Aging is universally associated with a progressive decline in both physical and metabolic function across a diverse range of species from nematodes to humans. Moreover, progressive reductions in skeletal muscle mass, strength, and quality (referred to as sarcopenia) are often observed with aging. An associated problem is decline in maximal aerobic capacity, and all of these factors together contribute to the physical frailty of older people. In light of the rapidly expanding aging population, sarcopenia and related disorders are emerging as a major public health problem of the 21st century. This is particularly pertinent considering the loss of independence that is associated with frailty and falls that increase the risk of fractures. Another consequence of the sarcopenia of aging is a deleterious change in body composition resulting in many metabolic alterations leading on to metabolic syndrome and increased cardiovascular disease risk. Indeed, sarcopenia has received considerable attention by both researchers and clinicians over the last two decades. Muscle changes with age include reduction in fiber numbers, motor units, and a relative loss of type II fibers with a preservation of type I fibers (1) that may result from reductions in transcript levels of myosin heavy chain isoforms IIa and IIx without any decline of isoform I as reported in older people (2). Thus, a relative increase of type I fibers occurs with age, but these fibers are lower in abundance of mitochondria (3) than those in long-distance runners who also have a relatively high proportion of type I fibers but with high abundance of mitochondria. Reductions in skeletal muscle protein abundances (the balance between protein synthesis and degradation) are a key contributing factor to the development of sarcopenia. Mechanistically, it has been extensively reported that skeletal muscle protein synthesis is reduced in aging adults (2, 4, 5). The reduction in skeletal muscle mitochondrial protein synthesis (6) occurs in conjunction with reduced mitochondrial capacity for ATP production (3). Thankfully, skeletal muscle protein synthesis and reduced mitochondrial function are responsive to physiological interventions such as exercise training and dietary interventions (5, 7, 8). However, there remains a critical need for well-designed clinical investigations that examine the potential of various interventions designed to increase muscle protein synthesis to prevent and treat sarcopenia.

Extensive research efforts have been spent to determine whether replacement of many hormones that decline with age may mitigate sarcopenia. Therapies with GH (9), testosterone (10), and dehydroepiandrosterone (10) have been disappointing. Oral ingestion of essential amino acids (EAAs) stimulates muscle protein synthesis in the young (11–13) and elderly (11–13), and does not seem to impact muscle (limb) proteolysis, although EAAs, when given iv, reduce muscle proteolysis (14). Similar results for muscle protein synthesis have been attained during infusion of a commercially available amino acid (AA) mixture, and the effects were not exclusive to muscle, also including a stimulation of protein synthesis and inhibition of proteolysis within the splanchnic bed (15). AA intake can be most cost effectively achieved by increasing protein intake, but such studies demonstrated an increase in nitrogen balance without an improvement in muscle function (8). Another concern emerging from the aforementioned study (8) is that high-protein diets may deteriorate renal clearance rate in elderly people. Hence, it would be a great advantage if EAA could increase muscle mass and function without any adverse effect in elderly people. Nonetheless, considering that there would seemingly be a small, acute increment in total muscle protein during assimilation of an EAA supplement, it seems plausible that repeated ingestions would, over time, lead to a measurable increase in muscle size, and, therefore, performance.

In open-label studies, positive results for chronic EAA supplementation in the elderly were reported for increased lean body mass (LBM) (16), leg strength (16), handgrip strength (17), and walking performance (16, 17). Of note though, it is unclear whether the participants in the aforementioned studies had in...
increased their physical activity levels, which could have contributed to their positive outcomes. Supporting the results in the open-label studies, in a placebo-controlled study of chronic supplementation with EAA in the elderly, similar results were attained for improved handgrip strength and walking performance (18). Due to the limited number of placebo-controlled, double-blinded studies, it was not yet conclusively known if chronic EAA administration would improve LBM and muscle strength. Furthermore, it was not yet known if the ability of EAA to promote protein synthesis would wane over time, or if the effect would be sustained and, therefore, potentially lead to changes in muscle mass and strength over the course of chronic supplementation. In this issue of *The Journal of Clinical Endocrinology and Metabolism*, Dillon et al. (19) have reported results from a placebo-controlled, double-blinded study of EAA supplementation in the elderly. The main strength of this report is the controlled study design rather than use of an open-label format, and the authors carefully investigated the effects of chronic EAA supplementation upon muscle protein synthesis, LBM, and maximal strength.

The study by Dillon et al. (19) demonstrated that 3 months of EAA supplementation resulted in a small (4%) increase in LBM. A limitation of the study (19) is the use of changes in total LBM as a surrogate for changes in skeletal muscle mass; it is recognized that appendicular bone-free lean tissue has been endorsed as a valid estimation for appendicular skeletal muscle mass; however, the relationship between total LBM and total muscle mass is more tenuous. Second, LBM assessment by dual-energy x-ray absorptiometry scanning fails to differentiate between extracellular water and lean tissue, and aging individuals may have increased propensity for water retention (20). As such, the changes in LBM in response to 3 months of EAA may have been due to tissue fluid retention rather than an increase in skeletal muscle mass *per se*. Unfortunately, the authors decided only to report the changes in total lean tissue, which includes all lean tissue. Therefore, it is not possible to determine whether the increase in LBM was specifically localized to the skeletal muscle depot or to other lean tissue depots (*e.g.*, splanchnic tissue), though this could have been reasonably inferred if appendicular LBM was reported and shown to have increased. Finally, despite demonstrating a statistically significant increase in LBM, 3 months of EAA supplementation failed to increase skeletal muscle strength [one repetition maximum (1RM)]. The lack of an EAA effect upon 1RM could be due to inevitable experimental variability in the measurements but could also suggest that minimal muscle improvements occurred with EAA supplementation. There are other metabolic functions of muscle such as mitochondrial function that also decline with age. It is possible that aerobic exercise (that mostly stimulates metabolic functions) and resistance exercise (that enhances strength) may need to be combined with other general anabolic agents such as EAA to reveal any functional effects of the supplements.

Despite the issues we have raised, the results of this study are still encouraging and suggest that there is some promise for efficacy of chronic EAA supplementation. This is especially the case because the authors demonstrated a chronic effect upon muscle protein synthesis, which could be expected to favor muscle anabolism in the absence of an increased proteolysis rate. In addition, the measurement of mixed muscle protein synthesis leaves some uncertainty on whether EAA increased synthesis of all muscle proteins or some proteins that may have specific function or functions. Future studies of longer duration in a larger population are needed to conclude whether EAA supplementation in elderly individuals may prevent or reverse sarcopenia. Clinical trials are needed, testing different doses and formulations, to really hone in on the full potential (or lack thereof) of EAA supplementation. Such studies should also address potential adverse effects such as renal dysfunction, any increment of growth of dormant tumors, especially in the gut and liver, because AAs have been shown to have a profound anabolic effect in the splanchnic bed. It remains uncertain whether proteins such as clotting factors synthesized in liver also may be increased by the general anabolic effect of EAA. In addition, more assessments of performance are needed, such as maximal aerobic capacity in addition to 1RM measurements, because EAs may potentially increase the volume of skeletal muscle mitochondria in addition to their potential to increase the abundance of contractile proteins. As stated previously, although exogenous AA administration leads to increased protein synthesis in muscle, it also promotes protein synthesis and reduced proteolysis within the splanchnic bed (15). Hence, it is especially imperative to confirm that increases in LBM actually occur within skeletal muscles because the AAs may be anabolic in nonmuscle tissues, which may not be relevant to the issue of sarcopenia. Therefore, in subsequent studies it ought to be tested if appendicular LBM by dual-energy x-ray absorptiometry and/or appendicular muscle cross-sectional area by computed tomography or magnetic resonance imaging is increased.

In summary, the results of Dillon et al. (19) provide promising preliminary results indicating that EAA may provide protection against sarcopenia in healthy aging adults. However, this study (19) does not yet provide conclusive evidence that elderly individuals should consume dietary supplements of EAA, though it paves the way for future placebo-controlled, double-blinded long-term studies designed to investigate beneficial and adverse effects of AA supplementation, including changes in skeletal muscle protein synthesis, skeletal muscle mass, and ultimately functional outcomes (*e.g.*, skeletal muscle strength and endurance).

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