Family Practice 2012; **29**:i44–i48
doi:10.1093/fampra/cmr063

Sarcopenia in the elderly

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Received 19 April 2011; Revised 22 July 2011; Accepted 29 July 2011.

Sarcopenia is the age-related loss of muscle. It leads to loss of muscle power, which in the end results in frailty and disability. There are numerous causes of sarcopenia. Treatment consists of resistance exercise and a leucine-enriched essential amino acid protein supplement. There is an emerging role for testosterone and other anabolic steroids. An activin II receptor soluble fusion protein is showing great potential to increase muscle mass and bone mineral density.

Keywords. Ageing, geriatric medicine, muscle strength.

Sarcopenia (poverty of flesh) was a term applied by Irwin Rosenberg to define the loss of muscle mass that occurs with advancing age. The loss of muscle mass was first noted by famous English neurologist, MacDonald Critchley, who pointed out that this loss of muscle mass was most marked in the hands and the feet. Today, sarcopenia is considered to be a loss of muscle mass in an older person, which is 2 SDs less than the mean for young persons.[1] Sarcopenia can be considered for muscle, what osteoporosis is to bone. Sarcopenia is commonly associated with infiltration of fat into the muscle (sarcopenic obese) and an increase in connective tissue. Sarcopenia is very common, with a prevalence of ~5% in persons aged 65 years and as high as 1 in two persons over the age of 80 years. Sarcopenia is commonly associated with disability and has been estimated to cost the US health system ~$18.4 billion a year.[2]

Sarcopenia leads to a decline in muscle strength and power. However, there are numerous other factors that lead to a decrease in strength.[3,4] These include altered muscle energetics, changes in tendon insertion with increased collagenation leading to an altered angle of pannation, altered nerve motor unit input to muscle altering muscle coordination and decreased blood flow due to decreased nitric oxide release in the capillary bed of the muscle. Fat infiltration into muscle (myosteatosis) is associated with decreased strength and an increase in the prevalence of disability.[5] Strength also is not directly related to the muscle power, i.e. the product of muscle force (torque) and velocity (speed). This can be defined as dynapenia.

Inability to develop adequate muscle power is one of the causes of frailty.[6,7] A person with frailty can be considered to have a general condition so borderline that any stressor will lead her\him to have a poor outcome, such as hospitalization, disability or death.[8] The features of frailty are fatigue, inability to climb one flight of stairs, inability to walk one block, more than five illnesses and loss of weight.[9,10] It should be considered a condition of predisability and is half as common as sarcopenia. The cascade from sarcopenia to disability is shown in Figure 1.

Epidemiology

Numerous epidemiological studies using different methods of measurement and cut-off points have attempted to establish the prevalence of sarcopenia.[11,12] In general, it appears that 5–13% of persons aged 60–70 years and 11–50% of persons in their 80s have sarcopenia. It is estimated that there are 3.6 million persons in the USA with sarcopenia.

Sarcopenia is associated with a high predictive value for disability.[2,13,14] There is an even higher association of disability in persons with obese sarcopenia.[15] While some authorities consider muscle loss in cancer sarcopenia, in almost all cases, it is better classified as cachexia or myopenia.[16,17]

Clinically, DEXA or ultrasound appears to be the best measures of sarcopenia. Ultrasound has the added advantage of being able to measure changes in tendons as well. MRI or CT gives excellent muscle measurements and delineate fat infiltration but are very expensive. Bioelectrical impedance measures have questionable value in individuals, in view of the uncertainty regarding their level of hydration. Midarm muscle circumference or calf circumference is cheap but inaccurate measures of muscle mass.

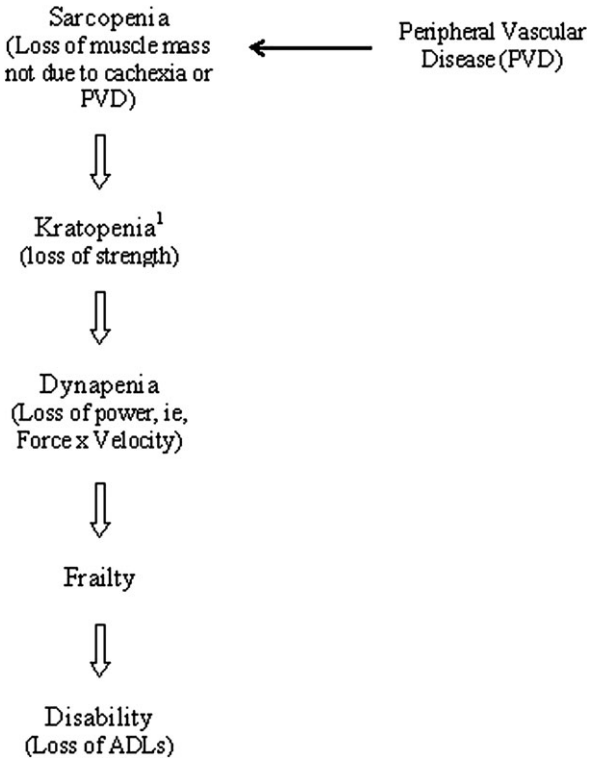

FIGURE 1 *Pathway from sarcopenia to disability.* [1]*From* Kratos, the Greek god of strength

Causes and management of sarcopenia

There are numerous causes of sarcopenia (Fig. 2). Overall, the most prominent cause of sarcopenia is inactivity. Exercise (muscle contraction) causes the release of muscle growth factors [insulin growth factor (IGF-Ea) and mechanogrowth factor] to activate satellite cells and protein synthesis. This leads to muscle regeneration. All these processes are less active with ageing (Fig. 3).

Adequate nutrient intake is essential to maintain muscle mass.[18] Thus, the decline in food intake with ageing plays a role in the development of sarcopenia. In particular, maintenance of muscle mass requires adequate protein intake. It is postulated that to maintain muscle mass, older persons require at least 1.2 g/kg of protein a day. A number of studies have shown that leucine-enriched mix of essential amino acids increase protein synthesis to a greater extent than other forms of protein. They do this by activating the muscle target of rapamycin pathway, which is a key regulator of anabolism. Protein acts synergistically with exercise to increase muscle mass. Typical foods containing leucine include milk, cheese, beef, tuna, chicken, peanuts, soybeans and eggs[19] (www.dietaryfiberfood.com/leucine-rich.php).

Creatine is essential for forming phosphocreatine, which is an extramitochondrial energy store. Creatine increases both lean mass and knee extension/flexion power in older persons.[20] It also decreases muscle cramps. Creatine causes fluid retention, which can be disconcerting in older persons as it results in peripheral oedema.

Testosterone secretion in males declines at the rate of ~1% per year after 30 years of age.[21] In females, testosterone declines rapidly between the ages of 20 and 45 years. These changes parallel the rate of decrease in the clean and jerk weightlifting world records (Fig. 4). In epidemiological studies, testosterone is a major factor in both the decline in muscle mass and to a lesser extent the decline in strength. Testosterone activates both the protein synthesis/degeneration pathway as well as channelling mesenchemal stem cells to satellite cells and inhibiting the pathway to pre-adipocyte progenitor cells.[22] A number of studies have shown that testosterone in low doses increases muscle mass and in higher doses muscle strength.[23] This is similar to the effect seen with other anabolic steroids, such as nandrolone. A series of recent studies have suggested that testosterone may be helpful in the management of frailty, though with the side effect of oedema.[24] In the studies so far conducted, testosterone therapy in frail persons has been associated with a lower mortality rate than placebo. Ostarine is a potent oral selective androgen receptor molecule. In healthy older men and women, it increased their ability to stair climb as well as increasing muscle mass.[25] A pilot study showed that testosterone together with a caloric supplement reduced hospitalizations in a frail older population.[26]

In older persons, growth hormone increases nitrogen retention, body mass and muscle mass.[27] There is no increase in strength. Long-term treatment leads to unacceptable side effects. Animal studies have suggested that genetically increasing muscle IGF-1 will increase muscle mass in mice.[28]

25(OH) vitamin D levels fall longitudinally with ageing.[29] Low levels of 25(OH) vitamin D in older persons are associated with sarcopenia, falls, hip fracture and mortality.[30] When levels are low, vitamin D replacement reverses the functional deterioration. A plasma level of 30 ng/ml (70 nmol) is considered an appropriate lower level.

Deletion of the myostatin gene in mice, cows, dogs and humans results in muscle hypertrophy.[31] Attempts to develop drugs directed against myostatin have so far been unsuccessful.

Myostatin activates the activin II receptor (AIIR). A fusion soluble decoy protein to the AIIR has been developed. Preliminary studies in humans have shown a marked increase in muscle mass, a decrease in fat mass and an increase in bone anabolism and bone mineral density [www.acceleronpharma.com (accessed on 10 December 2010)].

Elevated pro-inflammatory cytokines, especially interleukin-6 and tumour necrosis factor alpha, lead to

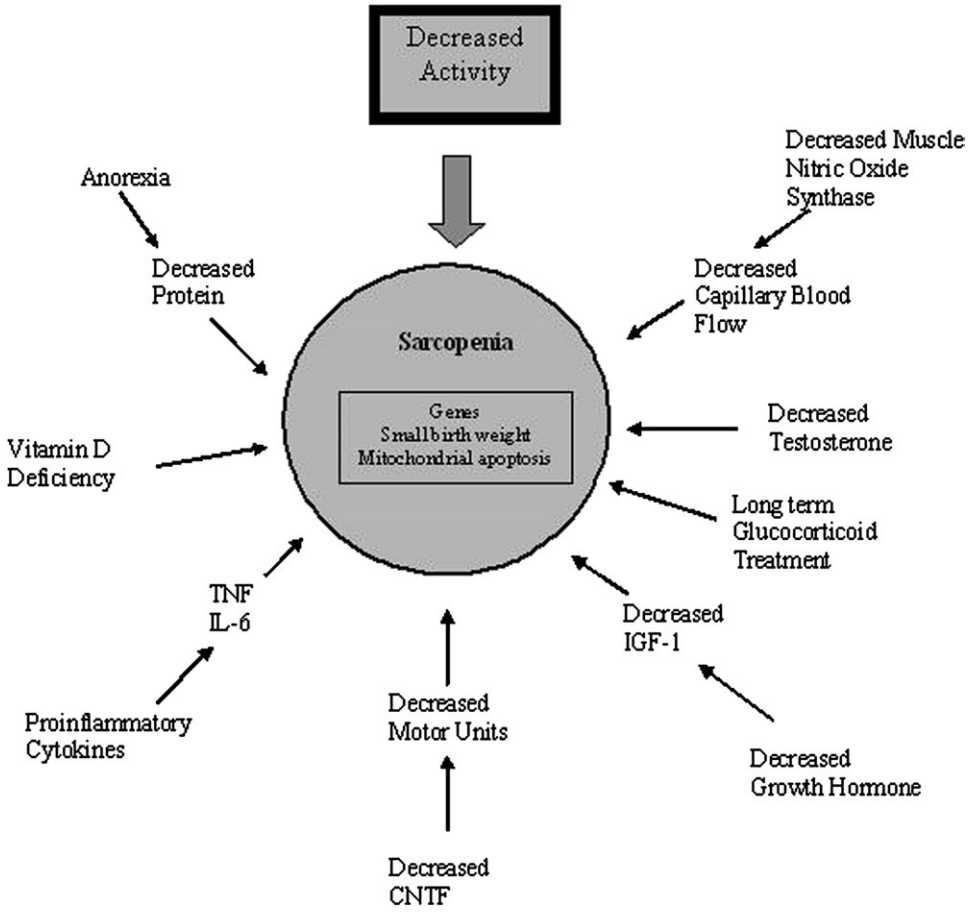

FIGURE 2 *Causes of sarcopenia. CNTF, ciliary neurotropic factor; TNF, tumour necrosis factor; IL-6, interleukin-6*

loss of muscle mass and a decline in function.[32] Attempts to lower cytokines to inhibit muscle loss have to date been unsuccessful.

There is a decline in motor units with ageing.[33] This decline leads to a reduced coordination in muscle function and a reduction in muscle mass. This decline in motor units appears to be related to the decline in ciliary nerve trophic factor (CNTF). In animals, CNTF increased muscle mass.

Peripheral vascular disease and/or loss of nitric oxide in the capillary beds leads to reduced vasodilation. It can also lead to sarcopenia. Peripheral vascular disease should be ruled out as a cause in persons with sarcopenia.

Numerous genetic allelic variations have been associated with body mass and strength. These include myostatin, CNTF, vitamin D receptor, angiotensin-converting enzyme, androgen receptor gene and cycline-dependent kinase inhibitor. In addition, it has been clearly shown that size at birth is a clear predictor of the development of sarcopenia at 70 years of age.[34]

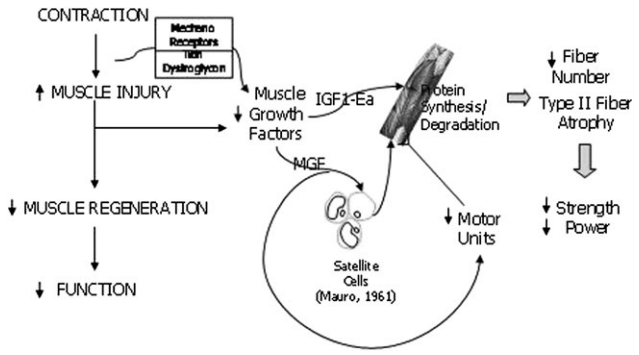

FIGURE 3 *Ageing, exercise and muscle injury*

Conclusions

A number of groups have attempted to create a consensus definition for sarcopenia. This is due to the fact that muscle loss alone is insufficient to explain the clinical syndrome. The European Working Group on Sarcopenia in Older People defined sarcopenia as both low muscle mass and low muscle function.[35] The International Association of Nutrition and Ageing similarly stressed the importance of function in the definition.[36] Both these definitions overlap with the definitions for frailty.[9,10] The Society of Sarcopenia and Cachexia compromised by suggesting that the condition be called sarcopenia with limited mobility.[37]

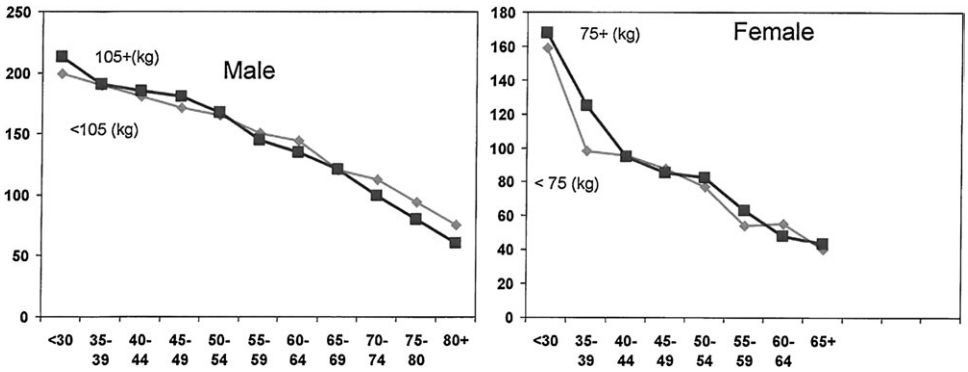

FIGURE 4 *World clean and jerk weightlifting records www.masterweightlifting.org*

TABLE 1 *Potential treatments for sarcopenia*

Nutrients	Leucine-enriched essential amino acids
Anabolics	Testosterone
	Selective androgen receptor molecules
	Ghrelin[a]
Proteolysis inhibitors	Angiotensin-converting enzyme inhibitors, e.g. prindopril
Exercise	Resistance exercise

[a]Insufficient evidence at present for anabolic effects in sarcopenia.

Resistance exercise and an adequate protein intake are the cornerstones of the management of sarcopenia. Based on the pathophysiology outlined above, a number of drugs have been used to treat sarcopenia (Table 1). At present, testosterone and selective-androgen receptor molecules appear to be the best available drugs to treat sarcopenia. While its safety profile has been questioned, the available studies suggest that testosterone treatment for up to a year is relatively safe in frail older individuals.[24] Testosterone should be combined with a leucine-enriched essential amino acid protein supplement for the best effect.[26] The AIIR decoy protein appears to have great potential. However, its diverse effects on other tissues raise the probability of some side effects. Some angiotensin-converting enzyme inhibitors also increase muscle mass and function, but this is not a universal effect.

Acknowledgements

Conflict of interest: advisory boards for Amgen, Sanofi-Aventis, GTx and Lilly.

Declaration

Funding: none.
Ethical approval: there were no IRB approvals required for this review article.

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