Attenuation of Adverse Effects of Aging on Skeletal Muscle by Regular Exercise and Nutritional Support

Abstract: *Beginning early in midlife, natural/primary aging is inevitably associated with a progressive reduction in muscle mass and function. This process can progress with aging to a substantial loss of strength, particularly in the lower extremities, reducing mobility. This condition, commonly referred to as sarcopenia, can result in frailty, reducing one's ability to live independently. This article reviews the underlying biological process contributing to the development of sarcopenia and the roles of regular exercise and nutritional support for attenuating aging-associated muscle loss as well as risk and management of sarcopenia and associated frailty.*

Keywords: skeletal muscle; sarcopenia; oxidative stress; exercise; dietary habits

Skeletal Muscle Functions

Skeletal muscle constitutes the largest soft-tissue mass of the human body. More than 600 muscles contribute about 40% of the total body mass of an average, healthy, young adult man and

about 25% of that of a comparable young woman.¹ The principal function of skeletal muscle is to initiate body movements, particularly locomotion. In addition, muscle tone is essential for maintaining body posture and balance against the force of gravity. Muscle contractile force on bone via tendon attachments also is an important

total resting metabolism, which is markedly increased by the metabolic demands on active muscles during physical exertion. Heat generated, as a byproduct of muscle conversion of chemical energy from food substrates to mechanical energy, is important for body temperature regulation, particularly in a cool environment. Skeletal muscle also

Thus, a reduction in muscle mass with aging results not only in decreased mechanical functions of the body but also in adverse metabolic consequences.

contributor to bone strength and health. Furthermore, muscular contractions are required for respiration and to augment cardiovascular function by enhancing venous return of blood to the heart. In addition, skeletal muscle is a significant contributor to metabolic regulation of the body. Muscle mass generally is responsible for about 20% of the body's

plays a central role in regulation of glucose homeostasis. Furthermore, proteins, which make up 20% of the wet weight of muscle, provide a reserve source of amino acids and energy in the advent of chronic energy deprivation or debilitating medical conditions. Thus, a reduction in muscle mass with aging results not only in decreased mechanical

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functions of the body but also in adverse metabolic consequences. These include reduced resting metabolic rate, which contributes to adipose tissue accumulation and glucose intolerance, increasing the risk of developing type 2 diabetes and cardiovascular disease (CVD).

Aging-Related Muscle Decline

Skeletal muscle mass and strength generally peak by the mid-20s to 30 years of age. This is followed, generally beginning at age 30 to 50 years, by a progressive decline of about 1% per year until age 70 years, following which the rate of loss accelerates to about 3% per year.¹ Thus, the primary aging process generally results in a lifetime loss of more than 30% of one's peak muscle mass. This process can further progress in elderly individuals to the development of frailty, resulting in an inability to independently perform activities of daily living. Frailty also is associated with increased morbidity and premature mortality. However, there is marked variability between individuals in both development of peak muscular mass and strength and in the rate of loss with primary aging. This variability is attributable to genetic and other innate biological factors as well as extrinsic environmental and lifestyle contributions, especially physical activity (PA) and nutritional factors, which are discussed below. Additional secondary contributors to development of frailty with aging include disuse and disease states.

The term *sarcopenia*, meaning in Greek, "deficiency of flesh," refers to the loss of skeletal muscle bulk and functions, attributed to primary aging.² Various diagnostic criteria have been proposed to define this condition in epidemiological and clinical research studies. However, during the past decade, international consensus conferences have endorsed a definition based on the criterion first proposed by Baumgartner et al.³ This criterion is modeled after the 1996 World Health Organization's (WHO's) widely used

criterion for osteoporosis (a medical condition commonly accompanying sarcopenia).⁴ This involves the use of dual-energy absorptiometry (DEXA) imaging. The diagnosis of sarcopenia by this consensus requires the presence of a reduction in DEXA-assessed appendicular (arm plus leg) muscular mass (adjusted for height) of 2 or more standard deviations (SDs) below the mean of young (20- to 30-year-old) reference persons of the same sex and ethnicity. In addition, the diagnosis requires demonstration of the presence of an associated muscle-related functional impairment—for example, documented reduced strength and/or limited mobility (eg, reduced walking speed on a 4-m or 6-minute walk test). Furthermore, secondary causes of accelerated loss of muscle mass, such as cachexia caused by starvation, chronic disease, or prolonged immobilization must be excluded. The European Working Group on Sarcopenia⁵ also has proposed classifying the relative severity of sarcopenia into 3 stages, again analogous to the whole classification of severity of osteoporosis: that is, presarcopenia, sarcopenia, and severe sarcopenia. *Presarcopenia*, or so-called myopenia (analogous to osteopenia), refers to those with a 1 SD but less than a 2 SD reduction in appendicular muscle mass on DEXA. The *sarcopenia* stage meets the WHO 2 SD reduction in appendicular muscular mass plus the presence of some nondebilitating reduction in strength or mobility. *Severe sarcopenia* requires meeting the sarcopenia criteria plus the presence of marked debilitating impairments in muscular strength and mobility, resulting in the so-called frailty syndrome. Manifestations of physical frailty include difficulty in rapidly rising from a chair or bed, an inability to independently perform routine activities of daily living, and a high risk of falls and associated osteoporotic-related fractures. Severe sarcopenia or frailty also is associated with a high risk of comorbidities and premature mortality

Public Health Impact of Sarcopenia

With the progressive aging of the American population, sarcopenia has emerged as a major public health problem. Its estimated prevalence in the United States is currently between 13% and 24% in adults <70 years of age and >50% in those 80 years or older.³ The current economic impact of providing at-home or assisted-living care facility and hospital expenses for those with severe sarcopenia and fragility is estimated to be close to 20 billion dollars annually in the United States.⁴

Biological Mechanisms

Over the past several decades, in vitro, animal, and human research has resulted in enormous advances in the identification of multiple intrinsic biological mechanisms as well as extrinsic lifestyle contributors to development of sarcopenia. Intrinsic mechanisms include anatomical, cellular, biochemical, chromosomal, and other molecular processes elaborated below.^{1,6,7}

Anatomical Changes

The progressive reduction in muscle mass with primary aging is associated with the following morphological changes:

1. a reduction in muscle fiber number and size and a shift in fiber type distribution;
2. a reduction in progenitor stem cell number and activity, resulting in impairment of repair of injuries; and
3. multiple adverse neuromuscular changes (elaborated on below).

Muscle Fiber Change. Necropsy studies, involving whole human skeletal muscles, have yielded data on fiber type changes with aging, which differ from earlier studies based only on biopsies of specific muscles. These recent studies reveal an aging-related reduction in the number of both type I (slow twitch, oxidative) and type IIb (fast-twitch,

glycolytic) fibers; however, there appears to be a greater reduction in size (atrophy) of type II than of type I fibers. Furthermore, there is postulated to be an associated increase in relative number of intermediate type IIa (fast-twitch, oxidative-glycolytic) fibers, postulated to be derived from IIb fibers.⁸ The functional implications of these findings are a greater reduction with primary aging in muscular strength and power (force $\times$ velocity) than of muscular oxidative capacity and endurance.

Reduced Satellite Cell Activity and Associated Muscle Repair. Satellite cells are the principal muscle adult progenitor/stem cells,⁹ which are located on the periphery of muscle fibers (hence, the term *satellite*). These and other adult stem cells, unlike mature myocytes, are capable of mitotic division. On their activation, in response to muscle injury, they proliferate and migrate to the injury site and repair the injury by fusion to existing fibers and/or by regeneration and replacement of damaged fibers. Furthermore, they can bond together to create new nucleated microfilaments. Their activation also is required to increase the cross-sectional area and size of muscle fibers (ie, to initiate hypertrophy). Aging results in both a reduction in the number and activity of satellite cells, thereby decreasing the body's ability to repair muscle injuries, to replace damaged or necrotic fibers, and to respond to resistance training by hypertrophy.¹⁰ Loss of these progenitor cells is via both genetically programmed cell death (apoptosis) and by their damage from oxidative stress and inflammatory cytokines, as discussed later in this article.

Neuromuscular Changes. Central nervous system stimulation initiates the electrical and biochemical stimulation required to induce skeletal muscle contractions. Aging results in multiple adverse neuromuscular changes, which interfere with these processes and significantly contribute to the development of sarcopenia.^{1,7} These

include the loss of α motor neurons (α MNs), which innervate muscle fibers and disturbances at the neuromuscular junctions (NMJs). α MNs innervate a varying number of muscle fibers, predominantly of the same types (and thereby similar contractile functions) to constitute motor units. Denervated fibers are subsequently lost; however, some are reinnervated by neighboring α MN. This results in a decrease in the number and an increase in the size of motor units. These adaptations result in a decline with aging in fine motor skills as well as the speed and quality of the signal transmitted from the nerves to the muscles.⁷ Axons of α MN synapse at the NMJ with muscle fibers. When an action potential electrical signal reaches the NMJ, calcium (Ca) is released from muscle sarcoplasmic reticulum. Ca in turn induces the release at the NMJ of acetylcholine (Ach). This provides the signal to postreceptors to initiate muscle contractions by opening of Ca channels. The subsequent binding of Ca to troponin initiates the cross-linkage of actin and myosin to induce contractions. The speed at which the Ca is released and pumped back to the sarcoplasmic reticulum also contributes to the speed and forcefulness of muscle contractions. Structural changes with aging at the NMJ partially block the Ach message transmission between the nerves and muscles. In addition, there is an aging-induced impairment of Ca release and reuptake by the sarcoplasmic reticulum.

Molecular and Biochemical Contributors

Over the past several decades, research has revealed multiple intrinsic biological, molecular, and biochemical mechanisms involved in the etiology of the aging process, which contribute to the development of sarcopenia. These are summarized in Table 1 and discussed below. The identification of these mechanisms provides potential intervention targets for pharmacological and nonpharmacological preventive and therapeutic interventions.

Table 1.

Molecular and Biochemical Contributors to Aging-Related Development of Sarcopenia.

1. Apoptosis
2. Accelerated oxidative stress
3. Inflammation
4. Protein glycation
5. Accumulation of damaged muscle proteins
6. Reduced anabolic hormone activity
7. Reduced autophagy
8. Reduced protein synthesis
9. Reduced muscle blood supply

Apoptosis

Aging is associated with a genetically programmed loss of body cells. This process, called apoptosis, is often referred to as cell suicide programmed by a biological clock.^{7,11} Apoptosis results in a noninflammatory-related loss of myocytes as well as of progenitor stem cells and α MN. Acceleration of this process is postulated to play a key role in the etiology of sarcopenia.¹¹ Both biological and environmental factors, which cause gene mutations (ie, alterations in the nucleotide sequences of gene DNA) and epigenetic (Greek, literally meaning "above genetics") alterations are contributors. Epigenetic modifications refer to direct alterations to the DNA and histone protein making up chromatin (eg, methylation of the DNA or acetylation of the histones).¹² Major contributors to both genetic mutations and epigenetic changes, which accelerate apoptosis, are discussed next.

Oxidative Stress

"The free radical theory of aging," first proposed in 1956 by Harman¹³ is

currently widely considered as a major contributor to the etiology of sarcopenia.^{2,14} Reactive oxygen species (ROS) are byproducts primarily of the mitochondrial Krebs citric acid cycle, oxidative phosphorylation of chemical substrates to generate adenosine triphosphate (ATP). Physiologically, ROS are essential signaling molecules targeting genes to regulate essential cell functions. ROS also upregulate the body's antioxidant (redox) defense system. These endogenous antioxidants include superoxides, catalase, and the glutathione peroxidase system. However, aging is associated with an imbalance between generation of ROS as well as of nitrogen oxidative species (NOS) and the body's intrinsic antioxidative defense system, favoring oxidative stress.¹⁵ ROS- and NOS-induced damage to muscle macromolecules is postulated to play a major role in the development of sarcopenia. Negative effects include damage at multiple sites on DNA, intracellular and extracellular proteins, and polyunsaturated fatty acid components of cell membrane phospholipids. The latter target results in generation of lipid peroxidases that initiate a chain reaction, generating additional ROS.¹⁶

Because of the proximity of mitochondria to the cell nuclei, nuclear DNA is an early target for ROS-induced damage and mutagenicity, as is the mitochondrial gene DNA.¹⁵ Damage to mitochondrial gene DNA reduces the formation of or structurally alters 13 of the Krebs cycle enzymes. Oxidative damage also occurs at multiple sites on amino acids of target proteins and/or causes protein unfolding, making them functionally inactive. Mitochondrial targeted proteins include the enzymes required for β oxidation of fatty acids and for ATP generation by the Krebs cycle and its associated electron transport system. Alterations in these skeletal muscle mitochondrial functions are postulated to be major contributors to adverse impact of aging on both muscular and cardiorespiratory endurance. Furthermore, ROS damage to anaerobic

enzymes in the muscle sarcoplasm (especially lactate dehydrogenase) also adversely affects muscular performance, especially power output.

Inflammation

A large body of research has demonstrated that proinflammatory cytokines play an important role in muscle wasting and their functional decline with aging.¹⁷⁻¹⁹ Senescent muscle commonly is a site for inflammatory processes induced by ROS damage and necrosis of damaged cells. Furthermore, fragile atrophic muscle fibers are easily injured, which induces an additional inflammatory response. Proinflammatory cytokines circulating in the blood include C-reactive proteins (CRPs), interleukins 2 and 6 (IL-2, IL-6), and particularly tumor necrosis factor α (TNF- α), which are expressed by genes of injured muscles and by infiltrating leukocytes.¹⁸ It should be noted that these cytokines also play pivotal roles in the etiology of CVD and other chronic diseases, which contribute to so-called secondary aging effects or comorbidities.

Protein Glycation

Glycation is another intrinsic source of muscle protein damage.²⁰ This process involves nonenzymatic cross-linkage of protein components with glucose. Glycation is potentiated by aging, because of increased blood glucose levels commonly associated with reduced glucose clearance caused by muscle atrophy, increased adiposity, and associated insulin resistance (IR).

Accumulation of Damaged Muscle Proteins

Multiple causes have been identified for the aging-related accumulation of damaged myofibrillar contractile and enzymatic mitochondrial and sarcolemma proteins, which contribute to the development of sarcopenia. These include not only the multiple causes of induced damage previously described but also reduced turnover and replacement of damaged proteins with advanced age.^{21,22} It appears that practically all intracellular proteins show

evidence of at least one form of damage with aging. These changes are postulated to be important contributors to malfunction of practically all the body's biological systems. A major contributor to accumulation in muscle and other senescent tissues of damaged protein is reduced autophagy (literally derived from a Greek word meaning "self-eating").^{23,24} This process involves proteolysis of damaged proteins (as well as other damaged macromolecules and dysfunctional mitochondria and other organelles) via several lysosomal- and proteosomal-dependent mechanisms. Damage to the actual enzymes contributing to the catabolic processes involved in autophagy are postulated to be involved in the disturbed cellular housekeeping and, hence, the development of sarcopenia.

In addition to reduced proteolysis, there is strong evidence that reduced protein synthesis also contributes to cellular accumulation of damaged, dysfunctional proteins in aging muscle.²⁵⁻²⁷ This is particularly evident in a reduction in synthesis of muscle mitochondrial and myosin heavy-chain proteins.²⁸ This anabolic resistance, related to aging, includes impaired muscle protein synthesis in response to food ingestion, amino acid administration, and exercise as well as in response to anabolic hormones (as described below). Mechanisms postulated to contribute to impairment in protein synthesis in aging muscle include the following²⁸:

- a negative feedback caused by the reduced turnover of damaged proteins;
- ROS and inflammatory cytokine damage to mitochondrial and nuclear DNA;
- translation errors in converting the DNA message into mitochondrial messenger RNA (mRNA);
- errors in translating the mRNA message into protein synthesis by dysfunctional ribosomes (protein-synthesizing cell factories); and
- reduced responsiveness to anabolic signals, including food and amino acid intake and PA.

Reduced Anabolic Hormone Activity

Aging is associated with significant changes in both the rate of endocrine gland secretions and/or the responsiveness of their cell receptors.²⁹ These changes are postulated to play a significant role in muscle aging. Aging-related hormonal changes include reduced levels of and physiological responsiveness to the anabolic, muscle-building, peptide hormones—namely, somatotropin or growth hormone (GH), insulin-like growth factor-1 (IGF-1), and the sex hormonal steroids, that is, testosterone and related androgens as well as estrogens. Mechanisms of the activity of these anabolic hormones are briefly discussed below.

Growth hormone and IGF-1. They are responsible for the postnatal growth and development of multiple target tissue, including skeletal muscle. Secretion of GH is maximized at puberty. This is followed by a progressive decline by age 30 years, at about a rate of 1% per year. In elderly individuals, GH levels are 5% to 20% lower than in young adults.²⁹ The growth-promoting properties of GH levels are mediated by the activity of IGF-1. The principal source of circulating IGF-1 is the liver; however, skeletal muscle also has GH receptors, which express IGF-1. There is observational evidence that the aging-related decline in blood levels of GH and associated reduced IGF-1 levels are major contributors to the development of sarcopenia. However, the use of injectable (subcutaneous) human GH treatment for elderly individuals in an attempt to improve muscle mass is controversial because of insufficient evidence of efficacy and adverse side effects.

Testosterone. Gonadal and adrenal cortical-derived testosterone and related androgens increase skeletal muscle protein synthesis with effects on muscles modulated by genetic factors and dietary and exercise habits.^{30,31} In men, serum levels of testicular-derived total and unbound bioavailable testosterone levels decline, beginning at age 30 years, at a rate of 1% and 2% per year, respectively.

Furthermore, testicular response to pituitary gonadotropin stimulation also is diminished in older men. In women, circulating levels of androgens of adrenal cortical origin also rapidly decline, beginning in early adulthood.³¹ Numerous studies of testosterone replacement therapy in elderly men have been performed over the past decade. Placebo-controlled clinical trials have shown that testosterone replacement therapy can increase muscle mass and grip strength in elderly men with sarcopenia, especially in those with low blood levels; however, the potential risks, including increased risk of prostate cancer, must be weighed against the potential benefits.^{30,32}

Estrogen. Although a great deal is known about the physiological effects of androgens on skeletal muscles, relatively little is known regarding the effects of their female ovarian steroid sex hormone counterparts. Recent research in animals and humans has provided strong evidence indicating that estrogens also play important roles in the regulation of physiological and metabolic functions of skeletal muscle and that estrogen deficiency is a contributor to a decline in strength with aging.³³ Women actually begin losing muscular strength at an earlier age than men.³⁴ This is postulated to be related to a decline in secretion of ovarian estrogen even prior to menopause, which generally occurs in American women around 50 years of age. A meta-analysis of observational studies that compared muscle strength in about 10 000 postmenopausal women who were receiving estrogen replacement therapy (ERT) and those who were not receiving ERT found a small positive association of ERT with muscular strength.³⁴ Furthermore, a meta-analysis of experimental studies in rodents showed a stronger muscular force generation in estrogen-replete as compared with estrogen-deficient animals. Skeletal muscle in both rodents and humans also has specific estrogen receptors. In addition, it appears from the current literature that in both rodents and humans, estrogen differs from

androgens in the mechanisms involved in reducing aging effects on the skeletal muscles.^{33,34} Androgens, as mentioned, increase muscular strength primarily by enhancing protein synthesis and inducing hypertrophy (ie, by increasing muscle quantify). In contrast, estrogen appears to enhance muscle strength by improving its capability to generate force (ie, by improving muscle quality). It is postulated that this action is directly related to positive effects on contractile protein functions. However, the routine use of ERT alone or in combination with progestins for postmenopausal women is not recommended, despite its apparent beneficial effects of maintaining muscle strength and reducing menopausal symptoms as well as helping prevent osteoporosis. This is because of potential serious side effects, including vascular thrombosis and increased risk of malignancies of the breast and uterine endometrium.

Increased Insulin Resistance

Insulin is a pancreatic β -cell-derived peptide hormone that, in addition to regulating glucose and fat metabolism and their storage, also has a positive anabolic effect on body proteins and appears to increase skeletal muscle protein storage, primarily by inhibiting its proteolytic breakdown.³⁵⁻³⁷ In addition, in some, but not in all studies, feeding of protein or amino acid supplements to exercising individuals increases insulin-induced muscle protein synthesis by facilitating the translation of mRNA by ribosomes, particularly if it is consumed during the immediate postexercise period.³⁹

It is widely recognized that aging is associated with a progressive impairment in glucose handling by increasing IR³⁹⁻⁴¹. Postulated unifying explanations for this relationship are as follows: (1) reduction in mass of skeletal muscle and other active metabolic active tissues, (2) the endocrine changes previously discussed, (3) increased oxidative stress and mitochondrial dysfunction, and (4) environmental contributors, including smoking, physical inactivity, and eating habits. Current research suggests that IR precedes the development of sarcopenia

during healthy aging and is postulated to play a fundamental role in its development. Furthermore, IR is an independent predictor of aging-related chronic diseases, including type 2 diabetes, CVD, and malignancies.⁴⁴

Reduced Blood Supply

Aging results in progressive cardiovascular changes.^{38,39} As previously reviewed in this Journal,⁴³ these include a reduction in muscle blood flow, decreasing oxygen and nutrient delivery, and an aging-related reduction in cardiac output as well as adverse effects on both macrovascular and microvascular tissue blood supply.^{44,45} Macrovascular changes include a progressive reduction of distensibility and increased stiffness of major conduct arteries, beginning in the third decade of life. The resulting vascular stiffness is generally considered the hallmark of vascular aging. A consequence is reduced cushioning of the pulse wave velocity following each heartbeat. The resulting increased shear stress results in irreversible damage to the microvasculature and a reduction in capillary density of skeletal muscles. In addition, blood flow to the lower extremities declines with primary aging (independent of the reduction in muscle mass), apparently because of enhanced adrenergic-induced vasoconstriction.⁴⁶ Furthermore, there is a progressive reduction in vascular endothelium-related vasodilatation with aging. Endothelial dysfunction (ED) is further potentiated by reduced circulating estrogen in women, physical inactivity, and all the classic and novel risk factors for CVD as well the negative effects of oxidative stress and inflammatory cytokines. ED also is postulated to be an initiating factor in the development of atherosclerosis and is potentiated throughout its development.

Role of Exercise in Prevention and Management of Sarcopenia

Observational studies have consistently identified an inverse association between

a sedentary lifestyle and development of sarcopenia and frailty as well as other common medical conditions contributing to secondary aging and all-cause mortality.^{47,48} Furthermore, exercise training, even in older physically frail individuals, has been demonstrated to improve muscle mass and strength as well as muscular and cardiovascular endurance and to reduce comorbidities associated with secondary aging.^{7,49-51} Although the relative impact of regular exercise for attenuating aging-related muscle loss appears to be greatest after age 40 to 50 years, it is an important preventive measure against sarcopenia throughout the lifespan. During youth, regular exercise is required for achieving and maintaining one's peak potential muscle mass and strength. However, exercise cannot abolish all the negative impacts of primary aging on skeletal muscle. Even elite master's level athletes, who train and compete at a high level for most of their lives, inevitably experience a significant reduction in muscle mass with aging.⁵² An optimal comprehensive exercise training program to reduce risk of sarcopenia or as therapy ideally should include the following components:

1. resistance training following the classic pattern of 2 to 3 days per week of 8 to 10 upper- and lower-body exercises via machinery, weight lifting, and/or elastic bands in a gym or at home;
2. moderate to vigorous, aerobic/ cardiorespiratory endurance training at least 3 to 5 days per week for 30 to 60 minutes per session via walking, stationary or outdoor cycling, or swimming; and
3. flexibility and balance training, generally as a component of the warming up and cooling down for each exercise session, to reduce risk of falls and associated musculoskeletal injuries.

Furthermore, it is recommended in addition to formal exercise training that individuals perform a minimum of 150 min/wk of informal/lifestyle PA to further

reduce the risk of cardiometabolic diseases—for example, walking and working around the house and/or yard—because prolonged sitting appears from observational studies to be an independent risk factor for CVD. Even for otherwise physically active adults,⁵⁶ it should be avoided (eg, by using a standup desk instead of sitting or by interrupting sitting at least once every hour via a few minutes of standing or walking).⁵⁴ A brief review of biological mechanisms for the postulated protective effects of regular exercise against sarcopenia follows.

Biological Mechanisms for the Beneficial Effects of Exercise

Over the past several decades, animal, human, and in vitro research has provided a substantial body of evidence, identifying multiple plausible biological mechanisms for the effectiveness of exercise in reducing the risk of sarcopenia and as a component of its therapy. Based on this research, it is postulated that both resistance and aerobic exercise training can attenuate many of the molecular and biochemical processes involved in muscle decline with aging listed in Table 1. These postulated pleiotropic effects of exercise training include those described below.

Reduced Apoptosis

As mentioned, an accelerated rate of apoptosis by multiple mechanisms is postulated to be a key contributor to development of sarcopenia as well as to disuse atrophy of muscle. There is growing evidence that aerobic exercise training can reduce apoptotic signaling in both skeletal and heart muscle.¹¹ Several signaling pathways favorably affected by exercise training are currently under investigation, including the role of mitochondrial involvement in attenuation of aging-associated muscle damage. Exercise training is also postulated to reduce muscle fiber damage and necrosis by multiple adaptations discussed below.

Reduced Oxidative Stress

Regular moderate-intensity aerobic exercise has been shown in rodent and human models to both attenuate oxidative stress and promote endogenous antioxidant defenses.^{55,56} These adaptations not only provide benefit to skeletal muscle but systemically reduce damage to other types of cells and tissues. Aerobic, anaerobic, and resistance modes of exercise all appear to provide these benefits. However, in the elderly population, simply being moderately active (eg, 150 min/wk of walking) appears to substantially reduce oxidative damage. The term *hormesis* refers to the duality of regular moderate intensive and volume of exercise in reducing oxidative stress, whereas heavy physical exertion increases generation of potentially damaging ROS germinators from excessive mitochondrial respiratory chain activity.^{57,59} This term is borrowed from a pharmacological concept, according to which a large dose of a substance is toxic, whereas a lower dose has beneficial therapeutic effects.

Anti-inflammation Effects

Multiple plasma biomarkers of systemic inflammation are positively associated with primary aging. These include inflammatory cytokines, especially CRP, hepatic production of which is related to leucocyte cytokine activity. Exercise training significantly reduces circulating CRP as well as other inflammatory cytokines.^{59,60} In addition, regular exercise can increase a number of anti-inflammatory cytokines, such as IL-10, released by immune system cellular components, which inhibits the production of the potent proinflammatory cytokine, TNF- α .

Exercise training also can reduce skeletal muscle vulnerability to injury and its associated inflammatory response by improving its functional capacity and flexibility. In addition, it reduces the risk of falls and related injuries in elderly individuals. Furthermore, both aerobic and resistance training appeared to induce an increase in satellite and other

muscle adult stem cells to initiate repair and regeneration of damaged muscle.^{7,61}

Improved Insulin-Glucose Dynamics

There is strong supporting evidence that both aerobic and resistance training help maintain blood glucose homeostasis by multiple mechanisms, in addition to increasing muscle mass, thereby reducing protein glycation. Exercise training enhances glucose uptake by muscles in response to insulin as well as independent of insulin. It also promotes both glucose oxidation and its storage as glycogen.^{62,64} Furthermore, randomized controlled clinical trials have demonstrated that aerobic exercise reduces the risk of type 2 diabetes in those with prediabetic glucose levels and makes an important contribution to diabetes management.^{64,67} Exercise-induced improved insulin sensitivity also is postulated to improve muscle blood flow, in addition to enhancing liver glycogen synthesis and reducing hepatic glucose output. It should be noted, however, that these exercise-induced improvements in insulin-glucose dynamics are short-lived, and last only a few days. Thus, consistency in exercise performance is required for maintenance of this effect.

Enhanced Quality and Quantity of Muscle Proteins and Mitochondria

At all stages of life, exercise training enhances both the quality and quantity of muscle contractile and enzymatic proteins and of muscle mitochondria. Mechanisms include enhanced autophagic removal of damaged dysfunctional proteins and mitochondria in addition to stimulating anabolic signals for their replacement with healthy new ones.^{65,68} Because of a strong exercise-induced positive anabolic effect, muscle protein synthesis exceeds its turnover, resulting in a net gain. This includes the contractile protein myosin-ATPase as an enzyme required for release of ATP to provide energy for initializing contractions as well as mitochondrial and sarcoplasmic enzymes required for

aerobic and anaerobic metabolisms, respectively. These positive anabolic responses to exercise training are primarily attributed to increased circulating levels and activity of anabolic hormones, especially Human Growth Hormone (HGH) and associated muscle-derived IGF-1.⁶⁹ In addition, exercise training enhances the insulin-mediated response to absorption and circulation of essential amino acids, particularly of the branched chain amino acid, leucine, thereby reversing the decline to its responsiveness associated with aging. Aerobic exercise training also upgrades the quality, quantity, and functionality of muscle mitochondria.^{70,73} Damaged, dysfunctional mitochondria are removed by a form of autophagy called macrophagy. Replacement is with an enhanced volume of healthy new mitochondria and an enhanced network. The primary mechanism responsible for this mitochondrial upgrade is postulated to be an exercise training-induced upregulation of a protein called PGC- α (peroxisome activated receptor gamma coactivator-1- α).^{72,73} PGC- α is a coactivator of the *PPAR* gene. Activation of this gene also is postulated to be responsible for muscle fiber-type changes with aging, a reduction in oxidative damage to aging muscle, and enhanced muscle insulin sensitivity. Defects in this gene have been implicated in the pathophysiology of many of the health problems contributing to secondary aging. These include obesity, type 2 diabetes, and atherosclerotic CVD. Risk for all these conditions is postulated to be reduced by regular aerobic PA.

Skeletal Muscle Hypertrophy

Resistance training is the most effective approach known for increasing muscle hypertrophy and strength at all stages of life, including in frail, elderly individuals.^{7,74} However, the increase in muscle mass and strength with resistance training is specific to the muscle groups involved in the training and is less effective in older, as compared with younger people, and in older women as compared with men of the same age. Furthermore, a larger

volume of exercise is required for maintenance of induced hypertrophy in older as compared with younger adults.⁷⁴ As discussed later in the section on nutritional support, there is evidence accumulating that an increase in protein intake in proximity to an exercise session can enhance training-induced muscle hypertrophy. The associated training-induced muscle fiber hypertrophy appears to primarily affect the type 11b slow twitch fibers, which are primarily affected by aging. There is concern, however, based on recent studies that simultaneous sessions of aerobic and resistance training may blunt the hypertrophy response to resistance training.⁷⁵ This observation requires confirmation, and if it is correct, there is a need to establish the optimal period between sessions of these 2 forms of exercise.

Biological mechanisms contributing to the development of skeletal muscle hypertrophy in response to resistance training include enhanced protein anabolism and an increase in satellite and other myogenic progenitor stem cell number and activity.⁶⁸ As mentioned, satellite cells induce hypertrophy by fusing to existing myofibers, in addition to their role in repairing or replacing injured muscle cells.¹⁰ Another mechanism, postulated to contribute to resistance training-induced hypertrophy, is the reduction in the release by muscle fibers of myostatin, a muscle parakine that inhibits satellite cell proliferation.⁶⁸ In addition to inducing muscle hypertrophy, resistance training strengthens the tendons of the exercised muscle, particularly at their junction with bone.

Positive Neuromuscular Adaptations

Neuromuscular adaptations to exercise training also are postulated to significantly contribute to the prevention and management of sarcopenia.⁷⁶ Exercised muscles release several polypeptide neurotrophins and upregulate their muscular receptors. These include brain-derived neurotrophic factor. These neurotrophins have multiple beneficial effects on muscle motor units, which include the following:

1. Reduced loss via apoptosis of α MN
2. Increased number of terminal branches of motor nerve
3. Increased synapses at NMJs
4. Increased flow of Ca and the neurotransmitter, Ach across the NMJs

These neuromuscular adaptations enhance development of muscle hypertrophy and speed and force of contractions and, hence, muscle power.

Enhanced Muscle Blood Supply

In addition, exercise training reduces the risk of sarcopenia by significantly enhancing cardiovascular system functions and muscle blood flow at all stages of life.⁷⁷ During each acute bout of aerobic exercise, there is an increased perfusion to skeletal muscle composed predominantly of type 1 slow-twitch, highly oxidative fiber.⁸⁰ Thus, the delivery of oxygen and nutrients to muscles with a high mitochondrial density for aerobic metabolism is enhanced. Mechanisms for this hyperemic response include local metabolic changes, training-induced alterations in neurohumoral regulations of vascular tone in small-resistance arteries and structural alterations in peripheral vasculature (ie, vascular remodeling and angiogenesis).^{77,78}

Furthermore, aerobic exercise training counteracts vascular endothelial cell dysfunction associated with aging and reduces modifiable risk factors for CVD causing ED, including physical inactivity. Exercise-induced increased shear stress on vascular endothelial linings increases synthesis release and duration of action of NO, a potent vasodilator. In addition, in sedentary older persons, aerobic exercise training has consistently been demonstrated to maintain and enhance the compliance/elasticity of the aorta and other major elastic arteries as well as the blood flow in major arteries via multiple antiatherogenic and antithrombotic effects.^{43,44}

Aerobic exercise training also has been consistently demonstrated to promote skeletal muscle (as well as myocardial)

angiogenesis—that is, increased capillary density per unit of muscle mass.^{43,77}

Increased skeletal muscle capillarization appears to be specifically associated with the motor units recruited during exercise training. Angiogenesis is postulated to be induced by exercise training either by proliferation of vascular endothelial cells from existing capillaries and their differentiation into new sprouting capillaries or by circulating endothelial progenitor cells forming new capillaries. Stimulus for both these processes is postulated to be related to exercise-induced NO-induced release of vascular endothelial growth factors from vascular endothelium.⁷⁸

Nutritional Strategies

In addition to regular PA, other behavioral strategies are generally recognized as effective for reducing the rate of aging processes as well as for promotion of general health. These include the following: healthy eating habits; not smoking; alcohol in moderation, if used; adequate sleep; and maintaining optimal body weight. Table 2 summarizes current nutritional recommendations postulated to reduce the risk of sarcopenia and comorbidities.^{79,81}

Healthy Nutritional Habits

These include regular energy-balanced meals, consisting of an adequate intake of whole grains, fruits and vegetables, low-fat/fat-free dairy products, and daily servings of other protein-rich animal products (including lean meat, poultry, and fish) and/or protein-rich beans, nuts, and legumes, with a limited intake of total saturated and trans fats, cholesterol, sugar, and salt to reduce the risk of CVD.

There is only limited research on the contribution of nutrition to help achieve peak muscle mass; however, undernutrition during childhood has been associated with increased risk of frailty in older adults.⁷⁹ Furthermore, observational studies report an increased risk of sarcopenia with a low food energy intake later in life, particularly in older adults, which generally is

Table 2.

Nutritional Recommendations to Reduce Risk of Sarcopenia and Comorbidities.

1. Follow national guidelines for a healthy balanced diet
2. Adequate food energy intake
3. Increased requirement for good quality proteins
4. Maintenance of adequate circulating vitamin D levels from sun exposure diet, and/or supplements.
5. Adequate intake of food sources of exogenous antioxidants

associated with insufficient intake of protein, vitamin D, and antioxidants.⁷⁹⁻⁸¹ A brief review of supporting evidence of these nutritional concerns follows.

Adequate Food Energy Intake

American adults typically experience a progressive increase in body weight of 25 to 30 pounds between physical maturity and 50 to 55 years of age. This is primarily attributed to fat accumulation resulting from a reduction in PA. Generally, this is followed by a progressive decline in body weight caused by a loss of both fat and fat-free mass usually associated with reduced food energy intake.⁸²⁻⁸⁵ This reduction in food intake is attributed primarily to an aging-associated decline in appetite and the consumption of smaller meals as well as less snacking. This phenomenon has been termed the *anorexia of aging*.⁸⁶ Multiple physiological mechanisms are postulated to be associated with the genesis of this condition. Psychological and social factors associated with aging also are strong contributing factors to reduced food intake. Thus, elderly people are generally at increased risk of malnutrition. Estimates of the prevalence of undernutrition in older community-dwelling adults varies according to the various criteria used but is consistently high.

Although in animal models, caloric restriction extends the life span, in elderly humans, anorexia of aging appears to have detrimental consequences. These include

accelerating the loss of muscle mass and strength (increasing risk of falls), increased susceptibility to infections, increased health care requirements, and an increased mortality rate.^{84,85} In fact, the association between body mass index (BMI) and mortality has consistently been shown to have a U- or J-shaped configuration, with better health outcomes and longevity observed for elderly men and women in the overweight category of the current BMI classifications (ie, 25 to 29 kg/m²). Furthermore, a longitudinal study in Hong Kong showed that a weight reduction of 2 kg over a 2-year period in older adults increased the relative risk of mortality 5-fold, whereas a weight gain was not associated with increased mortality, following statistical adjustment for age, health status, income, and baseline BMI.⁸⁵ In addition, other observational studies have reported that the lowest mortality rate in Americans 65 to 85 years of age occurs in those who were classified as mild to moderately obese but were also aerobically fit, as compared with those who were not overweight or obese but were not fit.⁸⁶ Thus, based on these data with respect to body weight for successful aging, including reducing risk of sarcopenia, the emphasis should be on intake of sufficient energy from nutrient-rich food for weight maintenance rather than on weight reduction in the absence of chronic disease indications in obese elderly individuals.

Increased Protein Intake

Adequacy of intake of high-quality protein is extremely important for reducing the risk of sarcopenia as well as for its management.^{79,81,87,90} In addition, adequate protein intake appears to optimize responsiveness of skeletal muscle to exercise training.⁸⁹ Longitudinal observational studies, involving older community-dwelling men and women, have demonstrated via DEXA imaging, a strong association between a deficient protein intake (adjusted for energy intake) at baseline and subsequent increased rate of loss of lean body mass.⁹⁰ In addition, because aging blunts the anabolic response to the postabsorptive surge in blood amino acid levels following protein ingestion, there is growing support for raising the recommended daily allowance (RDA) for protein in older adults from 0.8 g per kg of body weight to 1.0 g per kg or more. Such an increase is postulated to reduce the rate of decline of muscle mass with aging, but currently, this remains to be proven.

In addition, the quality of protein in terms of essential amino acid content and digestibility also should be taken into consideration. High-quality protein can be obtained from reduced-fat/fat-free dairy products; egg whites; meat, poultry, and seafood; and via combinations of plant sources—for example, soy products plus whole grains. However, experimental administration to animals as well as humans of high-quality protein or amino acid supplements alone have yielded mixed results in terms of independently attenuating aging-related muscle loss or for restoring reduced muscle mass.

On the other hand, there is growing evidence that suggests that feeding high-quality protein or supplementation during a resistance training program increases the resulting muscle hypertrophy as compared with resistance training alone. An optimal anabolic response, based on dose-response study evidence, is associated with administration of 20 g or more of dairy protein either during or immediately following each training session.⁸⁷⁻⁹⁰

Whey, derived as a byproduct of cheese processing, appears to be the most effective dairy protein, as an anabolic stimulant. It is rapidly digested, resulting in an accelerated rise in blood levels of all the essential amino acids. It is also rich in the branched-chain amino acid leucine, which is postulated to be the most potent amino acid anabolic trigger for protein synthesis. Furthermore, there is evidence that the induced augmented anabolic response to a resistance training session from protein ingestion persists for 24 to 48 hours and is increased by sufficient increments of protein during this window of opportunity. Additional research is clearly needed to confirm these interesting, potentially important findings.

Adequate Vitamin D Blood Levels

During the past decade, there has been an enormous surge in published research on the postulated contributions of vitamin D to health promotion and disease prevention,⁹¹ far beyond its long-recognized role in body calcium homeostasis and bone health. This includes the findings from a wide range of human, animal, and cellular research studies on the impact of vitamin D on skeletal muscle function and metabolism and adverse health conditions associated with deficiency states and their responsiveness to replacement therapy. Technically, vitamin D is not a true vitamin. It is instead a precursor of a steroid hormone obtained in humans predominantly (>90%) via a nondietary source—that is, by photosynthesis in the skin from 7-dehydrocholesterol (DHC) on sun exposure to sunlight-derived ultraviolet B (UV-B). The derived prohormone, cholecalciferol (D_3), is also provided by a limited number of food sources, particularly fish and fish oil supplements (eg, cod liver oil). It is also obtained in a limited amount from fortified dairy and cereal products. Enrichment of food products is, generally, with vitamin D_2 or (ergocalciferol), derived by UV-B exposure of plant sterols (eg, in mushrooms). Both forms of vitamin D

are immediately transported by a carrier protein to the liver, where they are converted to 25-hydroxy D —25 (OH) D —plasma levels of which serve as a biomarker commonly used to assess adequacy of vitamin D stores. A second hydroxyl group is subsequently added primarily by the kidneys to form 1,25 (OH) $_2$ D (calcitriol) the active steroid hormone derivative of vitamin D. Genomic and nongenomic vitamin D receptors (VDRs) for calcitriol are present in most tissues and cells of the body, including skeletal muscle.⁹⁵ It is estimated that about 2000 genes regulated by calcitriol are responsible for a wide range of biological actions. Activation of VDR in skeletal muscle increases the expression of the contractile proteins actin and myosin as well as other proteins located in fiber sarcoplasm.⁹⁵ Calcitriol is postulated to contribute to many additional processes favorably affecting muscle strength and attenuating aging-related muscle loss and to attenuate aging-related muscle loss by multiple mechanisms, including the improved neuromuscular functioning by enhancing Ca uptake, increased membrane phospholipid composition, improved insulin sensitivity, and anti-inflammatory effects.^{92,96}

Hypovitaminosis D has been defined by National Health and Nutrition Examination Survey (NHANES) as a serum 25 (OH) D level of <15 ng/mL or 37.5 nmol/L. The prevalence of vitamin D deficiency increases with age in Americans, reaching a prevalence of 70% in adults 60 years and older.⁹⁸ Observational studies have consistently reported an association between reduced 25 (OH) D levels in community-dwelling adults and chronic muscular skeletal pain (myalgia), low muscle mass on DEXA and osteopenia imaging, reduced upper- and lower-body strength and power, about a 4-fold increase in frailty, and increased risk of fall-related injuries.^{92,96}

Contributing factors to reduced 25 (OH) D with aging include limited sun exposure in both community-dwelling and assisted-living individuals. Furthermore, aging skin has reduced

7-DHC levels and hence reduced ability to synthesize vitamin D_3 on UV-B exposure, particularly in those with dark skin or on using sunscreen, especially in the fall and winter seasons in northern latitudes in North America. In addition, elderly individuals commonly have a low dietary intake of major natural or fortified sources of vitamin D (ie, fatty fish and dairy products). Reduced gastrointestinal absorption of vitamin D with aging and a decline in nuclear VDR in skeletal muscle may be additional contributors to the above observational study findings. The RDA for vitamin D and tolerable upper-limit levels vary in different age groups with 600 to 800 IU (15 to 20 μ g) daily considered sufficient to optimize bone health. However, for most of the US population, a higher vitamin D intake (1000 to 2000 IU) appears to be required to maintain 25 (OH) D at optimal levels (ie, >30 ng/L or >75 nmol/L), particularly in older adults.

There have been only a limited number of large controlled randomized trials that have studied the effects of vitamin D supplementation on muscle mass and function as well as incidence of falls in healthy community-dwelling elderly individuals.^{97,98} These trials have yielded mixed results, which is understandable given the differences between studies in regard to entry criteria, dosage of vitamin D supplements, and measurement criteria. It appears from meta-analyses of these trials that elderly individuals, who are the most deficient in vitamin D levels, and those with the poorest baseline strength and mobility are the most likely to exhibit significant improvements in study parameters with vitamin D supplementation. Stockton et al⁹⁸ in their meta-analysis, based on data primarily related to reduced incidence of falls and associated fractures, recommend the titration of the dosage of a vitamin D supplement required to attain a proposed optimal level of serum 25 (OH) D of 30 ng/mL or more. Furthermore, it is clearly evident that those with severe vitamin D deficiency (15–20 ng/mL) stand to gain the most in terms of muscular benefits from vitamin D supplementation. Large

randomized controlled clinical trial research is required to determine the role of vitamin D supplementation alone and in combination with exercise training for the prevention and management of sarcopenia and frailty.

Food-Derived Antioxidants

Oxidative stress, contributing to loss of muscle mass with aging, is counterbalanced by both the body's endogenous antioxidant enzyme defense system and by exogenous dietary antioxidants. Antioxidants present in fruits and vegetables include ascorbic acid, β carotene and other carotenoids with or without provitamin A activity (eg, lutein and lycopene), flavonoids and other polyphenol phytochemicals (eg, resveratrol in the skin of red grapes and berries), and the minerals selenium and zinc. In addition, vitamin E/tocopherols are derived in the diet primarily from vegetable oils. A low intake of these dietary antioxidants is common in elderly individuals.

A positive association has been reported in longitudinal observational studies between blood biomarkers of exogenous antioxidant states and skeletal muscle function, and risk of sarcopenia in older men and women.⁹⁹⁻¹⁰¹ For example, in the Italian Chianti Aging Study,¹⁰⁰ which involved 929 men and women older than 65 years, high plasma levels of total carotenoids (generally regarded as a biomarker for fruit and vegetable intake) and other dietary antioxidants was associated with reduced risk of developing severe walking disability over a 6-year observational period. This association persisted after adjustment for potential confounding variables, including PA habits, skeletal muscle strength, physical performance, and reduced comorbidities. However, there have only been a limited number of randomized controlled trials to determine the effects of antioxidant nutrients or phytochemical supplements on muscle strength and other functions in elderly individuals.¹⁰¹ Furthermore, existing studies have yielded mixed results and raised questions regarding the usefulness of antioxidant

supplements in reducing the risk of sarcopenia. Also, there is concern that administration of antioxidant supplements may impede physiological adaptations to exercise training. In addition, there are safety concerns, including possible increased risk of malignancies, particularly in cigarette smokers, because immune defense system cells use blasts of ROS to destroy malignant cells. Thus, public health authorities and gerontologists recommend limiting antioxidant intake to dietary sources with supplements primarily reserved for prevention and management of age-related macular degeneration, a common cause of nontraumatic blindness in elderly individuals.

Conclusions

Aging is associated with multiple molecular and biochemical skeletal muscle changes, which contribute to the development of sarcopenia and, ultimately, frailty. A lifelong comprehensive exercise program and healthy eating habits are postulated to attenuate many of these biological processes, reducing the risk and/or improving these conditions, thereby improving quality of life of elderly individuals. However, controlled clinical trials are required to prove these postulated beneficial lifestyle benefits. Nevertheless, the potential benefits of these lifestyle recommendations, as compared with risks, makes them worth pursuing in the interim.

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