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Dr. Munin is a consultant with Ipsen, Inc. Dr. Kortebein is an employee of Novartis Pharmaceuticals Corporation. Doctors Buzanowska and Berry have reported no relationships with proprietary entities producing health care goods or services.

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Sarcopenia: A Primer for Physiatrists

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Case Vignette

RM is an 82-year-old woman who presents to the UPMC Physical Medicine and Rehabilitation Clinic for a follow-up appointment due to persistent fatigue and weakness. She had completed a two-week inpatient rehabilitation stay following a seven-day intensive care admission for pneumonia with acute respiratory distress syndrome. While she had been fully independent previously, RM was discharged home from rehabilitation at a modified independent level for household ambulation using a wheeled walker, and a rollator with a seat for community ambulation.

Today, she reports she is receiving physical therapy once per week at home, but still feels "weak." She has difficulty rising from a chair and negotiating stairs. She also reports that she seems to tire quickly and has to take frequent rest breaks when she is walking around her home and performing her activities of daily living (ADLs). Her children have been taking turns staying with her to provide supervision and assistance with ADLs. She had one non-injurious fall at home since discharge. On examination, she has normal strength and sensation in the upper and lower extremities with negative Romberg testing. She has trouble rising from a chair, and her Short Physical Performance Battery (SPPB) score is 7 placing her at more than a two-fold higher risk of rehospitalization compared with a normal older adult.[1]

RM wants to know what she can do to return to her prior level of independence. She is fearful that she is becoming a burden on her family, and is worried that she will "have to be put in a home." Her daughter has heard the term "sarcopenia" in the news, and wonders if this condition might apply to her mother.

Definition and Epidemiology

Sarcopenia is a condition that should be of interest to virtually all physiatrists, as it adversely impacts skeletal muscle and physical function, both areas of physiatric expertise. In addition, physiatrists will be seeing an increasing number of older patients with sarcopenia and related conditions.

Sarcopenia was originally defined as the age-related loss of muscle mass.[2] However, over the years, the term has evolved in the literature to encompass a loss of strength and/or function in addition to muscle loss.[3-5] For example, a recent consensus statement on sarcopenia proposed the inclusion of functional measures, such as gait speed, in the evaluation and diagnosis of sarcopenia.[3] While some authors have advocated for the use of a separate term — dynapenia — describing the age-related loss of muscle strength and power,[4] most authors in this area utilize the expanded definition of sarcopenia.

The origin of this alternate terminology (i.e., dynapenia) stems from the well-known fact that declines in mass and strength are not proportionate, and that decreased strength in the aged typically exceeds losses in muscle mass.[5] In addition, it has long been recognized that muscle strength is not solely dependent on muscle size.[6] While sarcopenia may be a new term, it is important to distinguish this disorder from the related conditions anorexia and cachexia. Anorexia is weight loss of all body components (i.e., muscle and fat) due to reduced caloric intake, while cachexia is associated with an underlying illness, typically with an increased inflammatory component, that results in a loss of muscle mass with or without a loss of fat mass or weight change.[7]

At the current time, there are no standard diagnostic criteria for sarcopenia, although several have been proposed.[3-5] Utilizing osteoporosis as a paradigm, sarcopenia has been defined as a reduction in skeletal muscle mass as compared to young adult reference values using either relative muscle mass (RMM) or a skeletal muscle index (SMI). The RMM is calculated by taking an individual's appendicular skeletal muscle mass as measured by dual x-ray absorptiometry (DEXA), divided by the square of their height.

Sarcopenia has been defined as an RMM more than two standard deviations below a young reference population.[9] In contrast, the SMI is calculated by dividing an individual's total muscle mass, as measured by bioelectric impedance analysis (BIA), by their total body mass. According to proposed criteria, subjects have class I sarcopenia when their SMI falls between one and two standard deviations below the mean, and class II sarcopenia when their SMI falls more than two standard deviations below the mean.[10] Additional measures of muscle mass in the literature include mid-thigh and mid-arm circumference, as measured by either computerized tomography (CT) or magnetic resonance imaging (MRI), although these measures have not generally been incorporated into the diagnostic criterion proposed to date.[3]

In one of the first attempts to examine the prevalence of sarcopenia, Baumgartner et al reported that 15% of males and 24% of females aged 65 to 70 years had sarcopenia as measured by RMM, and that 50% of both sexes >80 years were sarcopenic.[9] Ianuzzi-Sucich et al studied another U.S. population and reported that 53% of men and 31% of women over the age of 80 years had sarcopenia.[11] Using data from the U.S. Third National Health and Nutrition Exam Survey (NHANES III), Janssen et al reported that 50% of men and 72% of women over the age of 80 met criteria for sarcopenia as measured by the SMI.[10] Interestingly, the reported prevalence in non-U.S. populations has generally been lower. In a population of Danish women, only 12% of individuals over 70 years were identified as sarcopenic using RMM/SMI,[12] while in a Taiwanese population, Chien et al noted a prevalence of about 20% in subjects over 80 years.[13]

Multiple studies have reported that sarcopenia is independently associated with physical disability and functional impairment, including impaired ambulation and the inability to rise from a chair.[5,10] Further, the diagnosis of sarcopenia has been independently associated with the use of a walker and falls, even when adjusted for age, obesity, and medical comorbidities.[8,13] Slow gait speed has been used as one criterion for sarcopenia, and has been independently associated with ADL disability as well.[14] Thus, sarcopenia has a clear detrimental impact on physical function in older adults, and this will become a significant societal concern in the coming decades, due to the burgeoning older adult population.

Pathophysiology

The etiology of sarcopenia has not been fully elucidated; however it is clearly a multifactorial process with dysfunction of skeletal muscle and the nervous system most predominant.

Skeletal Muscle

While the mechanical properties of aged skeletal muscle appear to be the same as that of younger muscle, the contractile force of older muscle is mildly impaired due to alterations in the excitation-contraction coupling system.[15] In addition, lipid infiltration of aged human skeletal muscle is well documented, and is thought to adversely impact muscle contractile function. Although the mechanism of this process is incompletely understood, it appears that the deposition of lipid within skeletal muscle may reduce oxidative capacity. It also has been noted that muscle satellite cells (i.e., skeletal muscle cell precursors) not only decrease in number with age, thus limiting the overall regenerative capacity of muscle, but also may express an adipocytic phenotype.[16]

The maintenance of skeletal muscle mass requires that the rate of muscle protein synthesis be in balance with the rate of muscle protein degradation. While aging itself has been postulated to be an independent factor contributing to a reduction in muscle protein synthesis, the general consensus is that there is no decline in muscle protein synthetic capacity with aging.[7] However, hormonal changes with aging, including declines in anabolic factors such as testosterone, growth hormone, and IGF-1 (insulin-like growth factor 1) are felt to be key contributors to sarcopenia. In addition, many older adults have a chronic low-level inflammatory process (unrelated to infection or illness) with elevated levels of inflammatory cytokines, such as TNF-α (tumor necrosis factor alpha) and IL-6 (interleukin 6).This inflammatory milieu results in an augmentation of muscle degradation.[17] Insufficient protein intake is quite common among older adults, and this is most certainly a significant factor affecting muscle protein synthesis. In fact, it has been proposed that the current recommended dietary allowance for protein (0.8 g/kg/d) should be increased by 50% or more (1.2 to 1.5 g/kg/d).[18]

Reactive oxygen species generated from oxidative metabolism cause internal cell damage, particularly to mitochondrial DNA (mtDNA). While the role of altered mtDNA is still under investigation, studies indicate that skeletal muscle apoptosis and net muscle fiber loss, as well as compromised muscle cellular respiration may result.[19] Finally, some studies have found that there may be an age-associated loss of intrinsic muscle fiber elasticity, and that the tendons of older individuals are more compliant compared to younger subjects; this abnormal tendon elasticity can result in decreased force transmission to bone.[17]

Nervous System

The aging process generally affects all levels of the nervous system, from the cortex, spinal cord, and peripheral nerves down to the neuromuscular junction. Dysfunction at each of these levels contributes to the decline in skeletal muscle mass and function in aging humans.

As the healthy human brain ages, there is a global loss of brain tissue, although it appears that this loss is not uniform. In a study comparing young and older (>80 years) individuals, it was found that the primary sensory and motor cortices of older subjects had the greatest volume loss.[20] In addition, other studies have found that in older humans there is a reduction in the cell-body size of premotor cortex neurons, and cortical atrophy near the primary motor cortex. Normal aging also has been noted to result in a decline in neurotrophic factors within the motor cortex, increased GABA-mediated intracortical inhibition resulting in hypoexcitability, and reduced cortical plasticity.[21] These changes result in impaired descending drive to the corticospinal tract and alpha-motor neurons.

Aging also has been shown to result in a decline in spinal cord excitability and a loss of alpha-motor neurons. There is a more pronounced loss of type II (fast twitch) motor units; as such, the remaining type I (slow twitch) motor units reinnervate the denervated type II muscle fibers (see Figure 1 on Page 4). Thus, while there is little change in the average cross-sectional area (CSA) of type I muscle fibers, type II fiber CSA has been noted to decrease substantially with age.[22]

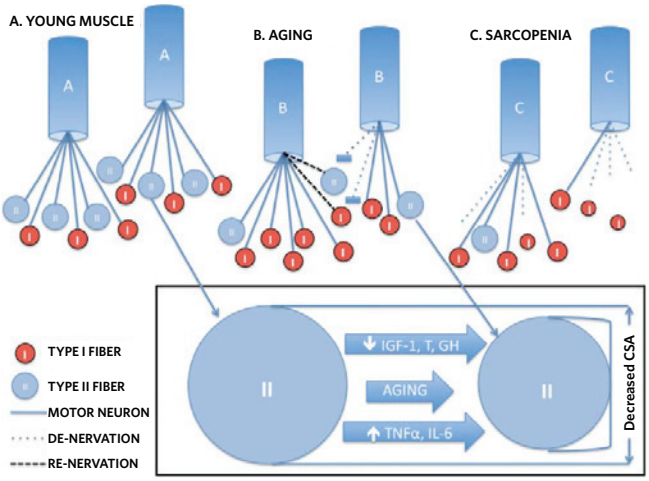

FIGURE 1: **Effect of age on the motor unit, depicting young, aging, and aged sarcopenic fibers.** This drawing depicts the pronounced denervation of type II fibers and the incorporation of type I muscle fibers into surviving motor units in older subjects. In addition, there is impaired recruitment in sarcopenic subjects, as well as biochemical changes that cause type II fibers to decrease in cross-sectional area (CSA) due to the effects of systemic inflammatory factors (IGF-1, GH, TNFα, IL-6). Source: Lang, et al. (2010), *Osteoporos Int.* "Sarcopenia: etiology, clinical consequences, intervention and assessment."

Diagnosis

The diagnosis of sarcopenia in clinical practice has been confounded by the fact that even the definition remains controversial. As noted, while sarcopenia was originally defined as the age-related loss of muscle mass, the term has been expanded over the years to incorporate muscle strength and physical function (e.g. gait speed). In addition, there is not even a consensus as to whether the diagnosis of sarcopenia should include an age cutoff. Nonetheless, in the past several years a number of groups have proposed diagnostic criteria for sarcopenia.[3-5] There is consensus across these three recent criteria (see Table 1) regarding low muscle mass, while there is divergence with the gait speed cutoff and the use of a strength measure. It also is important to note that these groups recognized that sarcopenia needs to be distinguished from other recognized medical disorders (e.g. specific muscle diseases, peripheral vascular disease, central or peripheral nervous system diseases, and cachexia).

While the diagnosis of sarcopenia in clinical practice remains an inexact science, physiatrists can play an instrumental role in the evaluation of these patients by utilizing their diagnostic expertise in neurologic and musculoskeletal disorders to exclude other conditions that impact ambulation and function. Abellan Van Kan et al have suggested an algorithmic approach for identifying older adults with sarcopenia in clinical practice based on the current working group definitions[23] (see Figure 2 on Page 5). For example, a spine physiatrist will be able to readily determine that an older patient's slow gait speed is due to neurogenic claudication, and thus obviate an evaluation for sarcopenia (see Table 2 on Page 5). As the interest in sarcopenia continues to grow, there will most certainly be opportunities for physiatrists to become engaged in the diagnostic evaluation of these patients.

Treatment

Resistance Exercise

Resistance exercise is the only intervention that has consistently demonstrated evidence of benefit, and is recommended for both sarcopenia prophylaxis and treatment. Progressive resistance exercise training in older adults has been shown to improve muscle strength to the

TABLE 1:

Proposed Sarcopenia Diagnostic Criteria

ESPEN Special Interest Groups[3]	European Working Group on Sarcopenia in Older People[4]	Sarcopenia With Limited Mobility[5]
1) Low Muscle Mass: > 2 SD below mean young reference population	1) Low Muscle Mass: > 2 SD below mean young reference population	1) Low Muscle Mass: > 2 SD below mean young reference population
2) Low Gait Speed: <0.8 m/sec	2) Low Gait Speed: <0.8 m/sec (or low grip strength if gait speed >0.8 m/sec)	2) Low Gait Speed: < 1 m/sec

FIGURE 2: **Sample algorithm for diagnosing sarcopenia in the office.**[23]

same degree as younger individuals in addition to improving functional activities such as gait speed, and stair climbing ability.[24] Resistance exercise (RE) guidelines explicitly designed for older adults provide clear recommendations for novice to experienced exercisers.[25] While standard RE regimens typically include two to three sets of 10 to 15 repetitions, improvements in muscle strength in older adults can be achieved with as little as one resistance exercise training session per week. Initial resistance may be as low as 40% to 50% of maximum (e.g. one repetition maximum), however, programs should generally be progressive in nature with a goal resistance of 70% to 80% of 1-RM. Table 3 (see Page 6) is a sample resistance exercise program for an older adult with sarcopenia, utilizing resistance exercise equipment as may be found in a physical therapy or fitness facility. An alternative program utilizing other resistance training equipment or methods (e.g. resistance bands, body-weight exercises) may be developed in conjunction with a physical therapist.

In general, resistance exercise is safe for older individuals although there are some absolute contraindications, such as decompensated heart failure and severe aortic stenosis. Cardiac screening may be necessary for some individuals based on AHA guidelines.[26]

Nutrition

Protein supplementation may increase muscle strength, although no definite functional benefit has been found. While the primary goal of adequate protein intake is to maintain (or augment) muscle mass, resistance exercise is necessary to improve strength and function. As noted, the current recommended dietary allowance for protein is 0.8 g/kg/d, although it has been suggested that this should be increased to 1.2 or even 1.5 g/kg/d; unfortunately, about 40% of individuals over 70 years of age do not meet even the current lower recommendation. Essential amino acid (EAA) supplementation for three months has been shown to improve walking capacity and isometric muscular strength, although EAAs are not readily available commercially. Thus, foods rich in protein that may be recommended for older patients include lean meats, low fat dairy products (e.g. milk), nuts, and soy products (e.g. tofu); commercially available protein supplements (e.g. Ensure, Boost) may be considered as well.

TABLE 2:
Differential Diagnosis of Decreased Muscle Mass and Decreased Gait Speed

Differential diagnosis of decreased muscle mass	Differential diagnosis of decreased gait speed
Sarcopenia	Neurogenic claudication/spinal stenosis
Anorexia	Knee/hip osteoarthritis
Cachexia	Low back pain (e.g. facet arthropathy)
	Myopathy
	Myositis, including polymyalgia rheumatica
	Demyelinating inflammatory neuropathy
	Peripheral neuropathy
	Neuromuscular junction disorder
	Malignancy
	Anemia

TABLE 3:

Sample Progressive Resistance Training Program Prescription

Sets	Repetitions per Set	Intensity	Frequency
1 set: Novice exerciser 2 to 4 sets: Experienced exerciser	10 to 15	40% to 50% of 1RM (very light to light intensity) Goal: Gradual progression to 70% to 80% 1-RM	2 to 3x a week (non-consecutive days)
Exercises: Upper extremity: Bench press, seated row, elbow flexion/extension; Lower extremity: Leg press (squat/lunges), knee extension/flexion			
Note: Exercises should be selected based on clinical indication.			
Note: 1-RM = maximum weight a person can lift through a full range of motion one time for a given exercise. Sample 1-RM calculation: W/(1-0.02 x R) with W = weight/resistance, and R = number of repetitions.[24,25]			

Medications/Supplements

Although not well studied in sarcopenic populations, other potential therapeutic interventions include the use of hormonal therapies (e.g. testosterone, estrogens, growth hormone), nutritional supplements (e.g. vitamin D, creatine) and angiotensin-converting enzyme inhibitors (ACE-I). The evidence supporting these therapies is weak and the risks often outweigh the benefits.[27] For example, Basaria et al[28] reported that testosterone supplementation in older men with mobility limitation and low testosterone levels was associated with improvements in muscle strength and stair-climbing power. However, the trial was stopped due to an increased frequency of adverse cardiovascular events in the testosterone group. The current Endocrine Society Practice Guideline recommends testosterone replacement therapy only in men diagnosed with androgen deficiency who experience symptoms and signs unequivocally consistent with low testosterone levels.[29]

Clinical Vignette Outcome

While RMs generalized weakness was most certainly due to her ICU illness and prolonged hospitalization, further evaluation was completed to determine whether she met criteria for sarcopenia. Given her ICU stay, critical illness myopathy and polyneuropathy also were considerations; however these were excluded with electrodiagnostic testing.

RM's gait speed from her initial SPPB was 0.7 m/s, and she underwent DEXA testing for assessment of appendicular muscle mass; her SMI was calculated at 4.9 kg-m-2 (> 2 SD below lower limit of reference normal values). Based on these measurements, she was diagnosed with sarcopenia.[4]

After being medically cleared for an exercise program based on American Heart Association guidelines, she was prescribed a course of outpatient physical therapy, including a progressive resistance exercise training program for key muscle groups of the lower and upper extremities (seated leg press, knee flexion and extension, chest press, seated row, bicep curls, and triceps extensions). Exercises were to be performed two days per week with two sets of 10 to 15 repetitions at an intensity of 50% of her calculated 1-RM (completed by her physical therapist) with a goal of 70% to 80% of her 1-RM. In addition, she initiated an aerobic exercise program comprised of a 10-minute walk with a five-minute warm up and five-minute cool down three days per week, with a goal of 20 to 30 minutes. She also was referred to a dietitian for recommendations on optimizing her protein intake (goal 0.8-1.2 g/kg/d).

When seen at her three-month follow-up visit, RM had completed her physical therapy program and transitioned to a home resistance and aerobic exercise program at a local gym. She had progressed to an intensity of 75% 1-RM with all of her resistance exercises and was walking for 25 minutes (excluding warm up/cool down) three days per week. On functional testing, her SPPB score had improved to 11. She reported that she no longer required hands-on assistance with her activities of daily living and was ambulating in her home without an assistive device, but continued to use the rollator in the community for safety. While she had not fallen, she did not feel that she was back to her baseline and moved in with her daughter where more consistent supervision was available. She was advised to continue her current exercise program with a goal of returning to her premorbid-level of function.

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