INTRODUCTION

Some of the most serious consequences of aging are its effects on skeletal muscle. The term *sarcopenia* is widely used to describe the progressive loss of muscle mass and quality with increasing age. Sarcopenia is characterized by a gradual decline in strength and a slowing of movement that increases the risk of injury from sudden falls and the need for assistance for the frail elderly to accomplish even the most basic tasks required for independent living. Although sarcopenia affects the elderly regardless of ethnicity, gender, or wealth, it should be recognized that health status, physical activity, and nutrition, can play an important role in slowing the rate of physical decline and preserving functional independence and quality of life.

As the proportion of older persons in the population continues to escalate, sarcopenia will have widespread implications and place increasing demands on public health. Even though it is generally agreed that the effects of aging on skeletal muscle are inevitable, there is debate as to whether these deleterious changes can be stopped or reversed. Therapeutic strategies are needed to slow the effects of aging on skeletal
muscle, and to restore and preserve muscle size and strength so that quality of life can be maintained or improved. In this review, we discuss the importance of physical activity in slowing the effects of aging, but emphasize the fact that exercise alone will not prevent the sarcopenia. We also describe some of the other contributing factors that affect muscle quantity and quality, such as age-related changes in circulating levels of muscle anabolic hormones and growth factors. Neural influences in the preservation of muscle size and strength are also described as well as some of the interventions that have been proposed for the preservation of motor units and neurotransmission during aging. In addition, the importance for continued research into the development and testing of safe and efficacious strategies that can be applied clinically for combating sarcopenia are be reiterated.

**UNDERLYING MECHANISMS OF AGE-RELATED CHANGES IN SKELETAL MUSCLE**

With advancing age, there is a slow but progressive loss of skeletal muscle mass that results in gradual decline in muscle function. The underlying mechanisms responsible for these age-related changes in muscle quantity and quality involve a complex interaction of many factors that affect neuromuscular transmission, muscle architecture, fiber composition, excitation-contraction (E-C) coupling, and metabolism. There continues to be considerable research investigating strategies that can reduce or reverse these age-related changes in skeletal muscle structure and function, especially muscle atrophy and weakness, and a number of these interventions will be described. Sarcopenia in men and women is associated with significant changes in body composition, which involve a decrease in body mass and skeletal muscle mass with increased fat and reduction of the muscle force. Sarcopenia is not limited to humans, since most mammals are affected by the progressive loss of muscle mass with advancing age including, but not limited to, rats, mice, cats, rabbits, dogs, and horses. One of the major issues is whether the decline in muscle force producing capacity is due to a loss of contractile protein resulting from loss of individual muscle fibers, or to a decrease in the ability of the remaining myofibers to produce force, i.e. an age-related decrease in
specific force \((sP_o)\) or the force per cross-sectional area.\(^3\)\(^{-6}\) Differences in basal muscle protein turnover may also explain the age-related loss in muscle mass in humans.\(^7\)\(^{,8}\) Several studies have investigated these age-related effects at the single muscle fiber (cellular) level and some of them reported decreases in the maximum force producing capacity \((P_o)\), specific force \((sP_o)\) or force per cross-sectional area, and maximum velocity of shortening.\(^9\)\(^{-11}\) Alterations in the mechanisms of excitation-contraction (E-C) coupling are thought to contribute to the changes in muscle contractility with age.\(^12\)\(^{,13}\) These age-related alterations include: a reduction in the amount of Ca\(^{2+}\) available for triggering contraction and a reduction in Ca\(^{2+}\) release due to dihydropyridine (DHPR)-ryanodine receptor (RyR) uncoupling,\(^14\) impairment of sarcoplasmic reticulum (SR) Ca\(^{2+}\)-pump function,\(^15\) abnormalities in the regulation of RyRs\(^16\) and decreased turnover of Ca\(^{2+}\)-ATPase and RyR protein.\(^17\)

Other general age-related systemic changes such as alterations in levels of anabolic hormones and neuronal function also deleteriously affect skeletal muscle and other tissues. The decline in overall body function further impacts upon the loss of muscle mass and much of this is due to a decreased capacity for exercise.\(^18\) While there is compelling evidence that problems with reinnervation can lead to impaired function of regenerated muscles, the proposal that the capacity of muscle precursor cells for new muscle formation (myogenesis) \textit{in vivo} is not a limiting factor in healthy individuals, even in very old age, is controversial.\(^18\)\(^{,19}\) There is consistent evidence that the rate of myoblast activation may be a little slower in older muscles, but cross-transplantation experiments of whole muscle grafts between young (2 months) and old (24 months) mice, show no marked differences in the overall capacity of these cells to become activated and fuse to form new muscle (Grounds \textit{et al.}, manuscript in preparation). Under tissue culture conditions, many studies show a reduced replicative capacity of myoblasts derived from aged compared with adult muscles of mice and humans. However, the extent to which this behavior under \textit{in vitro} conditions accurately reflects the more complex \textit{in vivo} situation is unclear. For example, extraction of myoblasts may be less efficient from aged muscles that contain more interstitial connective tissue, and myoblasts conditioned by the aged environment may have a sub-optimal response to tissue culture conditions that have been optimized for cells extracted from younger muscles. Elegant \textit{in vivo}
parabioisis experiments where the circulatory systems of young and aged mice are joined, reveal that systemic factors from young mice can enhance the rate at which myoblasts in old muscle respond to muscle injury, supporting the idea of no intrinsic difference of the response of satellite cells with age, although clearly the aged environment modifies their capacity to respond (T. Rando, personal communication). These observations raise the possibility that administration of (yet to be identified) systemic factors could be used to boost the regenerative response of aged muscle under certain conditions.

Undoubtedly, factors that contribute to the age-related decrease in muscle mass and function include changes in endocrine and cytokine levels, a decline in food intake and energy balance, age-related changes in skeletal muscle metabolism and biochemistry, and especially decreased physical activity and impaired neuronal function. Before describing some of the hormonal and growth factor approaches that have been proposed for treating sarcopenia, we must first discuss the most effective intervention for slowing the rate of loss of muscle function with advancing age, namely exercise. We will outline the role of exercise in preserving muscle mass and strength, and identify the best exercises that can slow the rate of sarcopenia and improve overall muscle function in older adults.

**EXERCISE AND AGING**

Maintenance of skeletal muscle mass is highly dependent on muscle activity (muscle contraction), which initiates signal transduction pathways responsible for protein synthesis and muscle growth. It is well-recognized that reduced physical activity contributes to the age-related loss of muscle mass, accelerates osteoporosis and sets up a vicious cycle of increasing disability and impaired mobility. The loss of functional independence can lead to depression and is painful for the individual and their families and carers. Thus, physical fitness, especially muscle strength, is critical for the preservation of functional independence, the promotion of good health, and improved overall quality of life for the elderly. Home-based exercise programs have proved successful for improving functional independence and have been advocated in the elderly with benefits for reducing nursing home and health care costs;
e.g. a six month physical activity program of balance exercises and strength training reduced the level of disabilities in muscle strength, balance, and mobility by 45% in frail elders living at home.\textsuperscript{24} In addition to the widely recognized effects on physiological functions, regular exercise has been shown to have a protective effect against depression.\textsuperscript{25} Resistance exercise (or strength training) has been shown to be the most effective way to actively avoid losing muscle strength with age and improve the ability to perform the tasks of daily living, even in nonagenarians.\textsuperscript{26} Lack of strength, especially around the ankle, predisposes elderly individuals to falls\textsuperscript{27} and to the fear of falls, which results in the decrease of their physical activities.\textsuperscript{28,29} Improved strength due to resistance training may lead to reduced fears about the likelihood of falling, increased confidence about posture and response time and improved balance.\textsuperscript{30} Although improvements in strength and power can be demonstrated in the elderly following training, the greatest benefits of exercise are likely to be seen when it is incorporated early in life (well before the age of 50 years) and maintained for as long as possible in order to produce the desired preventive effect.\textsuperscript{22} Exercise intensity is also an important factor, with the greatest benefits being observed when resistance training involves more intense, higher velocity lifting of heavier rather than lighter loads,\textsuperscript{26} although such intense exercise may not be possible for a considerable proportion of older people especially the frail elderly. Furthermore, flexibility training such as yoga, balance training such as tai chi, and swimming, which are milder forms of exercise can be beneficial.\textsuperscript{2} An exercise prescription involving resistance training for muscle strength, aerobic exercise for maintaining cardiovascular fitness, as well as flexibility and balance exercises, has been proposed as the best combination for maintaining independent living.\textsuperscript{31}

Use it or Lose it? Exercise Alone Will Not Prevent Sarcopenia

Despite the obvious benefits bestowed by exercise training, it must be made clear that exercise alone cannot prevent age-related changes in skeletal muscle function. Even elite Master’s level athletes who train and compete at the highest levels, for a significant portion of their lifespan, simply do not perform as well as they did when they were younger, and
they still exhibit obvious age-related losses in muscle mass and strength. An active lifestyle, while likely to slow the relentless effects of aging on muscle structure and function, will not prevent sarcopenia completely. Thus, the popular adage “use it or lose it” when applied to aging, is only partly true, and other factors such as age-related changes in circulating levels of muscle anabolic hormones and growth factors must also be considered when developing effective strategies to combat sarcopenia.

**Innervation and Neurotrophic Factors**

Contraction of skeletal muscle occurs in response to stimulation at the neuromuscular junction by signals from nerves. Many age-related changes in the central nervous system are deleterious for innervation of skeletal muscle and much muscle wasting may be the result of functional denervation. Neuromuscular function declines with age and while involvement of many neurotrophic and/or myotrophic candidate molecules has been proposed, studies show no clear association between the age-related changes in muscle mass, neurotransmission and levels of neurotrophic factors such as nerve growth factor, neurotrophin-3 (NT-3), neurotrophin-4 (NT-4), brain-derived neurotrophic factor (BDNF), or glial-derived neurotrophic factor. Local blockade of neuromuscular transmission decreases levels of NT-4 mRNA in skeletal muscle, whereas increased levels of mRNA of NT-4, NT-3 and BDNF occur in response to increased activity of skeletal muscle. Ciliary neurotrophic factor (CNTF) and insulin-like growth factor-1 (IGF-I) both have myotrophic and neurotrophic effects and in mammals, both show a decline in synthesis with age. IGF-1 is clearly very important for maintaining muscle mass (discussed later) but may also directly affect motor neurons, since administration of low doses of IGF-1 in combination with glycosaminoglycans dramatically prevent the motor neuron loss in wobbler mice, that are a model for motor neuron disease.

Although CNTF has myotrophic effects, it is most well-known for its neurotrophic properties. CNTF stimulates axonal sprouting and reinnervation of denervated myofibers. As CNTF is the main neurotrophic factor that shows decreased levels with advancing age, it is one of the most likely candidates contributing to age-related impairment of neurotransmission.
and muscle sprouting in response to transient denervation that result in the deterioration of muscle performance. CNTF participates in the survival of motor neurons and reduces denervation atrophy of skeletal muscles. In preliminary experiments in old rats, CNTF levels were restored by exogenous CNTF administration, and a strong correlation was found between CNTF production and muscle performance. Follow-up studies in rats and humans support the notion of a strong relationship between CNTF and age-related changes in muscle mass and function. Of related interest to sarcopenia is the clinical administration of neurotrophic factors to maintain neuronal function and for treating neuromuscular diseases. Reports of success with respect to rescue of skeletal muscle function have been claimed, although many of these are unsubstantiated. It has been shown that administration of CNTF retards the adverse progressive motor neuron dysfunction and improves muscle strength in wobbler mice and also accelerates regeneration of transected sciatic nerve and muscle re-innervation in rats. While innervation is clearly essential for skeletal muscle contraction (required for maintenance of muscle mass), relatively little is known about the muscle-derived factors that maintain neuromuscular contact and function and their decline with age.

Systemic Changes in Circulating Hormones and Other Factors

Age-related changes in body composition are commonly attributed to alterations of systemic endocrine function in aging individuals leading towards hormonal imbalances. Studies examining steroid (testosterone, oestradiol/noretisterone acetate, dehydroepiandrosterone) treatment in healthy individuals have not provided major health benefits and several undesirable side effects have been identified, including a greater risk for cardiovascular disease and some cancers. In March 2004, the United States Department of Health and Human Services (HHS) issued warnings to companies that manufacture, market and distribute products containing androstenedione, which was stated to act like a steroid once it was metabolized and could therefore pose similar health risks as anabolic steroids. Androstenedione (also called “anabolic steroid precursor” or “andro”) is produced naturally in humans and can be converted in the body to testosterone. Generally, androstenedione is advertised as a...
dietary supplement that can enhance athletic performance based on its claimed anabolic and androgenic properties, which stimulate muscle growth and increase production of testosterone. A press release from the United States Food and Drug Administration (FDA) reported that androstenedione when taken over time and in sufficient quantities, may increase the risk of serious and life-threatening diseases, and subsequently a number of athletic organizations, including the International Olympic Committee, banned use of androstenedione.

**Growth Hormone/IGF-I**

Of particular interest in relation to sarcopenia is the decreased activity of the growth hormone (GH)/IGF-I axis. Although it was a widely held notion that sarcopenia was directly related to an age-related decline in GH secretion, this view has been contested and numerous studies in humans do not support a benefit of GH administration on muscle protein synthesis. Synthetic peptides that cause the release of GH (GH secretagogues, e.g. benzoazepines and their analogs) have been used clinically but their efficacy is unclear, as are the benefits of commercial hormone replacement therapies.

The growth factor IGF-I, seems to be particularly important for maintaining muscle mass in the elderly. The mechanisms by which IGF-I maintains muscle mass and might prevent age-related muscle atrophy have been reviewed elsewhere. It is now recognized that there are several isoforms of IGF-I, some present in the circulation, and others are expressed locally in skeletal muscle and other tissues. Of particular importance for maintaining muscle mass are the two IGF-I isoforms produced locally in myofibers, which arise from differently spliced mRNA precursors. Aging is associated with decreased serum levels of IGF-I and also down-regulation of the local IGF-I in muscle. Muscles of old rats and humans have less robust upregulation of one of the muscle specific IGF-I isoforms (mechano growth factor or MGF) in response to physical overload, compared to young individuals. Since MGF is involved in myoblast proliferation, this might help to partly explain muscle wasting in elderly. IGF-1 produced locally within muscles in response to exercise is responsible for hypertrophy and maintaining muscle mass and transgenic over-expression of the other muscle specific
IGF-I isoform (Class 1 Ea isoform) in muscles of mice prevents or reduces the age-related loss of muscle mass\(^6\) and the extent of damage in dystrophic myofibers.\(^6,10\) The challenge is to translate these experimental benefits of muscle restricted elevated IGFs to the clinical situation. It is noted that systemic administration of IGFs is not recommended as this results in hypertrophy of cardiac muscle and heart failure and also prostate cancer.\(^2\)

**Treating Sarcopenia is not Simply “Hormone Replacement Therapy”**

On the basis of the evidence presented, simple hormone “top up” strategies to restore hormone levels in the elderly have not been successful, especially if they have not been performed in conjunction with a resistance exercise program.\(^65–68\) Developing supplementation strategies with different combinations of low-dose anabolic compounds has merit for attenuating the loss of muscle mass and improving muscle function in the elderly, and this has received some attention.\(^68\) In 2002, a report was convened by the Therapeutic Goods Administration (TGA) to assess the findings regarding the safety of the US Women’s Health Initiative (combined Hormone Replacement Therapy, HRT) trial. The TGA Report made recommendations regarding the relative benefits and risks of combined HRT (estrogen and progestin) for post-menopausal women, and concluded that the benefits did not outweigh the risks for side effects, including coronary heart disease. Furthermore, recent evidence also indicates that there may be increased risks of combined therapy in accelerating other age-related pathologies such as Alzheimer’s disease.\(^69\)

**β\(_2\)-Adrenoceptor Agonists**

It has long been known that some β\(_2\)-adrenoceptor agonists (β\(_2\)-agonists), agents that stimulate the β\(_2\) receptors of the sympathetic nervous system and which are widely used to treat asthma, have powerful anabolic effects on skeletal muscle. The application of β\(_2\)-agonists (particularly clenbuterol) for increasing muscle mass and performance and their adverse effects has been reviewed elsewhere.\(^70\) Clenbuterol mediates hypertrophy of skeletal muscle\(^71,72\) and inhibits denervation-induced atrophy
through its action on β2-adrenergic receptors. However, the use of clenbuterol is limited by numerous undesirable side effects, including sweating, tachycardia, tremors, effects on the central nervous system and serious heart complications that may be lethal.

At an equimolar dose to clenbuterol, another β2-agonist, fenoterol, has a 10–15% greater anabolic effect on rat fast-twitch (EDL) and slow-twitch (soleus) muscles. In a follow-up study, 4 weeks of daily administration of fenoterol completely ameliorated the age-related loss of muscle mass and strength in aged (28 month old) F344 rats and this was attributed to hypertrophy of existing fibers and not by increased myofiber number. This was one of the first studies to demonstrate complete restoration of both muscle mass and strength to (adult) control levels following β2-agonist administration. Aging is also characterized by a slowing of movements, due to factors such as muscle remodeling, where denervated fast fibers become reinnervated by slow motoneurons. One advantage of treating sarcopenia using β2-agonists over other anabolic agents, relates to the ability for some of these β2-agonist to cause fiber type transitions within skeletal muscles, typically from slow- to fast-twitch. Thus powerful β2-agonists such as fenoterol may not only prevent the loss of muscle mass and strength, but may also help retain a higher proportion of fast-twitch fibers that will attenuate the characteristic slowing of contraction in aged mammals.

Despite the positive attributes of β2-agonists for treating sarcopenia, there are several deleterious side effects especially when administered in high doses. Given that β2-agonist act via the β2-adrenoceptors, and there exists a population of these adrenoceptors in the heart, it is difficult (perhaps impossible) to separate the hypertrophic effects on skeletal muscle from those on the heart. Not surprisingly, cardiac hypertrophy has been observed in nearly all studies that have examined the effects of β2-agonist administration on skeletal muscle. Most studies have employed high doses in order to produce skeletal muscle hypertrophy and therefore have also resulted in significant (and potentially deleterious) increases in cardiac mass. This has so far limited the clinical potential of β2-agonists for sarcopenia. To prevent or reduce these detrimental effects on tissues other than skeletal muscle, the challenge is to devise treatments that utilise different β2-agonists that are capable of eliciting skeletal muscle hypertrophy at low doses, and following short duration treatments.
Risks and Benefits of Muscle Anabolic Therapies for Sarcopenia

For anabolic therapies, it could be argued that concerns regarding potential pharmaceutical toxicity and safety issues are usually only related to high doses. Although the use of powerful muscle anabolic agents will likely have dose-related side effects, developing low-dose, short-term treatment strategies are likely to have less toxic effects and their clinical merit is worthy of testing. This will require extensive pre-clinical and clinical studies to determine the optimum dosage and regimen of administration that will produce significant improvements in muscle mass and strength without causing deleterious side effects such as cardiovascular complications or tumor formation.

As society faces an increasing burden of aging-related health issues, the need to develop safe and effective therapies for sarcopenia to promote independent living is deserving of immediate attention. Unlike HRT for post-menopausal women where, under some circumstances, risks may outweigh benefits, the potential benefits for successful treatment of sarcopenia with short-term low-dose muscle anabolic agent may be effective in restoring muscle mass and far outweigh the possible risks.23

Myostatin

Myostatin, a member of the transforming growth factor-beta superfamily, is another circulating growth factor that has attracted much attention since the absence of myostatin results in increased muscle size, known as double muscling, in mice and cattle.75 Myostatin is a negative regulator of myogenesis and suppresses myoblast proliferation76 and myogenic differentiation.77 High serum and muscular levels of myostatin are associated with the cachexia (wasting) associated with HIV-infected men.78 It has been postulated that age-related deficits in both GH and testosterone may lead to an increase in myostatin expression and a disassociation in autocrine IGF-I effects on muscle protein synthesis, both of which could contribute to sarcopenia.79 Experiments in mice show that blocking myostatin with antibodies80 and silencing of the myostatin gene results in decreased fat content.81 Whether strategies to decrease
myostatin activity might reduce muscle sarcopenia in humans remains speculative.

**Vitamin D**

The importance of circulating vitamin D in maintaining muscle mass and strength is often overlooked and vitamin D deficiency is extremely prevalent in the elderly. Vitamin D is formed from calciferol that is mainly produced in the skin in response to sunlight. Levels of vitamin D and muscle strength decline with age. Indeed, low levels of vitamin D are associated with reduced physical performance, muscle strength and physical function, and increased risk of falls in older people. With age there is a decreased ability to manufacture vitamin D, resulting in marked deficiency, leading to muscle atrophy with selective loss of type IIB muscle fibers and other disorders. Fifty per cent of subjects with vitamin D deficiency display hip fractures. Since pain, weakness, and fear of falling are all factors that may cause older people to restrict their outdoor activities, it is quite possible that low vitamin D levels result from illness and disuse that limits outdoor activities and exposure to sunlight. While studies have found that vitamin D supplementation is a simple, safe, and low cost intervention that may reduce the number of bone fractures, a recent review concluded that there was insufficient evidence that vitamin D supplementation alone could improve physical performance in older people, and that confirmation of a benefit from vitamin D combined with calcium supplementation would only come from larger, well-designed clinical trials. It is suggested that vitamin D may act by stimulating IGF-I signaling. Clearly vitamin D deficiency should be carefully monitored in the elderly; it is readily diagnosed and appears to be reversed by administration of calcium and vitamin D supplements.

**Inflammatory Cytokines**

Another important circulating cytokine that severely affects skeletal muscle is the pro-inflammatory cytokine tumor necrosis factor-alpha (TNF-α). Increased inflammation is associated with many age-related problems (e.g. arthritis, inflammatory myopathies, coronary heart disease, cancers) and
the associated elevated of TNF-α and interleukin-6 (IL-6) can directly contribute to loss of skeletal muscle tissue in aging humans. The role of TNF-α and other inflammatory cytokines in extensive muscle wasting (cachexia) associated with severe inflammatory situations like cancer and acquired immunodeficiency syndrome has attracted considerable attention. Increased plasma TNF-α and IL-6 are often observed in healthy elderly people and higher levels of these cytokines are associated with lower muscle mass and strength in well-functioning older men and women. TNF-α expression is also elevated locally in skeletal muscles of the elderly and inflammation, measured as high levels of inflammatory markers IL-6, C-reactive protein and IL-1RA, and is significantly associated with poor physical performance and muscle strength in older persons. A relationship between IL-6 and levels of growth factors, such as IGF-I, and the preservation of muscle mass in the elderly has recently been proposed and sarcopenia in men was found to reflect a withdrawal of anabolic stimuli (such as growth hormone/IGF-I), but in women was due to increased catabolic stimuli (such as cellular IL-6). Increasing evidence supports the idea that the effects of TNF-α on muscle atrophy may also be mediated in part via interference with IGF-I signaling. Attempts to minimize cachexia have focused on anti-inflammatory drugs to block TNF-α action. This might be done by blocking the function of TNF-α with either specific antibodies such as Remicade (Infliximab®) or by soluble receptors marketed as Etanercept (Enbrel®). Remicade is a highly specific anti-inflammatory intervention and it clearly delays and reduces the breakdown of muscles from dystrophic mdx mice. Remicade is very successful clinically in the treatment of inflammatory diseases like rheumatoid arthritis; while it can have some side effects it might be useful for amelioration of inflammatory cytokine induced muscle loss with aging. Reduction of serum TNF-α by administration of L-carnitine has been proposed to prevent muscle loss secondary to heart failure, since L-carnitine reduces TNF-α serum levels in rats with experimentally induced chronic heart failure: however, such L-carnitine treatment did not significantly increase muscle size. Since high levels of TNF-α result in cachexia and act by increasing protein degradation as well as directly interfering with IGF-1 signaling, reduced TNF-α combined with either elevated IGF to increase overall protein synthesis, or a high protein diet, may have additive benefits.
Metabolism, Energy Balance and Nutrition

Imbalance between energy intake and energy expenditure is considered to be one of the main reasons for decreased lean body mass. This aspect includes altered food intake, combined with changes in basic metabolic rate and biochemistry. Aging is associated with dramatic changes in the biochemistry and enzymatic activity of skeletal muscle resulting (among other effects) in reduced capacity to synthesize new proteins, up-regulation of pathways leading to increased protein breakdown (catabolism), and increased oxidative cell damage. There are strong advocates that suggest that an optimum intake of micronutrients and metabolites, which varies with age and genetic constitution, would tune up metabolism and give a marked increase in health, particularly for the poor, young, obese and elderly, at little cost.

The use of specific amino acid supplements and their derivatives has recently attracted much attention to reduce muscle protein breakdown and increase muscle mass. Supplementation with a nutrient mixture of β-hydroxy-β-methylbuturate (HMB), a metabolite of leucine, has beneficial effects for increasing muscle strength, and administration of HMB to elderly individuals involved in strength-training, resulted in increased muscle strength as well as a significant decrease in fat mass.

Another nutritional supplement which has attracted attention for increasing muscle mass and strength is creatine. Supplementation with creatine has been advocated for older individuals because creatine enhances muscle strength and explosive power after only 5–7 days in young adults. Creatine supplementation in normally active older men (59–72 years of age) increased several indices of muscle performance, including functional tests, without adverse side effects and it was concluded that creatine may be a useful therapeutic strategy for older adults to attenuate loss in muscle strength and performance.

Caloric restriction, which refers to a nutritive dietary regimen low in calories, is one of the very few interventions that extends longevity in animal models. This extends life expectancy by 30–40% if initiated early in the animal’s life, and by about 20% if started in middle age. In a recent study of aged (26–28 month old) F344 rats, long-term (life-long) caloric restriction was an effective intervention against the loss of muscle function with age. It is proposed that the main mechanism responsible
for such longevity is reduced reactive oxygen species formation and thus reduced oxidative damage to cellular structures. The other mechanism, which underlies life-extending benefits of caloric restriction, is its ability to reduce fat deposition and maintain insulin sensitivity. These observation must be balanced against the requirement for a healthy high protein diet to maintain muscle mass, and a progressive loss of appetite that can lead to “anorexia of aging” and weight loss is a major cause of muscle wasting in the elderly.

CONCLUSION

There is clearly a profound need for therapeutic strategies that can slow the effects of aging on skeletal muscle structure and function; namely to restore muscle size and strength in the frail elderly so that their quality of life can be maintained or improved. Physical activity, particularly resistance (strength) training, can play an important role in slowing the effects of aging, but exercise alone will not prevent the gradual decline in muscle quantity and quality. Other factors, such as nutrition and age-related changes in circulating levels of muscle anabolic hormones and growth factors, must also be considered when developing strategies to combat sarcopenia. Neurotrophic strategies may also be an area of focus since many of these factors have myotrophic as well as neurotrophic effects and healthy innervation is clearly crucial for skeletal muscle structure and function. Although we have identified many promising candidates and strategies that have potential for ameliorating sarcopenia and improving muscle function in the elderly, few pharmacological interventions seem justified at this stage. Much research is needed to test the safety and efficacy of various exciting experimental strategies before any of them could be recommended for potential clinical application.

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