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Aging and sarcopenia

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Sarcopenia is the loss of skeletal muscle mass resulting in a reduction of physical strength and ability to perform activities of daily living. Loss of muscle and strength with aging results in frailty leading to an elevated risk of suffering a fall, difficulty recovering from illness, prolongation of hospitalizations, and long-term disability requiring assistance in daily living. Further, the reduction of muscle mass and physical strength leads to diminished quality of life, loss of independence, and mortality[1]. This loss of independence represents a high economic healthcare burden and area of high medical need. Sarcopenia also results when rapid muscle loss and reduced physical strength occurs due to disease-induced cachexia, immobilization, or drug-induced sarcopenia. The Institute of Medicine, a division of the National Academy of Sciences declared "frailty associated with old age" a priority area for national healthcare and an area that required increased research to deal with this healthcare issue[2].

Today, there are ~34M persons aged 65 and over – almost 13 percent of all Americans – and this number will grow to ~70M by 2030, representing 20% of the population[3]. Worldwide, the individuals who will become the frail elderly will more than double from ~321M in 1990 to ~799M in 2025. As a consequence of the expansion of this population segment along with increased longevity, the number of the elderly who will become sarcopenic and frail and require long-term institutionalization will consume an ever-expanding share of healthcare funds. In the US, 1.5M persons aged 65+ years are institutionalized each year, and 33% of these individuals are put into long-term healthcare facilities solely due to their physical frailty and their inability to maintain prerequisite activities of daily living, with most frail elderly facing >2 years of self-care disability at the end of life.

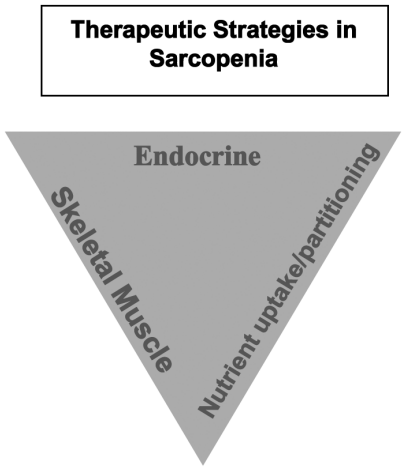

Figure 1.

No effective and safe therapy is now available to prevent or restore muscle loss in these conditions. Currently, the standard of care for sarcopenia is either nutritional supplements and appetite enhancers or exercise to maintain or improve muscle strength. In spite of these treatment options, many elderly still lose muscle strength and function and are subsequently at risk for the deleterious outcomes of frailty. Anabolic steroids are also occasionally prescribed but are limited due to a poor efficacy and safety profile.

Emerging therapeutic strategies to prevent and treat sarcopenia can be divided into three categories: 1) nutrient uptake/partitioning, 2) skeletal muscle, and 3) endocrine (Figure 1).

Improved nutrient uptake is the first line therapy in the treatment of sarcopenia, but has very limited efficacy. Significant breakthroughs are occurring in focusing on skeletal muscle targets that will treat sarcopenia, for example, myostatin[4]. Also, the loss of neuromuscular junction integri-

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ty in aging may be a major contributor to sarcopenia and extends the focus beyond the muscle to also include innervation[5]. Devising new therapies to maintain neuromuscular innervation with aging may provide substantial clinical benefit. Finally, endocrine strategies for the treatment of sarcopenia have been delineated. Two notable endocrine approaches include selective androgen receptor modulators (SARMs) and growth hormone secretagogues.

Growth hormone secretion and pulsatility decline with age, most notably after the age of 50 years of age. Growth hormone replacement to subjects with growth hormone deficiency has been shown to improve muscle mass. However, it is less clear if growth hormone replacement is efficacious in elderly sarcopenic subjects. With the discovery of orally active compounds that selectively stimulate growth hormone secretion, it is feasible in elderly sarcopenic subjects to test the hypothesis that restoring growth hormone secretion and pulsatility to young adult levels may increase muscle mass and physical performance.

CP-424,391 is an orally active growth hormone secretogogue or gherlin receptor agonist[6]. In preclinical models, CP-424,391 stimulates growth hormone secretion in pituicytes and increases growth hormone secretion in rats and dogs. CP-424,391 was evaluated in single and multiple dose clinical trials and demonstrated increased growth hormone secretion leading to increased IGF-1 levels. Further, CP-424,391 was evaluated in longer term trials in elderly frail subjects where body composition and physical performance were evaluated.

In conclusion, therapeutic strategies for the treatment and prevention of sarcopenia are under investigation. Future studies will ascertain the ability of these strategies to alter the course of sarcopenia to determine if improvement in body composition and physical performance will have a beneficial outcome in the growing elderly population.

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