Cell 22 (2), e13770.
Cauley, J.A., 2015. An overview of sarcopenic obesity. J. Clin. Densitom. 18 (4), 499–505.
Churchward-Venne, T.A., Burd, N.A., Phillips, S.M., 2012. Nutritional regulation of muscle protein synthesis with resistance exercise: strategies to enhance anabolism. Nutr. Metab. 9 (1), 40.
Coggan, A.R., Spina, R.J., Rogers, M.A., King, D.S., Brown, M., Nemeth, P.M., et al., 1990. Histochemical and enzymatic characteristics of skeletal muscle in master athletes. J. Appl. Physiol. 68 (5), 1896–1901, 1985.
Coggan, A.R., Spina, R.J., King, D.S., Rogers, M.A., Brown, M., Nemeth, P.M., et al., 1992. Skeletal muscle adaptations to endurance training in 60- to 70-yr-old men and women. J. Appl. Physiol. 72 (5), 1780–1786, 1985.
Coker, R.H., Hays, N.P., Williams, R.H., Wolfe, R.R., Evans, W.J., 2015. Bed rest promotes reductions in walking speed, functional parameters, and aerobic fitness in older, healthy adults. J. Gerontol A. Biol. Sci. Med. Sci. 70 (1), 91–96.
Conboy, I.M., Conboy, M.J., Wagers, A.J., Girma, E.R., Weissman, I.L., Rando, T.A., 2005. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. Nature 433 (7027), 760–764.
Conley, K.E., Amara, C.E., Jubrias, S.A., Marcinek, D.J., 2007. Mitochondrial function, fibre types and ageing: new insights from human muscle in vivo. Exp. Physiol. 92 (2), 333–339.
Corsi, M., Alvarez, C., Callahan, L.F., Cleveland, R.J., Golightly, Y.M., Jordan, J.M., et al., 2018. Contributions of symptomatic osteoarthritis and physical function to incident cardiovascular disease. BMC Muscoskel. Disord. 19 (1), 393.

Currier, B.S., McLeod, J.C., Banfield, L., Beyene, J., Welton, N.J., D'Souza, A.C., et al., 2023. Resistance training prescription for muscle strength and hypertrophy in healthy adults: a systematic review and Bayesian network meta-analysis. Br. J. Sports Med. 57 (18), 1211–1220.
Della Peruta, C., Lozanoska-Ochser, B., Renzini, A., Moresi, V., Sanchez Riera, C., Bouché, M., et al., 2023. Sex differences in inflammation and muscle wasting in aging and disease. Int. J. Mol. Sci. 24 (5).
Deutz, N.E., Bauer, J.M., Barazzoni, R., Biolo, G., Boirie, Y., Bosy-Westphal, A., et al., 2014. Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. Clin. Nutr. 33 (6), 929–936.
Devries, M.C., Breen, L., Von Allmen, M., MacDonald, M.J., Moore, D.R., Offord, E.A., et al., 2015. Low-load resistance training during step-reduction attenuates declines in muscle mass and strength and enhances anabolic sensitivity in older men. Phys. Rep. 3 (8).
Dideriksen, K.J., Reitelseder, S., Petersen, S.G., Hjort, M., Helmark, I.C., Kjaer, M., et al., 2011. Stimulation of muscle protein synthesis by whey and caseinate ingestion after resistance exercise in elderly individuals. Scand. J. Med. Sci. Sports 21 (6), e372–e383.
Distefano, G., Goodpaster, B.H., 2018. Effects of exercise and aging on skeletal muscle. Cold Spring Harb. Perspect. Med. 8 (3).
Fang, W.Y., Tseng, Y.T., Lee, T.Y., Fu, Y.C., Chang, W.H., Lo, W.W., et al., 2021. Triptolide prevents LPS-induced skeletal muscle atrophy via inhibiting NF-κB/TNF-α and regulating protein synthesis/degradation pathway. Br. J. Pharmacol. 178 (15), 2998–3016.
Farsijani, S., Morais, J.A., Payette, H., Gaudreau, P., Shatenstein, B., Gray-Donald, K., et al., 2016. Relation between mealtime distribution of protein intake and lean mass loss in free-living older adults of the NuAge study. Am. J. Clin. Nutr. 104 (3), 694–703.
Fede, C., Fan, C., Pirri, C., Petrelli, L., Biz, C., Porzionato, A., et al., 2022. The effects of aging on the intramuscular connective tissue. Int. J. Mol. Sci. 23 (19).
Ferrucci, L., Fabbri, E., 2018. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat. Rev. Cardiol. 15 (9), 505–522.
Ferrucci, L., Harris, T.B., Guralnik, J.M., Tracy, R.P., Corti, M.C., Cohen, H.J., et al., 1999. Serum IL-6 level and the development of disability in older persons. J. Am. Geriatr. Soc. 47 (6), 639–646.
Franceschi, C., Bonafè, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., et al., 2000. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann. N. Y. Acad. Sci. 908, 244–254.
Goldspink, G., Fernandes, K., Williams, P.E., Wells, D.J., 1994. Age-related changes in collagen gene expression in the muscles of mdx dystrophic and normal mice. Neuromuscul. Disord. 4 (3), 183–191.
Gomez-Cabrera, M.C., Arc-Chagnaud, C., Salvador-Pascual, A., Brioche, T., Chopard, A., Olaso-Gonzalez, G., et al., 2020. Redox modulation of muscle mass and function. Redox Biol. 35, 101531.
Gram, M., Dahl, R., Dela, F., 2014. Physical inactivity and muscle oxidative capacity in humans. Eur. J. Sport Sci. 14 (4), 376–383.
Guo, Y., Guan, T., Shafiq, K., Yu, Q., Jiao, X., Na, D., et al., 2023. Mitochondrial dysfunction in aging. Ageing Res. Rev. 88, 101955.
Hackney, K.J., Ploutz-Snyder, L.L., 2012. Unilateral lower limb suspension: integrative physiological knowledge from the past 20 years (1991-2011). Eur. J. Appl. Physiol. 112 (1), 9–22.
Hales, C.M.S.J., Martin, C.B., Kohen, D., 2019. Prescription Drug Use Among Adults Aged 40–79 in the United States and Canada. NCHS Data Brief, Hyattsville, MD: National Center for Health Statistics no 347.
Halloway, S., Buchholz, S.W., Wilbur, J., Schoeny, M.E., 2015. Prehabilitation interventions for older adults: an integrative review. West. J. Nurs. Res. 37 (1), 103–123.
Hepple, R.T., 2018. When motor unit expansion in ageing muscle fails, atrophy ensues. J. Physiol. 596 (9), 1545–1546.
Holm, L., van Hall, G., Rose, A.J., Miller, B.F., Doessing, S., Richter, E.A., et al., 2010. Contraction intensity and feeding affect collagen and myofibrillar protein synthesis rates differently in human skeletal muscle. Am. J. Physiol. Endocrinol. Metab. 298 (2), E257–E269.
Holwerda, A.M., van Loon, L.J.C., 2022. The impact of collagen protein ingestion on musculoskeletal connective tissue remodeling: a narrative review. Nutr. Rev. 80 (6), 1497–1514.
Huang, Z., Zhong, L., Zhu, J., Xu, H., Ma, W., Zhang, L., et al., 2020. Inhibition of IL-6/JAK/STAT3 pathway rescues denervation-induced skeletal muscle atrophy. Ann. Transl. Med. 8 (24), 1681.
Hwang, A.B., Brack, A.S., 2018. Muscle stem cells and aging. Curr. Top. Dev. Biol. 126, 299–322.
Irving, B.A., Lanza, I.R., Henderson, G.C., Rao, R.R., Spiegelman, B.M., Nair, K.S., 2015. Combined training enhances skeletal muscle mitochondrial oxidative capacity independent of age. J. Clin. Endocrinol. Metab. 100 (4), 1654–1663.
Izquierdo, M., Merchant, R.A., Morley, J.E., Anker, S.D., Aprahamian, I., Arai, H., et al., 2021. International exercise recommendations in older adults (ICFSR): expert consensus guidelines. J. Nutr. Health Aging 25 (7), 824–853.
Järvinen, T.A., Józsa, L., Kannus, P., Järvinen, T.L., Järvinen, M., 2002. Organization and distribution of intramuscular connective tissue in normal and immobilized skeletal muscles. An immunohistochemical, polarization and scanning electron microscopic study. J. Muscle Res. Cell Motil. 23 (3), 245–254.
Jackson, A.A., Gibson, N.R., Lu, Y., Jahoor, F., 2004. Synthesis of erythrocyte glutathione in healthy adults consuming the safe amount of dietary protein. Am. J. Clin. Nutr. 80 (1), 101–107.
Ji, Y., Li, M., Chang, M., Liu, R., Qiu, J., Wang, K., et al., 2022. Inflammation: roles in skeletal muscle atrophy. Antioxidants 11 (9).
Joanisse, S., Nederveen, J.P., Baker, J.M., Snijders, T., Iacono, C., Parise, G., 2016a. Exercise conditioning in old mice improves skeletal muscle regeneration. Faseb. J. 30 (9), 3256–3268.
Joanisse, S., Nederveen, J.P., Snijders, T., McKay, B.R., Parise, G., 2016b. Skeletal muscle regeneration, repair and remodelling in aging: the importance of muscle stem cells and vascularization. Gerontology 63 (1), 91–100.
Johnson, M.A., Polgar, J., Weightman, D., Appleton, D., 1973. Data on the distribution of fibre types in thirty-six human muscles. An autopsy study. J. Neurol. Sci. 18 (1), 111–129.
Jornayvaz, F.R., Shulman, G.I., 2010. Regulation of mitochondrial biogenesis. Essays Biochem. 47, 69–84.
Joseph, A.M., Adhihetty, P.J., Buford, T.W., Wohlgemuth, S.E., Lees, H.A., Nguyen, L.M., et al., 2012. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell 11 (5), 801–809.
Koopman, R., van Loon, L.J., 2009. Aging, exercise, and muscle protein metabolism. J. Appl. Physiol. 106 (6), 2040–2048, 1985.
Kortebein, P., Ferrando, A., Lombeida, J., Wolfe, R., Evans, W.J., 2007. Effect of 10 days of bed rest on skeletal muscle in healthy older adults. JAMA 297 (16), 1772–1774.
Kortebein, P., Symons, T.B., Ferrando, A., Paddon-Jones, D., Ronsen, O., Protas, E., et al., 2008. Functional impact of 10 days of bed rest in healthy older adults. J. Gerontol A. Biol. Sci. Med. Sci. 63 (10), 1076–1081.
Kosek, D.J., Kim, J.S., Petrella, J.K., Cross, J.M., Bamman, M.M., 2006. Efficacy of 3 days/wk resistance training on myofiber hypertrophy and myogenic mechanisms in young vs. older adults. J. Appl. Physiol. 101 (2), 531–544, 1985.
Kouw, I.W.K., Groen, B.B.L., Smeets, J.S.J., Kramer, I.F., van Kranenburg, J.M.X., Nilwik, R., et al., 2019. One week of hospitalization following elective hip surgery induces substantial muscle atrophy in older patients. J. Am. Med. Dir. Assoc. 20 (1), 35–42.
Kragstrup, T.W., Kjaer, M., Mackey, A.L., 2011. Structural, biochemical, cellular, and functional changes in skeletal muscle extracellular matrix with aging. Scand. J. Med. Sci. Sports 21 (6), 749–757.
Kumar, V., Selby, A., Rankin, D., Patel, R., Atherton, P., Hildebrandt, W., et al., 2009. Age-related differences in the dose-response relationship of muscle protein synthesis to resistance exercise in young and old men. J. Physiol. 587 (1), 211–217.
Lamboley, C.R., Wyckelsma, V.L., Dutka, T.L., McKenna, M.J., Murphy, R.M., Lamb, G. D., 2015. Contractile properties and sarcoplasmic reticulum calcium content in type I and type II skeletal muscle fibres in active aged humans. J. Physiol. 593 (11), 2499–2514.
Lexell, J., 1995. Human aging, muscle mass, and fiber type composition. J. Gerontol A. Biol. Sci. Med. Sci. 50 (Spec No), 11–16.
Li, M., Ogilvie, H., Ochala, J., Artemenko, K., Iwamoto, H., Yagi, N., et al., 2015. Aberrant post-translational modifications compromise human myosin motor function in old age. Aging Cell 14 (2), 228–235.
Liang, H., Ward, W.F., 2006. PGC-1alpha: a key regulator of energy metabolism. Adv. Physiol. Educ. 30 (4), 145–151.
Lim, C., Kim, H.J., Morton, R.W., Harris, R., Phillips, S.M., Jeong, T.S., et al., 2019. Resistance exercise-induced changes in muscle phenotype are load dependent. Med. Sci. Sports Exerc. 51 (12), 2578–2585.
Linssen, W.H., Stegeman, D.F., Joosten, E.M., Binkhorst, R.A., Merks, M.J., ter Laak, H.J., et al., 1991. Fatigue in type I fiber predominance: a muscle force and surface EMG study on the relative role of type I and type II muscle fibers. Muscle Nerve 14 (9), 829–837.
Lukjanenko, L., Karaz, S., Stuelsatz, P., Gurriaran-Rodriguez, U., Michaud, J., Dammone, G., et al., 2019. Aging disrupts muscle stem cell function by impairing matricellular WISP1 secretion from fibro-adipogenic progenitors. Cell Stem Cell 24 (3), 433-46. e7.
Mahase, E., 2024. GLP-1 agonists: US sees 700% increase over four years in number of patients without diabetes starting treatment. Bmj 386, q1645.
Mamerow, M.M., Mettler, J.A., English, K.L., Casperson, S.L., Arentson-Lantz, E., Sheffield-Moore, M., et al., 2014. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. J. Nutr. 144 (6), 876–880.
Marcucci, L., Reggiani, C., 2020. Increase of resting muscle stiffness, a less considered component of age-related skeletal muscle impairment. Eur. J. Transl. Myol. 30 (2), 8982.
Mashinchian, O., Pisconti, A., Le Moal, E., Bentzinger, C.F., 2018. The muscle stem cell niche in health and disease. Curr. Top. Dev. Biol. 126, 23–65.
Mays, P.K., McAnulty, R.J., Campa, J.S., Laurent, G.J., 1991. Age-related changes in collagen synthesis and degradation in rat tissues. Importance of degradation of newly synthesized collagen in regulating collagen production. Biochem. J. 276 (2), 307–313. Pt 2.
McGlory, C., von Allmen, M.T., Stokes, T., Morton, R.W., Hector, A.J., Lago, B.A., et al., 2018. Failed recovery of glycemic control and myofibrillar protein synthesis with 2 wk of physical inactivity in overweight, prediabetic older adults. J. Gerontol A. Biol. Sci. Med. Sci. 73 (8), 1070–1077.
McKendry, J., Stokes, T., McLeod, J.C., Phillips, S.M., 2021. Resistance exercise, aging, disuse, and muscle protein metabolism. Compr. Physiol. 11 (3), 2249–2278.
McKendry, J., Lowisz, C.V., Nanthakumar, A., MacDonald, M., Lim, C., Currier, B.S., et al., 2024a. The effects of whey, pea, and collagen protein supplementation beyond the recommended dietary allowance on integrated myofibrillar protein synthetic rates in older males: a randomized controlled trial. Am. J. Clin. Nutr.
McKendry, J., Coletta, G., Nunes, E.A., Lim, C., Phillips, S.M., 2024b. Mitigating disuse-induced skeletal muscle atrophy in ageing: resistance exercise as a critical countermeasure. Exp. Physiol. 109 (10), 1650–1662.
McLeod, J.C., Currier, B.S., Lowisz, C.V., Phillips, S.M., 2024. The influence of resistance exercise training prescription variables on skeletal muscle mass, strength, and

physical function in healthy adults: an umbrella review. J. Sport Health Sci. 13 (1), 47–60.
Melov, S., Tarnopolsky, M.A., Beckman, K., Felkey, K., Hubbard, A., 2007. Resistance exercise reverses aging in human skeletal muscle. PLoS One 2 (5), e465.
Mikkelsen, U.R., Dideriksen, K., Andersen, M.B., Boesen, A., Malmgaard-Clausen, N.M., Sørensen, I.J., et al., 2015. Preserved skeletal muscle protein anabolic response to acute exercise and protein intake in well-treated rheumatoid arthritis patients. Arthritis Res. Ther. 17, 271.
Miljkovic, N., Lim, J.Y., Miljkovic, I., Frontera, W.R., 2015. Aging of skeletal muscle fibers. Ann. Rehabil. Med. 39 (2), 155–162.
Miller, S.L., Wolfe, R.R., 2008. The danger of weight loss in the elderly. J. Nutr. Health Aging 12 (7), 487–491.
Miller, B.F., Olesen, J.L., Hansen, M., Døssing, S., Crameri, R.M., Welling, R.J., et al., 2005. Coordinated collagen and muscle protein synthesis in human patella tendon and quadriceps muscle after exercise. J. Physiol. 567 (Pt 3), 1021–1033.
Miquel, J., Economos, A.C., Fleming, J., Johnson Jr., J.E., 1980. Mitochondrial role in cell aging. Exp. Gerontol. 15 (6), 575–591.
Mitch, W.E., Goldberg, A.L., 1996. Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. N. Engl. J. Med. 335 (25), 1897–1905.
Mitchell, W.K., Williams, J., Atherton, P., Larvin, M., Lund, J., Narici, M., 2012. Sarcopenia, dynapenia, and the impact of advancing age on human skeletal muscle size and strength; a quantitative review. Front. Physiol. 3, 260.
Moore, D.R., Tang, J.E., Burd, N.A., Rerecich, T., Tarnopolsky, M.A., Phillips, S.M., 2009. Differential stimulation of myofibrillar and sarcoplasmic protein synthesis with protein ingestion at rest and after resistance exercise. J. Physiol. 587 (Pt 4), 897–904.
Moore, D.R., Churchward-Venne, T.A., Witard, O., Breen, L., Burd, N.A., Tipton, K.D., et al., 2015. Protein ingestion to stimulate myofibrillar protein synthesis requires greater relative protein intakes in healthy older versus younger men. J. Gerontol A. Biol. Sci. Med. Sci. 70 (1), 57–62.
Moro, T., Brightwell, C.R., Volpi, E., Rasmussen, B.B., Fry, C.S., 2020. Resistance exercise training promotes fiber type-specific myonuclear adaptations in older adults. J. Appl. Physiol. 128 (4), 795–804, 1985.
Mosole, S., Carraro, U., Kern, H., Loefler, S., Fruhmann, H., Vogelauer, M., et al., 2014. Long-term high-level exercise promotes muscle reinnervation with age. J. Neuropathol. Exp. Neurol. 73 (4), 284–294.
Murgia, M., Toniolo, L., Nagaraj, N., Ciciliot, S., Vindigni, V., Schiaffino, S., et al., 2017. Single muscle fiber proteomics reveals fiber-type-specific features of human muscle aging. Cell Rep. 19 (11), 2396–2409.
Murphy, C.H., Oikawa, S.Y., Phillips, S.M., 2016. Dietary protein to maintain muscle mass in aging: a case for per-meal protein recommendations. J. Frailty Aging 5 (1), 49–58.
Nauenberg, E., Ng, C., Zhu, Q., 2023. A tale of two countries: changes to Canadian and U. S. Senior population projections due to the pandemic-implications for health care planning in Canada and other western countries. J. Popul Ageing 16 (1), 27–41.
Nederveen, J.P., Joanisse, S., Snijders, T., Ivankovic, V., Baker, S.K., Phillips, S.M., et al., 2016. Skeletal muscle satellite cells are located at a closer proximity to capillaries in healthy young compared with older men. J. Cachexia, Sarcopenia Muscle 7 (5), 547–554.
Nederveen, J.P., Joanisse, S., Thomas, A.C.Q., Snijders, T., Manta, K., Bell, K.E., et al., 2020. Age-related changes to the satellite cell niche are associated with reduced activation following exercise. Faseb. J. 34 (7), 8975–8989.
Nilwik, R., Snijders, T., Leenders, M., Groen, B.B., van Kranenburg, J., Verdijk, L.B., et al., 2013. The decline in skeletal muscle mass with aging is mainly attributed to a reduction in type II muscle fiber size. Exp. Gerontol. 48 (5), 492–498.
Norton, C., Toomey, C., McCormack, W.G., Francis, P., Saunders, J., Kerin, E., et al., 2016. Protein supplementation at breakfast and lunch for 24 Weeks beyond habitual intakes increases whole-body lean tissue mass in healthy older adults. J. Nutr. 146 (1), 65–69.
Nowotny, K., Grune, T., 2014. Degradation of oxidized and glycoxidized collagen: role of collagen cross-linking. Arch. Biochem. Biophys. 542, 56–64.
Nunes, E.A., Stokes, T., McKendry, J., Currier, B.S., Phillips, S.M., 2022. Disuse-induced skeletal muscle atrophy in disease and nondisease states in humans: mechanisms, prevention, and recovery strategies. Am. J. Physiol. Cell Physiol. 322 (6). C1068-c84.
Ochala, J., Frontera, W.R., Dorer, D.J., Van Hoecke, J., Krivickas, L.S., 2007. Single skeletal muscle fiber elastic and contractile characteristics in young and older men. J. Gerontol A. Biol. Sci. Med. Sci. 62 (4), 375–381.
Oikawa, S.Y., McGlory, C., D'Souza, L.K., Morgan, A.K., Saddler, N.I., Baker, S.K., et al., 2018. A randomized controlled trial of the impact of protein supplementation on leg lean mass and integrated muscle protein synthesis during inactivity and energy restriction in older persons. Am. J. Clin. Nutr. 108 (5), 1060–1068.
Oikawa, S.Y., Holloway, T.M., Phillips, S.M., 2019. The impact of step reduction on muscle health in aging: protein and exercise as countermeasures. Front. Nutr. 6, 75.
Palmer, C.S., Anderson, A.J., Stojanovski, D., 2021. Mitochondrial protein import dysfunction: mitochondrial disease, neurodegenerative disease and cancer. FEBS Lett. 595 (8), 1107–1131.
Paoletti, A., Pencharz, P.B., Rafii, M., Tomlinson, C., Kong, D., Xu, L., et al., 2024. Protein intake affects erythrocyte glutathione synthesis in healthy adults aged ≥60 years in a repeated-measures trial. Am. J. Clin. Nutr. 119 (4), 917–926.
Paterson, D.H., Warburton, D.E., 2010. Physical activity and functional limitations in older adults: a systematic review related to Canada's Physical Activity Guidelines. Int. J. Behav. Nutr. Phys. Activ. 7, 38.
Pavan, P., Monti, E., Bondí, M., Fan, C., Stecco, C., Narici, M., et al., 2020. Alterations of extracellular matrix mechanical properties contribute to age-related functional impairment of human skeletal muscles. Int. J. Mol. Sci. 21 (11).
Phillips, B.E., Williams, J.P., Gustafsson, T., Bouchard, C., Rankinen, T., Knudsen, S., et al., 2013. Molecular networks of human muscle adaptation to exercise and age. PLoS Genet. 9 (3), e1003389.
Phillips, S.M., Paddon-Jones, D., Layman, D.K., 2020. Optimizing adult protein intake during catabolic health conditions. Adv. Nutr. 11 (4). S1058-s69.
Piasecki, M., Ireland, A., Jones, D.A., McPhee, J.S., 2016. Age-dependent motor unit remodelling in human limb muscles. Biogerontology 17 (3), 485–496.
Pillon, N.J., 2023. Mitochondrial response to inactivity-induced muscle disuse and exercise training. Eur. J. Appl. Physiol. 123 (2), 243–245.
Pinckaers, P.J.M., Trommelen, J., Snijders, T., van Loon, L.J.C., 2021. The anabolic response to plant-based protein ingestion. Sports Med. 51 (Suppl. 1), 59–74.
Pišot, R., Marusic, U., Biolo, G., Mazzucco, S., Lazzer, S., Grassi, B., et al., 2016. Greater loss in muscle mass and function but smaller metabolic alterations in older compared with younger men following 2 wk of bed rest and recovery. J. Appl. Physiol. 120 (8), 922–929, 1985.
Polyzos, S.A., Margioris, A.N., 2018. Sarcopenic obesity. Hormones (Basel) 17 (3), 321–331.
Prattichizzo, F., De Nigris, V., Spiga, R., Mancuso, E., La Sala, L., Antonicelli, R., et al., 2018. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res. Rev. 41, 1–17.
Purslow, P.P., 2020. The structure and role of intramuscular connective tissue in muscle function. Front. Physiol. 11, 495.
Quinn, K.L., Stall, N.M., Yao, Z., Stukel, T.A., Cram, P., Detsky, A.S., et al., 2019. The risk of death within 5 years of first hospital admission in older adults. CMAJ (Can. Med. Assoc. J.) 191 (50), E1369–E1377.
Rafii, M., Paoletti, A., He, H., Porto, B., Szwiega, S., Pencharz, P.B., et al., 2024. Dietary lysine requirements of older adults stratified by age and sex. J. Nutr.
Rebelo-Marques, A., De Sousa Lages, A., Andrade, R., Ribeiro, C.F., Mota-Pinto, A., Carrilho, F., et al., 2018. Aging hallmarks: the benefits of physical exercise. Front. Endocrinol. 9, 258.
Robinson, M.M., Dasari, S., Konopka, A.R., Johnson, M.L., Manjunatha, S., Esponda, R. R., et al., 2017. Enhanced protein translation underlies improved metabolic and physical adaptations to different exercise training modes in young and old humans. Cell Metabol. 25 (3), 581–592.
Rommersbach, N., Wirth, R., Lueg, G., Klimek, C., Schnatmann, M., Liermann, D., et al., 2020. The impact of disease-related immobilization on thigh muscle mass and strength in older hospitalized patients. BMC Geriatr. 20 (1), 500.
Rooyackers, O.E., Adey, D.B., Ades, P.A., Nair, K.S., 1996. Effect of age on in vivo rates of mitochondrial protein synthesis in human skeletal muscle. Proc. Natl. Acad. Sci. U.S. A. 93 (26), 15364–15369.
Rowan, S.L., Rygiel, K., Purves-Smith, F.M., Solbak, N.M., Turnbull, D.M., Hepple, R.T., 2012. Denervation causes fiber atrophy and myosin heavy chain co-expression in senescent skeletal muscle. PLoS One 7 (1), e29082.
Santilli, V., Bernetti, A., Mangone, M., Paoloni, M., 2014. Clinical definition of sarcopenia. Clin. Cases Miner. Bone Metab. 11 (3), 177–180.
Sayer, A.A., Syddall, H.E., Martin, H.J., Dennison, E.M., Roberts, H.C., Cooper, C., 2006. Is grip strength associated with health-related quality of life? Findings from the Hertfordshire Cohort Study. Age Ageing 35 (4), 409–415.
Schaap, L.A., Pluijm, S.M., Deeg, D.J., Visser, M., 2006. Inflammatory markers and loss of muscle mass (sarcopenia) and strength. Am. J. Med. 119 (6), 526.e9-17.
Shefer, G., Van de Mark, D.P., Richardson, J.B., Yablonka-Reuveni, Z., 2006. Satellite-cell pool size does matter: defining the myogenic potency of aging skeletal muscle. Dev. Biol. 294 (1), 50–66.
Short, K.R., Bigelow, M.L., Kahl, J., Singh, R., Coenen-Schimke, J., Raghavakaimal, S., et al., 2005. Decline in skeletal muscle mitochondrial function with aging in humans. Proc. Natl. Acad. Sci. U.S.A. 102 (15), 5618–5623.
Silva, A.M., Shen, W., Heo, M., Gallagher, D., Wang, Z., Sardinha, L.B., et al., 2010. Ethnicity-related skeletal muscle differences across the lifespan. Am. J. Hum. Biol. 22 (1), 76–82.
Smeuninx, B., Elhassan, Y.S., Sapey, E., Rushton, A.B., Morgan, P.T., Korzepa, M., et al., 2023. A single bout of prior resistance exercise attenuates muscle atrophy and declines in myofibrillar protein synthesis during bed-rest in older men. J. Physiol.
Sousa-Victor, P., García-Prat, L., Muñoz-Cánoves, P., 2022. Control of satellite cell function in muscle regeneration and its disruption in ageing. Nat. Rev. Mol. Cell Biol. 23 (3), 204–226.
Spina, R.J., Chi, M.M., Hopkins, M.G., Nemeth, P.M., Lowry, O.H., Holloszy, J.O., 1996. Mitochondrial enzymes increase in muscle in response to 7-10 days of cycle exercise. J. Appl. Physiol. 80 (6), 2250–2254, 1985.
Srikanthan, P., Karlamangla, A.S., 2011. Relative muscle mass is inversely associated with insulin resistance and prediabetes. Findings from the third National Health and Nutrition Examination Survey. J. Clin. Endocrinol. Metab. 96 (9), 2898–2903.
Suetta, C., Hvid, L.G., Justesen, L., Christensen, U., Neergaard, K., Simonsen, L., et al., 2009. Effects of aging on human skeletal muscle after immobilization and retraining. J. Appl. Physiol. 107 (4), 1172–1180.
Suetta, C., Frandsen, U., Mackey, A.L., Jensen, L., Hvid, L.G., Bayer, M.L., et al., 2013. Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. J. Physiol. 591 (15), 3789–3804.
Szwiega, S., Pencharz, P.B., Rafii, M., Lebarron, M., Chang, J., Ball, R.O., et al., 2021. Dietary leucine requirement of older men and women is higher than current recommendations. Am. J. Clin. Nutr. 113 (2), 410–419.
Tan, S., Li, W., Wang, J., 2012. Effects of six months of combined aerobic and resistance training for elderly patients with a long history of type 2 diabetes. J. Sports Sci. Med. 11 (3), 495–501.
Tang, J.E., Moore, D.R., Kujbida, G.W., Tarnopolsky, M.A., Phillips, S.M., 2009. Ingestion of whey hydrolysate, casein, or soy protein isolate: effects on mixed muscle protein

synthesis at rest and following resistance exercise in young men. J. Appl. Physiol. 107 (3), 987–992, 1985.
Traylor, D.A., Gorissen, S.H.M., Phillips, S.M., 2018. Perspective: protein requirements and optimal intakes in aging: are we ready to recommend more than the recommended daily allowance? Adv. Nutr. 9 (3), 171–182.
Trommelen, J., Holwerda, A.M., Senden, J.M., Goessens, J.P.B., J, V.A.N.K., Gijsen, A.P., et al., 2020. Casein ingestion does not increase muscle connective tissue protein synthesis rates. Med. Sci. Sports Exerc. 52 (9), 1983–1991.
Ubaida-Mohien, C., Lyashkov, A., Gonzalez-Freire, M., Tharakan, R., Shardell, M., Moaddel, R., et al., 2019. Discovery proteomics in aging human skeletal muscle finds change in spliceosome, immunity, proteostasis and mitochondria. Elife 8.
Ueno, M., Maeshige, N., Hirayama, Y., Yamaguchi, A., Ma, X., Uemura, M., et al., 2021. Pulsed ultrasound prevents lipopolysaccharide-induced muscle atrophy through inhibiting p38 MAPK phosphorylation in C2C12 myotubes. Biochem. Biophys. Res. Commun. 570, 184–190.
Verdijk, L.B., Koopman, R., Schaart, G., Meijer, K., Savelberg, H.H., van Loon, L.J., 2007. Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. Am. J. Physiol. Endocrinol. Metab. 292 (1), E151–E157.
Verdijk, L.B., Gleeson, B.G., Jonkers, R.A., Meijer, K., Savelberg, H.H., Dendale, P., et al., 2009. Skeletal muscle hypertrophy following resistance training is accompanied by a fiber type-specific increase in satellite cell content in elderly men. J. Gerontol A. Biol. Sci. Med. Sci. 64 (3), 332–339.
Visser, M., Goodpaster, B.H., Kritchevsky, S.B., Newman, A.B., Nevitt, M., Rubin, S.M., et al., 2005. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J. Gerontol A. Biol. Sci. Med. Sci. 60 (3), 324–333.
Volpi, E., Campbell, W.W., Dwyer, J.T., Johnson, M.A., Jensen, G.L., Morley, J.E., et al., 2013. Is the optimal level of protein intake for older adults greater than the recommended dietary allowance? J. Gerontol A. Biol. Sci. Med. Sci. 68 (6), 677–681.
von Haehling, S., Morley, J.E., Anker, S.D., 2010. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle 1 (2), 129–133.
Wall, B.T., Gorissen, S.H., Pennings, B., Koopman, R., Groen, B.B., Verdijk, L.B., et al., 2015. Aging is accompanied by a blunted muscle protein synthetic response to protein ingestion. PLoS One 10 (11), e0140903.
Watanabe, J.H., Kwon, J., Nan, B., Reikes, A., 2024. Trends in glucagon-like peptide 1 receptor agonist use, 2014 to 2022. J. Am. Pharmaceut. Assoc. 64 (1), 133–138 (2003.
Webb, M., Sideris, D.P., 2020. Intimate relations-mitochondria and ageing. Int. J. Mol. Sci. 21 (20).
Wilkinson, S.B., Phillips, S.M., Atherton, P.J., Patel, R., Yarasheski, K.E., Tarnopolsky, M. A., et al., 2008. Differential effects of resistance and endurance exercise in the fed state on signalling molecule phosphorylation and protein synthesis in human muscle. J. Physiol. 586 (15), 3701–3717.
Wohlgemuth, R.P., Brashear, S.E., Smith, L.R., 2023. Alignment, cross linking, and beyond: a collagen architect's guide to the skeletal muscle extracellular matrix. Am. J. Physiol. Cell Physiol. 325 (4). C1017-c30.
Yannakoulia, M., Mamalaki, E., Anastasiou, C.A., Mourtzi, N., Lambrinoudaki, I., Scarmeas, N., 2018. Eating habits and behaviors of older people: where are we now and where should we go? Maturitas 114, 14–21.
Zanders, L., Kny, M., Hahn, A., Schmidt, S., Wundersitz, S., Todiras, M., et al., 2022. Sepsis induces interleukin 6, gp130/JAK2/STAT3, and muscle wasting. J Cachexia Sarcopenia Muscle 13 (1), 713–727.
Zhu, D., Li, X., Tian, Y., 2022. Mitochondrial-to-nuclear communication in aging: an epigenetic perspective. Trends Biochem. Sci. 47 (8), 645–659.
Zoe Caplan, M.R., 2023. The Older Population: 2022.