

**HIGHLIGHTED TOPIC** | *Regulation of Protein Metabolism in Exercise and Recovery*

## Aging, exercise, and muscle protein metabolism

**René Koopman<sup>1,2</sup> and Luc J. C. van Loon<sup>1</sup>**<sup>1</sup>*Department of Human Movement Sciences, Nutrition, and Toxicology Research Institute Maastricht, Maastricht University, Maastricht, The Netherlands; and* <sup>2</sup>*Basic and Clinical Myology Laboratory, Department of Physiology, The University of Melbourne, Melbourne, Victoria, Australia*

**Koopman R, van Loon LJ.** Aging, exercise, and muscle protein metabolism. *J Appl Physiol* 106: 2040–2048, 2009. First published January 8, 2009; doi:10.1152/jappphysiol.91551.2008.—Aging is accompanied by a progressive loss of skeletal muscle mass and strength, leading to the loss of functional capacity and an increased risk of developing chronic metabolic disease. The age-related loss of skeletal muscle mass is attributed to a disruption in the regulation of skeletal muscle protein turnover, resulting in an imbalance between muscle protein synthesis and degradation. As basal (fasting) muscle protein synthesis rates do not seem to differ substantially between the young and elderly, many research groups have started to focus on the muscle protein synthetic response to the main anabolic stimuli, i.e., food intake and physical activity. Recent studies suggest that the muscle protein synthetic response to food intake is blunted in the elderly. The latter is now believed to represent a key factor responsible for the age-related decline in skeletal muscle mass. Physical activity and/or exercise stimulate postexercise muscle protein accretion in both the young and elderly. However, the latter largely depends on the timed administration of amino acids and/or protein before, during, and/or after exercise. Prolonged resistance type exercise training represents an effective therapeutic strategy to augment skeletal muscle mass and improve functional performance in the elderly. The latter shows that the ability of the muscle protein synthetic machinery to respond to anabolic stimuli is preserved up to very old age. Research is warranted to elucidate the interaction between nutrition, exercise, and the skeletal muscle adaptive response. The latter is needed to define more effective strategies that will maximize the therapeutic benefits of lifestyle intervention in the elderly.

sarcopenia; nutrition; exercise training; muscle hypertrophy

AT PRESENT, MANY DISCUSSIONS focus on the public health implications of global aging. The latter should not be a surprise, as demographics show that the world's population aged 60 yr and over will triple within 50 yr, from 600 million in the year 2000 to more than 2 billion by 2050. Two-thirds of the elderly people are presently living in the developed world, and this will continue to rise up to 75%. Due to greater longevity, the subpopulation of elderly people aged 80 yr and over is presently the fastest growing subpopulation in the developed world (130). This global aging will have a major impact on our healthcare system due to increased morbidity and greater need for hospitalization and/or institutionalization. Good health is essential for older people to remain independent and to continue to actively take part in family and community life. Life-long health promotion is warranted to prevent or delay the onset of noncommunicable and chronic metabolic diseases, like heart disease, stroke, cancer, and diabetes.

One of the factors that plays an important role in the loss of functional performance and, as such, the capacity to maintain

a healthy, active lifestyle is the progressive loss of skeletal muscle mass with aging, or sarcopenia (7, 42, 85) (see Fig. 1). Lean muscle mass generally contributes up to ~50% of total body weight in young adults but declines with aging to 25% when reaching an age of 75–80 yr (108, 109). The loss of muscle mass is typically offset by gains in fat mass. The loss of muscle mass is most notable in the lower limb muscle groups, with the cross-sectional area of the vastus lateralis being reduced by as much as 40% between the age of 20 and 80 yr (79). On a muscle fiber level, sarcopenia is characterized by specific type II muscle fiber atrophy, fiber necrosis, fiber-type grouping, and a reduction in type II muscle fiber satellite cell content (62, 76, 78, 79, 81, 82, 117, 119). The loss of skeletal muscle mass is accompanied by the loss of muscle strength, a decline in functional capacity (6, 21, 45, 75, 77, 83, 94, 134), and a reduction in whole body and skeletal muscle oxidative capacity (89, 90, 108). The absolute decline in muscle mass and muscle oxidative capacity, in combination with a greater fat mass, contributes to the greater risk of developing insulin resistance and/or type 2 diabetes due to the reduced capacity for blood glucose disposal and a greater likelihood of excess lipid deposition in liver and skeletal muscle tissue. The latter will also lead to hyperlipidemia,

Address for reprint requests and other correspondence: L. J. C. van Loon, Dept. of Human Movement Sciences, Maastricht Univ., PO Box 616, 6200 MD Maastricht, The Netherlands (e-mail: L.vanLoon@HB.unimaas.nl).

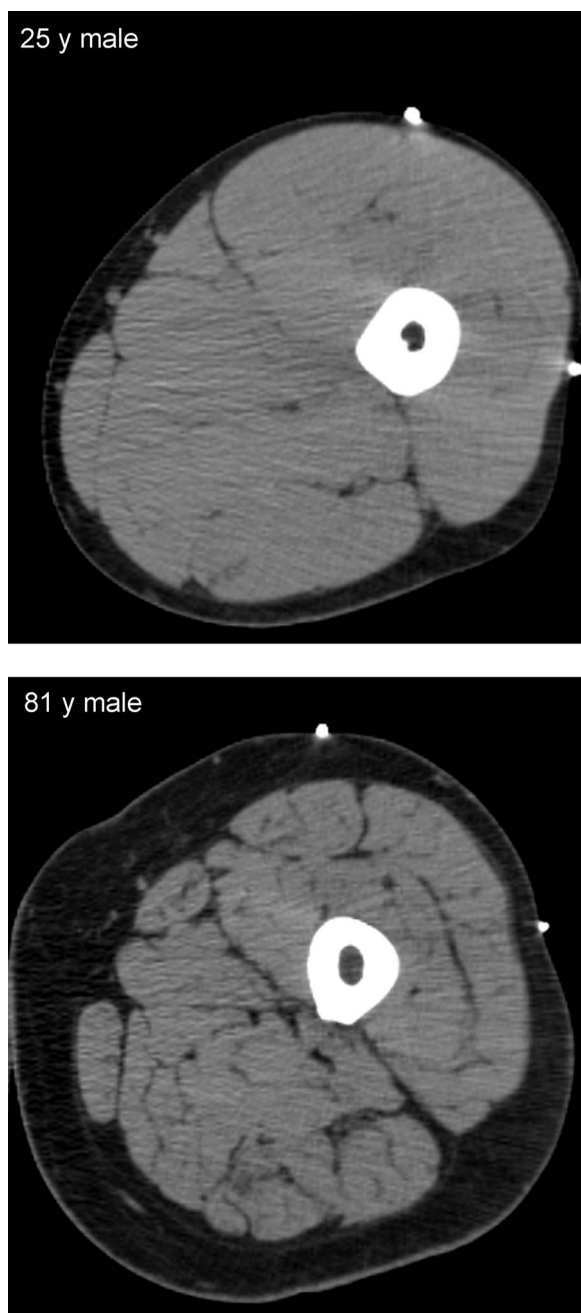


Fig. 1. Computed tomography (CT) scan of the upper leg (midhigh level) in a young and old subject, matched for body mass and height. Note the reduced muscle area, increased subcutaneous fat, and increased fat and connective tissue infiltration into the muscle in the elderly subject.

hypertension, and cardiovascular comorbidities. Therefore, it is evident that preventing, attenuating, and/or reversing the decline in skeletal muscle mass should form a main target in interventional strategies to promote healthy aging.

#### MUSCLE PROTEIN METABOLISM IN THE ELDERLY

The age-related loss of skeletal muscle mass is facilitated by a combination of factors, which include a less than optimal diet (23, 25, 27) and a sedentary lifestyle (89). The decline in muscle tissue with aging must be attributed to a disruption in

the regulation of skeletal muscle protein turnover, leading to a structural imbalance between muscle protein synthesis and degradation. In an attempt to unravel the proposed impairments in muscle protein metabolism in the elderly, many research groups first assessed basal muscle protein synthesis and/or protein breakdown rates in both young and elderly subjects (4, 29, 58, 63, 64, 93, 105, 109, 124–128, 135, 136). Some groups observed substantially lower basal mixed, myofibrillar, and/or mitochondrial muscle protein synthesis rates in the elderly vs. the young (4, 58, 105, 109, 127, 128, 135, 136). However, more recent studies have failed to reproduce these findings and generally show little or no differences in basal muscle protein synthesis rates between the young and old (29, 63, 64, 93, 124–126). The apparent discrepancy in the reported basal muscle protein synthesis rates in the young vs. the elderly might, at least partly, be attributed to differences in health status, habitual physical activity, and/or dietary habits between the selected young and elderly subjects. Furthermore, it should be noted that the assessment of fractional muscle protein synthetic rate *in vivo* in humans has its methodological limitations. The sensitivity of the measurement and large intersubject variance in basal muscle protein synthesis rates limit the ability to detect small, but physiologically relevant differences between groups. In contrast, a 30–40% lower basal protein synthesis rate, as observed previously in the elderly (4, 58, 105, 109, 127, 128, 135, 136), is unlikely representative of a normal physiological condition. Without a similar, concomitant decline in muscle protein breakdown rate, such protein synthesis rates would be accompanied by rapid muscle wasting. Therefore, the hypothesis that basal fasting protein synthesis and/or breakdown rates are not (substantially) impaired with aging generally receives more support (126). Nonetheless, it should be noted that even minor differences in basal muscle protein synthesis and/or breakdown rate (<10%) would be clinically relevant when calculating their impact over one or more decades before sarcopenia becomes evident. Therefore, more sensitive methods should be developed to assess both basal muscle protein synthesis and breakdown rates *in vivo* in humans. In particular, more work is needed to develop valid methods to assess muscle protein breakdown rates in various settings. Due to methodological limitations, the regulation of muscle protein breakdown, as opposed to protein synthesis, has received relatively little attention. Nonetheless, as basal (fasting) muscle protein synthesis rates do not seem to differ substantially between the young and elderly, many research groups have since refocused on the proposed disturbances in the muscle protein synthetic response to the main anabolic stimuli, *i.e.*, food intake and physical activity.

#### FOOD INTAKE AND MUSCLE PROTEIN METABOLISM

It has been well established that protein turnover in skeletal muscle tissue is highly responsive to nutrient intake (102). Ingestion of amino acids and/or protein strongly stimulates muscle protein synthesis and inhibits protein breakdown, resulting in a positive net protein balance in both the young and elderly (92, 93, 102, 121, 125). Interestingly, data from recent studies suggest that the muscle protein synthetic response to the ingestion of smaller, meal-like amounts of amino acids (29, 64) is attenuated in the elderly compared with young controls.

The latter is now believed to represent one of the key factors responsible for the age-related decline in skeletal muscle mass.

The mechanisms that might be responsible for the proposed anabolic resistance to protein and/or amino acid administration in the elderly remain to be elucidated. In addition, it is unclear whether the blunted muscle protein synthetic response to food intake is also accompanied by an attenuated postprandial decline in muscle protein breakdown in the elderly (56). Cuthbertson et al. (29) reported that signaling protein concentrations differ between old and young muscle and showed an attenuated rise in the activation of key signaling proteins in the mammalian target of rapamycin (mTOR) pathway after ingesting 10-g essential amino acids (EAAs) in the elderly vs. the young. These findings seem to be in line with previous observations by Guillet et al. (55) and suggest that an anabolic signal might not be sensed and/or transduced as well in muscle tissue of elderly compared with younger subjects (13, 29). The EAAs (114, 122), and leucine in particular (91, 111), seem to represent the main anabolic signal responsible for the postprandial increase in muscle protein synthesis. In accordance, recent studies demonstrate 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 (63, 103). Leucine has been shown to stimulate net protein accretion via insulin-dependent as well as -independent pathways. There is still considerable controversy regarding the proposed role of insulin in regulating the postprandial muscle protein anabolic response (29, 51, 56, 95, 98, 123, 124). Some propose that insulin is rather permissive instead of modulatory, and that plasma insulin levels of  $\sim 10\text{--}15\ \mu\text{U/ml}$  are sufficient to allow a maximal muscle protein synthetic response (13, 29). However, evidence has been provided suggesting that muscle protein synthesis is resistant to the anabolic action of insulin in the elderly (98, 124). The latter seems to be attributed to a less responsive impact of physiological hyperinsulinemia on the increase in skeletal muscle blood flow and subsequent amino acid availability in aged muscle (50, 98). The latter would also agree with a reduced activation of the mTOR signaling pathway and with the lesser increase in the muscle protein synthetic rate following amino acid/protein ingestion in the elderly (29).

Furthermore, the presence of impairments in dietary protein digestion and/or amino acid absorption might also be (partly) responsible for a blunted muscle protein synthetic response to amino acid/protein ingestion in the elderly (16). It has been proposed that the digestion rate of protein is an independent regulating factor of postprandial protein anabolism (30). Impaired protein digestion and/or absorption might attenuate and/or reduce the appearance rate of dietary amino acids in the circulation, thereby lowering the postprandial muscle protein synthetic rate. Furthermore, amino acid uptake in the splanchnic area has been shown to be elevated in the elderly (16, 125), which implies that less of the ingested amino acids are available for muscle protein synthesis (14). Evidence to support the existence of differences in digestion and absorption kinetics and the subsequent muscle protein synthetic response to dietary protein intake between young and elderly humans remains lacking. The latter is largely due to the restrictions set by the methodology that has been used to assess the appearance rate of amino acids from the gut into the circulation. As free amino acids and protein-derived amino acids exhibit a different timing and efficiency of intestinal absorption (17), simply adding

labeled free amino acids to a protein-containing drink does not provide an accurate measure of the digestion and absorption kinetics of the ingested dietary protein (15). To accurately assess the appearance rate of amino acids derived from dietary protein, the labeled amino acids need to be incorporated in the dietary protein source (8, 17, 31). A series of studies that have applied, specifically produced, intrinsically labeled protein have been instrumental in the development of the fast vs. slow protein concept (8, 14, 30–32). These studies show that ingestion of a slowly digested protein (casein) leads to a more positive protein balance compared with the ingestion of a fast digestible protein (whey) or a mixture of free amino acids in healthy, young subjects (30). However, in the elderly, the postprandial protein anabolic response turned out to be the opposite. Ingestion of a fast protein (whey) was shown to result in greater net protein retention compared with a slow protein (casein) when provided in healthy, elderly men (8, 14, 31, 32). The latter might be attributed to the proposed anabolic resistance of the muscle protein synthetic machinery to become activated in elderly muscle. In accordance, it has been 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 (2, 3). In agreement, pulse feeding did not lead to greater protein retention than spread feeding when applied in young females (2).

All of these findings agree with the concept that the postprandial muscle protein synthetic response is set off by a specific nutritional signal, most likely the postprandial rise in plasma availability of one or more specific EAAs and/or the concomitant insulin response, allowing the amino acids to reach the extracellular matrix of the target tissue, and that the sensitivity and/or capacity of this signaling process is impaired with aging. Much effort is presently being directed toward the discovery of such an extracellular amino acid sensing mechanism in skeletal muscle tissue. The latter will further our understanding of the proposed impact of the anabolic response to food intake in the etiology of sarcopenia.

#### EXERCISE AND MUSCLE PROTEIN METABOLISM

Physical activity, in particular resistance-type exercise, is a powerful stimulus to promote net muscle protein anabolism, resulting in specific metabolic and morphological adaptations in skeletal muscle tissue. Resistance-type exercise training can effectively increase muscle strength, muscle mass and, as such, improve physical performance and functional capacity (37). Following a single bout of resistance-type exercise, muscle IGF-I gene expression is temporally increased (28), whereas myostatin expression is reduced (89). As a result, mRNA translation is enhanced (104), and DNA transcription is increased, via activation of transcription factors like MyoD and myogenin (133) (see Fig. 2).

A single bout of resistance-type exercise accelerates muscle protein synthesis rates within 2–4 h (96). Increased protein synthesis rates have been reported to persist for up to 16 h in trained (112) and 24–48 h in untrained individuals (28, 96, 112) following a single bout of exercise. The increase in mixed muscle protein synthesis rates following resistance-type exercise is largely attributed to an increase in myofibrillar protein synthesis (127, 131, 136). Interestingly, muscle protein break-

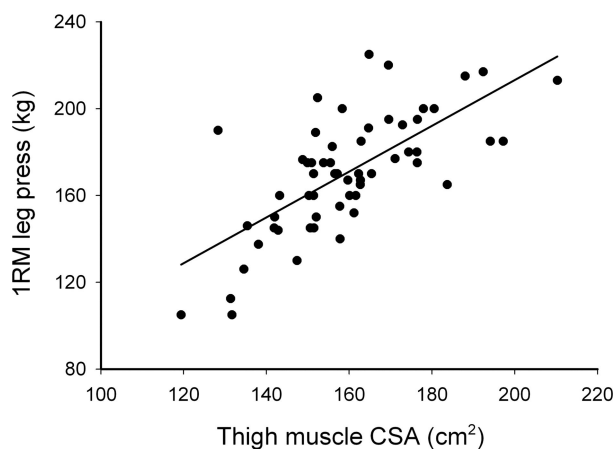


Fig. 2. Scatterplot of the correlation between total thigh muscle cross-sectional area (CSA) measured by CT scan and one-repetition maximum (1 RM) leg press strength. Data were measured in 60 elderly men, aged 65–86 yr.  $r = 0.70$ ;  $P < 0.001$  (Verdijk LB, Beelen M, Snijders T, Kuipers H, van Loon LJC, unpublished observations).

down is also stimulated following exercise, albeit to a lesser extent than protein synthesis (11, 96). The latter results in an improved net muscle protein balance that persists up to 48 h in untrained individuals (96). Although a single bout of resistance-type exercise stimulates muscle protein synthesis to a greater extent than protein degradation, net muscle protein balance remains negative in the absence of nutrient intake (96). Consequently, both exercise and nutrition are required to obtain a positive protein balance and, as such, allow muscle hypertrophy. Carbohydrate and protein/amino acid ingestion during recovery from exercise forms an effective strategy to stimulate muscle protein synthesis, inhibit protein degradation, and, as such, to enable net muscle protein accretion. Ingestion of carbohydrate during postexercise recovery has been shown to improve net leg amino acid balance (18), which has been attributed to the concomitant increase in circulating plasma insulin concentrations (106). In accordance, the elevation of plasma insulin levels has been shown to increase net muscle protein anabolism *in vivo* in humans (53, 60). However, insulin should not be regarded as a primary regulator of muscle protein synthesis, as insulin exerts only a modest effect on muscle protein synthesis in the absence of elevated amino acid concentrations (29). In rodent models, it has been reported that an increase in circulating plasma insulin concentrations does not further enhance mRNA translation initiation during postexercise recovery (38, 52, 65). In a recent attempt to assess whether carbohydrate coingestion is required to maximize postexercise muscle protein synthesis, we observed no surplus effect of carbohydrate coingestion on postexercise muscle protein synthesis under conditions in which ample protein is ingested (67). Although carbohydrate coingestion does not seem to be required to maximize postexercise muscle protein synthesis rates, it is likely that carbohydrate coingestion can further inhibit the postexercise increase in muscle protein breakdown (18), thereby improving net protein balance (18, 106).

There is a substantial amount of evidence showing that protein/amino acid administration effectively stimulates muscle protein synthesis. Hyperaminoacidemia, following intravenous amino acid infusion, increases postexercise muscle protein synthesis rates and prevents the exercise-induced increase

in protein degradation (12). In a more practical, physiological setting, oral administration of repeated boluses of a protein and/or amino acid mixture ingested following resistance-type exercise also substantially increases muscle protein synthesis rates (70, 72). Furthermore, ingestion of a large, single bolus of protein and/or amino acids (30–40 g) following exercise also effectively accelerates postexercise muscle protein synthesis rates (113). Moreover, ingestion of smaller amounts of EAAs or intact protein with and without carbohydrate have all been shown to augment postexercise protein synthesis rates and improve net protein balance (19, 33, 34, 87, 99, 112, 132). In short, it has been well established that postexercise amino acid/protein ingestion represents an effective strategy to augment the anabolic response to exercise.

It has been suggested that the timing of amino acid/protein intake is instrumental to further optimize the anabolic response to exercise (9, 36, 115). As a result, several research groups have studied the efficacy of protein/amino acid ingestion before and/or during exercise to further augment muscle protein synthesis. Recently, we reported that protein ingestion before and during endurance- (68) and resistance-type (9) exercise stimulates whole body (9, 68) and mixed muscle protein synthesis (9) during exercise. The latter is in agreement with the observation that protein intake before exercise augments activation of the mTOR pathway during subsequent postexercise recovery (69). Protein ingestion before and/or during exercise may further enhance muscle protein anabolism by blunting the exercise-induced increase in protein breakdown. Interestingly, a recent study by Fujita et al. (48) showed no additional benefits of the ingestion of small amounts of EAAs before resistance-type exercise on postexercise muscle protein synthesis rates, despite significantly elevated phosphorylation of S6 kinase 1 (S6K1) and 4E-binding protein 1 (4E-BP1). In addition, a recent study from our laboratory showed no effect of protein ingestion before, during, and after exercise on muscle protein synthesis measured during subsequent overnight recovery (10). The latter might be attributed to the fact that subjects were studied in the fed state, performing exercise in the evening after receiving a standardized diet throughout the day. Clearly, more research is warranted to assess the impact of timing of food intake on the skeletal muscle adaptive response to exercise.

As discussed previously, the increase in extracellular leucine concentration has been proposed to represent an important nutritional signal that drives the postprandial increase in muscle protein synthesis (66). Therefore, it has been suggested that ingestion of additional leucine during postexercise recovery could further accelerate postexercise muscle protein synthesis rates. Recently, Dreyer et al. (33) reported that ingestion of a leucine-enriched EAA and carbohydrate mixture following resistance-type exercise enhances mTOR signaling and muscle protein synthesis *in vivo* in humans. However, previous observations in our laboratory showed no surplus value of additional leucine supplementation in either young or old subjects when a substantial amount of protein was being ingested during postexercise recovery (70, 71).

#### AGING AND THE ANABOLIC RESPONSE TO EXERCISE

There is substantial evidence that muscle protein synthesis is responsive to exercise in both the young and elderly. In studies

performed in young and elderly individuals, resistance- and endurance-type exercise have been shown to stimulate mixed muscle protein synthesis (35, 49, 74, 107, 128, 136). Both young and elderly humans show a substantial increase in MyoD and myogenic regulatory factor 4 and a reduction in myostatin gene expression following exercise (100). Although some studies have reported subtle differences in changes in gene expression and anabolic signaling (57), early studies indicate that the protein synthetic response to resistance-type exercise does not differ considerably between the young and elderly (58, 136). In contrast, a more recent study shows anabolic resistance of anabolic signaling (i.e., 4E-BP1 and S6K1) and muscle protein synthesis to resistance-type exercise in elderly men compared with young controls, with measurements being performed in the postabsorptive state (74). In addition, it has recently been suggested that gene expression of proteolytic regulators, such as atrogen-1, are elevated in old compared with young muscle at rest, and gene expression increased even further in response to resistance-type exercise in the elderly (101). These findings suggest that the regulation of ubiquitin proteasome-related genes involved with muscle atrophy might be altered in the elderly. More work is needed to assess the impact of exercise and specific exercise modalities on postexercise muscle protein synthesis and breakdown rates and associated myocellular signaling in the young and elderly.

We have previously shown that muscle protein synthesis rates tend to be lower in elderly (~75 yr) compared with young controls under conditions in which resistance-type exercise is followed by food intake (70). However, combined ingestion of carbohydrate and protein during recovery from physical activity resulted in similar increases in mixed muscle protein synthesis rates in young and elderly men (70). In line with these findings, Drummond et al. (35) recently reported similar post-exercise muscle protein synthesis rates over a 5-h recovery period in young vs. elderly subjects following 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 postexercise recovery, the young subjects showed a substantial increase in muscle protein synthesis rate, which was not observed in the elderly. The latter may be attributed to a more pronounced activation of AMP-activated protein kinase and/or reduced extracellular regulated kinase 1/2 activation during exercise, which seems to be in line with the recently reported attenuated rise in 4E-BP1 phosphorylation following resistance-type exercise in the elderly (74). The mechanisms responsible for the delayed intramyocellular activation of the mTOR pathway remain unclear, but might include differences in muscle recruitment, muscle fiber-type composition, 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 the young and the elderly.

#### EXERCISE TRAINING IN THE ELDERLY

For obvious methodological considerations, studies investigating the mechanisms responsible for the muscle protein anabolic response to food intake and/or exercise generally focus on the acute skeletal muscle adaptive response. However, the clinical relevance of nutritional and/or exercise intervention

in the elderly naturally resides in the long-term impact on skeletal muscle mass and strength, and the implications for functional capacity and the risk of developing chronic metabolic disease. In accordance with the previously discussed work, it has been well established that the ability of the muscle protein synthetic machinery to respond to anabolic stimuli is preserved until very old age (40, 47). Resistance-type exercise interventions have been shown to be effective in augmenting skeletal muscle mass, increasing muscle strength, and/or improving functional capacity in the elderly (1, 5, 20, 39–41, 44, 46, 47, 54, 59, 61, 73, 80, 84, 117, 118, 120). In addition, endurance-type exercise activities have been shown to enhance skeletal muscle oxidative capacity, resulting in greater endurance capacity (109, 110).

Despite numerous studies addressing the need for protein and/or carbohydrate ingestion before, during, and/or after exercise to allow net muscle protein accretion, there is remarkably little evidence that dietary cointerventions can further augment the adaptive response to prolonged exercise training in the elderly. Even 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 (23, 25, 88). The current Recommended Dietary Allowance (RDA) for habitual protein intake of  $0.8 \text{ g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  (97, 116) has been suggested to be marginal to allow lean mass accretion following resistance exercise training in the elderly (26). Moreover, it has been suggested that the RDA is even insufficient for long-term maintenance of skeletal muscle mass in sedentary elderly (27). However, more recent work by the same group indicates that dietary protein requirements do not increase with age, and that a dietary protein allowance of  $0.85 \text{ g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$  is adequate (24).

In accordance, when habitual dietary protein intake is standardized at  $0.9 \text{ g}\cdot\text{kg}^{-1}\cdot\text{day}^{-1}$ , exercise-induced increases in muscle mass become apparent, and a further increase in protein intake does not seem to have any additional effect (61). The latter might explain why most studies fail to observe any additional benefit of nutritional cointervention on the skeletal muscle adaptive response to prolonged resistance-type exercise training in the elderly (22, 40, 41, 43, 47, 54, 59, 61, 86, 118, 129). However, the absence of any benefits of nutritional cointervention may well be attributed to a less than optimal timing of amino acid and/or protein supplementation that was applied in these studies. Esmarck et al. (36) concluded that an early intake of a protein-containing supplement immediately after each bout of resistance-type exercise, as opposed to 2 h later, is required for skeletal muscle hypertrophy to occur following 12 wk of intervention in the elderly. However, the absence of any hypertrophy in the control group receiving the same supplement 2 h after cessation of each exercise bout seems to be in conflict with previous studies that show muscle hypertrophy following resistance training without any dietary intervention. Nevertheless, the proposed importance of nutrient timing is supported by more recent studies investigating the impact of amino acid or protein coingestion before, during, and/or after exercise on the acute muscle protein synthetic response (9, 115). To study the proposed impact of timed protein supplementation during prolonged exercise intervention, we recently compared increases in skeletal muscle mass and strength following 3 mo of resistance-type exercise training, with or without protein ingestion before and immediately

after each exercise session in elderly men (118). However, timed protein supplementation before and after each exercise bout did not further increase skeletal muscle hypertrophy in these healthy, elderly men who habitually consumed  $\sim 1.0$  g protein $\cdot$ kg $^{-1}\cdot$ day $^{-1}$ .

Altogether, the available data suggest that sufficient habitual protein intake ( $\sim 0.9$  g $\cdot$ kg $^{-1}\cdot$ day $^{-1}$ ), combined with a normal meal pattern (i.e., providing ample protein 3 times per day), will allow substantial gains in muscle mass and strength following resistance-type exercise training in the elderly. Additional amino acid and/or protein supplementation does not seem to provide large surplus benefits to exercise intervention in healthy, elderly men. Clearly, acute studies showing benefits of timed protein supplementation provided in an overnight fasted state do not necessarily reflect long-term benefits of specific nutritional cointervention. The latter is indicative of the complexity of the skeletal muscle adaptive response to exercise and nutrition. Nutrient availability throughout day and night likely plays an important role in the differential response to acute vs. long-term exercise intervention. We speculate that potential benefits of (timed) protein supplementation in the elderly might be restricted to specific elderly subpopulations, e.g., malnourished or frail elderly, and various patient populations. More research is necessary to study the interaction between exercise and nutrition in the elderly and the implications for the acute and long-term adaptive response to intervention. So far, it is evident that the combination of resistance-type exercise training with or without postexercise protein administration represents a feasible and effective strategy to improve muscle mass, strength, and functional performance in the elderly.

## CONCLUSIONS

The loss of skeletal muscle mass with aging is associated with reduced muscle strength, the loss of functional capacity, and an increased risk of developing chronic metabolic disease. The progressive loss of skeletal muscle mass does not seem to be attributed to age-related changes in basal muscle protein synthesis and/or breakdown rates. Recent work suggests 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 proposed anabolic resistance to food intake and/or physical activity, resistance-type exercise substantially stimulates net muscle protein accretion when protein is ingested before, during, and/or following exercise in both the young and the elderly. In accordance, prolonged resistance-type exercise training has proven an effective interventional strategy to prevent and/or treat the loss of muscle mass and strength in the elderly. Research is warranted to provide more insight in the interaction between nutrition, exercise, and the skeletal muscle adaptive response. The latter is needed to define more effective nutritional, exercise, and/or pharmaceutical interventional strategies to prevent and/or treat sarcopenia.

## GRANTS

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