Prioritizing skeletal muscle health for successful aging

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Kevin A. Murach, Ph.D. at the University of Arkansas, talks us through prioritizing skeletal muscle health for successful aging, beginning with a primer on skeletal muscle aging

Skeletal muscles are the motors for locomotion and breathing.

They are also secretory organs that communicate throughout the body via secreted factors, crucial for thermoregulation (e.g., shivering), storage depots for amino acids, and a metabolic sink for carbohydrates and fat. Healthy skeletal muscle is essential for whole-body health throughout the lifespan and is a major factor in the proportion of life spent in good health (a.k.a. healthspan).

As we age, skeletal muscle tissue is progressively lost due to a process called age-related sarcopenia. The development of age-related sarcopenia, especially in individuals with a sedentary lifestyle, can begin well before middle age in most skeletal muscles. Reductions in the size of individual muscle cells (i.e., muscle fibers), the total number of muscle fibers, and the proportion of power-producing “fast-twitch” fibers, alongside more denervated fibers and non-contractile material (e.g., fatty infiltration and fibrosis), collectively lead to reduced muscle performance and metabolic dysfunction as aging progresses.

Power is the product of force and velocity. An age-associated inability to produce power combined with deteriorating muscle quality underlies compromised recovery from inevitable episodes of illness or hospitalization that occur throughout life. These negative health events, unfortunately, tend to increase in frequency over time, compounding the deleterious effects of aging. Age-related sarcopenia and its sequelae are, therefore, major contributors to a loss of independence and increased morbidity and mortality.

Fortunately, skeletal muscle is a highly plastic and adaptable tissue. It contains a population of regenerative stem cells, is exceedingly resilient to stress, and may even have a “memory” of prior healthful states. (1) As such, fortifying muscles throughout life may be our best strategy for promoting successful aging.

The most potent natural therapy for combating aging in humans: Muscular exercise

Aging is the number one risk factor for most chronic diseases that cause disabilities and death. The “geroscience hypothesis” states that understanding and combating the ubiquitous process of aging will effectively reduce all manner of specific diseases. (2)

What is the most effective therapy for treating ageing? Muscular exercise. The benefits of exercise are systemic, but many of the positive effects are owed specifically to improvements in skeletal muscle. [3]

Exercise causes skeletal muscle to become stronger, more powerful, fatigue resistant, metabolically flexible, less prone to damage, and better able to recover from injury. These favorable muscular characteristics resulting from exercise could help prevent falls or mitigate loss of function resulting from hospitalization, thereby increasing independence and quality of life throughout the lifespan.

Furthermore, factors released by skeletal muscle in response to exercise may be responsible for delaying the onset of age-related genetic conditions, such as Alzheimer's disease. [4] It is never too late to begin structured exercise, as positive adaptations can be realized even if initiated late in life [5-7]; however, an early start may help extend healthspan.

Different types of exercise confer qualities that tend to emphasize one characteristic versus another: endurance for muscle metabolic health versus resistance for strength and power production.There is now a growing recognition that divergent modes of exercise complement and reinforce each other. [8] A prudent approach is to incorporate different exercise modalities into a structured program, emphasising activities that are enjoyable to the individual, to promote adherence and consistency – the keys to exercise success.

Muscular exercise to guide countermeasures against the deleterious effects of aging

A little bit of exercise – even a few minutes a day – can go a very long way for improving skeletal muscle health. [9] Nevertheless, an exercise program requires some time and discipline that not everyone can commit to. Alternatives to exercise, such as "geroprotector" medications, which are objectively less effective than muscular exercise, have recently risen in popularity. These drugs could foster aspects of muscle health but may have unwanted side effects.

Some geroprotector drugs can also blunt the beneficial effects of endurance or resistance exercise in healthy individuals when used combinatorially. [10-12] It is unrealistic to expect that the myriad beneficial effects of exercise can be distilled into a single pill or pharmaceutical. However, muscular exercise can be used as an instrument to understand the molecular mechanisms of what dictates a youthful skeletal muscle phenotype and inform therapeutic approaches.

With contemporary descriptions of the "hallmarks of aging" [13, 14], specific molecular triggers that can slow signs of aging have come into sharper focus. For example, the genetically controlled induction of several epigenetic reprogramming "Yamanaka" factor genes in vivo has been shown to reverse some hallmarks of aging in mice. [15] Such work inspired my laboratory to explore what epigenetic reprogramming factors are induced by exercise in skeletal muscle.

Of several known factors, we found MYC was specifically induced by exercise in skeletal muscle [16] and was among the most powerful factors controlling the muscle molecular response to resistance exercise in humans. [17] Using a genetically inducible mouse model, we demonstrated that brief pulses of MYC specifically in skeletal muscle fibers were sufficient to drive cellular muscle growth in vivo [17] and initiate muscle epigenetic changes. [16] Knowledge gained from harnessing the timed induction of a powerful gene, such as MYC, could potentially lead to improved strategies for combating sarcopenia and/or boosting the efficacy of exercise in old age. [18]

Skeletal muscle health and the “fountain of youth”

There are numerous examples where targeted experimental dysregulation of skeletal muscle health directly controls systemic health and longevity in model systems. [19-21] Data from humans also point to several aspects of muscle function as strong determinants of all-cause mortality and healthspan. [22-25] Exercise impacts skeletal muscle from the whole muscle to the gene. Exercise can even slow biological aging in skeletal muscle, according to epigenetic aging “clocks” [5,16], which are used as molecular biomarkers of health status.

The beneficial effects of exercise on skeletal muscle cannot be overstated, and the impact of healthy skeletal muscle on successful aging should not be underestimated. The maintenance of skeletal muscle health throughout the lifespan may be the closest approximation to a mythical “fountain of youth” for promoting healthspan.

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