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Age-related changes in muscle architecture and metabolism in humans: The likely contribution of physical inactivity to age-related functional decline

N.F. Shur a,b,c,1, L. Creedon a,c,1, S. Skirrow a,e, P.J.Atherton a,c,d, I.A. MacDonald a,c,e, J. Lund a,c,d, P.L. Greenhaff a,b,c,e,*

a MRC/Versus Arthritis Centre for Musculoskeletal Ageing Research, UK
b Versus Arthritis Centre for Sport, Exercise and Osteoarthritis, The University of Nottingham, UK
c National Institute for Health Research (NIHR) Nottingham Biomedical Research Centre, UK
d School of Medicine, University of Nottingham Medical School, Royal Derby Hospital, Derby DE22 3Df, UK
e School of Life Sciences, University of Nottingham Medical School, Queen’s Medical Centre, Nottingham NG7 2UH, UK

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A B S T R A C T

In the United Kingdom (UK), it is projected that by 2035 people aged >65 years will make up 23 % of the population, with those aged >85 years accounting for 5 % of the total population. Ageing is associated with progressive changes in muscle metabolism and a decline in functional capacity, leading to a loss of independence. Muscle metabolic changes associated with ageing have been linked to alterations in muscle architecture and declines in muscle mass and insulin sensitivity. However, the biological features often attributed to muscle ageing are also seen in controlled studies of physical inactivity (e.g. reduced step-count and bed-rest), and it is currently unclear how many of these ageing features are due to ageing per se or sedentarism. This is particularly relevant at a time of home confinements reducing physical activity levels during the Covid-19 pandemic. Current knowledge gaps include the relative contribution that physical inactivity plays in the development of many of the negative features associated with muscle decline in older age. Similarly, data demonstrating positive effects of government recommended physical activity guidelines on muscle health are largely non-existent. It is imperative therefore that research examining interactions between ageing, physical activity and muscle mass and metabolic health is prioritised so that it can inform on the “normal” muscle ageing process and on strategies for improving health span and well-being. This review will focus on important changes in muscle architecture and metabolism that accompany ageing and highlight the likely contribution of physical inactivity to these changes.

1. Introduction

Ageing is associated with progressive changes in skeletal muscle mass, metabolism and functional capacity, which are associated with a decline in independence and increased total mortality (Srikanthan and Karlsmangla, 2014). Given that by 2035, people aged >65 years will make up 23 % of the UK population, with those aged >85 years accounting for 5 % of the total population (Office for National Statistics), it is paramount that studies into the effects of ageing on muscle mass and metabolism are investigated. Some features of ageing may in fact be partly reversible. Busse was the first to suggest the idea of primary and secondary ageing (Busse, 1969); primary ageing refers to the intrinsic time-related biological process not contingent on stress, trauma or disease, whilst secondary ageing is physiological decline that occurs secondary to environmental and lifestyle influences such as diet and physical activity. Factors contributing to secondary ageing by their nature therefore may be partly reversible. As people age physical activity levels tend to decline (Milanovic, Pantelic et al. 2013). Studies in older people to date have not measured baseline physical activity levels in a detailed quantified manner. Similarly, studies comparing young and old have not matched groupings for habitual physical activity levels (Frontera et al., 2000) and it is also debatable whether the decline in muscle mass and quality in older people during inactivity follows the same trajectory as younger individuals, with studies reporting opposite

* Corresponding author at: Division of Physiology, Pharmacology and Neuroscience, School of Life Sciences, The Medical School, University of Nottingham, Queen’s Medical Centre, Nottingham NG7 2UH, UK.
E-mail address: paul.greenhaff@nottingham.ac.uk (P.L. Greenhaff).
1 Joint first author.

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Ageing is associated with insidious declines in skeletal muscle mass, termed sarcopenia, as well as a decline in strength and quality, termed dynapenia (Mitchell et al., 2012). However, there is little agreement on the rate of decline of muscle mass according to age, due to a paucity of longitudinal studies. Cross sectional studies comparing younger cohorts considered to be of peak muscle mass (age 18–45) with older cohorts (age 65–90) have highlighted differences in muscle mass between young and older individuals ranging from 8 to 45% (Tzankoff and Norris, 1977; Mitchell et al., 2012). However, cross-sectional studies assume that their young and old participants are fairly matched, while other factors such as intergenerational differences may also have an influence. Of the few longitudinal studies that have been conducted in this area, one showed a leg lean muscle mass loss of 0.7–0.8% per year, during a 7 year follow up of individuals in their 70 s (Koster et al., 2011). A large cross-sectional study has described a linear loss of muscle mass in later life, accelerated after the age of 60 years (Kyle et al., 2001), whilst others have reported a reduction in muscle mass starting as early as 30 years of age (Janssen et al., 2000). The rate of muscle mass loss has also been reported to be accelerated in the lower body; being twice as high as the upper body response (Janssen et al., 2000). A bed rest study in healthy older adults (mean age 67 years) found a greater loss of lean tissue compared to young individuals after 28 days, particularly of the lower extremities, associated with a negative urinary nitrogen balance (Kortebein et al., 2007), whilst another study showed greater loss of quadriceps muscle volume in the young volunteers in response to 14 days immobilization compared to older volunteers (mean age 67 years; Suetta et al., 2009).

Muscle mass is regulated by the balance of muscle protein synthesis (MPS) and muscle protein breakdown (MPB). This equilibrium has a diurnal variation and is predominantly stimulated by food intake (Wilkinson et al., 2015) and physical activity (Kumar et al., 2009). The anabolic effects of nutrition are primarily driven by amino acids from dietary proteins, which are incorporated into skeletal muscle (Atherton and Smith, 2012). One mechanism proposed to contribute to chronic muscle mass loss during ageing is anabolic resistance, or specifically, the inability to stimulate MPS or inhibit MPB following feeding or an exercise stimulus. Cuthbertson compared rates of MPS in 44 healthy young and old men in response to essential amino acids (EAA) and found that the elderly showed a blunted myofibrillar protein fractional synthetic rate in response to EAA compared with the young (Cuthbertson et al., 2005). In particular, they found the phosphorylation of mammalian target of rapamycin (mTOR) at Ser2448 and p70S6K and downstream translational regulators increased less in the elderly in response to EAA
compared to young, indicating a reduction in the ability of aged muscle to “sense” a nutrient signal. Similarly, Kumar found a blunted MPS response 1–2 h after resistance exercise training (RET) in elderly men compared to young as well as a reduction in phosphorylation of anabolic signalling molecules (Kumar et al., 2009). In a study measuring chronic MPS using “heavy water” (D<sub>2</sub>O) stable isotope tracer, Brook et al. found a blunted hypertrophic response to a 6 week RET programme which occurred secondary to reduced rates of chronic MPS in older individuals compared to young (Brook et al., 2016). This appeared to be multifactorial in nature, reflecting blunted ribosomal biogenesis and translational efficiency and lower anabolic hormone concentrations. Interestingly, a longitudinal study of 20 weeks RET in healthy young (18–28 years), middle aged (45–55 years) and older participants (65–75 years) demonstrated that only younger individuals increased muscle mass in response to RET (Phillips et al., 2017). This suggests an age-related failure of muscle hypertrophy which occurs earlier in life than previously reported. However, well controlled longitudinal studies are missing in order to conclusively determine whether anabolic resistance is a causative factor in sarcopenia.

Age related loss of quadriceps muscle cross-sectional area has been associated with loss of muscle mitochondrial ATP production capacity, due at least in part to a decline in mitochondrial volume density (Brokeley et al., 2014). This will impact negatively muscle metabolic resilience, i.e. the ability of skeletal muscle metabolism to respond to and recover from a physiological stress, in particular muscle contraction. Muscle metabolic resilience can also be negatively affected by a reduction in intrinsic mitochondrial function, i.e. ATP production per mitochondrial unit caused by, for example, reactive oxygen species and defective autophagy (Gonzalez-Freire et al., 2015). Collectively, physiological ageing appears to be associated with muscle mass loss and declines in metabolic capacity and resilience which will limit functional ability, and in turn may accelerate further age-related decline.

### 2.2. Muscle strength and power

The magnitude of strength loss seen in ageing is consistently greater than the degree of muscle mass loss demonstrated in studies of hand-grip (Dey et al., 2009) and lower limb strength (Delmonico et al., 2009). In a 5-year follow-up of 1678 older participants, strength, measured as knee extensor torque, declined 2–5 times more than the loss of cross sectional area of the thigh (Delmonico et al., 2009). Similarly, Frontera noted a 20–30 % decline in strength of knee flexors and extensors with an average 16 % loss in quadriceps CSA in older men over 12 years follow up (Frontera et al., 2000). In this study however, there was a significant difference in weekly habitual physical activity levels between year 1 and follow up (Frontera et al., 2000). Nevertheless, the fact that exercise training intervention can increase whole-body and leg insulin sensitivity (Delia et al., 2019; Søgaard et al., 2018) and oxidative capacity (Brokeley et al., 2014) in older volunteers strongly points to muscle deconditioning, occurring secondary to age related declines in physical activity levels, being an important contributor.

As people age, they inherently become less active, which may predispose to increases in adiposity and a reduction in whole-body lean mass (Dela et al., 1996). However, changes in muscle mass are complex as obesity has been shown to preserve muscle mass due to the greater muscle loading required to ambulate (Murton et al., 2015). There is a large body of evidence that adiposity is linked with insulin resistance (Lanza et al., 2008), visceral adiposity (Ross et al., 2002) and subcutaneous adiposity having the most significant associations with insulin resistance (Kelley et al., 2000) and Smith et al., 2001). Studies utilising the hyperinsulinaemic clamp technique in healthy older volunteers have shown that whole body insulin-stimulated glucose disposal in healthy individuals is not reduced by age per se but is probably explained by a relative increase in body fat compared with young (Dela et al., 1996). At a muscle level, intra-myocellular lipid (IMCL) accumulation also appears to have a significant negative impact on muscle insulin sensitivity, with the size, location and composition of the lipid droplets all appearing to diminish insulin sensitivity (Gemmink et al., 2017). Some suggest that ageing combined with increasing adiposity exacerbates insulin resistance (Kohrt et al., 1993; Seals et al., 1984; Basu et al., 2003), but it is very difficult to control for confounding variables in such...
studies. Indeed, recent evidence showing older lean volunteers displayed IMCL content and insulin sensitivity to that of younger volunteers (Chee et al., 2016), strongly suggests muscle insulin resistance and lipid accumulation often observed in older individuals are likely due to lifestyle factors rather than inherent aging of skeletal muscle per se. Indeed, obese older individuals were markedly insulin resistant and had more than twofold greater IMCL in the sub-sarcolemmal region compared to their older lean counterparts.

Mitochondrial dysfunction has been linked to lipid induced insulin resistance through the comparison of young healthy volunteers and older healthy volunteers. Petersen et al. (2003) identified that a reduction in mitochondrial respiratory capacity was associated with a greater muscle fat content (Petersen et al., 2003). However, this could simply reflect the impact of reduced habitual physical activity on muscle deconditioning and energy balance with ageing, rather than a causative effect of lipid accumulation on mitochondrial function. Nevertheless, evidence suggests that an increase in IMCL content has detrimental effects on mitochondrial fuel selection resulting in the inability of mitochondria to switch from lipid to glucose oxidation during insulin stimulation (Petersen et al., 2015). Importantly, much of the existing research that has been undertaken looking at the link between insulin resistance and mitochondrial dysfunction has not been definitive. For example, some studies have not normalised mitochondrial function measurements for the decline in muscle mitochondrial content that accompanies age. Whatever the drivers, adiposity is associated with alterations of both muscle lipid stores and mitochondrial dynamics. Furthermore, research showing changes in lipid droplet morphology, mitochondrial dynamics and improvements in insulin sensitivity after gastric bypass surgery suggests an association between these events (Kristensen et al., 2018), but the mechanistic links are not yet resolved (Dela and Helge, 2013) and may not be age related per se.

Age related insulin resistance has been linked to an age-related decline in insulin stimulated muscle GLUT4 content in both males and females (Houmard et al., 1995), and this relationship persisting despite adjusting for whole-body adiposity, regional adiposity, and cardiorespiratory fitness. This age-related decline in muscle GLUT4 content was also observed in the fast twitch fibres of the vastus lateralis, but not the slow twitch fibres, when comparing older and younger participants (Gaster et al., 2000). In contrast, Dela and colleagues (Dela et al., 1994) and Cox and colleagues (Cox et al., 1985) found no age-related differences in muscle GLUT4 protein abundance. Furthermore, Cox et al. identified similar relative increases in muscle GLUT4 protein content, irrespective of age, following a short-term exercise programme (Cox et al., 1985). The current evidence linking GLUT4 protein content with the age-related decline in insulin sensitivity is inconclusive and may simply be explained by habitual physical activity levels given exercise training is able to stimulate muscle GLUT4 protein content in young and older volunteers.

3. Inactivity related muscle events

3.1. Models of inactivity

Mechanistic insight into the rate and magnitude of decline in muscle mass, muscle architecture and glucose disposal in response to physical inactivity is lacking. A recent upper limb immobilization study suggests changes in glucose disposal in response to immobilization is rapid and specific to the inactive limb (Burns et al., 2021), but precise mechanisms are unclear. This is a major gap in our understanding that needs to be addressed in controlled human volunteer studies given the poor generalisation from rodents that possess poor metabolic stability compared with humans (Demetrius, 2005). An appreciation of the different models of inactivity used to study this gap is therefore important. Several different models of physical inactivity, ranging in severity, have been developed to study the effects of inactivity in healthy human volunteers. These models allow the exploration of short and long-term physical inactivity and energy balance and the effects that these have metabolic health, providing useful insight into their physiological mechanisms (Fig. 2).

Spaceflight, or a microgravity environment, is an extreme model of inactivity; the lack of load bearing activity results in reduced muscular contraction leading to substantial functional and metabolic adaptations. However, the opportunity to study physiological changes during spaceflight is limited due to the cost and complexity of studies; the number of studies is few and often of varying duration. Therefore, data remains hard to interpret because of the small sample size, the variations in flight duration and the lack of regulation in diet and exercise.

Bed rest is a widely accepted model of physical inactivity; generally, all activities are performed in a horizontal or -6 degree head-down tilt position, minimising use of all muscles and bringing about significant physiological adaptations similar to those observed during spaceflight. A substantial number of bed rest studies have been performed ranging from 3 to 120 days duration (Leblanc et al., 1992; Ferrando et al., 1996; Smorawitski et al., 2000). These studies on the whole have shown, to a varying degree, a reduction in skeletal muscle mass, strength and whole body insulin sensitivity, with this effect being demonstrated after just 7 days (Dirks et al., 2016). Bed rest is an extreme stimulus when compared to the degree of physical inactivity encountered by the general population. However, they allow the impact of an intervention such as dietary energy content and composition, exercise or a pharmacological agent, to be examined. An alternative model of whole-body physical inactivity is ‘dry’ water immersion, which is often used as a model of weightlessness. It involves immersing the subject in thermoneutral water; however subjects are protected from water contact with a thin elastic waterproof fabric. ‘Dry’ water immersion produces similar physiological effects to those observed during bed rest, but the effects are often of greater magnitude and occur at a faster rate (Shenkman et al., 1997; Navasiolava et al., 2010).

Limb immobilisation and unilateral lower limb suspension extensively restricts motion in a targeted limb but allows maintenance of everyday activities. Limb immobilisation studies use a cast to fully immobilise the targeted limb, whilst in unilateral lower limb suspension studies, as originally described by Berg et al, the treatment limb is flexed and suspended above the ground with the use of a shoulder harness (Berg et al., 1991). Both models evoke muscular adaptations similar to those induced by bed rest; but these adaptations are mostly confined to the immobilised limb, allowing the localised effects of physical inactivity to be studied. The benefit of limb immobilisation is that the participant’s contralateral limb can serve as an internal control, drastically reducing a number of potential inter-participant variables. The use of limb immobilisation in research has more clinical relevance than bed rest due to it being a commonly used technique in the treatment of fractures, which are common throughout all age groups.

Studies involving reduced ambulatory activity normally achieved through a reduction in daily step counts is a model most realistic to the free-living state (Tudor-Locke and Bassett, 2004). There have been several examples of well controlled experiments of reduced step count which have demonstrated reductions in muscle mass, postprandial MPB and insulin sensitivity after 14 days of <1500 steps per day (Breen et al., 2013; Krogh-Madsen et al., 1985).

3.2. Many of the physiological features of ageing also appear to be major features of inactivity

Declines in muscle mass and strength attributed to ageing have been reproduced in young volunteers subjected to reduced step count or immobilisation. This implies that you can make a young person physiologically age simply by making them immobile or inactive using the models of physical inactivity outlined above. Two-weeks of full leg immobilisation in young men (aged 18–30) led to a –4.7 % decline in quadriceps lean mass and a –27 % reduction in isometric strength from the pre-immobile state (Jones et al., 2004). Similarly, 3-days dry
immersion in 12 young participants (mean ± SD age 32 ± 5 years), resulted in an 11 % decline in maximal voluntary contraction and 2.4 % loss in quadriceps cross-sectional area (Demangel et al., 2017). This greater magnitude of voluntary strength loss was associated with some evidence of muscle fibre denervation in the form of increased neural cellular adhesion molecule positive fibre staining. The authors also reported a decrease in the proportion of IIa fibres and an increase in the proportion of hybrid fibres I/IIIX.

Muscle protein turnover is also altered secondary to immobilisation in the young. In a study of 9 healthy males undergoing 23 days of unilateral lower limb immobilisation, post-absorptive rates of MPS halved from day 0 to day 10 (0.047 % vs 0.022 %) and remained depressed at this rate until day 21 (de Boer et al., 2007). Apart from a fall in phosphorylation of focal adhesion kinase of 30 % (p < 0.01) by 10 days, there were no alterations in any of the proteins associated with protein anabolic signalling, implying that the signalling potential of skeletal muscle was not diminished at least in the fastest state. Furthermore, anabolic resistance to protein or amino acid administration, a characteristic finding shown in physiological studies of ageing, can be replicated in the young volunteers secondary to immobilisation irrespective of the dose administered (Glover et al., 2008). Kilroe and colleagues reported that changes in MPS are rapid, occurring after 2 days following lower limb immobilisation in young healthy volunteers using deuterated water to quantify cumulative myofibrillar protein synthesis rates, with greater reductions in the immobilised leg MPS when compared with the control leg after 7 days of immobilisation (Kilroe et al., 2020). This was associated with a reduction of 6.7 +/- 0.6 % in MRI derived quadriceps volume in the immobilised leg when compared to the non-immobilised leg.

Similarly, immobilisation and inactivity have been shown to induce deficits in whole body and leg glucose uptake under insulin stimulated conditions in young healthy adults. For example, whole-body and leg glucose uptake measured under hyperinsulinaemic euglycaemic clamp conditions declined following 7 days bed rest in young men, with the decline being of greatest magnitude in the legs (Mikines et al., 1991). In addition, bed rest had no impact upon hepatic insulin sensitivity in the same study. A less severe model involving a reduction in step count from ~10,000 to <1500 per day for 2 weeks was sufficient to reduce whole-body glucose uptake under insulin clamp conditions in young healthy men (Krogh-Madsen et al., 1985). The mechanism(s) responsible for immobilisation induced reductions in glucose disposal is currently unresolved but candidates include alterations in the signalling and/or translocation of GLUT4 to the plasma membrane (Zierath et al., 1996), immobilisation induced IMCL accumulation (Manini et al., 2007; Cree et al., 2010) through excessive free fatty acid supply secondary to positive energy balance and finally a decrease in mitochondrial content and/or mitochondrial function with subsequent alterations in carbohydrate metabolism (Abadi et al., 2009). A recent upper limb immobilisation study reported a decline in forearm glucose uptake within 24 h that was specific to the immobilised limb and was not accounted for by increased lipid availability (Burns et al., 2021). It is thought that the reduction in muscle contraction per se drives the cellular and molecular changes described however the specific mechanistic basis remains poorly understood.

Despite the apparent evidence of detrimental effects on muscle and metabolic health occurring secondary to ageing, we are not aware of any studies that have measured baseline levels of habitual physical activity in a precise quantifiable manner in volunteers and used these data to match study volunteers for habitual physical activity levels. Indeed, in studies where older individuals recruited have been highly physically active, age related muscle differences have been less apparent (Pollock et al., 2015). For example, in a cross-sectional study (Wroblewski et al., 2011) involving 40 high level master athletes aged 40–81 years, variation in muscle cross sectional area, lean mass and strength did not appear to be age related. Some have suggested the magnitude of adiposity in older adults predicts the decline in muscle mass and quality associated with poor metabolic health (Koster et al., 2011). This so called “sarcopenic obesity” has been questioned in studies demonstrating that obesity in older individuals is not associated with reduced in absolute lean tissue volume or strength (Murton et al., 2015), which the authors suggested was a logical outcome due to the increased contractile work performed by obese individuals in locomotor activities of daily living. Indeed, sarcopenic obesity may simply reflect that the relative increase in fat mass with obesity is greater than the relative increase in lean mass, but in absolute terms both increase.

4. Conclusion

Despite a large body of cross-sectional evidence detailing differences in muscle mass, muscle quality, body composition and insulin sensitivity associated with ageing, without accurate measurements of habitual physical activity levels it is difficult to conclude these differences are definitively due to ageing processes. Furthermore, in studies subjecting young healthy adults to inactivity and immobilisation, many of the muscle level responses attributed to ageing can be manifested. Current knowledge gaps therefore include the relative contribution that physical inactivity plays in the development of many of the features associated with poor muscle metabolic health in older age; including muscle centric mechanisms linking physical inactivity and/or sedentary time to impaired metabolic health. Similarly, data demonstrating positive
effects of government recommended physical activity guidelines (or indeed any other physical in/activity interventions relevant to preservation of health) on muscle specific health, the decline in which is strongly associated with functional deterioration in older adults, are largely missing. These are important knowledge gaps to address, as mitigation of some of the negative effects of secondary ageing due to inactivity or diet may be possible. Such an approach will also help identify the primary drivers of muscle ageing. Therefore, longitudinal intervention studies in humans to elucidate the contribution of both ageing and inactivity, and whether metabolic dysregulation with inactivity is additive to age and disease are warranted.

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Authors contributions

NFS and LC drafted the first draft of the manuscript. All authors revised subsequent drafts and approved the final version of the manuscript before submission.

Declaration of Competing Interest

The authors report no declarations of interest.

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