Ageing is accompanied by a progressive loss of skeletal muscle mass and strength, leading to the loss of functional capacity and an increased risk for developing chronic metabolic diseases such as diabetes. The age-related loss of skeletal muscle mass results from a chronic disruption in the balance between muscle protein synthesis and degradation. As basal muscle protein synthesis rates are likely not different between healthy young and elderly human subjects, it was proposed that muscles from older adults lack the ability to regulate the protein synthetic response to anabolic stimuli, such as food intake and physical activity. Indeed, the dose–response relationship between myofibrillar protein synthesis and the availability of essential amino acids and/or resistance exercise intensity is shifted down and to the right in elderly human subjects. This so-called ‘anabolic resistance’ represents a key factor responsible for the age-related decline in skeletal muscle mass. Interestingly, long-term resistance exercise training is effective as a therapeutic intervention to augment skeletal muscle mass, and improves functional performance in the elderly. The consumption of different types of proteins, i.e. protein hydrolysates, can have different stimulatory effects on muscle protein synthesis in the elderly, which may be due to their higher rate of digestion and absorption. Current research aims to elucidate the interactions between nutrition, exercise and the skeletal muscle adaptive response that will define more effective strategies to maximise the therapeutic benefits of lifestyle interventions in the elderly.

Sarcopenia: Nutrition: Exercise training: Muscle hypertrophy

Abbreviations: AA, amino acids; EAA, essential amino acids; mTOR, mammalian target of rapamycin; mTORCl, mTOR complex I; S6K1, S6 protein kinase.

Corresponding author: Dr René Koopman, fax +61 3 8344 5818, email rkoopman@unimelb.edu.au
It is therefore not surprising that the global ageing will have a major impact on our health-care system, as the number of frail elderly requiring hospitalisation and/or institutionalisation increases. Good health is essential for maintaining independence and to continue to actively enjoy family and community life. As such, lifelong health promotion is warranted to prevent or delay the onset of non-communicable and chronic (metabolic) diseases such as heart disease and stroke, cancer and diabetes. Preventing, attenuating and/or reversing the decline in skeletal muscle mass should be the main goal for interventional strategies to promote healthy ageing.

Ageing and protein turnover in skeletal muscle

The loss of skeletal muscle mass in the elderly is characterised by atrophy of type-II (fast) muscle fibres (Fig. 1(A)), fibre necrosis, fibre-type grouping and a reduction in satellite cell content in type-II muscle fibres. The loss of skeletal muscle mass is accompanied by the loss of muscle strength (Fig. 1(B)), a decline in functional capacity and a reduction in whole-body and muscle oxidative capacity. Together, these alterations at a muscle level have substantial health consequences, since they contribute to the greater risk of developing insulin resistance due to the reduced capacity for blood glucose disposal and a greater likelihood of excess lipid deposition in liver and skeletal muscle tissue leading to hyperlipidaemia, hypertension and cardiovascular co-morbidities.

The progressive muscle wasting with ageing must be due to a disruption in the regulation of skeletal muscle protein turnover, leading to a chronic imbalance between muscle protein synthesis and degradation. Although it was originally reported that healthy older adults had decreased rates of basal muscle protein synthesis, more recent studies have failed to reproduce these findings and generally show little or no differences in basal muscle protein synthesis rates between young and old adults. These discrepancies may be due to the standardisation of prior physical activity, selection of subjects or the selection of different precursor pools to calculate muscle protein synthesis. It seems unlikely that basal muscle protein fractional synthesis rates are diminished by 20–30% as reported previously and/or that muscle protein breakdown is elevated by as much as 50% in the elderly compared to younger adults. Such opposing alterations in the rates of protein synthesis and breakdown would be accompanied by more rapid muscle wasting than what is typically observed (3–8% per decade), and it therefore seems unlikely that basal muscle protein fractional synthesis rates could be diminished by 20–30% during ageing as reported previously. The relatively slow rate of muscle loss during ageing must mean that the mismatch between the average diurnal rate of muscle protein synthesis and breakdown is small. It is currently accepted that basal fasting protein synthesis and/or breakdown rates are not (substantially) different between young and elderly human subjects. To better understand the skeletal muscle wasting in the elderly, researchers have started to focus on the muscle anabolic response to anabolic stimuli such as physical activity, food intake and anabolic hormones such as insulin. It was well established that the protein turnover in skeletal muscle is highly responsive to exercise and nutrient intake in healthy young individuals. Interestingly, data from recent studies suggest that the muscle protein synthetic response to resistance exercise and following the ingestion of a small amount of amino acids (AA) with or without carbohydrate is reduced in the elderly when compared with young controls. The latter is believed to represent a key factor responsible for the age-related decline in skeletal muscle mass.

Anabolic response to exercise

Exercise is a powerful stimulus to promote net muscle protein anabolism, resulting in specific metabolic and morphological adaptations in skeletal muscle. Endurance training can increase whole-body and muscle oxidative capacity and endurance, whereas resistance exercise training can increase muscle mass and strength, and thus improve physical performance and functional capacity. It generally takes weeks to months before training-induced changes in skeletal muscle mass become apparent. The prolonged time course for hypertrophy is a reflection of the slow turnover rate of muscle proteins, i.e. about 1% per
day for contractile proteins. Although muscle hypertrophy occurs at a slow rate, a single bout of resistance exercise can rapidly (within 2–4 h) stimulate muscle protein synthesis, and increase protein synthesis rates, particularly the myofibrillar protein synthesis, which persist for up to 16 h in trained and 24–48 h in untrained individuals. Muscle protein breakdown is also stimulated following exercise, albeit to a lesser extent than protein synthesis, and results in an improved net muscle protein balance that persists for up to 48 h in untrained individuals.

It has been generally accepted that the increase in protein synthesis following exercise is due to increased mRNA translation. Many laboratories have shown that the signalling pathway involving a mammalian target of rapamycin (mTOR) complex I (mTORC1) plays a crucial role in the control of mRNA translation initiation and elongation. The activity of mTORC1 determines the activity of downstream effectors such as the 70-kDa S6 protein kinase (S6K1) and the eukaryotic initiation factor 4E-binding protein (4E-BP1). Both play key regulatory roles in modulating translation initiation, and control the binding of mRNA to the 40S ribosomal subunit. Studies have shown that the mTORC1 signalling pathway is activated following acute resistance exercise in healthy human subjects. Moreover, Drummond et al. showed elegantly that early acute contraction-induced increase in protein synthesis in human subjects can be blocked with rapamycin treatment indicating that mTORC1 signalling is crucial during the early post-exercise recovery. In addition, it was shown that the phosphorylation status of S6K1 following resistance exercise is a good marker for the long-term increase in skeletal muscle mass in rats and human subjects. Moreover, significant correlations were reported between S6K1 phosphorylation/activation and muscle protein synthesis following exercise in young healthy human subjects, highlighting the importance of this signalling pathway in the adaptive response to resistance exercise.

Ageing and the anabolic response to exercise

Muscle protein synthesis is responsive to resistance and endurance exercise in both young and elderly human subjects. Some studies have reported subtle differences in changes in gene expression and anabolic signalling, with early studies indicating that the protein synthetic response to resistance-type exercise did not differ considerably between the young and elderly. In contrast, an elegant study by Kumar et al. showed anabolic resistance of anabolic signalling (i.e. 4E-binding protein and S6K1) and muscle protein synthesis after resistance exercise (performed in the fasted state) in elderly men compared with young controls, which became apparent especially at higher exercise intensities. This study demonstrated that the sigmoidal response of muscle protein synthesis to resistance exercise of different (increasing) intensities was shifted downward in older men compared to younger men. Interestingly, this study shows that the linear relationship between S6K1 phosphorylation and muscle protein synthesis after resistance exercise, which is observed in young healthy adults, was not present in the elderly, indicating that anabolic signalling regulating mRNA translation is impaired in the older human subjects.

Compared to protein synthesis, not many studies have actually measured muscle protein breakdown using stable isotope tracers. Most studies rely on measurements of mRNA or protein expression of proteins involved in protein degradation such as Atrogin-1, MuRF-1, calpains and their regulators. It has been suggested that mRNA expression of proteolytic regulators, such as Atrogin-1, are elevated in muscles from old compared with young adults at rest and these levels increased even further in the elderly in response to resistance exercise. These findings from Raue et al. suggest that the regulation of ubiquitin proteasome-related genes involved in muscle atrophy might be altered in the elderly and protein breakdown may be increased in elderly human subjects. However, whether these changes in mRNA expression translate to actual changes in protein expression and altered proteasome activity has yet to be established. Thus, there is a paucity of data regarding the measurement of muscle protein breakdown in response to exercise in the elderly and it is clear that further research is needed to assess the impact of exercise and specific exercise modalities on post-exercise muscle protein synthesis and breakdown rates and associated myocellular signalling in young and elderly human subjects.

Anabolic response to food intake

Protein turnover in skeletal muscle is highly responsive to nutrient intake. Ingestion of AA and/or protein strongly stimulates muscle protein synthesis. Besides serving as a substrate for polypeptide biosynthesis, AA were shown to directly activate regulatory proteins in mRNA translation, while non-essential AA do not induce a substantial increase in muscle protein synthesis. In contrast, essential amino acids (EAA) increase muscle protein synthesis in the absence of increased non-essential AA availability. The branched-chain amino acid, leucine, is of particular interest since it has the unique ability to directly increase signalling through mTOR and its downstream targets 4E-binding protein and S6K1 and ribosomal S6. The EAA and leucine in particular seem to represent the main anabolic signals responsible for the post-prandial increase in muscle protein synthesis. The observations that EAA show a dose-dependent stimulation of muscle protein synthesis without increasing plasma insulin, and that carbohydrate ingestion does not affect protein synthesis, suggest that insulin is rather permissive instead of modulatory. Greenhaff et al. showed that insulin in the range of 30–150 μU/ml does not further stimulate muscle protein synthesis. In contrast to protein synthesis, muscle protein degradation seems to be very responsive to relatively small changes in insulin concentrations. Insulin levels of 15 μU/ml can almost maximally reduce muscle protein breakdown and there seems to be no further inhibition above 30 μU/ml. These data suggest that protein breakdown can be already maximally reduced by slightly increased insulin concentrations which can be achieved by the intake of a small breakfast in healthy young men.
Ageing and the anabolic response to food intake

Data from recent studies suggest that the muscle protein synthetic response to the ingestion of a small amount of EAA is attenuated in the elderly, and is now believed to represent one of the key factors responsible for the age-related decline in skeletal muscle mass. The so-called "anabolic resistance" in elderly human subjects was demonstrated by a rightward and downward shift of the dose–response relationship between myofibrillar protein synthesis and the availability of leucine in the plasma. Cuthbertson et al. showed that even a very large (40 g) dose of EAA is not able to bring the curve back to values for young subjects, suggesting that supplementation with extra protein, EAA or leucine will not be sufficient to restore the rate of muscle protein synthesis in older adults, relative to those found in the young.

The mechanisms responsible for the proposed anabolic resistance to protein and/or AA administration in the elderly are yet to be elucidated fully. Cuthbertson et al. reported decrements in amounts of signalling protein in the protein kinase B/mTORC1 pathway in old muscle and showed an attenuated rise in the activation of key signalling proteins in this pathway after ingesting 10 g EAA in the elderly compared to the young. These findings seem to be consistent with previous observations by Guillet et al., who showed reduced S6K1 phosphorylation following combined AA and glucose infusions in the elderly. Combined, these data suggest that anabolic signalling is impaired in skeletal muscles of older compared to younger adults, which may be in part due to insulin resistance in the elderly. Recent data suggest that muscle protein breakdown is not strongly inhibited by insulin in the elderly, whereas other reports suggested that muscle protein synthesis is resistant to the anabolic action of insulin in the elderly. It has been proposed that the anabolic resistance can be attributed to a less responsive impact of physiological hyperinsulinemia on the increase in skeletal muscle blood flow and subsequent AA availability in aged muscle, which would agree with the reduced activation of the phosphatidylinositol-3 kinase–protein kinase B–mTOR signalling pathway and with the lesser increase in the muscle protein synthetic rate after AA/protein ingestion in the elderly.

Another mechanism that has been suggested to contribute to the anabolic resistance to food intake in elderly men is an impairment in dietary protein digestion and/or absorption. Recent data show that the digestion rate of protein is an independent regulating factor of post-prandial protein anabolism. As such, it seems plausible to assume that any impairment in protein digestion and/or absorption will reduce the appearance rate of dietary AA in the bloodstream, thereby reducing AA delivery to the muscle and subsequently attenuating the muscle protein synthetic response. To accurately assess the appearance rate of AA derived from dietary protein, the labelled AA need to be incorporated in the dietary protein source. As free AA and protein-derived AA exhibit a different timing and efficiency of intestinal absorption, simply adding labelled free AA to a drink containing protein does not provide an accurate measure of the digestion and absorption kinetics of the ingested dietary protein. These methodological restrictions represent the main reasons why only a few researchers have investigated the differences in digestion and absorption kinetics of specific dietary protein sources and the disparity in anabolic response between young and elderly human subjects. These studies have suggested that AA utilisation in the splanchnic area is elevated in the elderly, which would imply that less of the ingested AA are available for muscle protein synthesis. We have recently repeated similar experiments, comparing the appearance rate of dietary L-[1-13C]-phenylalanine in the circulation following the intake of 35 g intact intrinsically labelled casein protein. Our data clearly show that splanchnic extraction is not altered significantly in elderly men, and that over a 3 and 6 h period the same amount of dietary phenylalanine appears in the circulation. Although we did not observe any impairment in digestion and absorption in the elderly, we observed substantially (about 12%) lower rates of whole-body protein synthesis and phenylalanine hydroxylation following protein ingestion in the elderly men compared to the young men (Fig. 2), calculated over the first 3 h, subsequent 3 h or total 6 h time period after protein ingestion. Consistent with these observations, we observed a 14% difference in muscle protein synthesis rates between young and elderly men over the 6 h period, although this difference did not reach statistical significance. Not all researchers have found impaired muscle protein synthetic response to protein intake in the elderly as similar protein synthetic rates were observed in young and elderly human subjects after ingestion of large amounts of carbohydrate and proteins, and following ingestion of large and small amount of beef. Discrepancies may arise from differences in timing of biopsy collection, the precursor...
pool used to calculate muscle protein synthesis or the age of the elderly volunteers studied. Clearly, more research is warranted to determine the extent of an anabolic resistance to food (i.e. intact protein) intake that exists in elderly human subjects.

Early work from the laboratory of Yves Boirie\(^{(82-84,92)}\) showed that ingestion of a slowly digested protein (casein) led to a more positive whole-body protein balance (averaged over a 7 h period) when compared with the ingestion of a fast digestible protein (whey) or a mixture of free AA in healthy, young subjects\(^{(83)}\). In contrast, ingestion of a fast protein resulted in greater (whole-body) net protein retention compared to a slow protein when provided to healthy, older men\(^{(82,84,92)}\). The latter response might be attributed to the reported anabolic resistance of the muscle protein synthetic machinery to become activated in the elderly. In accordance with the fast vs. slow protein concept, we tested the hypothesis that the ingestion of a casein protein hydrolysate, i.e. enzymatically pre-digested casein, would enhance protein digestion and the absorption rate in elderly men\(^{(93)}\). We expected that this enhanced AA uptake in the gut would result in a greater increase in plasma AA availability and might improve the post-prandial muscle protein synthetic response. Elderly men ingested 35 g intrinsically L-[1-\(^{13}\)C]phenylalanine labelled casein or casein hydrolysate and we assessed the appearance rate of dietary phenylalanine in the circulation and the subsequent muscle protein synthetic response. The ingestion of casein hydrolysate accelerated the appearance rate of dietary phenylalanine in the circulation, lowered splanchnic phenylalanine extraction, increased post-prandial plasma AA availability and tended to augment the subsequent muscle protein synthetic response \textit{in vivo} in human subjects, compared to the ingestion of intact casein\(^{(93)}\). The difference in the appearance rate of dietary protein between intact and hydrolysed casein was particularly evident in the first 3 h after the protein ingestion, with about 50\% more dietary phenylalanine appearing in the circulation after ingestion of the casein hydrolysate\(^{(95)}\). Consistent with these findings, it was reported that protein pulse feeding (providing up to 80\% of daily protein intake in one meal) leads to greater protein retention than ingesting the same amount of protein provided over four meals throughout the day (spread-feeding) in elderly women\(^{(94,95)}\). These findings may indicate that part of the proposed anabolic resistance in the elderly might be compensated for, in part, by enhancing AA availability during the post-prandial period.

\textit{Ageing and the anabolic response to combined exercise and nutrition}

We have shown previously that muscle protein synthesis rates are lower in the elderly (about 75 year) compared to young controls under conditions in which resistance-type exercise is followed by food intake\(^{(96)}\). However, combined ingestion of carbohydrate and protein during recovery from physical activity resulted in similar increases in mixed muscle protein synthesis rates, measured over a 6-h period, in young and elderly men\(^{(96)}\). Consistent with our findings, Drummond \textit{et al.}\(^{(67)}\) reported similar post-exercise muscle protein synthesis rates over a 5-h recovery period in young \textit{v.} elderly subjects following the ingestion of carbohydrate with an EAA mixture. However, their data indicated that the anabolic response to exercise and food intake was delayed in the elderly. During the first 3 h of post-exercise recovery, the young subjects showed a substantial increase in the muscle protein synthesis rate, which was not observed in the elderly. The delayed activation of muscle protein synthesis in the elderly may be attributed to a more pronounced activation of AMP-activated protein kinase and/or reduced extracellular-signal-regulated kinases 1/2 activation during exercise, which seems to be consistent with an attenuated rise in 4E-binding protein phosphorylation following resistance-type exercise in older adults\(^{(59)}\). These data highlight the importance of measuring muscle protein synthesis over different time periods (0–3 h and 3–6 h) following exercise and/or food intake to gain more information about impairments in activation of protein synthesis in the elderly. The mechanisms responsible for the delayed intracellular activation of the mTOR pathway in skeletal muscle remain unclear, but might include differences in muscle recruitment, muscle fibre-type composition, the capacity and/or sensitivity of the muscle protein synthetic machinery, the presence of an inflammatory state and/or the impact of stress on the cellular energy status of the cell between young and older adults.

\textit{Long-term interventions}

The clinical relevance of nutritional and/or exercise intervention in the elderly stems from the long-term impact on skeletal muscle mass and strength, and the implications for functional capacity. In accordance with the previously discussed findings, the muscle protein synthetic machinery is able to respond to anabolic stimuli, albeit maybe to a lesser extent\(^{(46)}\), until very old age\(^{(97,98)}\). Although it was suggested previously that elderly human subjects need more protein\(^{(99)}\), more recent studies by Campbell \textit{et al.}\(^{(100)}\), who performed very comprehensive nitrogen balance experiments, clearly showed that dietary protein requirements did not increase with age, and that a dietary protein allowance of 0.85 g/kg per day is adequate. Some researchers believe that the attenuated muscle protein synthetic response to food intake in the elderly can, at least partly, be compensated for by increasing the leucine content of a meal\(^{(34,101)}\). However, we have shown previously that additional leucine intake does not further increase muscle protein synthesis after exercise when ample protein is ingested by elderly men\(^{(102)}\). In addition, we investigated the effect of 3 months of leucine supplementation with main each meal (7.5 g/d) on skeletal muscle mass and strength and on glycemic control in healthy elderly men\(^{(103)}\). Consistent with our observations from our acute post-exercise study, we did not observe any effect of leucine supplementation on skeletal muscle mass and strength. In addition, no improvements in indices of whole-body insulin sensitivity blood-glycated Hb content, or the plasma lipid profile were observed. We concluded that long-term leucine supplementation (7.5 g/d) does not augment skeletal muscle mass or strength and does not improve glycaemic control or the blood lipid profile in healthy elderly men.
Resistance exercise training interventions were shown effective in augmenting skeletal muscle mass, increasing muscle strength and/or improving functional capacity in the elderly. Exercise was shown to enhance the skeletal muscle oxidative capacity, resulting in greater endurance capacity. Although the muscle regenerative capacity seems to decline at a more advanced age, the reduced satellite cell pool size does not compromise the capacity for muscle hypertrophy to occur even at an advanced age. Resistance exercise training was shown to increase muscle fibre size. Recently, Verdijk et al. assessed the effects of 12 weeks of leg resistance exercise training on fibre-type specific hypertrophy and satellite cell content in healthy, elderly men. Prolonged training resulted in a 28% increase in the size of type-II muscle fibres and a concomitant 76% increase in type-II muscle fibre satellite cell content in elderly males. The apparent differences in fibre size and/or satellite cell content between type-I and type-II muscle fibres prior to intervention were no longer evident after 12 weeks of training. Overall, these findings suggest that satellite cells are instrumental in the generation of new myonuclei to facilitate muscle fibre hypertrophy.

Protein/AA ingestion before, during and/or after exercise acutely stimulates muscle protein synthesis and reduces muscle protein breakdown to facilitate muscle fibre hypertrophy. Remarkably, little evidence exists that dietary interventions can further augment the adaptive response to prolonged exercise training in the elderly. The proposed importance of ample dietary protein intake in the long-term adaptive response to resistance training in the elderly has been a topic of intense debate. Some researchers suggest that the current RDA for habitual protein intake of 0.8 g/kg per day is marginal to allow lean mass accretion following resistance exercise training or even insufficient for long-term maintenance of skeletal muscle mass in sedentary elderly human subjects. However, others have shown that when habitual dietary protein intake is standardised at 0.9 g/kg per day, exercise-induced increases in muscle mass become apparent and further increases in protein intake does not provide any additional effect. In addition, data from Walrand et al. indicated that although increased protein intake in the elderly further improved nitrogen balance (by increasing AA oxidation), no beneficial effects on muscle protein synthesis and muscle function were observed. These observations might explain why most studies fail to observe any additional benefit of nutritional co-intervention on the skeletal muscle adaptive response to prolonged resistance exercise training in the elderly. However, it has been suggested that it is not the total protein amount per se, but the timing of protein intake that is crucial for its stimulatory effect on muscle protein synthesis and muscle fibre hypertrophy. Esmarck et al. concluded that the intake of a protein supplement immediately after each bout of resistance-type exercise was required for skeletal muscle hypertrophy to occur with a 12-week intervention in the elderly. Although the absence of any hypertrophy in the control group seems to conflict with previous studies that show muscle hypertrophy following resistance training without any dietary intervention, the proposed importance of nutrient timing is supported by recent studies investigating the impact of AA or protein co-ingestion prior to, during and/or after exercise on the acute muscle protein synthetic response. Verdijk et al. compared increases in skeletal muscle mass and strength following 3 months of resistance exercise training with or without protein ingestion prior to and immediately after each exercise session in elderly males. Timed protein supplementation prior to and after each exercise bout did not further increase skeletal muscle hypertrophy in healthy, elderly men who habitually consumed about 1-0 g protein/kg per day. Taken together, the available data suggest that sufficient habitual protein intake (about 0.9 g/kg per day) combined with a normal meal pattern (i.e. providing ample protein three times daily) will allow for substantial gains in muscle mass and strength with resistance exercise training in the elderly. Additional protein supplementation does not seem to provide large surplus benefits to the exercise intervention in healthy, elderly males. Additional protein intake may reduce subsequent voluntary food consumption in the elderly and consequently some have suggested that supplementation with EAA would be more efficient. Clearly, acute studies have shown benefits of timed supplementation with small (7–15 g) amounts of EAA on muscle protein synthesis. However, well-designed, double-blind, placebo-controlled long-term studies to investigate beneficial and adverse effects of long-term EAA supplementation in the elderly are yet to be performed.

Conclusions

The loss of skeletal muscle mass with ageing is associated with reduced muscle strength, the loss of functional capacity and an increased risk for developing chronic metabolic disease. The progressive loss of skeletal muscle mass does not appear to be attributed to age-related changes in basal muscle protein synthesis and/or rates of protein breakdown. Recent studies suggest that the muscle protein synthetic response to the main anabolic stimuli, i.e. food intake and/or physical activity, is blunted in the elderly. Despite this potential anabolic resistance to food intake and/or physical activity, resistance exercise training can stimulate net muscle protein accretion significantly. Prolonged resistance exercise training has proved to be an effective intervention for attenuating and/or treating the loss of muscle mass and strength in the elderly. Further research is warranted to provide insight into the interactions between nutrition, exercise and skeletal muscle adaptations in order to define more effective nutritional, exercise and/or pharmaceutical interventional strategies to prevent and/or treat sarcopenia.

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