Sarcopenia: A toolkit to guide diagnosis and treatment

by

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Submitted In partial fulfillment of the requirements

for the degree

Master of Science in Dietetics

MOUNT MARY UNIVERSITY

Date May 2021

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ABSTRACT

The negative impacts of sarcopenia come at a huge human and financial cost to individuals, their family, and society. The disease is better defined and identified now, but still under-treated. There is a need for education in the area of diagnosis and treatment of sarcopenia. As the definition and diagnosis are refined and operationalized, treatment is better addressed. The lack of consensus in these areas have hindered treating sarcopenia.

Muscle mass is regulated by the balance between muscle synthesis and breakdown, with the two major environmental influence on these processes being food intake and physical activity. Everyone loses muscle mass as part of the aging process, however, not all older adults meet the criteria for a sarcopenia diagnosis. There are individual differences in the rate of muscle mass loss, the age muscle mass starts to decline, and the extent to which strength and function are affected as part of the aging process. In older people muscle protein synthesis response to a single anabolic stimulus may be blunted. Adoption of multimodal strategies, particularly focusing on protein intake and physical activity, is the most plausible approach to treatment and prevention of sarcopenia.

Toolkits are a collection of resources on a particular topic that can be used in a variety of ways. Toolkits are available for certain diseases and are designed for use by healthcare professionals or for clients and patients. They are meant to be user friendly and to facilitate the translation of evidence into practice. This project aims to create a toolkit to guide healthcare professionals in the diagnosis and treatment of sarcopenia.

ACKNOWLEDGMENTS

I would like to thank my family, friends, and coworkers for their support through my undergraduate and graduate studies. Without their encouragement I would not have made it to this point.

I would especially like to thank Dr. Megan Baumler. She was instrumental in assisting me through the completion of this project. I never would have finished without her guidance.

I would finally, like to thank Mount Mary University and all of the professors I learned from. They helped shape me as a dietitian and grow as a person.

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Chapter 1: Introduction

The European Working Group on Sarcopenia in Older People (EWGSOP) developed a practical clinical definition and diagnostic criteria for age-related sarcopenia (1). Sarcopenia is defined by EWGSOP as a muscle disease involving muscle failure, rooted in adverse muscle changes that occur across a lifetime, and is further defined by low measures for three parameters: muscle strength, muscle quantity/quality, and physical performance as an indicator of severity (1). Other groups including the International Working Group on Sarcopenia (IWGS), The Asian Working Group for Sarcopenia (AWGS), and The Foundation for the National Institute of Health (FNIH) Sarcopenia Project have also developed similar definitions. The loss of muscle mass and function is a natural process that starts in the third decade of life and accelerates somewhere between age 65 and 80; disease states can further accelerate this process (1). Standardizing an operational and clinically applicable definition is important, not only for research purposes, but to develop prevention and treatment strategies. The development of definitions and guidelines to diagnose and treat sarcopenia has helped improve understanding of this condition.

The ICD-10 code for sarcopenia was assigned in 2016 (2). The ICD-10 system captures diagnosis codes, which are used for local and national analysis of healthcare data and reimbursement (3). For an ICD-10 code to be established, the condition must be real, understood, distinct, reasonably common, and useful

in broad-based data collection (3). The establishment of this code means the Centers for Disease Control and Prevention (CDC) recognizes sarcopenia as a separately reported condition (2). This code removes barriers to physicians diagnosing this condition, standardizes recognition of sarcopenia within the healthcare community, and allows access to more comprehensive data for research (3).

There are many factors that contribute to sarcopenia. It can be age related, obesity related, caused in part by disease states, related to cachexia, and/or related to inflammatory processes. Sarcopenia is largely attributed to aging in the absence of other apparent causes. Sarcopenia is divided into two categories: primary and secondary. Primary sarcopenia is considered "age-related" when no other specific cause is evident, while secondary sarcopenia involves other or additional causal factors (1).

Estimates on prevalence of sarcopenia range from 3% - 52% (3). The wide range accounts for differing criteria used for diagnosis and different populations, with community-dwelling older adults on the lower end and hospitalized or those in long-term care on the higher end (4,5,6). The largest risk factor for sarcopenia is increased age. Factors other than age affecting the prevalence of sarcopenia include: body mass index (BMI), sex, education level comorbid conditions, and ethnicity (4). As the elderly population continues to grow, sarcopenia is likely to become more prevalent.

Physical strength declines with sarcopenia that impairs ~~the~~ a person's ability to complete activities of daily living (1). Sarcopenia is associated with increased mortality independent of other risk factors (4). It is also associated with a significantly higher risk of nosocomial infection in the elderly (7). Nursing home residents affected with sarcopenia were found more likely to be functionally impaired and less likely to be involved in leisure time physical activities (6). Sarcopenia has potential to affect multiple areas and to create dysfunction. Any loss of function carries with it a risk of losing independence and reducing perceived quality of life. The loss of function accompanying sarcopenia makes the routine activities of daily life difficult or impossible to complete.

Sarcopenia also has financial consequences. It was estimated even a 10% reduction in sarcopenia could save $1.1 billion dollars in healthcare costs in the United States (US) in the year 2000 (8). At the present time, cost savings would likely be greater, given the overall rise in healthcare costs. As the aging population continues to grow and life expectancy increases, the cost of sarcopenia will likely increase.

Rationale

The negative impacts of sarcopenia come at a huge human and financial cost to individuals, their families, and society. The disease is better defined and identified now, but still under-treated. There is a need for professional medical staff education in the area of diagnosis and treatment of sarcopenia. As the

definition and diagnosis are refined and operationalized, treatment is improved. The lack of consensus in these areas have hindered treating sarcopenia.

There is ambiguity surrounding diagnosis and treatment of sarcopenia. The use of the recently established ICD-10 code is helpful in moving diagnosis and treatment forward, but does not address assessment, diagnosis, and treatment of the condition. Consensus regarding the definition of sarcopenia and diagnostic criteria for sarcopenia does not exist.~~,~~however, there are methods that can be used in the clinical setting to diagnose and address sarcopenia. There is a need for professional education in this area. ~~A~~ toolkit for practitioners may help facilitate diagnosis and treatment of sarcopenia.

Project

A toolkit designed for use by healthcare professionals will be developed.

Limitations

The inconsistencies in how sarcopenia is defined and/or which measures are studied make it difficult to develop clinical diagnosis and treatment protocols from the available research. There is a widely accepted definition that has been put forth by the EWGSOP, but it has been a work in progress and was recently updated in 2018 (1). There are similar definitions put forth by other organizations, and there is conflict within the differing definitions. If consensus can be reached it will drive better treatment of sarcopenia and more opportunities for further research. Assignment of an ICD-10 code and recognition of sarcopenia as a separate condition in 2016 was a huge step in this process (2).

Delimitations

Studies that include patients with sarcopenic obesity and sarcopenia related to a specific disease state or cachexia will be excluded. The scope of this project focuses on primary sarcopenia which affects relatively healthy older adults. The drivers of types of sarcopenia differ; therefore, treatments and benefit of treatments likely differ.

Assumptions

Existing research is assumed free of conflicts of interest or bias.

Definitions

Sarcopenia: (from EWGSOP) A muscle disease involving muscle failure, rooted in adverse muscle changes that occur across a lifetime (1). Sarcopenia is defined by low measures for three parameters: muscle strength, muscle quantity/quality, and physical performance as an indicator of severity (1).

Primary Sarcopenia: Age related sarcopenia; no other cause is apparent (1).

Secondary Sarcopenia: Sarcopenia involving causal factor(s) other than age (1).

Dynapenia: Muscle weakness (4).

Anabolic resistance: reflects the inability of skeletal muscle to maintain protein mass through the appropriate stimulation of protein synthesis (9)

Sarcopenic obesity: ~~is~~ a condition of reduced lean body mass in the context of excess adiposity, and is most often reported in older people (1).

Inflammaging: Age-associated state of low-grade systemic inflammation characterized by increased levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines (10).

Anorexia of aging: The overall decline in food intake that often happens with aging (11).

Frailty: Sarcopenia is a component of frailty. There is no single operational definition of frailty, it is widely accepted that frailty is:

- A clinical syndrome
- Indicates increased vulnerability to stressors leading to functional impairment and health outcomes
- Might be reversible with interventions
- Is useful in primary care

Frailty can be operationalized as a syndrome using Fried criteria, when 3 of 5 criteria are met: weakness often measured by grip strength, slowness measured by gait speed, low level of physical activity, exhaustion and poor endurance measured by self-report, and unintentional weight loss (12).

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Chapter 2: Review of the Literature

Introduction

Sarcopenia is a term coined by Irwin Rosenberg in 1989, from the Greek sarx for flesh and penia for loss (1). Skeletal muscle accounts for almost half of human body mass, and its contractions power body movements. Skeletal muscle function is essential to maintain homeostasis of glucose metabolism. The European Working Group on Sarcopenia in Older People (EWGSOP) published a widely used definition of sarcopenia in 2010 (2). The original definition put forth by EWGSOP identified sarcopenia as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with a risk of adverse outcomes such as: physical disability, poor quality of life (QOL), and increased mortality risk (2). The EWGSOP definition utilizes an algorithm with sex-specific thresholds (2, 3). Other groups including the International Working Group on Sarcopenia (IWGS), The Asian Working Group for Sarcopenia (AWGS), and The Foundation for the National Institute of Health (FNIH) Sarcopenia Project have also developed similar definitions and algorithms (3). EWGSOP recently updated and further enriched their definition. EWGSOP now defines sarcopenia as a muscle disease involving muscle failure, rooted in adverse muscle changes that occur across a lifetime (4). Sarcopenia is further defined by low measures for three parameters: muscle strength, muscle quantity/quality, and physical performance as an indicator of severity (4). Sarcopenia is now recognized as a disease state and was assigned an ICD-10 code in 2016 (5).

Adopting a standardized, operational, and clinically applicable definition is important, not only for research purposes, but to develop prevention and treatment strategies. Sarcopenia has been overlooked and undertreated in mainstream practice apparently due to the complexity of determining what variables to measure, how to measure them, and what cut-off points best guide diagnosis. The development of definitions and guidelines to diagnose and treat sarcopenia help to improve understanding of this condition.

Sarcopenia is largely attributed to aging without other causes. Loss of muscle strength and function is a natural part of the aging process, but sarcopenia is not diagnosed until muscle mass and function fall below defined thresholds (4). Sarcopenia is multifactorial in origin and its development can be related to lifestyle factors, nutritional status, vitamin D status, disease triggers, age-dependent biological changes, chronic inflammation, mitochondrial abnormalities, neurological changes, reduced satellite cells, insulin resistance, and hormonal alterations (6, 7). Sarcopenia can occur with or without obesity or cachexia, may occur with inflammatory processes, and is a factor in many disease states (7).

Sarcopenia is classified as primary or secondary. Primary sarcopenia is considered age related when no other specific cause is evident, while secondary sarcopenia involves additional causal factors such as systemic inflammatory, malignant, or endocrine disease (4). Sarcopenia is further divided by duration into acute and chronic categories, with acute lasting less than six months and chronic lasting over six months (4). EWGSOP guidelines also categorize

sarcopenia by severity. Probable or pre-sarcopenia is identified by low muscle strength; diagnosis of sarcopenia is confirmed by the additional presence of low muscle mass or quality (4). When low physical performance is identified in addition to low strength and low muscle mass/quality, sarcopenia is considered severe (4).

Sarcopenic obesity is a distinct condition and is considered separately from sarcopenia (4). Sarcopenic obesity is a condition of reduced lean body mass in the context of excess adiposity and is most often reported in older people (4). Obesity exacerbates sarcopenia, increases the infiltration of fat into muscle, lowers physical function, and increases the risk of mortality (4). It is estimated approximately 30% of men and 10% of women over the age of eighty have sarcopenic obesity (8).

Sarcopenia prevalence estimates vary, in part, due to inconsistent definitions and diagnostic criteria (4). Prevalence estimates are also dependent on the population studied and methods used to assess muscle mass (9). Prevalence estimates range from 3% - 52% across the lifespan (9).

Stephano Volpato et al. used data from the InCHIANTI study to determine prevalence in community dwelling elderly people using EWGSOP criteria to define the sarcopenic population (9). The study identified 16.7% were affected by pre-sarcopenia and 7.5% were affected by sarcopenia; sarcopenia prevalence increased steeply with age (9). Other studies that looked at this population found prevalence ranging from 1-29% (10).

Factors other than age affecting prevalence of sarcopenia include: Body mass index (BMI), gender, education level, comorbid conditions, and ethnicity (11). Goates et al. found Hispanics have the highest prevalence of sarcopenia and non-Hispanic (NH) blacks have the lowest (12). Prevalence was higher among older adults compared to younger and there was little difference between the sexes (12). As the elderly population continues to grow, sarcopenia will likely become more prevalent.

Elderly hospitalized and nursing home patients are often affected by sarcopenia. Martone et al. looked specifically at the hospital population using data from the GLISTEN project (13). Prevalence of sarcopenia at admission was found in 34.7% of patients with a mean age of 81 years of age (13). Among the patients who did not have a diagnosis of sarcopenia at admission, ~~they found~~ 14.7% met the EWGSOP diagnostic criteria by the time of discharge, about half of this patient population (13). Francisco et al. studied a nursing home population and found 32.8% affected by sarcopenia (14).

Sarcopenia is recognized as a debilitating condition with potentially devastating consequences. Multiple studies correlate sarcopenia and disability; the likelihood of disability increases with severity of sarcopenia (7). Age-related changes in muscle cause alterations that translate to decreases in bulk muscle mass, strength, and function leading to reduced physical performance, disability, frailty, and an increase in fall related injuries (15). Individuals with sarcopenia have approximately twice the odds of hospitalization (12). The decline in strength associated with sarcopenia impacts the ability to complete activities of daily living

(ADLs), making them difficult or impossible to complete independently (14). Sarcopenia is associated with increased mortality independent of other mortality risk factors and is associated with a significantly higher risk of nosocomial infection in the elderly (16, 17). Nursing home residents affected with sarcopenia were found more likely functionally impaired and less likely involved in leisure time physical activities (14). Sarcopenia has potential to create dysfunction, and any loss of function carries a risk of losing independence and reducing perceived QOL.

Data estimating the cost of sarcopenia is relatively scarce. Janssen et al. estimates in the year 2000 direct costs of sarcopenia were 18.5 billion dollars spent on hospitalizations, nursing home placements, and home healthcare (18). This represents $860 for every man and $933 for every woman diagnosed with sarcopenia (18). Sarcopenia is also associated with multiple comorbidities resulting in much higher costs (11). More recently Sousa et al. estimates sarcopenia increased costs of hospitalization by 58.5% for patients aged less than 65 years and 34% for those aged 65 years or older (19). One estimate based on costs in the year 2000 reveals a 10% reduction in sarcopenia could save $1.1 billion dollars in healthcare costs in the US (18). Goates et al. recently examined the cost of sarcopenia and estimates the total annual cost of hospitalizations for those with sarcopenia is $40.4 billion; over double the estimate from the year 2000 (12). As the aging population continues to grow and life expectancy increases, the costs associated with sarcopenia are likely to increase.

Background

Physiology

Age-related changes impact the strength and power of muscles and may signal the beginning of mobility limitations observed in patients affected with sarcopenia (20). Studies have demonstrated an association of muscle mass with strength and changing muscle quality in later life (12). Though sarcopenia interacts with many body functions it primarily affects skeletal muscle. The processes affected by age related muscle changes include denervation, mitochondrial function, inflammatory processes, and hormonal changes (15). Endocrine and inflammatory factors increase protein degradation, and some hormones that promote protein synthesis decrease with aging (15).

Skeletal muscle is made up of multinucleated cells that proliferate and differentiate into skeletal muscle fibers. Muscle fibers consist of contractile proteins made up of myosin, actin, and other regulatory proteins. Muscle fibers are organized into filaments arranged in bands called sarcomeres. Sequences of sarcomeres are myofibrils. The number of parallel myofibrils corresponds to the force a muscle can generate (15).

Muscles are innervated by motor neurons (15). The motor unit includes motor neurons plus the muscle fiber they innervate (15). Fibers in a motor unit contract, and the nerve impulse reaches the neuromuscular junction generating power (15). There are three types of motor units: slow, fast-fatigable, and fast fatigue-resistant (15). Slow motor units are rich in mitochondria, express type I

myosin, and are suited for endurance activities or precise finite motor activities (15). Fast-fatigable motor units have the greatest number of fibers, largest cross-sectional area (CSA), express type IIx myosin, are relatively mitochondria poor using more energy from glycogen stores (15). Fast-fatigable units are best suited for activity such as weightlifting or sprints (15). Fast fatigue-resistant units express both type I and IIx myosin and are intermediate between slow and fast-fatigable motor units in terms of CSA and velocity of contraction (15).

Muscles are built by protein synthesis which is stimulated by the intake of amino acids (AA) from dietary protein. Leucine is the primary driver of protein synthesis (15). Protein breakdown is suppressed by insulin, and increase in muscular lipid infiltration contributes to insulin resistance (15). When protein breakdown exceeds the rate of synthesis, atrophy occurs. Exercise extends the anabolic effects of dietary protein and contributes to building muscle (15). Lower activity levels contribute to muscle atrophy.

Etiology and Pathogenesis

Skeletal muscle has multifactorial changes throughout the aging process. Muscle loss is a significant consequence of aging. Typically, from age 20 to 80 years, there is an approximate 30% reduction in muscle mass and decline in CSA of about 40% (7, 21). The rate of muscle mass loss is estimated at 1-2% annually after the age of fifty; in conjunction with strength losses of 1.5%, that rate increases to 3% annually after the age of sixty years (21). Physical strength generally peaks in the thirties (22). Loss of muscle mass and strength typically

become pronounced around the age of fifty, accelerate in the sixties, and more acceleration is expected after the age of seventy (22).

Aging muscle triggers underlying cellular changes that can result in weakening of factors that promote muscle anabolism. These changes can also trigger increased expression of agents that contribute to muscle catabolism (15). The disruption in balance between muscle anabolism and catabolism cause muscle loss over time. At the molecular level, there is a decrease in skeletal muscle protein synthesis and an increase in protein breakdown (7). These changes are manifested in loss of CSA, denervation, and adaptive changes in proportions of fast and slow motor units within the muscle tissue resulting in less fast units overall (15). Skeletal muscle atrophy due to aging is characterized by two factors: decreased CSA of individual muscle fibers and decreased numbers of muscle fibers (23). The type and number of muscle fibers decline, there is reduction in cross-bridging between fibers, and there are changes in tendon stiffness (7). All these changes contribute to loss of function in sarcopenia.

Neurodegeneration occurs with aging and contributes to muscle degeneration. The numbers of nerve fibers decrease with preferential loss in motor neurons supplying fast motor units (15). The number of muscle neurons decrease with aging, which leads to denervation of muscle fibers, followed by an adaptive partial re-innervation to remaining neurons (23). Myelin sheaths degenerate and there are age-related changes in neuromuscular junctions which cause a decrease in number but increase in size and terminal area of the junctions (15). Synaptic vesicles decrease, neurotransmitters increase, and

terminal axon branching increases (15). Age-related changes are likely adaptivevdue to aging, allowing viable motor units to recruit denervated muscle fiber (15). The changes contribute to less efficient function and impact muscle force (23).

Another common occurrence in aging muscle is infiltration by lipid (7, 15). Both increased total body fatness and lipid infiltration of muscle tissue are prevalent in older people and increases with advancing age (7, 15). An average adult can expect to gain approximately a pound of fat and lose about a half pound of muscle annually between thirty and sixty years of age (23).

Insulin-like growth factor 1 (IGF-1) promotes protein synthesis in skeletal muscle. Skeletal muscles have receptors that bind insulin and IGF-1 to regulate proliferation, differentiation, synthesis, and fusion of skeletal muscle precursor cells (15). IGF-1 can be produced by the interaction of growth hormone (GH) in the liver, or by processes within skeletal muscle (15). IGF-1 production declines with aging, and the decrease in IGF-1 contributes to decreased protein synthesis, decreased muscle function, and may compromise motor neuron function (15).

Sarcopenia may include an age-associated state of low-grade systemic inflammation which is termed inflammaging (25). Inflammaging is characterized by increased levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines (25). Higher levels of age-associated pro-inflammatory markers are detected in a majority of older individuals, even in the absence of other risk factors and clinically active diseases (24). Epidemiological studies have found Inflammaging is a risk factor for cardiovascular disease (CVD),

cancer, chronic kidney disease (CKD), dementia, depression, disability, sarcopenia, frailty, and premature death (25). Muscle degradation accelerates in chronic inflammatory diseases associated with atrophy, such as cancer cachexia and some autoimmune disorders (15). Many patients with frailty have chronic inflammation, especially those affected with sarcopenia (25).

The loss of skeletal muscle in sarcopenia may result, in part, from inflammation related to circulating levels of interluken-6 (IL-6) and tumor necrosis factor alpha (TNF-α). Increased expression of these cytokines appear common in aging skeletal muscle (15,20,23). The ubiquitin-proteasome pathway is important for protein degradation and this pathway is promoted by inflammatory cytokines such as TNF-α and IL-6, as well as hormones such as cortisol and angiotensin. TNF-α is pro-inflammatory cytokine related to metabolic disorders and wasting syndromes seen with chronic disease (23). TNF-α expression stimulates muscle atrophy through apoptosis, likely contributes to loss of muscle fibers in sarcopenia, and promotes both decreased protein synthesis and increased protein degradation (15, 23). Some studies reported a higher level of IL-6 in those with sarcopenic obesity (23). Physical activity is associated with lower levels of TNF-α (23).

C-reactive protein (CRP) is produced by the liver, is recognized as a marker of systemic inflammation, and increased levels can be triggered by cellular damage induced by injuries or disease (23). CRP levels trend up with age, and high CRP is associated with low muscle mass independent of age, lifestyle, and body composition (23). Several studies have shown CRP levels to

be higher in patients with sarcopenic obesity (23). Studies have also shown an association between physical activity and lower CRP (23).

Oxidative metabolism generates reactive oxygen species (ROS) which accumulate over time causing damage to cell components such as mitochondria and DNA (15). Alterations to mitochondrial DNA increase with age, and frequency of abnormal mitochondrial regions are higher in skeletal muscle affected by sarcopenia (15). The role of mitochondrial DNA alterations in sarcopenia is under investigation, possibly contributing to skeletal muscle cell apoptosis and negative effects to cellular respiration contributing to loss of maximal oxygen consumption (VO2 max) (15).

Identifying Sarcopenia - Measurement Methods

Definitions of sarcopenia are based on muscle mass, strength, and function. A wide variety of tests and tools are available for identifying sarcopenia. Appropriate methods for measurement must be identified for both research and clinical practice areas. The various measurement methods are not uniformly suitable for both research and clinical settings.

Tool selection depends on the patient/population, access to technology, setting, and purpose of testing. High cost, radiological concerns, and inconvenience contribute to low usage of tools such as Dual Energy X-ray Absorptiometry (DXA), Computed Tomography (CT), and Magnetic Resonance Imagery (MRI) in the clinical setting.

Anthropometrics and screening questionnaires are economical and can be used to identify at risk or individuals with sarcopenia. Bioelectrical Impedance Assessment (BIA) and kinetic dynamometry can be used to assess status before, during, and after treatment. Any of these methods may be used in the clinical or research setting.

Screening

Sarc-F

Sarc-F is a rapid questionnaire used to screen for sarcopenia using self-reported information and is a convenient and inexpensive way to screen patients (4, 26). This tool has low to moderate sensitivity and very high specificity to predict low muscle strength (4). Sarc-F utilizes a 0 to 2 point scoring system based on five areas: strength, assistance walking, chair rise, stair climb, and falls and is summarized in the following chart. The sum of the 5 areas yields the Sarc-F score with 0-3 being healthy and 4+ being symptomatic (27). A project is underway to validate and translate SARC-F into multiple world languages (4).

Sarc-F scoring

AREA	0	1	2
Strength – difficulty carrying 10 pounds	No difficulty	Some difficulty	Very difficult or unable to complete

Walking across room	No difficulty	Some difficulty	Very difficult, requires aids, or unable to complete
Chair Rise – ability to transfer from chair or bed	No difficulty	Some difficulty	Very difficult, requires aids, or unable to complete
Stair climb – 10 steps	No difficulty	Some difficulty	Very difficult or unable to complete
Falls in past one year	No falls	1-3 falls	4 or more falls

(26)

The Sarc-F tool is an appropriate starting point to identify sarcopenia.

Ishii's Score

Ishii's score is a rapid screening test for sarcopenia using an equation-based score derived from simple measures of age, grip strength and calf circumference, and was developed in an Asian population (4, 27).

Men = 0.62 (age-64) – 3.09 (grip strength – 50) - 4.64 (calf circumference – 42)

Women = 0.80 (age-64) – 5.09 (grip strength – 34) – 3.28 (calf circumference – 42) (27).

SAR-QoL questionnaire

SAR-QoL is a self-administered questionnaire for people already diagnosed with sarcopenia. It identifies and predicts complications that may later impact the patients' quality of life (4). This questionnaire comprises 55 items transcribed into 22 questions specific to muscle mass and muscle function (28). SAR-QoL has been validated, translated into multiple languages, and may be used in clinical practice or research settings (4, 28).

Anthropometrics and estimating muscle quantity

Muscle quantity can be estimated using a variety of techniques. Muscle quantity can be reported as total body skeletal muscle mass (SMM), appendicular skeletal muscle mass (ASM), or as muscle CSA of specific muscle groups or body locations (4). Anthropometric measurements such as BMI, arm muscle CSA predictions, calf circumference, and skin-fold thickness are simple, but lack precision and are dependent upon the skill of the person taking the measurements (4). BMI is a better measure of nutritional status than of muscle mass in the older population (4). Calf circumference has been shown to predict performance and survival in older people with a cutoff point of <31 cm and may be used as a diagnostic proxy in settings where other diagnostic methods are unavailable (4).

Bioelectrical impedance (BIA)

BIA equipment, hand-held or scale-like devices, derive an estimate of total lean mass, based on whole-body electrical conductivity by using an equation that

is calibrated with a reference of DXA-measured lean mass in a specific population (4). BIA estimates volume of body fat and lean body mass, but not appendicular muscle mass (22). Estimates of muscle mass differ by which equipment is used, however, raw measures produced by the different devices, along with the cross-validated Sergi equation, standardize the measures (4). BIA prediction models are most relevant to the populations in which they have been derived; the Sergi equation is based on older European populations (4). Age, ethnicity, and hydration status can affect the measurements (4). BIA accuracy is validated in sarcopenia diagnosis, but it is hoped newer BIA equipment may be more accurate and able to obtain measures of appendicular muscle mass (22).

Muscle Mass (ASM) or Muscle Quality by DXA scan

DXA is a widely used gold-standard, but costly procedure, that provides a measure of muscle mass, and is usually limited to use in research (4). To obtain a complete picture of body composition, a four-component model comprised of total body water, protein, mineral, and fat mass is required (3). As a three-component model combining protein and minerals into solids, DXA is superior to standard densitometry, which differentiates only between fat mass and fat-free mass (3). SMM and ASM can be adjusted for body size using DXA measurements (4). DXA can distinguish protein and mineral from fat and water but cannot evaluate intramuscular fat which can account for 5-15% of observed fat in obese people (3). DXA measurements also can be influenced by hydration status, and different brands of DXA equipment yield inconsistent results (4).

Computed Tomography (CT) and Magnetic Resonance Imagery (MRI)

CT and MRI have high accuracy and consistency but are expensive, lack portability, require specially trained staff, and are usually limited to use in the research setting (3, 4, 22). CT has a smaller margin of error than DXA, but CT lacks well defined cut-off points for low muscle mass (4). Both CT and MRI are more sensitive to small changes in muscle mass than DXA (4).

Ultrasound

Ultrasound is a valid and reliable technique used to measure muscle quantity, to identify muscle wasting, and ~~also~~ as a measure of muscle quality (4). The use of ultrasound is being expanded in clinical practice to support the diagnosis of sarcopenia in older adults, and protocols are being developed to facilitate use (4). Ultrasound assesses muscle quality by evaluating muscle echogenicity (4). Assessment of pennate muscles such as quadriceps can detect a decrease in muscle thickness and cross-sectional areas suggesting a potential for use of this tool in clinical practice (4). Ultrasound has the advantage of being able to assess both muscle quantity and quality.

Hand-grip strength by Isokinetic dynamometry

Low hand grip strength is a powerful predictor of poor patient outcomes. Isokinetic dynamometry is the gold standard for the measurement of muscle strength accomplished with relative ease using relatively inexpensive equipment. (3, 4, 22). Accurate measurement of grip strength requires use of a calibrated handheld dynamometer under well-defined test conditions with interpretive data

from appropriate reference populations (4). The Jamar dynamometer is a validated and widely used tool for measuring grip strength (4). Because of its ease of use and cost isokinetic dynamometry is suitable for use in clinical or research settings.

Short Physical Performance Battery (SPPB)

Physical performance is defined as an objectively measured whole-body function related to locomotion that involves muscles, nervous system function, and balance (4). The SPPB is an objective assessment tool for evaluating lower extremity functioning in older persons (3). The SPPB combines the results of balance, gait speed, and chair stand tests to give an overall physical performance score (3, 4).

Other physical performance assessments

Other validated physical performance assessments used to identify sarcopenia include: walking tests, gait speed measurements, and timed up and go (TUG) test (4). TUG has also been found to predict onset of disability and mortality (4, 22). TUG is an assessment of ambulation and dynamic balance. It has a demonstrated association with decreased physical and mental function, mood status, and low fat-free mass (22). Gait speed is considered a quick, safe, and reliable test for sarcopenia, predicts adverse outcomes related to sarcopenia, and is used in practice (4). The 400 meter walking test and/or the six-minute walk assess endurance and walking ability (4). These physical performance tests can be performed in most clinical or research settings.

Potential Biomarkers

It is unlikely that there will be a single biomarker to identify sarcopenia. Potential biomarkers could include markers of the neuromuscular junction, muscle protein turnover, behavior-mediated pathways, inflammation-mediated pathways, redox-related factors, hormones, and other anabolic factors (4). The development of a panel of biomarkers for identification of sarcopenia should be considered (4). Currently sarcopenia biomarkers under investigation include IL-6, C-terminal agrin fragment, follistatin, and transforming growth factor beta (TGFβ) family members such as: myostatin, activin A, growth and differentiation factor (GDF), bone morphologic proteins; brain-derived neurotrophic factor; and irisin (29).

Creatine dilution test

Creatine is produced by the liver and kidney and is also ingested from a diet rich in meat. Creatine is taken up by the muscle cells where a portion is irreversibly converted to phosphocreatine, a high-energy metabolite. Excess circulating creatine is changed to creatinine and excreted in urine. The excretion rate of creatinine is a promising proxy measure of estimated whole-body muscle mass (4). A creatine dilution test uses an oral dose of deuterium-labelled creatine and urine measures to calculate muscle mass. Test results have been shown to correlate with measures from BIA and DXA (4). This method is predominantly used in research at this time.

Possible therapeutic intervention strategies - Non-nutritional

Hormonal and pharmacologic approaches

Hormonal therapy is supplementation with androgens or hormones with anabolic properties that naturally decline with age (29). This represents a possible avenue of treatment for sarcopenia (29).

Decline in serum testosterone is a natural part of aging with an expected decline in testosterone in men from the third to ninth decade (7, 29). There is evidence to support a relationship between decline of testosterone in elderly men and loss of muscle strength and function (15). Transdermal testosterone replacement has been shown to increase skeletal muscle mass and strength in some studies; while other studies have demonstrated testosterone treatment can increase lean mass and decrease fat mass (15,20,29). Though these changes in muscle are positive, they do not necessarily increase muscle strength or function. It is questionable whether the benefits of treatment with testosterone are sustainable due to the observation that improvements in muscle size and function reversed within six months of ending low dose therapy (30). Supplemental dehydroepiandrosterone (DHEA) has been studied due to its ability to increase the ratio of circulating testosterone in both men and women (29). Oxandrolone is asynthetic androgenic steroid similar to naturally occurring testosterone. Oxandrolone is taken orally and is less hepatotoxic than other options, and is also being studied and shows some promise as a therapeutic strategy to treat sarcopenia (29). Additional study of testosterone replacement for sarcopenia treatment is indicated.

There is a natural decline in estrogen in menopausal women. Menopause and age-related reduction in estrogen in women may impact muscle strength because estrogen is converted to testosterone which has an anabolic effect on muscle protein synthesis (15). This is an area that requires more study, and estrogen replacement therapy is not currently used as treatment for sarcopenia.

GH assists with regulation of the growth and differentiation of skeletal muscle; production decreases as part of the aging process (7, 23). GH is being proposed as a possible treatment for sarcopenia (25). GH exerts an indirect anabolic effect on muscle by stimulating production of IGF-1 in the liver (25). Inflammation and aging are associated with reduced synthesis and activity of IGF-1, which is essential for muscle regeneration and maintenance of muscle integrity (25). Studies suggest GH levels are increased with physical activity (23). GH secretion is suppressed with sarcopenic obesity and is usually accompanied with a decrease in IGF-1 (23). More study is needed. GH supplementation is not currently used as treatment for sarcopenia.

Selective androgen receptor modulators (SARMs) are a class of androgen receptor ligands that may be therapeutic for many conditions including sarcopenia (31). Several steroidal and non-steroidal SARMs have undergone trials and have shown favorable effects on increasing lean body mass and increasing strength (31). Other SARMs have shown benefits in treating muscle wasting occurring with cancer and other conditions (29, 30). SARMs are a possible treatment for sarcopenia due to their specificity and relatively few

negative side-effects; they have exhibited potent anabolic effects on skeletal muscle (20, 29).

Though not a primary driver of sarcopenia, myostatin is a powerful negative regulator of muscle growth (32, 33). The absence of myostatin has increased muscle mass in cattle and mice (29). Some studies have suggested myostatin increases with age in humans (33). Inhibition of myostatin may hold promise in the treatment of sarcopenia by counteraction of myogenic regulatory factors that promote the differentiation and proliferation of myocytes (31). There are multiple pharmacologic strategies to disrupt myostatin such as: neutralizing antibodies, propeptides, soluble activing type IIB (ActRIIB) receptors, and interacting proteins (32). Bimagrumab is a monoclonal antibody that binds to ActRIIB receptors, GDF11, and activin-A (31). Trials have shown increases in muscle mass in younger people, improvement in atrophy in casted adult legs, and improved gait speed in those with sporadic inclusion body myositis, a rare muscle disease (30). It is possible Bimagrumab could prove a useful treatment for sarcopenia. There appears to be therapeutic potential in the use of antibody-directed inhibition of myostatin for treatment of sarcopenia.by inhibiting protein degradation (32, 33). Further study is needed.

Angiotensin-converting enzyme (ACE) inhibitors are generally used to treat hypertension (HTN) and cardiovascular disease. ACE inhibitors may also exert a beneficial effect on skeletal muscle through multiple mechanisms (33, 34). ACE inhibitors may improve muscle function through improvements in endothelial function and metabolic function. Anti-inflammatory effects and

angiogenesis improves muscle blood flow (33). ACE inhibitors increase mitochondrial numbers and IGF-1 levels which could improve muscle function (33). More study is needed to determine if ACE inhibitors can be used in sarcopenia treatment.

Physical Activity

Physical activity (PA) is any level in bodily movement that results from skeletal muscle activation and leads to an increase in energy expenditure (35). Exercise is any activity requiring physical effort, and is carried out to sustain or improve health and fitness. Bed rest due to illness or injury or a sedentary lifestyle can result in rapid muscle mass and strength loss in the elderly (36). Research has shown sedentary behavior, is more common in older adults, and is associated with morbidity and mortality (3). PA is especially important to preserve muscle strength and function in the elderly because it can slow muscle losses (36). Exercise promotes myofibrillar protein synthesis (6). Exercise also lessens effects of impaired insulin sensitivity, mitochondrial dysfunction, acceleration of myonuclear apoptosis, and inflammation (35).

Because inactivity is linked to loss of muscle mass and strength, it is reasonable to believe increasing levels of physical activity has protective effects. Impact exercise such as walking and aerobic exercise exert a benefit in overall health, but resistance training (RT) appears the most beneficial to improve sarcopenia (15). RT increases type 2 muscle fiber size and improves satellite muscle recruitment in older persons (15, 36). It is possible both aerobic and RT are protective against sarcopenia, in part, because of their anti-inflammatory and

antioxidative effects (25). Exercise has a role in muscle protein synthesis; PA may be effective for both prevention and treatment of sarcopenia. More research is required to develop appropriate exercise prescriptions to treat sarcopenia.

Possible therapeutic intervention strategies - Nutritional

Protein is critical to maintaining muscle mass. Optimal protein can be defined as the minimum amount of protein that results in the maximum anabolic response, and thus, can help maintain or improve muscle mass and function over time (37). Studies suggest the Recommended Daily Allowance (RDA) of 0.8 gm of protein per kg of body weight -is inadequate to sustain muscle in older adults, due in part, to the anabolic resistance of aging muscle (36). Anabolic resistance is a reduced sensitivity to AAs which are responsible for maintenance of muscle mass and function (37). Because of metabolic changes, older persons may make less muscle protein than younger persons from the same amount of dietary protein (38). More recent recommendations for older adults are for protein intake of 1.0-1.2 g/kg body weight per day (36, 39). This higher level of intake is thought to be the optimum amount to maintain skeletal muscle health without affecting renal function in older adults (36).

Anorexia of aging is the overall decline in food intake that often happens with aging (36). Compared to younger adults, older adults often eat less food, including less protein (40). Consequences of lower intake include potential weight loss, loss of muscle mass, and difficulty obtaining adequate micro and macro nutrients (36). The imbalance created between anabolic resistance to AAs and inadequate intake contributes to muscle loss and sarcopenia. For older

people with decreased intake it is particularly important to consume a diet providing adequate nutrition. Figure 1 illustrates the contributors to negative outcomes associated with sarcopenia.

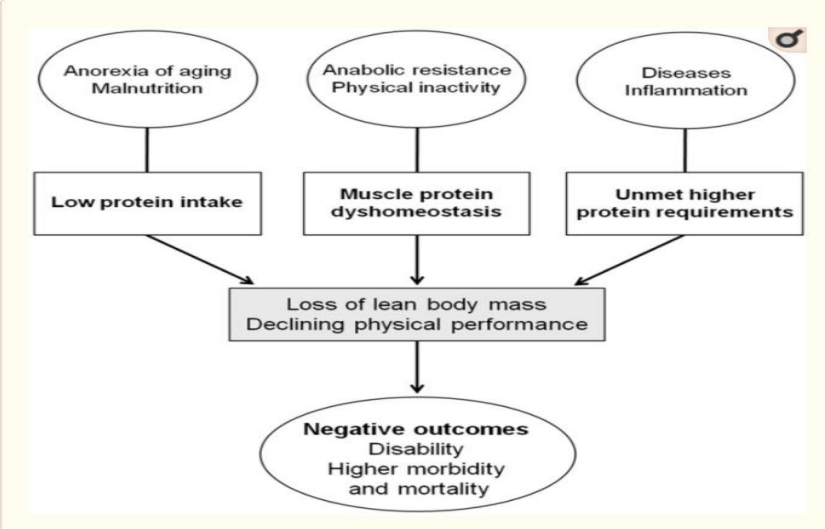

Figure 1 (40)

Supplementing protein may be of value in the prevention and treatment of sarcopenia. Greater dietary protein intake may be necessary for promotion of muscle health in older individuals compared to younger persons (40). Studies have not demonstrated detrimental effects of higher levels of protein intake in healthy older adults (36). It is possible muscle protein synthesis (MPS) is highest post-prandial and that AAs circulating after a meal are more significant than the total daily AA intake (42). Supplements can deliver a bolus of AA and increase circulating AA's much like a meal does. Older persons have a high risk of inadequate protein intake; one study shows 32-41% of women and 22-38% of

men older than 50 years ingested less than the RDA for protein (38). Supplementing protein is one way to ensure older adults, especially those who have difficulty eating, consume adequate protein.

There is much debate and study about the types of protein, timing of protein intake, protein and AA supplementation, and supplementation of other substances to enhance the effects of protein (36). The branched-chain amino acid leucine produces anabolic effects in muscle by stimulating the mammalian target of rapamycin (mTOR) pathway (37, 40). Leucine activates a major complex in the anabolic pathway called mTOR 5-7. Decreased leucine concentrations signal mTOR that not enough dietary protein is available to synthesize new skeletal muscle so it deactivates. For this reason, leucine, and its metabolite ß-hydroxy-ß-methylbutyrate (HMB), have generated much interest and study (36). Higher amounts of leucine and other AAs are needed to stimulate MPS in older adults due to anabolic resistance (40). Other amino acids of interest for study include lysine and arginine (36).

Animal proteins are shown to have higher digestibility than plant proteins which may make their AAs more available for MPS (40, 43). Ingestion of meal-like amounts of animal protein strongly stimulates skeletal muscle protein synthesis since animal-based sources of protein contain more leucine, lysine, and methionine; all crucial to MPS (43, 44). Eating higher quantities of plant-based proteins may compensate for the lower AA content in plant foods; it is not necessary to consume meat to obtain adequate AAs. Given the anorexia of aging

seen in older adults, protein supplementation may be helpful, especially with a high plant-based diet (40, 43).

Whey protein may be the most effective stimulator of MPS. Whey contains a considerably higher amount of leucine compared to casein or soy protein (43, 44). Whey protein may more effectively increases postprandial protein retention than casein (44). Whey protein appears to be digested and absorbed faster resulting in higher peak leucine appearance, which may contribute to more efficient MPS stimulation (44, 45). There appears to be a greater utilization of whey protein in older adults.

Creatine is a nutritional supplement that is popular with body builders for building muscle. There is some evidence that supplementation with creatine monohydrate can have a positive effect in older adults with sarcopenia (36, 46). It is possible creatine supplementation can increase lean muscle tissue and improve performance (46). The effects of creatine appear to be amplified when combined with exercise, protein, and/or conjugated linolenic acid (CLA) (46). Creatine appears less effective in secondary sarcopenia (46). More study of creatine use in the elderly is needed.

The level of 25(OH) vitamin D declines with age (46). Low vitamin D levels are associated with low muscle strength (34, 46). Sarcopenia is twice as likely diagnosed in older adults with levels of 25(OH) vitamin D below 25 nmol/L than in those with concentrations higher than 50 nmol/L (46). Some studies suggest the incidence of frailty is increased with low vitamin D status and that falls are more frequent (34). Though vitamin D supplementation does raise

levels of 25(OH) vitamin D, studies examining the effect of vitamin D supplementation upon sarcopenia yield inconsistent results (46). Vitamin D efficacy appears more effective if subjects have both low vitamin D levels and is combined with other nutrients (47). Vitamin D may be protective against sarcopenia, in part, because of its anti-inflammatory and antioxidative effects (25). More study of the efficacy of vitamin D supplementation is needed.

Polyunsaturated fats (PUFAs) are components of the phospholipids of cells, including muscle cells. The anti-inflammatory properties of omega-3 (n-3) fatty acids, particularly eicososapentenoic acid (EPA) and docosahexaenoic acid (DHA), are suggested to be beneficial in improving muscle mass, strength, and function. A small randomized controlled study of n-3 fatty acid supplementation for 8 weeks showed an increased in the rate of MPS in older adults, suggesting that n-3 fatty acids may be an effective addition when addressing the age-related loss of muscle mass (39)

Oxidative stress is believed to have a role in the development of sarcopenia, and observational studies have suggested better physical function among older adults with higher antioxidant status (34). Cesari et al. used data from the InCHIANTI Study to show positive associations between higher plasma concentrations of antioxidants from dietary vitamin C and β-carotene and skeletal muscle mass (49). When compared to younger adults, satellite cells from older adults have more apoptotic signals, and reduced antioxidant activity of catalase and glutathione transferase in satellite cells isolated from elderly subjects has been observed (29). The decrease in antioxidant capacity may reduce the

regenerative ability of aged satellite cells, but it is unclear if increased antioxidant intake from foods or supplements are helpful in treating sarcopenia (29). More study of antioxidants and sarcopenia is needed.

Ursolic Acid-is a folk remedy for diabetes and hyperlipidemia, and is a component of apple peels and other plants (33). Some studies suggest urosolic acid may reduce skeletal muscle atrophy by stimulating IGF-1 and insulin, and possibly affecting gene expression that contributes to muscle atrophy (33). More study is needed to determine if supplementing urosolic acid is beneficial to mitigate sarcopenia.

Conclusion

Muscle mass is regulated by the balance between muscle synthesis and breakdown, with the two major environmental influences on these processes being food intake and physical activity. Everyone loses muscle mass as part of the aging process, however, not all older adults meet the criteria for a sarcopenia diagnosis. There are individual differences in the rate of muscle mass loss, the age at which muscle mass starts to decline, and the extent to which strength and function are affected as part of the aging process. In older people muscle protein synthesis response to a single anabolic stimulus may be blunted. Adoption of multimodal strategies, particularly focusing on protein intake and physical activity, is the most plausible approach to treatment and prevention of sarcopenia.

Current Research - Nutritional and Exercise-Based Approaches to Treatment of Sarcopenia

Sarcopenia is a common condition that will continue to affect many elderly people. The US population of older people is expanding. The financial cost of sarcopenia is significant. The human costs of sarcopenia are serious and more difficult to quantify. Reduced quality of life, loss of productivity, and loss of independence and autonomy can impact the lives of those affected with sarcopenia. This underscores the importance of understating and utilizing effective prevention and treatment strategies for sarcopenia.

Standardizing and operationalizing the definition of sarcopenia has been a first step in finding effective prevention strategies and treatments for sarcopenia. The assignment of the ICD-10 code for sarcopenia establishes it as a distinct reportable disease state. Though there are many possible approaches to treating and preventing sarcopenia; the primary evidence-based treatments are lifestyle modification focusing on diet and exercise. The purpose of this literature review is to exam the effect and efficacy of nutritional interventions and exercise for prevention and/or treatment of sarcopenia.

Protein intake from food in community- dwelling elderly subjects

Huang et al. looked at the association between protein intake and muscle mass in a community-dwelling older population (50). The purpose of this cross-sectional study was to determine if there was an association between dietary protein intake and low muscle mass (LMM) and if total and/or vegetable protein is

associated with LMM (50). 327 ambulatory Taiwanese volunteers aged 65 – 85 participated in the study, and the researchers collected dietary, demographic and health information, and did body and muscle mass measurements (50). The study found the LMM group exercised less and had a higher incidence of diabetes mellitus (DM) ~~more~~; ~~but~~ other nutritional biomarkers, major disease, and lifestyle habits revealed no significant differences (50). Total protein density and vegetable protein density (density = % of total energy), were significantly lower in the LMM group (total protein density 14.5% +/- 2.9% vs 15.5% +/- 3.1%, p= 0.007 and vegetable protein density 7.0% +/- 2.4% vs 8.1% +/- 3.0%, p= 0.004) (50). No significant differences were found in animal protein, total energy, carbohydrates, and vitamin-mineral supplements, but there was higher fat intake and fat density in~~n~~ the LMM group (p+ 0.012, p+ 0.028) (50). The participants were grouped into quartiles and odds ratios (OR) were shown adjusted for confounders (50). Participants in the lowest total protein density and vegetable protein density quartiles have higher risk for LMM than those in the highest quartile (50). Participants with the lowest mean total protein intake (11.7%) had almost three times the risk for LMM compared to those with the highest mean protein intake (18.3%) (50). Participants with the lowest mean vegetable protein intake (4.9%) had over twice the risk for LMM compared with those with the highest mean vegetable protein intake (10.9%) (50). This study suggests higher protein intake supports higher muscle mass in older adults, even if that protein is vegetable protein.

The Huang et al. study was a large study that used validated tools to measure anthropometrics, body composition, and to complete dietary assessment. Limitations included use of the food frequency questionnaire (FFQ). Though a validated method administered by a registered dietitian (RD), it is subject to measurement errors due to inaccurate participant reporting. The sample was not a representative sample of the population and may have included a more health-aware population than is usual. A causal relationship cannot be established using an observational study and a long-term prospective study is warranted. The study looked at LMM which is one major component of sarcopenia, but did not look at muscle function or quality, so applications for prevention or treatment of sarcopenia are limited.

Nilsson et al. conducted an observational study to find associations between dietary protein intake, muscle mass, and physical activity in older community-dwelling women (51). Included were 106 non-smoking women aged 65-70, free of coronary disease and DM, and without disability related to mobility (51). Skeletal muscle mass index was calculated using bioelectric impedance analysis (BIA), physical function was assessed by aerobic and strength tests and self-reported perceived exertion, subjects self-reported physical activity, and BMI was calculated (51). Protein intake was captured using a 6-day food record, and subjects were grouped into lower and higher protein intake (51). Average daily protein intake of the entire sample was 1.03 +/- 0.26 g/kg BW (51). Participants were categorized as either low protein intake, based on lower RDA threshold of 0.8 gm/kg BW or high protein intake, based on higher RDA threshold of 1.1

gm/kg BW (51). The women in the low protein intake group were found to have higher BMI, lower physical function, and lower skeletal muscle mass index (SMI) regardless of total energy intake (51). When the groups were sub-divided, SMI was significantly lower in participants with protein intake of < 0.8 gm/kg BW than in those with protein intake >1.1 gm/kg BW (51). Comparing participants with protein intake < 0.8 gm/kg BW to those with protein intake >/= 1.1 gm/kg BW, the former showed higher likelihood of having physical limitations (OR 5.48, 95% confidence interval: 1.34 – 22.43) even after SMI adjustment (51). This study suggests women with higher protein intake have higher SMI and higher physical function; ~~and that~~ failing to meet the lower RDA guidelines for protein intake is detrimental to both muscle mass and physical function in elderly women.

The Nilsson et al. study had adequate sample size that reached 80% power, and used validated tools to measure anthropometrics, body composition, and to complete dietary assessment and protein intake. Statistical adjustments were made to account for differences in body composition compounding the link between protein intake and muscle function. Limitations included use of the dietary recall, a validated method, though subject to measurement errors due to inaccurate participant reporting~~.~~. The food record was not administered by an RD; qualifications of the nutritionists providing instruction are undefined. The sample was not a representative sample of the population, in that, the women studied were active; the results may not translate to a sedentary population. The study did not specifically look at sarcopenia; however, because it examined muscle mass and physical function, it could be applied to sarcopenia. The study

suggests higher protein intake may assist in prevention and/or treatment of sarcopenia. A causal relationship cannot be established using an observational study and further study is warranted.

The Haaf et al. cross-sectional study investigated whether protein intake, protein distribution, and physical activity are associated with muscle strength, muscle function, and overall quality of life in 140 over-65 years old community-dwelling people (52). Subjects were selected from two studies; one study had participants with higher baseline physical activity levels to provide variety in the current study; participants were divided into tertiles based upon overall protein intake and protein intake distribution within meals (52). The studies used different validated methods for collecting dietary protein intake, assessed physical activity and quality of life using questionnaires, collected anthropometric data, calculated BMI, assessed strength based on hand grip strength, and assessed physical function using the SPPB (52). The average daily protein intake of all participants was 1.08 +/- .26 gm/kg BW (52). Participants were split into groups by daily protein intake with the low group consuming <1 gm/kg BW and the high group consuming >/= 1 gm/kg BW (52). There was no association found between higher protein intake and muscle strength or function, and higher protein intake had no association with quality of life (52). They also observed no association between protein distribution and muscle strength, muscle function, or quality of life, but gait speed was significantly higher in the spread (most even protein intake) distribution group (52). They found concurrent higher protein intake and higher physical activity was positively associated with quality of life

(52). Overall results of this study do not show benefit of higher protein intake on physical function. It does suggest the combination of physical activity and higher protein intake could improve overall quality of life in the elderly.

The Haaf et al. study had a large sample size with a high mean age (80 yr.+) and included a broad range of physical activity. It used validated tools to measure anthropometrics, body composition, muscle strength and functioning, and to capture physical activity levels, quality of life, and dietary intake. Statistical adjustments were made to identify under and over reporting of dietary intake. The use of participants from two large studies provided variety (47). Different methods were used to capture dietary intake and physical activity which could contribute to inconsistent results, though the methods were comparable and coded and calculated in the same manner for this study (47). The participants were elderly, but not sarcopenic, so results may not translate to that population,and some studies have shown less impact of protein intake on function of healthy elderly adults than those that are frail or meet the definition of sarcopenic (34, 47). The average daily protein intake of this sample was above the RDA of 0.8 gm/kg BW and the contrast between high and low was small which may make the results less applicable to a typical sarcopenic population. A causal relationship cannot be established using a cross-sectional study and further study is warranted.

Protein Supplementation in community- dwelling elderly subjects

Chale et al. studied the effects of whey protein concentrate supplements (WPC) and RT in 80 sedentary community-dwelling older adults in an

experimental study (53). Measurements at baseline and at the 6-month completion of study were done including: body composition determined by DXA and CT scan, strength determined by leg press and knee extension testing, diet based on 3-day food records, and physical functioning determined by SPPB with separate 400 meter walk, chair rise, and stair climb assessments (53). The exercise protocol was supervised and progressive RT, the intervention supplement was whey-based and provided 40 gm protein daily in 2 divided doses; the control placebo was isocaloric without protein (53). Total lean body mass increased in the WPC and control groups, but not significantly, and total body fat mass did not change in any group (53). Muscle CSA increased significantly by the end of the study, but there was no significant difference between groups (53). All measures of strength and physical functioning improved significantly in both groups except the 400 meter walk, but again, there was no significant difference between groups (53). This study showed RT increased the strength and muscle function in the participants and had some positive effects on body composition, but it did not appear that WPC supplementation had significant impact.

The Chale et al. study is a strong randomized study with a sample size reaching power of 80%. Anthropometrics, body composition, and physical performance were measured using validated methods. Adherence to the supplement was monitored. Though the study did not specifically focus on adults with sarcopenia, the results of this study likely translate and can be applied to sarcopenia because of the focus on effect of exercise and WPC supplementation

on muscle strength and function. The WPC supplement did not show efficacy and further studies using different sources of protein and amino acid configurations are warranted.

Protein Supplementation in community- dwelling elderly subjects with frailty

Tieland et al. conducted a 24-week, experimental trial to study the effect of protein supplementation on physical performance and muscle mass in a frail elderly population (54). Though there is no single operational definition of frailty, it is widely accepted that frailty is: 1) a clinical syndrome, 2) indicates increased vulnerability to stressors leading to functional impairment and health outcomes, 3) might be reversible with interventions, and 4) is useful in primary care (55). Frailty can be operationalized as a syndrome using Fried criteria, when 3 of 5 criteria are met: weakness often measured by grip strength, slowness measured by gait speed, low level of physical activity, exhaustion and poor endurance measured by self-report, and unintentional weight loss (55). There are similarities between sarcopenia and frailty with overlap in ~~regards to~~ diminished strength and function. Frailty also encompasses deficits in multiple organ systems, as well as psychological, cognitive, and social functioning (55).

Tieland et al. studied 65 frail elderly participants who were divided into a control and intervention group; the control group was given a vanilla flavored protein free powder packet to take twice daily, ~~and~~ the intervention group was given a vanilla flavored 15 gm protein powder packet to take twice daily (54). Skeletal muscle mass was assessed by DXA, muscle fiber size assessed by

biopsy, strength and physical performance were assessed at baseline, 12 weeks, and 24 weeks using SPPB (54). At the end of the 24-week period, skeletal muscle mass and muscle fiber size showed no significant change, muscle strength improved in both groups, but significantly in the intervention group, and performance improved significantly in the intervention group only (54). Baseline dietary protein intake averaged 1 gm/kg body weight (BW) for both groups; with the addition of the protein supplement, the intervention group averaged 1.5 gm/kg daily protein intake (54). This study demonstrates protein supplementation is effective for increasing performance and muscle strength in frail elderly people but did not show efficacy for increasing muscle mass or fiber size.

The Tieland et al study is a strong randomized and double blinded study with a sample size reaching power of 80%. Anthropometrics, body composition, and physical performance were measured using validated methods. The study showed the effect of protein supplementation on frail adults. Sarcopenia can be a component of frailty but is a different and separate condition. The results of this study likely are applicable to sarcopenia because the study specifically looked at and found results regarding the effect of supplementation on muscle mass and performance.

Protein Supplementation in nursing home elderly subjects with frailty

Bonnefoy et al. looked at the effect of exercise and protein supplementation on body composition, strength, and muscle function in frail elderly nursing home residents in an experimental study (56). This 9-month clinical trial had a factorial design comparing the effect on ~~the~~ nutritional and

functional status of: exercise (1 hr./3x wk. strength, balance, and flexibility) with a control memory activity and powdered nutritional supplements (200 kcal, 15 gm protein + vitamin and minerals, drink twice daily) with a placebo (no vitamins, minerals, kcal or protein twice daily) (56). Participants were randomized into four groups: supplement plus memory activity, supplement plus exercise, placebo plus memory activity, and placebo plus exercise (56). Strength of quadriceps was assessed by muscular testing, physical function was assessed by gait velocity and chair rise test, and body composition was determined using labelled water and calculations (56). Participants were analyzed at baseline, 3 months, and 9 months (56). There were no significant changes in quadriceps strength between groups with exercise at 3 or 9 months, but there was significant improvement in the supplemented groups at 3 months (56). Fat free mass (FFM) did not significantly change in any group but showed tendency to increase in the supplemented group and decrease in the placebo group at 3 and 9 months (56). There was a significant increase in BMI in the supplemented group at 3 or 9 months (56). Exercise significantly improved chair rise time at 9 months; there were no other significant changes in function (56). This study suggests there is benefit to supplementing calories and protein. Supplementation had some positive effect on strength at 3 months, and it had a positive effect when combined with exercise programs (56). These measures could improve some aspects of sarcopenia.

The Bonnefoy et al study was a long-term study with a small sample size that did not reach adequate power. The authors acknowledge it was difficult to

motivate the chosen residents to participate in the study; adherence to supplementation and the exercise program was low and drop-out rate was high. Anthropometrics and body composition were measured using validated methods. The exercise program was not well described and the qualification of those conducting the exercise program was not specified. The study sample were frail nursing home residents which may not translate to the general elderly population. Sarcopenia is a component of frailty but a different and separate condition, but the results of this study likely can be applied to sarcopenia. A larger and stronger study is warranted.

Protein and Vitamin D Supplementation in community- dwelling elderly subjects without malnutrition

Bauer et al. conducted an experimental study to examine the impact of a whey-based, vitamin D and leucine-enriched protein powder to determine whether a specific ONS could result in improvements in measures of sarcopenia in independent-living, non-malnourished older adults (57). The intervention group received a vitamin D and leucine enriched whey protein powder and the control group received an isocaloric protein-free powder; both groups added these powders to their regular diets twice daily for 13 weeks (57). Primary outcomes were handgrip strength and SPPB score; secondary outcomes were individual outcomes of the SPPB (chair stand test, gait speed, balance), and muscle mass by DXA scan (57). Outcomes were measured at baseline, 7 weeks, and 13 weeks (57). There were no significant differences between groups in SPPB score of hand grip strength (57). Significant gains in muscle mass and significant

improvement in chair stand ability were noted in the intervention group (57). The results suggest supplementation alone can benefit muscle mass and some components of muscle function in older adults without increasing physical activity.

Bauer et al. conducted a strong study with a sample size reaching power of 80%. Anthropometrics, body composition, and physical performance were measured using validated methods. Adherence to the ONS was monitored. Dietary changes were not encouraged to show full effect of supplementation with ONS. Though the study did not specifically focus on adults with sarcopenia, the results of this study likely translate and can be applied to sarcopenia because of the focus on muscle mass and function. Nutrica Research and Nutrica Advanced Medical Nutrition financially supported and provided products for this study. The randomized, double-blinded, and controlled study design allows for inferences regarding causal effects of the supplement.

Protein Supplementation in community- dwelling elderly subjects with malnutrition and sarcopenia

Cramer et al. examined the impact of high-protein ONS in >/= 65 years of age malnourished men and women with sarcopenia (58). The experimental and control groups were given ONS with similar energy content; the experimental ONS contained more protein, more vitamin D, and CaHMB (58). Both groups were given dietary counseling to consume at least 0.8 gm protein/kg of body weight per day; otherwise, the diet was ad lib (58). Leg strength, gait speed, handgrip strength, body composition determined with DXA scan, SMI and muscle

quality (MQ) based on DXA scan and calculations, diet records, and logs of daily ONS consumption were collected at baseline, and every 6 weeks through the 24-week study (58). Both groups showed improved leg strength by the end of the study, but in the experimental ONS group, those with mild-moderate sarcopenia, but not severe sarcopenia, showed a significant difference from the control ONS group, in leg muscle strength (58). Grip strength, gait speed, and MQ significantly improved in both groups but there was no significant difference between groups (58). This study demonstrated benefit of ONS but did not demonstrate much benefit to using the higher protein, vitamin D, and CaHMB enriched supplement.

The Cramer et al. study is strong with a large sample size reaching power of 80%. Anthropometrics, body composition, muscle-quality, and physical performance were measured using validated methods. Nutrition education was provided to encourage protein intake of 0.8 gm protein per day; however, it was not provided by an RD and qualifications of the provider(s) were not specified. Adherence to the ONS was monitored. The study stated it was specific to the effect of ONS on elderly men and women with sarcopenia, however, the only criteria used for sarcopenia was low skeletal muscle mass. The researchers did make a distinction between mild, moderate, and severe sarcopenia based on the presence of other criteria. The lead researcher was a consultant for Abbott Nutrition and Abbott Nutrition funded the study. Several other researchers were Abbott employees. The lead researcher was also supported by the US Dept. of Agriculture National Institute of Food and the Agriculture Hatch Project. The

experimental study design allows for inferences regarding causal effects of the supplement.

Amino Acid Supplementation in community- dwelling elderly subjects

Dillon et al. studied amino acid supplementation and its effect on muscle protein synthesis, lean body mass (LBM), and IGF-1 in older women over a 3-month period (59). The purpose of this experimental study was to determine if essential amino acid (EAA) supplementation improves lean body mass, muscle strength, and IGF-1 muscle protein expression, as well as whether the anabolic response to EAA ingestion is preserved after the 3-month supplementation period (59). Subjects took 15 gm EAA daily or a placebo and ate their normal diet for 3 months (59). Strength testing by bicep curl, triceps extension, leg extension, and leg curl were done on machines with one repetition maximum (IRM); assessments were completed at baseline and at the end of the study (59). Other testing and assessments completed at baseline and at the end of the study included: basal plasma amino acids blood test, muscle fiber biopsies, lean body mass evaluations with DXA scan, and muscle protein fractional synthesis rate (FSR) evaluated by blood testing and calculations after a 7 hour infusion of a stable isotope of phenylalanine (59). The group was habitually sedentary and encouraged to maintain their usual activity level throughout the study (59). LBM and basal IGF-1 protein expression increased in the intervention group; muscle strength and basal plasma amino acids did not change from baseline in either group (59). Muscle protein fractional synthesis rate (FSR) was improved in the intervention group only; ~~and~~ the magnitude of the response to EAA

supplementation was unaltered at the end of the 3-month period, showing anabolic response to EAA ingestion was preserved (59). This study suggests supplementing with amino acids maintains an acute anabolic response over time and could help prevent or treat the effects of sarcopenia.

The Dillon et al. study collected anthropometrics and body composition which were measured using validated methods. Muscle composition was evaluated using biopsy and biomarkers. The study showed the effect of EAA supplementation on healthy older female adults only; males were excluded to minimize the effect of testosterone on muscle function. Dietary habits were not assessed and dietary changes were not encouraged or required. This may make individual results of the supplementation inconsistent, however, it does demonstrate the effect of EAA supplementation on its own. The muscle biopsy and labs were invasive but allow for precise results. The randomized and blinded design of the study allows for inferences regarding causal effects of the supplement. The subjects in this study were healthy, but the effects of the supplementation on muscle synthesis and LBM may be applicable to prevention and treatment of sarcopenia. The authors highlight the effects of the supplement persisted throughout the study, but a longer study is needed to show if longer-term supplementation would persist.

Amino Acid Supplementation in community- dwelling elderly subjects with sarcopenia

Kim et al conducted an experimental study to examine the effects of exercise and EAA on body composition and physical function in community-

dwelling elderly women with sarcopenia (60). Participants were interviewed to collect demographic and health history, body composition was assessed using BIA, calf girth was measured, and function was assessed using walking speed and knee extension strength tests; body composition, strength, and function were assessed at baseline and the end of study (60). 155 women aged 75 years or older were randomly assigned into one of four groups: EAA, EAA with exercise, exercise only, or health education (1 class/mo. x 3 mo.) control group (60). Supplements contained 3 gm of leucine-rich amino acid mixture taken twice daily and the exercise group attended a 60 minute training class twice weekly (60). Walking speed significantly increased in all intervention groups. Leg muscle mass increased in both the supplemented and non-supplemented exercise groups, and knee extension strength increased in the supplemented exercise group (60). The data shows benefit of EAA supplementation on some aspects of muscle function, and benefits of exercise, both alone and with EAA supplementation, on muscle mass, strength, and function (60). The effects of EEA supplementation on muscle function suggest EAA supplementation could be beneficial to prevention and/or treatment of sarcopenia.

The Kim et al. is a study with an adequate sample size reaching power of 80%. Anthropometrics, body composition, and physical performance were measured using validated methods. Dietary habits were not assessed, and dietary changes were not encouraged or required, which may make individual results of the supplementation inconsistent, however, it does demonstrate the effect of EAA supplementation on its own. There was no placebo group and

further research could benefit from inclusion of a placebo ~~to~~ for comparison. The study was specific to the effect of EAA on women with sarcopenia, making results applicable to that population. The randomized and controlled study design allows for inferences regarding causal effects of the supplement and exercise.

Calcium ß-hydroxy-ß-methylbutyrate (CaHMB) supplementation in community- dwelling elderly subjects

Leucine is a critical AA within protein needed to build muscle and combat muscle loss. One of the primary mehcanicsms by which leucine prevents muscle wasting is its conversion to ß-hydroxy-ß-methylbutyrate (HMB) (40). Stout et al. conducted an experimental trial to study the effects of calcium ß-hydroxy-ß-methylbutyrate (CaHMB) with and without RT in 65 years or older ambulatory men and women (61). Researchers collected dietary information by 3-day diet recall, muscle quality using calculations, and body composition by DXA scan measuring fat mass, lean mass, regional leg lean mass, and regional arm lean mass (61). There were multiple strength assessments including handgrip strength, isokinetic leg strength, bench press, leg extension, leg press; ~~and~~ function was assessed by a get-up-and-go test which involves timed getting up from a chair, walking 3 meters, turn 180 degrees, walk back, turn 180 degrees and sit in chair again (61). Patients consumed an ad lib diet during the two 24-week phases in this trial (61). Phase 1 consisted of two non-exercise groups with the experimental group consuming 2 packets twice daily of powder containing 1.5 mg CaHMB and 4 carbohydrates, and the control group consuming two placebo packets of powder twice daily containing 4 carbohydrates (61). Phase two

consisted of the same supplementation regimen and added resistance exercise to both groups (61). Phase 1 of the study demonstrated the CaHMB supplementation alone improved total lean mass, strength, function, and muscle quality without RT, while Phase 2 demonstrated CaHMB and RT increased lean mass, decreased fat mass, and improved muscle quality (61). Both the CaHMB-supplemented and placebo group showed significant improvement in strength and function in phase 2 (61). The data shows muscle quality, strength, and lean mass can be improved with CaHMB supplementation with or without RT.

In the Stout et al. study, anthropometrics, muscle function, muscle quality, and body composition were measured using validated methods. Limitations included use of the dietary recall though it is a validated method, it is subject to measurement errors due to inaccurate participant reporting.. The food record was not administered by an RD; qualifications of the persons providing instruction are undefined. Dietary changes were not encouraged, to show full effect of supplementation with CaHMB. The study showed the effect of CaHMB supplementation on healthy older adults, and though they are not sarcopenic, the effects of the supplement on muscle quality, strength, and function suggest results are applicable to prevention and/or treatment of sarcopenia. The lead researcher is the science advisor for Abbott laboratories and Abbott provided a grant partially funding the study. The randomized and blinded design of the study allows for inferences regarding causal effects of the supplement, but the sample size was small.

Fish oil supplementation in elderly adults

The objective in the Rodacki et al. randomized controlled study was to investigate the chronic effect of fish oil supplementation on strength and functional capacity in older women (62). 45 healthy older women were randomized into three groups: strength training only, strength training supplemented with 2 gm fish oil daily for 90 days, and strength training supplemented with 2 gm fish oil daily for 150 days (60 days prior to strength training program and 90 days during) (62). The strength training program was designed to improve lower limb muscle strength and was supervised and conducted 3 times per week for 12 weeks (62). Participants were asked to maintain their normal diet and physical activity routines during this time, and diet was monitored to ensure no major changes were made (62). Muscle strength and function were assessed before and after the trial, and body mass and dietary habits remained unchanged from beginning to end in all groups (62). The peak torque and rate of torque development for all muscles (knee flexor and extensor, plantar and dorsiflexor) increased in all groups (62). The effect was greater in the supplemented groups than in the strength training only group, but activation level and electromechanical delay of the muscles changed only for the supplemented groups (62). Chair-rising performance in the supplemented groups was higher than in the strength training only group (62). Strength training increased muscle strength and improved function in all groups, however, the effect was greater in the supplemented groups (62). Supplementation for 150 days did not cause any additional effects (62).

The small sample used for Rodacki et al. is a limitation, even with a randomized controlled design. The study was limited to female participants as sex differences in response to strength training exist. The participants studied were not diagnosed with sarcopenia and were relatively healthy. The resulting gains in strength suggest strength training and supplementing with fish oil is beneficial for prevention of sarcopenia, given that, this population had significant gains and primary sarcopenia is an age-related condition. The study does not show a direct benefit to sarcopenia prevention nor treatment but does suggest fish oil is a good complement to a strength training program in elderly people.

Physical Activity in elderly adults

The Binder et al study randomized controlled study investigated the effect of progressive resistance training (PRT) on body fat mass and FFM on 91 community-dwelling sedentary and frail adults 78 years of age and older (63). Three-day diet records were used to evaluate dietary habits, participants were advised to maintain their normal diets, and calcium/vitamin D supplements were provided to control for variations in those nutrients (63). Muscle strength was tested prior to and after the study; ~~and~~ body composition was evaluated with DXA and MRI to measure fat mass and FFM before and after the study as well (63). Participants were randomized into exercise training or control groups. The exercise training group participated in three phases of 3-month and 3 times per week supervised group training consisting of warm-up, flexibility, balance, coordination, reaction speed, and RT exercises (63). The control group was given home exercise plans focusing primarily on flexibility, and were asked to

complete the exercises 2-3 times per week at home (63). After completion of PRT, exercise training participants had greater improvements than the control group in maximal voluntary force production for knee extension (mean delta +5.3 +/- 13 ft. /lb. vs +1.1 +/- 11 ft. /lb., p =.05), measured using isokinetic dynamometry (63). Total body FFM (measured using DXA) increased in the exercise training group, but not in the control group (mean delta +0.84 +/- 1.4 kg vs +0.01 +/- 1.5 kg, p =.005). Total, trunk, intra-abdominal, and subcutaneous fat mass (measured using DXA and MRI) did not change in response to PRT (63). The exercise training groups had significant gains in strength and FFM than the control group, but neither group decreased fat mass (63).

The small sample used for the Binder et al. study is a limitation, even with a randomized controlled design. Because the control group was performing home exercises, the extent of changes from supervised training may be underestimated compared to what would have been seen if the control group remained sedentary. Sarcopenia can be a component of frailty but is a different and separate condition, but the results of this study are likely applicable to sarcopenia. The results suggest this type of training program would be useful in preventing or treating sarcopenia, because the supervised exercise training did increase strength, and decreased strength is part of a sarcopenia diagnosis.

The Strasser et al randomized controlled trial explored systematic endurance training (ET) effect on muscle strength, and systematic effect of resistance training (RT) on VO2max in elderly adults (64). They sought volunteers from elderly care homes and clubs and randomized 42 people,

greater than 70 years old, into three groups: continuous 6-month ET program, continuous 6-month RT program, and a control group that was advised to not make lifestyle changes during the study (64). All were tested to measure aerobic power (VO2max) and maximum workload (Wmax), provided a medical history, and underwent anthropometric and fat mass measurements prior to starting the programs and again after completion (64). ET was performed on a cycle ergometer on three non-consecutive days every week and time was increased weekly and RT was supervised by a professional instructor and weights to train upper and lower body were increased throughout the program (64). After 6 months of RT, maximum strength increased by an average of 15% for leg press ($P < 0.01$), 25% for bench press ($P < 0.01$) and 30% for bench pull ($P < 0.001$); ET showed no effect on maximum strength except for the bench pull. Aerobic power improved by 6% in the ET group and by 2.5% in the RT group, neither of which was significant (64). Maximum workload improved significantly by 31% in the ET group ($P < 0.001$) and by 6% in the RT group ($P = 0.05$). ET resulted in a significant 5.3% reduction of body fat ($P < 0.05$), whereas only RT increased lean body mass by 1.0 +/- 0.5 kg (64). In this study, RT increased lean body mass and muscle strength in healthy elderly adults. ET appears to be effective for maintaining and improving maximum aerobic power in the elderly and should be viewed as a complement to RT (64). The loading intensity to promote hypertrophy should approach 60-80% of 1-RM with an exercise volume ranging from 3 to 6 sets per muscle group per week of 10-15 repetitions per exercise (64). ET should be performed on two days per week controlled by a heart rate

according to 60% of VO2max and an exercise volume ranging from 30 to 60 minutes per week (64).

The small sample used for the Strasser et al. study is a limitation, even with a randomized controlled design. The population was heavily weighted with women; sex differences exist in response to RT. The population studied was not diagnosed with sarcopenia and was relatively healthy. The resulting gains in strength suggest RT is beneficial for prevention of sarcopenia, given that, this population had significant gains and primary sarcopenia is an age-related condition. The study does not show a direct benefit of ET to sarcopenia prevention nor treatment, but does suggest ET is a good complement to an RT program.

The Rydwick et al. randomized controlled trial recruited volunteers from primary care providers, newspapers, and the local housing authority to examine the effect of physical training and nutrition intervention on frail elderly people (65). 96 volunteers 75 years of age or older were randomized into four groups: specific physical training, specific physical training with general diet instruction, specific physical training with individualized dietary counseling, and a control group that was given general lifestyle advice (65). Baseline measures included a physical examination, BMI calculation, medication lists, and type of walking aids (65). Habitual activity level was estimated by using Classification of Physical Activing, a six-graded ordinal scale including both training/exercise and domestic activity. Personal ADL was estimated using Functional Independence Measure (FIM) (65). These measurements were repeated immediately after the

intervention at 3 months, and at the second follow-up at 9 months. ADL data was also collected 24 months after baseline at the third follow-up (65). The groups that included specific physical training participated in a group class, planned by a physiotherapist, ~~and~~ led by a trained instructor and a physiotherapy assistant, for 1 hour twice weekly for 12 weeks (65). The classes included warm up, individualized RT, individualized strength training exercises, and functional training; ~~and~~ this period was followed by six months of home-based exercises. ~~and~~ The participants kept activity diaries (65). Nutritional treatment~~s~~ consisted of individual dietary counseling and supplements if needed, based on participant food diaries (65). The specific physical training with general diet instruction and control groups were given general nutrition advice to eat 3 meals per day with 2 small snacks between meals along with general food and fluid recommendations; the control group received recommendations to walk 3 times per week and try to be active 30 minutes each day (65). The four groups were comparable at baseline except that more walking aids were needed in the physical training with general diet instruction and control groups (65). There was an increase of the habitual physical activity level and walking duration at ~~1st~~ the first follow-up for the two training groups compared to the other groups. These increases remained at the second follow-up (65). The nutrition intervention did not show any significant results. There were no significant effects on ADL, however, there were moderate correlations between increases in physical activity level and ADL as well as between the amounts of home-based exercises and ADL for the two training groups (65). This study indicated that a physical training program alone

or in combination with the nutritional intervention program followed by monitored home-based exercises increased habitual physical activity level in frail elderly people (65).

The small sample and relatively high drop-out rate in the Rydwick et al. study is a limitation, even with a randomized controlled design. The population is described as frail as the study aimed to recruit subjects that met the Fried criteria for frailty. Sarcopenia can be a component of frailty but is a different and separate condition. The study did not examine the effect of increased habitual physical activity on muscle mass, strength, or function. The training was conducted by a professional team, which is a strength. The results do suggest this type of training program would be useful in preventing or treating sarcopenia, because the increased activity is likely to improve muscle mass, strength, and function.

Physical Activity and protein supplementation in elderly adults with sarcopenia

Shahar et al. conducted a quasi-experimental community-based study that looked at 65 subjects affected with sarcopenia, 60 years of age or older, who were divided into four groups: control, exercise, protein supplementation, and combined exercise with protein supplementation (66). The groups were not randomized; each group was taken from a different senior citizen club (66). Dietary history was established at baseline (66). The exercise group was supervised by professionals and the researchers. They received 60 minutes of "well rounded" moderately intensive activity, including 30 minutes of RT, twice

weekly for 12 weeks (66). The protein supplementation group received powdered soy protein in the amount required to maintain protein intake of the subjects at 1.5 gm protein/kg/day (66). Exercise and protein supplementation was provided at the same level to the group that received both interventions (66). Anthropometric measurements and tests of strength and function were conducted before and after the study; and blood was drawn before and after the intervention (66). There were no significant differences in the participants in terms of sociodemograpy, health profile, or health practices (66). Improvement in body composition was noted after the intervention in all but the control group, body weight and BMI decreased (66). There was no significant weight or BMI decrease in the control group (66). Protein supplementation had no effect upon fat-free mass (66). There were no significant changes in muscle mass in any group, but there was a trend toward increase in muscle mass in both interventions that utilized exercise (66). After the 12-week intervention, significant improvement was noted for body weight, strength, and function (66). There were no significant changes in oxidative stress markers in any group (66). This study suggests exercise and protein supplementation are beneficial to reduce body weight, improve fat-free mass, and to improve strength and function in elderly people affected with sarcopenia (66).

Because the Shahar et al. study is quasi-scientific causation cannot be attributed to the intervention with certainty, but it was well designed and implies positive effects of exercise and protein supplementation in line with many other studies. Soy protein was used for its high leucine content, however, whey

protein is better absorbed and possibly a more effective choice (44). Another limitation of this study is small sample and high dropout rate of 17%. There was unequal distribution of the sexes, but the study was controlled for sex. One major strength is the study used individuals affected by sarcopenia using criteria put forth from EWGSOP which allowed researchers to demonstrate likely improvements with the interventions in that population.

Summary and Conclusions

Many studies have brought forth evidence that older adults need more than the RDA protein intake of 0.8 gm per kg of body weight. Newer recommendations set the level at 1-1.2 gm per kg of body weight for healthy older adults and 1.3-1.5 gm per kg body weight for adults in disease states (39). There are varying opinions regarding whether plant-based protein can easily or adequately meet these protein needs; but a variety of protein sources should guarantee getting adequate AAs. Huang et al. demonstrated the value of protein intake in increasing muscle mass; particularly plant-based protein. Nilsson et al. demonstrated women with higher protein intake have higher SMI and higher physical function and that failing to meet the lower RDA guidelines for protein intake is detrimental to both muscle mass and physical function in elderly women.

Protein supplementation is an area of interest for prevention and/or treatment of sarcopenia. The anabolic signaling of amino acids in skeletal muscle may be triggered by the consumption of essential amino acids, particularly the branched chained amino acid leucine (67). Sarcopenia is usually

an older adult disease state. Protein intake can become challenging in later life. The more complete sources of protein are typically meat products. As teeth age and dental condition deteriorates the intake of meat can become problematic. Polypharmacy sometimes causes taste changes that make meat and proteins have off-flavors which can cause aversion. Meats can also present a cost challenge as they can be expensive. Many older adults rely on packaged foods and restaurant foods for ease and convenience. These options often do not provide adequate protein. Supplements can provide protein and targeted amino acid in an easy to consume form. The supplements sometimes present less of a challenge for the elderly because dentition is not an issue and supplements tend to be sweet which often works with the taste changes that accompany aging. Most of the studies examined in this review support the use of supplements to improve some or all markers of sarcopenia.

Tieland et al., Dillon et al., and Stout et al. studied the effects of amino acid supplementation on muscle mass and quality. Tieland demonstrated benefit to muscle mass and function with protein supplementation independent of other interventions. Dillon demonstrated some benefit to muscle size and function with amino acid supplementation on its own. Stout showed benefit of supplementing both with and without exercise. Dillon supplemented a variety of amino acids and Stout focused on CaHMB.

The remainder of the studies reviewed support the benefits of supplementation and exercise together as improving markers of sarcopenia such as muscle mass, muscle quality, muscle function, and physical performance.

Most agree the greatest benefit is achieved with a combined program involving physical resistance training and supplementation. Many studies suggest that resistance training on its own provides great benefit, but it appears the benefit is increased with the addition of protein supplements.

Intervention studies did not use consistent definitions of sarcopenia. Definitions that are based on some of the features of sarcopenia may make results misleading and difficult to interpret. With the implementation of the new operational definitions of sarcopenia and the classification of sarcopenia as a disease state, research will likely become easier to interpret and apply to this condition. Protein and amino acid supplementation appears to be a promising treatment for sarcopenia. This is an area that needs further and longer-term studies. It would also be beneficial to study the effects of real food protein sources versus the supplements.

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Chapter 3: Methodology

Toolkits are a collection of resources on a particular topic that can be used in a variety of ways. Toolkits are available for certain diseases and may be designed for use by healthcare professionals or for clients and patients. They are meant to be user friendly and to facilitate the translation of evidence into practice. Increased prevalence of and increased research on sarcopenia warrants the creation of a sarcopenia toolkit. Sample toolkits were reviewed as models to base the design on. The main inspiration for creation of the sarcopenia toolkit came from the CCQCC toolkits to address maternal quality care (Toolkits | California Maternal Quality Care Collaborative (cmqcc.org)). The content of the toolkit was assembled using data from the literature review. To the best of this author's knowledge, no such toolkit on sarcopenia exists, though there is a sarcopenia section within the CGA comprehensive geriatric assessment toolkit. The toolkit contains: cover page, sarcopenia education for healthcare professionals PowerPoint presentation with notes, two handouts for patient education, and a resource page to provide further helpful information.

Target Audience

The target audience for use of the toolkit is physicians and their office staff. The toolkit is provided for guidance in diagnosing and addressing primary sarcopenia in patients. The ICD-10 code for sarcopenia was created in 2016, however, it is

not widely used. Targeting this population for education will facilitate diagnosis of sarcopenia and use of the code allows for reimbursement and data collection.

Literature Review

A literature review was conducted to investigate documented evidence on the diagnosis and treatment of primary sarcopenia. The literature review was used as the basis for building the sarcopenia toolkit. The literature was searched between the dates of Jan 2000.and Jan 2021. Key search terms included: sarcopenia, sarcopenia exercise, sarcopenia treatment, and sarcopenia nutrition. Databases that were searched included PUBMED and Google scholar. Research articles were reviewed for relevance.

Toolkit components

The toolkit contains a PowerPoint for healthcare professional education and includes presentation notes. There are two sarcopenia handouts for patient education. Also included is a resource document which provides additional sources of professional education, patient education, and guidance for recognizing and diagnosing sarcopenia.

Envisioned Use

This toolkit could be used for guidance or primary physicians and their staff in diagnosing and treating primary sarcopenia in patients, with distribution to primary care physician offices. It is a rudimentary toolkit and would benefit from further development utilizing collaboration with other disciplines, such as physical therapy. The toolkit could be developed into a webpage.

Chapter 4 Toolkit

Sarcopenia Toolkit

Patient Handouts

What is Sarcopenia?

Sarcopenia is a disease that is often age-related. It involves a progressive and generalized loss of skeletal muscle and strength.

How does Sarcopenia affect people?

The loss of muscle mass contributes to a decline in physical function and performance. This can contribute to:

- Disability
- Poor Quality of Life
- Death

What causes Sarcopenia?

Age is a major factor in sarcopenia. Muscle mass loss is usually 1-2% per year after age 50. This loss speeds up with advancing age.

There are age-related changes in muscle tissue and fiber.

There are age-related changes in nerves that work with the muscles.

There are age-related changes in blood flow to the muscles.

What makes Sarcopenia worse or more likely?

- Inactivity and Sedentary Lifestyle
- Poor Nutrition
- Other Disease States and Inflammation

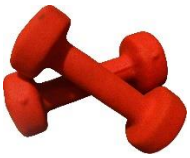
Please watch this short informative video on YouTube from the Alliance for Aging Research

- https://youtu.be/CAC2g03_-2

So I have Sarcopenia…what can I do about it?

Sarcopenia impacts most people as they age, but it can be prevented, progress slowed or even reduced.

See your doctor. Your doctor can help guide you in appropriate ways to treat sarcopenia. You may be referred to a Registered Dietitian and/or a Physical Therapist.



Physical Activity

All physical exercise is likely beneficial. Resistance training~~, such as exercise~~ using weights or bands~~,~~ has been shown to be the most effective form of exercise to combat sarcopenia. Resistance training may increase strength and lean muscle mass. This can help maintain good muscle function.

The American College of Sports Medicine (ACSM) recommends older adults should participate in muscle strengthening activities for the major muscle groups 2-3 times per week using moderate to vigorous intensity. They also recommend balance training exercise for general health and to maintain functional independence

*** Always check with your doctor before starting new exercise ***

Nutrition

Good nutrition is important for muscle maintenance and function. Protein is especially critical to keep muscles healthy.

Good sources of protein include

- Meats/chicken/fish
- Eggs
- Beans and lentils
- Nuts and seeds
- Protein shakes or bars

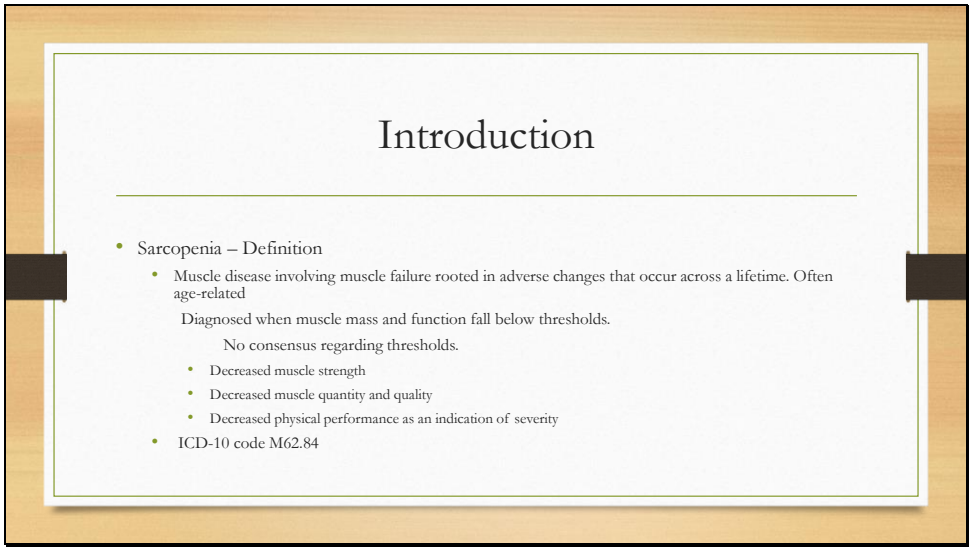
* A Registered Dietitian can guide you in how to meet your protein needs each day*

Vitamin D is important for maintaining muscles. A doctor can help you ~~in~~ decide whether a supplement is needed. Good sources of Vitamin D include:

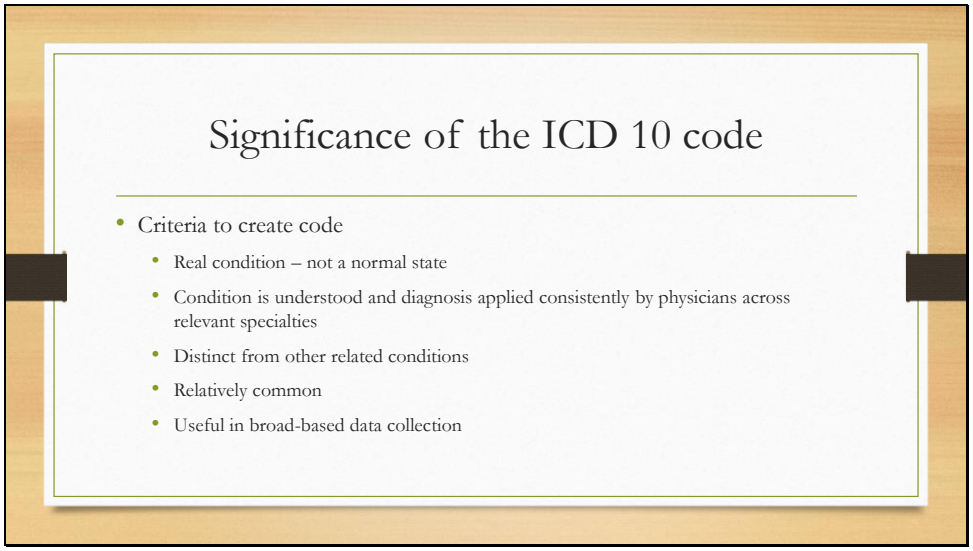
- Sunlight
- Fortified milk and juices
- Fatty fish (tuna, mackerel, salmon)
- Cod liver oil

Omega-3 fatty acids and some antioxidants also may help combat sarcopenia. The best strategy for getting these are from food first rather than supplements. Good sources are fatty fish, flaxseed, chia, seeds, nuts, and a variety of fruits and vegetables.

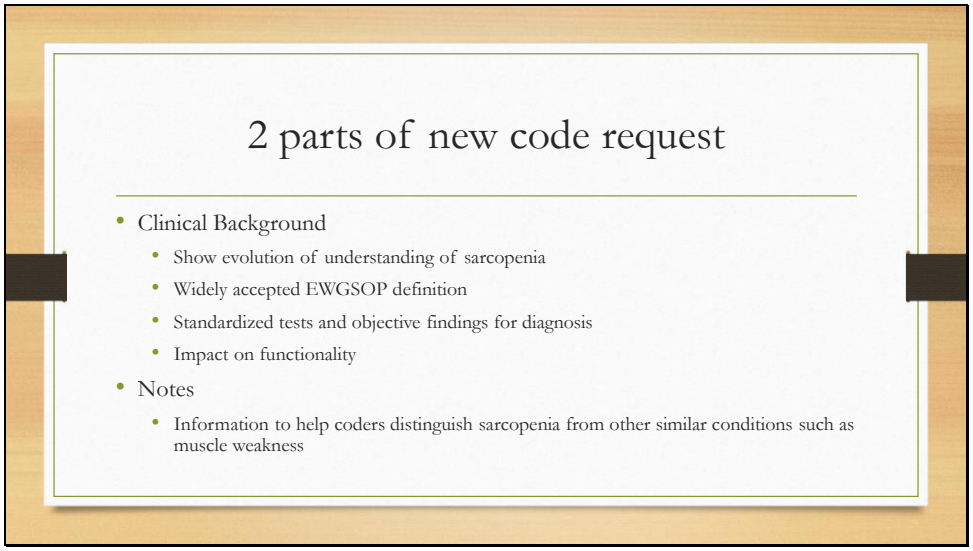
Sarcopenia PowerPoint for Healthcare Professional Education



Talking points: The definition of sarcopenia has evolved over time and still lacks consensus. The definition in this presentation is from the European Working Group on Sarcopenia in Older People (EWGSOP) which does have wide acceptance in both clinical and research settings. Other similar definitions of sarcopenia have been developed by international organizations, such as the European Working Group on Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS), the Asian Working Group for Sarcopenia (AWGS), and the Foundation for the National Institutes of Health (FNIH). These groups recommend~~ed~~ that sarcopenia should be defined by low muscle mass and strength and have some emphasis on function as well. Sarcopenia is recognized as a disease state with an ICD-10 code since 2016. Adopting a standardized, operational, and clinically applicable definition is important for both research and to develop prevention and treatment strategies. Although the criteria for diagnosis still lacks consensus, there are specific tests that can indicate a sarcopenia diagnosis The establishment of the ICD-10 code was a critical step sarcopenia diagnosis and treatment.

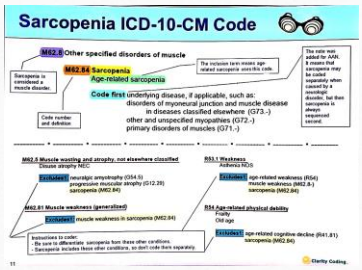


Talking points: This all contributes to accurate and more frequent diagnosis, allows for earlier interventions and better patient outcomes, and drives research



No further talking points

Anatomy of an ICD 10 code

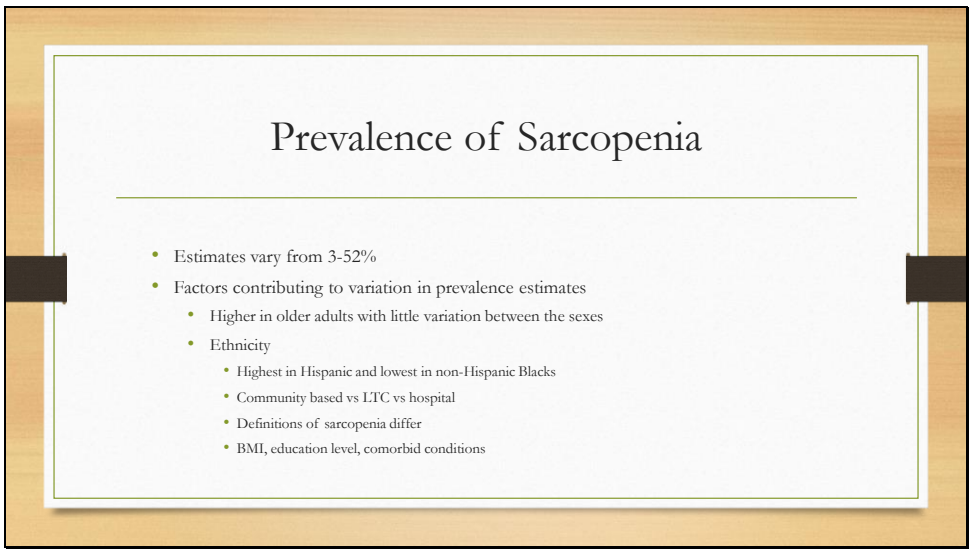


Talking points: Having an assigned ICD-10 code means the CDC recognizes sarcopenia as a separately recorded condition and removes barriers to diagnosis for physicians. The M indicates sarcopenia is considered a musculoskeletal disorder. Age-related sarcopenia is included under this ICD-10 code. The "code first" notes indicate that if sarcopenia is due to another disorder, it should be coded second (but should still be coded!) Some examples of related diagnoses are shown, such as muscle weakness/generalized weakness; ~~and~~ if these conditions are caused by primary sarcopenia, ~~then~~ the sarcopenia code should be used.

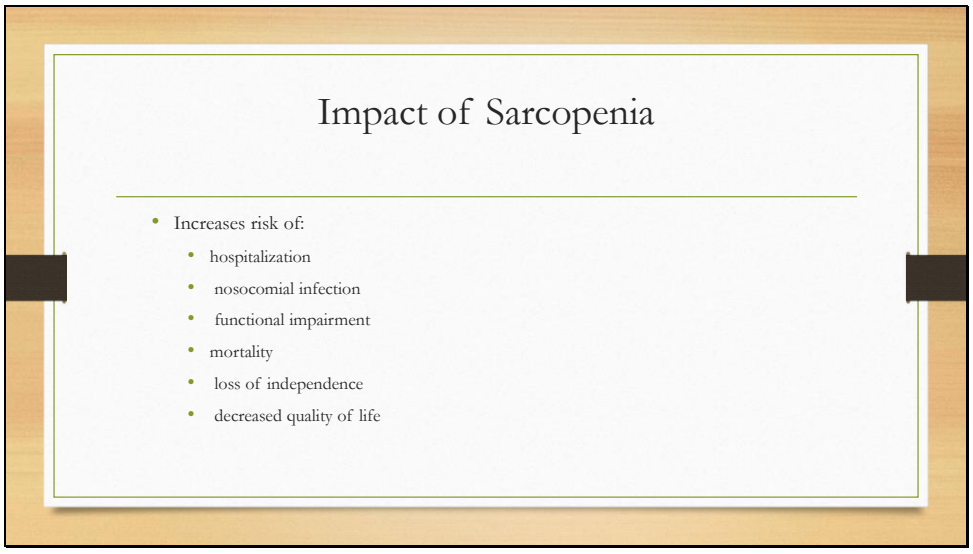
Classifications of Sarcopenia

- Severity
  - Probable or Pre-Sarcopenia
    - Low muscle strength
  - Sarcopenia
    - Low muscle strength AND reduced muscle mass
  - Severe Sarcopenia
    - Low muscle strength AND reduced muscle mass AND low physical performance

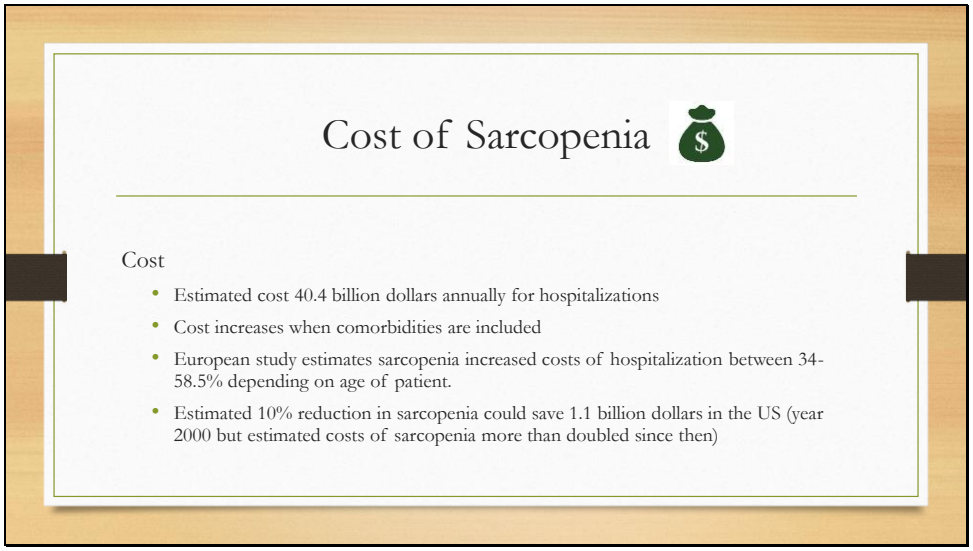
These classifications are from the EWGSOP. Although there is currently no~~t~~ consensus regarding the definition of "low," several groups propose cut-off points (Sarcopenia Project), other definitions use a decline in strength or performance rather than "low."



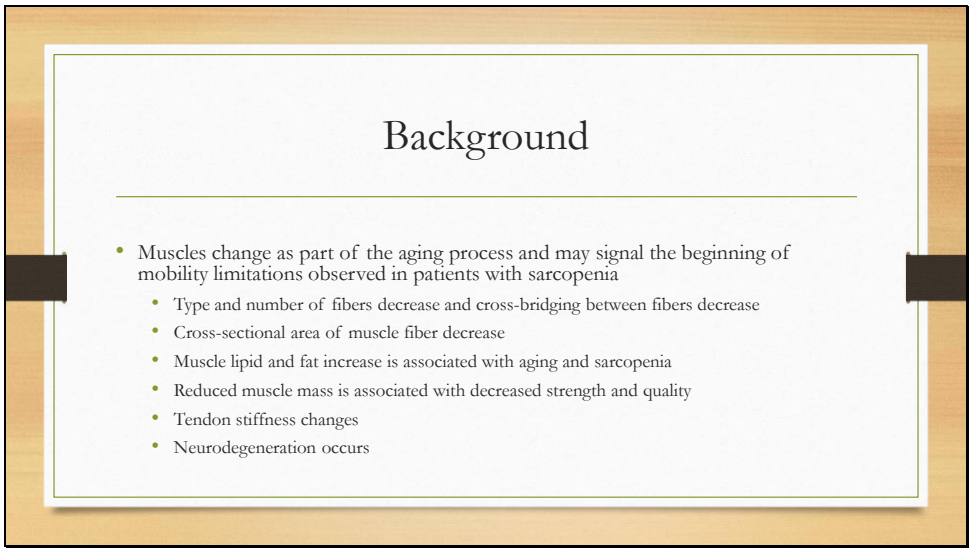
Talking points: The wide variation in prevalence estimates is largely due to differences in populations studied. Prevalence is generally lower in community dwelling adults and higher in adults in acute or long-term care environments. Prevalence estimates are also dependent upon the diagnostic criteria used.



Talking points: Some estimates have hospitalization risk as much as doubled if sarcopenia is present



Talking points: Data estimating the cost of sarcopenia is scarce. Direct costs are in the billions. The associated comorbidities drive the cost up. As the aging population continues to grow and life expectancy increases the costs of sarcopenia are likely to increase too.



Talking points: Some of these age-related changes are adaptive and while they allow continued overall function they can cause decreased function. Lifestyle changes can slow progression.

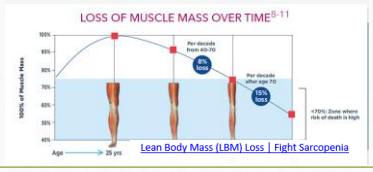
Background

- Processes affected by age-related muscle changes
  - Innervation
  - Mitochondrial function
  - Protein synthesis and degradation
  - Glucose utilization

No further talking points

Etiology of Sarcopenia

- Typically from age 20 to 80, there is a 30% reduction in muscle mass
- Rate of muscle mass loss estimated at 1-2% annually after age 50 in conjunction with annual strength losses of 1.5% accelerating to 3% after age 60



Talking points: This represents the natural progression of muscle mass loss due to aging. Muscle loss is a significant consequence of aging.

Etiology of Sarcopenia

- Aging
- Neurological Factors
- Inflammation
- Impaired Nutritional Status
- Genetics
- Hormones
- Insulin Resistance
- Vitamin D Status
- Decline in Physical Activity

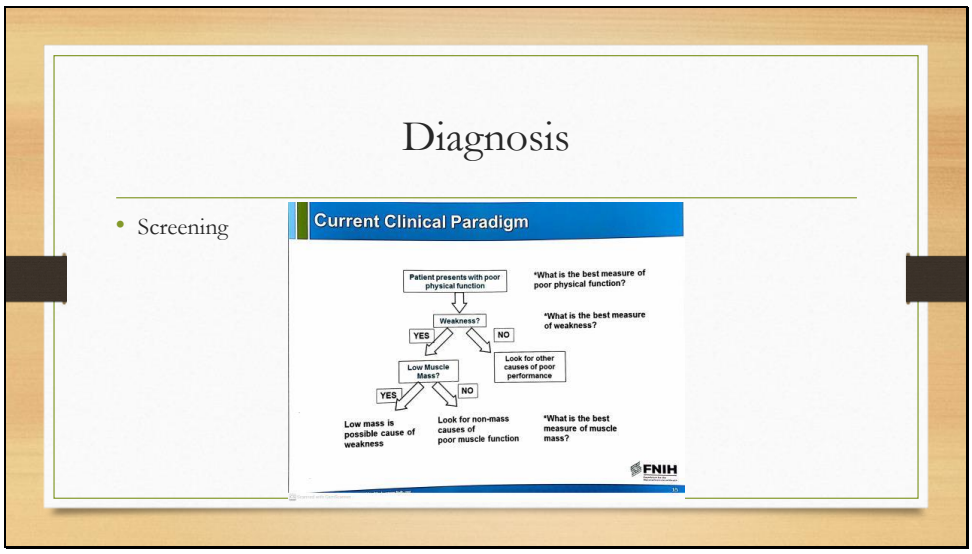
Lean Body Mass (LBM) Loss | Fight Sarcopenia

Talking points: Aging muscle triggers underlying cellular changes that can result in weakening of factors that promote muscle anabolism and ~~also~~ trigger increased expression of agents that promote muscle catabolism. That disruption in balance between anabolism and catabolism cause muscle loss over time. There are many contributors to sarcopenia and the combination leads to a loss of lean body mass and all contribute to a decrease in function. Many of these factors can be altered by lifestyle changes.

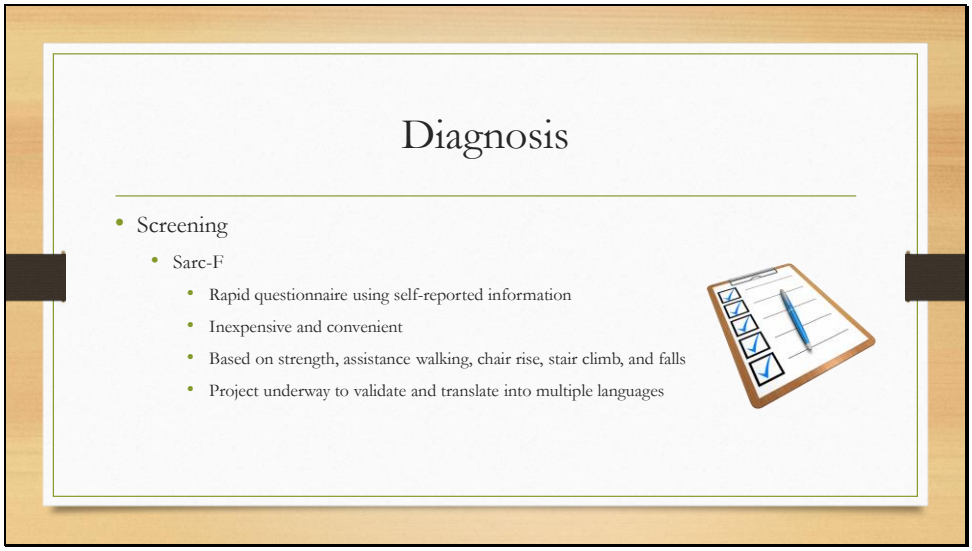
Etiology of Sarcopenia

- Inflammaging (age-associated state of low-grade inflammation)
- Decrease in muscle protein synthesis and increase in protein breakdown
- Manifestation
  - Loss of cross-sectional area of muscle
  - Denervation
  - Changes in motor-units resulting in less fast motor units overall

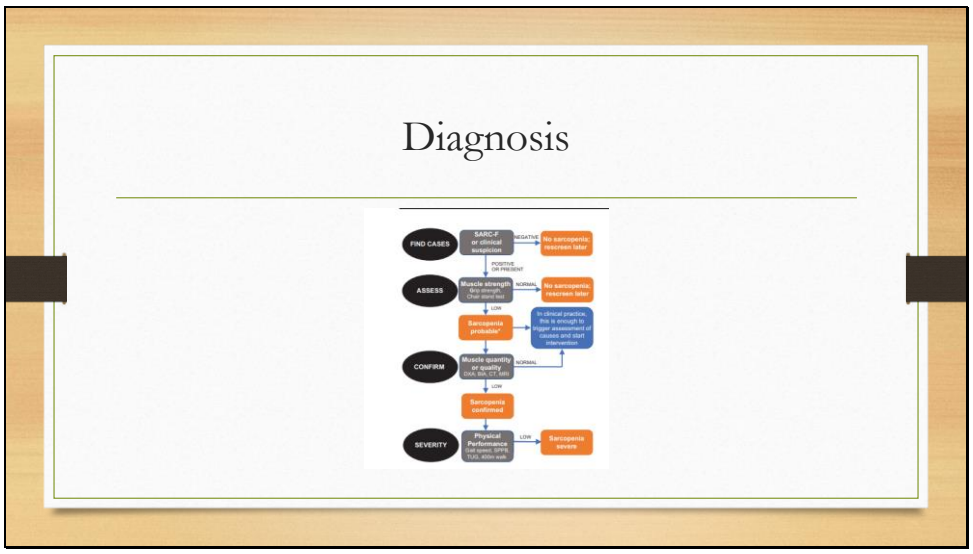
Talking points: Inflammaging is a relatively new concept. This refers to increased levels of pro-inflammatory cytokines and decreased levels of anti-inflammatory cytokines. Higher levels of age-associated pro-inflammatory markers are detected in the majority of older individuals even in the absence of other risk factors and clinically active diseases. Inflammaging is also a risk factor in many other diseases including cardiovascular disease, chronic kidney disease, cancer, chronic kidney disease, dementia, depression, frailty, and can contribute to premature death



Talking points: FNIH Sarcopenia Project suggests this screening. Patients with sarcopenia are likely to present to physician reporting poor physical function. If it is determined the patient has weakness, investigate further for low muscle mass, which would then indicate sarcopenia. To assess physical function ~~can~~ ask if patient noticed a decline such as inability to climb stairs, cannot open jars, cannot go grocery shopping because bags are too heavy, or cannot get out of a chair. Objective tests can also be used to determine functionality and they will be described later.

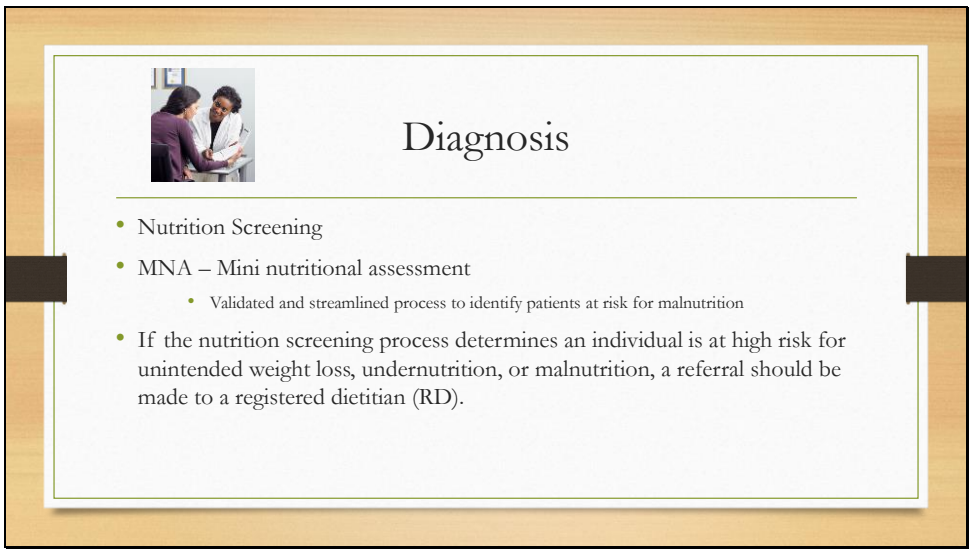


Talking points: All of the screening tools are helpful in identifying those who are at risk for sarcopenia and in determining patients that have sarcopenia. Tool selection depends on the patient/population, access to technology, setting, and purpose of testing. Cost is also a factor. A multidisciplinary team and approach are helpful when addressing sarcopenia and should include an RD, PT. and other interdisciplinary team memebers as applicable

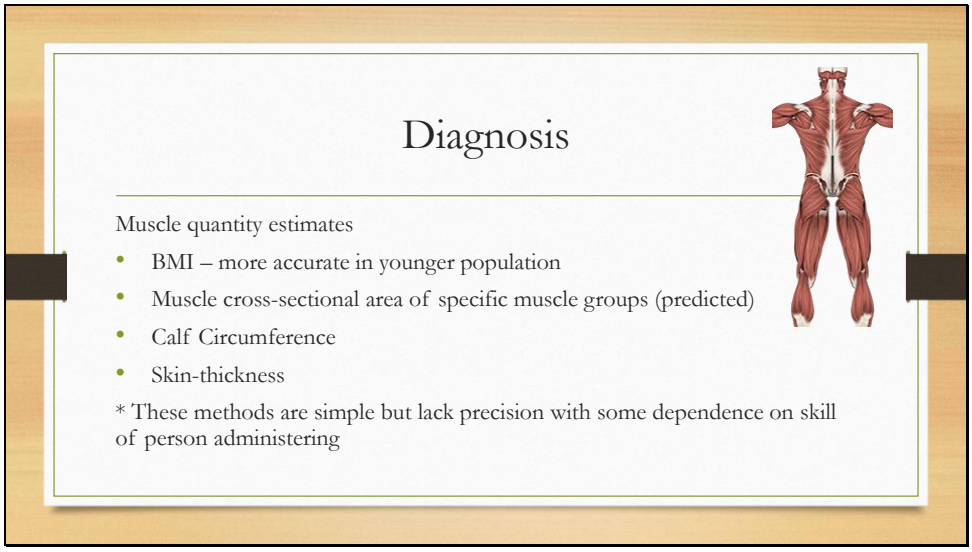


Talking points: This algorithm from EWGSOP can be useful in sarcopenia diagnosis, however, requires specialized equipment to assess muscle quality.

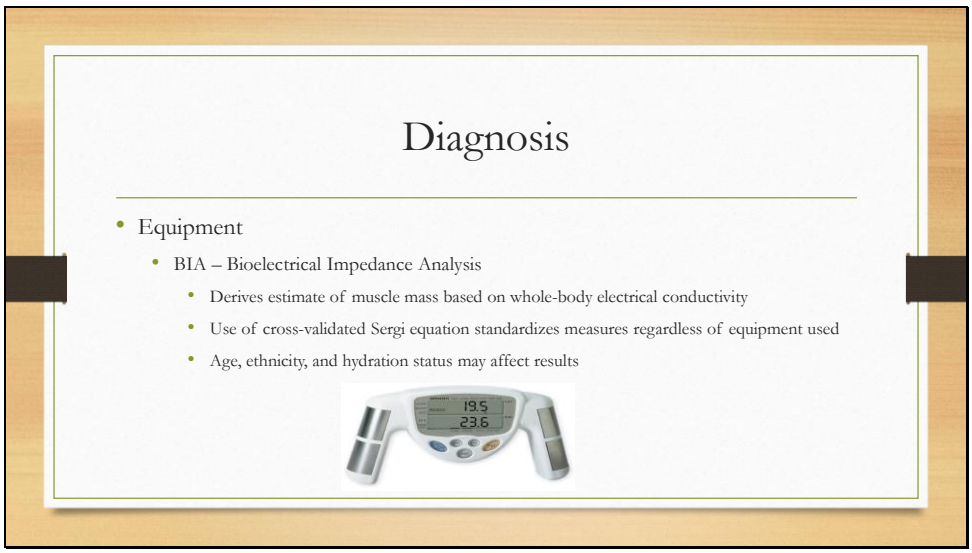
An example of the SAR-QoL tool and Ishiii's calculation can be found in the resources section of the toolkit



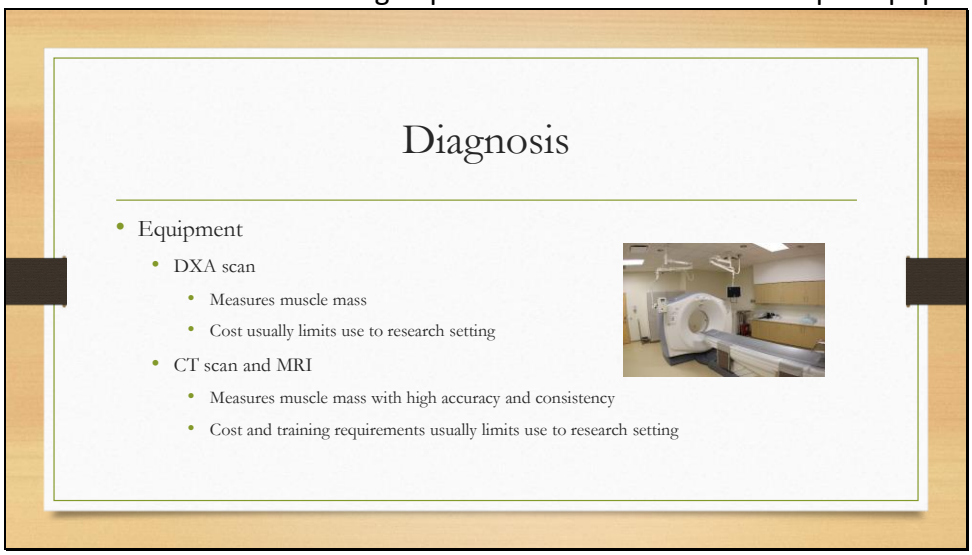
An example of the MNA is found in the resources section of the toolkit.



Talking points: Anthropometric measures such as these are simples but lack precision and are dependent on the skill of staff administering them. BMI is a better measure of nutritional status than of muscle mass in the older population. and It is less useful as a measure on its own in older population but can be used in parts of calculations useful in diagnosing sarcopenia. As noted earlier, fat infiltration of muscle increases with age. Calf circumference has been shown to predict performance and survival in older people with a cutoff point of <31; it may be used as a diagnostic proxy in settings where other diagnostic methods are unavailable. Other methods and cut-off points are provided in resource section of the toolkit



Talking points: BIA equipment is small hand-held or scale-like equipment that derive an estimate of total lean mass based on whole-body electrical conductivity by using an equation that is calibrated with a reference of DXA-measured lean mass in a specific population. BIA estimates volume of body fat and lean body mass, but not appendicular muscle mass. Estimates of muscle mass differ by which equipment is used, and raw measure produced by the different devices along with the cross-validated Sergi equation standardizes the measures. The Sergi equation is based on older European populations.



Talking points: DXA is widely used gold-standard but costly. It measures muscle mass but is usually only used in research settings. DXA measures are influenced by hydration status. CT and MRI are accurate but costly, ~~and~~ limited by lack of portability and require trained staff. They are more often used in research settings. Findings from the FNIH Sarcopenia Project find appendicular lean mass measured by DXA is not a good predictor of adverse health-related outcomes in community dwelling older adults and questions the value of DXA use in clinical practice for diagnosis of sarcopenia.

Diagnosis

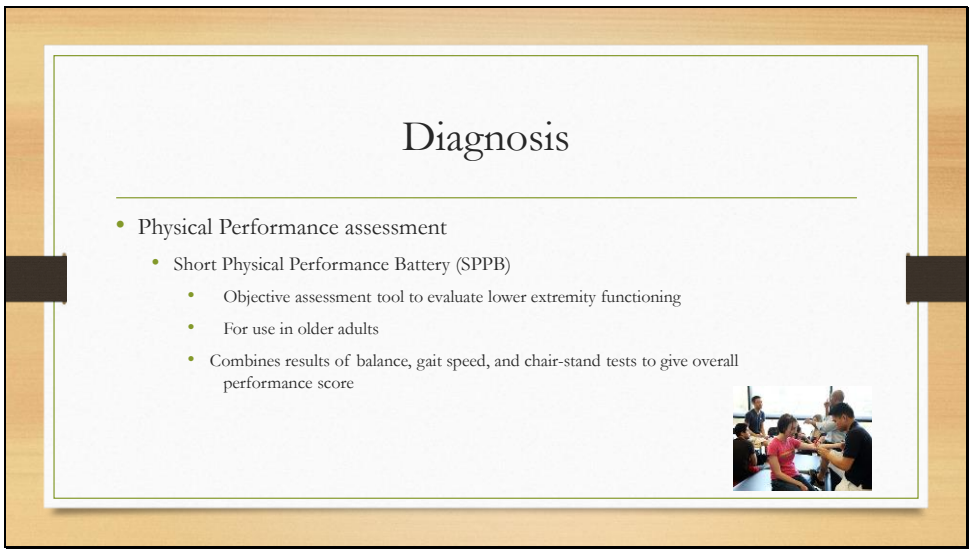
- Equipment
  - Ultrasound
    - Can measure muscle quantity, to identify muscle wasting, and to measure muscle quality
    - Valid and reliable
    - Not used in clinical practice, but has potential

Talking points: Protocols are being expanded that may make ultrasound more useful for diagnosis in clinical settings. Ultrasound offers the advantage of measuring both muscle quantity and quality.

Diagnosis

- Strength measures
  - Hand-grip strength by isokinetic dynamometry
    - Convenient
    - Relatively inexpensive equipment
    - Accurate measurement of hand-grip strength requires a calibrated hand-held dynamometer

Talking points: Low hand grip strength is a powerful predictor of poor patient outcomes. Isokinetic dynamometry is the gold-standard for the measurement of handgrip strength and can be accomplished with relative ease and inexpensive equipment. This makes it suitable for use in both clinical and research settings. FNIH Sarcopenia Project-proposes that muscle weakness as defined by low grip strength should be included in the definition of sarcopenia. Muscle weakness as defined by low grip strength is a predictor of adverse health-related outcomes such as mobility limitation, falls, ADL disability, and mortality in community-dwelling older adults.



An example of this tool can be found in the resource section of the toolkit
Talking points: SPPB can be performed in most clinical and research settings

Talking points: All of these physical performance tests can be performed in most clinical and research settings. Strength is one of many factors that affect walking speed. A reported decrease in ability to do these tasks is suggestive of sarcopenia. Findings from the FNIH Sarcopenia Project suggest "slowness" as defined by usual gait speed is a predictor of adverse health-related outcomes, and they suggest usual gait speed as an indicator of walking speed should be used in the definition of sarcopenia.
Further cut-off points and information are found in resource section of the toolkit.

Talking points: Older adults need more than ~~what~~ the RDA recommendation to maintain muscle; ~~and~~ protein is critical. The higher protein requirements of older adults is due in part to the anabolic resistance that is common to age related changes. Anabolic resistance is reduced sensitivity to amino acids which are responsible for maintenance of muscle mass and function. Older adults may produce less muscle from the same amounts of dietary protein than younger adults. Optimal protein intake can be defined as the minimum amount of protein that results in maximum anabolic response, and thus, can maintain or improve muscle mass and function over time. Appetite changes, taste changes, financial concerns, and dental issues can affect nutritional status of older adults and make getting adequate protein challenging. Supplements can assist in obtaining adequate nutrition.

Information regarding ONS is found in the resources section of the tool kit
Talking points: One study shows 32-41% of women and 22-38% of men older than 50 consumed less than the RDA for protein. Supplementation can deliver a bolus of amino acids and increase circulating amino acids much like from a meal ~~would~~ and may be more tolerable to someone with eating difficulty. Supplementing protein is one way to ensure older adults consume adequate protein. Whey protein may be the most effective stimulator of muscle protein synthesis. Animal proteins are better digested than plant proteins, however adequate protein can be obtained from a plant-based diet if the patient is able to consume adequate amounts.

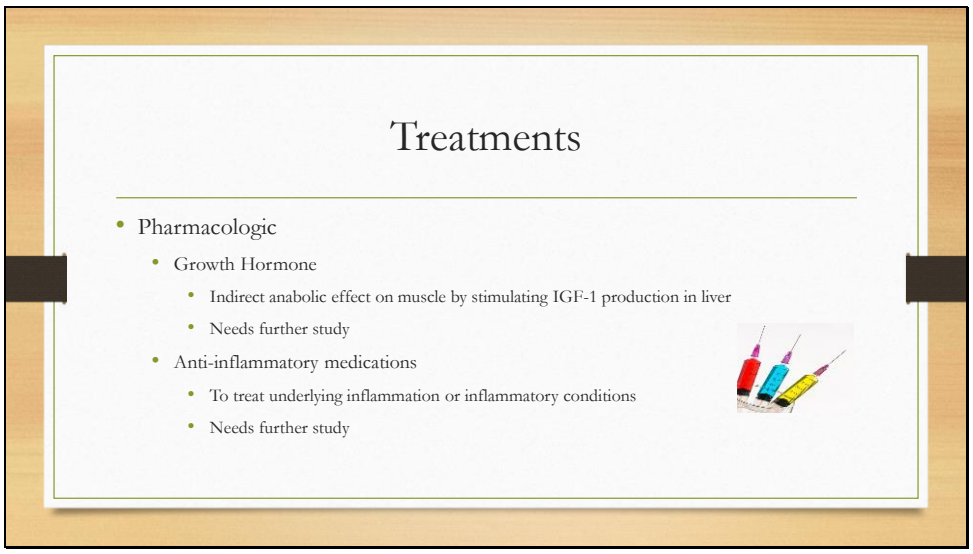
Talking points: The stimulation of mTOR pathway by leucine and its metabolite HMb has generated interest and study in supplementing these specific nutrients to assist in maintaining muscle. Higher amounts of leucine and HMb are needed to stimulate muscle protein synthesis in older adults due to anabolic resistance.

Talking points: Essential fatty acids, particularly DHA and EPA are beneficial in improving muscle mass and function. A diet that includes fatty fish can be encouraged. If dietary intake is insufficient a supplement could be beneficial. Vitamin D should be supplemented if levels are low. There is not enough current evidence to recommend creatine supplementation, but it may be beneficial. An RD is a great resource to help guide patients with their nutritional needs. A balanced diet is beneficial not only to preventing and treating sarcopenia, but for overall health status as well.

The pharmacologic agents discussed are not yet approved for use in sarcopenia. Diet, exercise, and lifestyle changes are effective. The following pharmacologic treatments are under study and may become treatments for sarcopenia in the future.

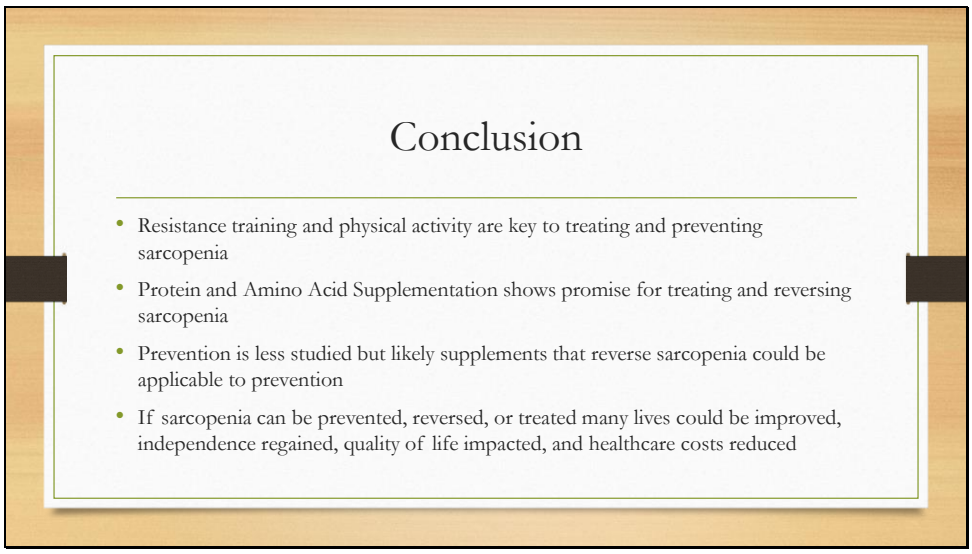
No additional talking points

Hormonal therapy should be addressed if there is a clinical need and may have a positive effect if sarcopenia is present



No additional talking points

Talking points: Any and all physical activity can benefit the patient and sarcopenia, as sedentary lifestyle is a risk factor. Resistance training has been shown to be most beneficial in sarcopenia. Referral to PT is beneficial for a full assessment of what is needed and what will best benefit the patient. Less deconditioned patients can be guided by physician as to what forms of exercise is medically appropriate. An exercise program should be personalized to address individual needs. Additional information is found in the resource section of the toolkit.



Muscle mass is regulated by the balance between muscle protein synthesis and breakdown, with the two major environmental influence on these processes being food intake and physical activity. Everyone loses muscle mass as part of the aging process, however, not all older adults meet the criteria for a sarcopenia diagnosis. There are individual differences in the rate of muscle mass loss, the age at which muscle mass starts to decline, and the extent to which strength and function are affected as part of the aging process. In older people muscle protein synthesis response to a single anabolic stimulus may be blunted. Adoption of multimodal strategies, particularly focusing on protein intake and physical activity, is the most plausible approach to treatment and prevention of sarcopenia.

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Resources to assist in the fight against Sarcopenia

Sarcopenia

International Osteoporosis Foundation | IOF

Information regarding sarcopenia, osteosarcopenia, nutrition

Aging in Motion - Advancing research and treatment of sarcopenia and age-related functional decline

The Aging in Motion (AIM) Coalition is a diverse group of patient, caregiver, health, and aging groups working together to press for greater levels of research and innovation to develop treatments in the area of sarcopenia and age-related functional decline.

CGA Toolkit Plus - Comprehensive Geriatric Assessment in Primary Care (cgakit.com)

This toolkit provides information regarding many areas of geriatric care, and includes a section with sarcopenia information, and includes tools for diagnosis, assessment, and treatment. There are some similarities to this toolkit in the sarcopenia section, but does not include the professional education piece, and some tools are different. It is a resource for holistic geriatric care and many of the issues and syndromes they address overlap with sarcopenia.

Senior wellness and fitness

Exercises for Older Adults to Stay Fit and Active (ncoa.org)

Exercise Plan for Seniors: Strength, Stretching, and Balance (healthline.com)

Senior Exercise Programs & Classes - SilverSneakers Fitness

Online workouts for seniors and how to pick the right one for you | CBC LifeSports Nutrition Guide | U.S. Anti-Doping Agency (USADA)

The complete Guide to Senior Health and Wellness – Senior Lifestyle

Information regarding supplements

nutrition-suggested-protein-supplements.pdf (hopkinsmedicine.org)

Sports Nutrition Guide | U.S. Anti-Doping Agency (USADA)

Abbott_WallChart.back (koppsrx.com)

nhs-product-guide-2019-online-hcp.pdf (nestlehealthscience.ca)

Videos

(597) Sarcopenia: Taking Charge of Your Muscle Health As You Age - YouTube

(597) Sarcopenia - YouTube

(597) How to Avoid Sarcopenia (Muscle Loss from Aging) - YouTube

Screening tools

Ishii's Score calculation

Men: 0.62 × (age − 64) − 3.09 × (HS − 50) − 4.64 × (CC − 42)

Women, 0.80 × (age − 64) − 5.09 × (HS − 34) − 3.28 × (CC − 42)

The cut-points for defining sarcopenia were ≥105 for men and ≥120 for women.

CC refers to calf circumference, HS refers to grip (hand) strength

SAR-QOL - Sar Qol.pdf

MNA - https://www.mna-elderly.com/forms/mini/mna_mini_english.pdf

Sergi Equation ASM (kg) =3.964 + (0.227 x RI) + (0.095 x weight) + (1.384 x sex (men = 11, women = 0) + (0.064 x Xc)

ASM = appendicular skeletal mass

RI = Resistance normalized for stature

Xc= Reactance

SBBP guides 9506 instructions.qxd (missouri.edu)

SPPB Guide

Short Physical performance battery assessment (ucsf.edu)

SARC F SARC-F Questionnaire - CGA Toolkit Plus (cgakit.com)

Diagnostic criteria

	Operationalization
European Working Group on Sarcopenia in Older People [20]	Low muscle mass (technique-specific cut-points) plus low physical function (gait speed ≤0.8 m/s) and/or low muscle strength (grip strength <30 kg in men and <20 kg in women)
FNIH Sarcopenia Project [16]	Low muscle mass (ALM < 19.75kg in men and <15.02 kg in women, or ALM_{BMI} <0.789 in men and <0.512 in women) plus low muscle strength (handgrip strength <26 kg in men and <16 kg in women)
International Working Group on Sarcopenia [22]	Low ALM/height^2 (≤7.23 kg/m^2 in men and ≤5.67 kg/m^2 in women) plus low physical function (gait speed <1.0 m/s)
Sarcopenia with limited mobility [23]	Low physical function (gait speed ≤1.0 m/s or <400 meters walked during 6 min) plus low appendicular lean mass (≥2 standard deviations below the mean measured in healthy persons aged 20-30 years old from the same ethnic group)
Special Interest Group: cachexia–anorexia in chronic wasting diseases [21]	Low muscle mass (≥2 SDs below the mean measured in young adults of the same sex and ethnic background) plus low physical function (gait speed <0.8 m/s)

ALM: appendicular lean mass; SD: standard deviation.

EWGSOP cut off points

Test	Cut-off points for men	Cut-off points for women	References
EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength			
Grip strength	**<27 kg**	**<16 kg**	Dodds (2014) [26]
Chair stand	**>15 s for five rises**		Cesari (2009) [67]
EWGSOP2 sarcopenia cut-off points for low muscle quantity			
ASM	**<20 kg**	**<15 kg**	Studenski (2014) [3]
ASM/height^2	**<7.0 kg/m^2**	**<5.5 kg/m^2**	Gould (2014) [125]
EWGSOP2 sarcopenia cut-off points for low performance			
Gait speed	**≤0.8 m/s**		Cruz-Jentoft (2010) [1] Studenski (2011) [84]
SPPB	**≤8 point score**		Pavasini (2016) [90] Guralnik (1995) [126]
TUG	**≥20 s**		Bischoff (2003) [127]
400 m walk test	**Non-completion or ≥6 min for completion**		Newman (2006) [128]

Variable	Clinical practice	Research studies	Video for practical instruction, reference
Case finding	SARC-F questionnaire Ishii screening tool	SARC-F	Malmstrom *et al.* (2016) [12] Ishii *et al.* (2014) [40]
Skeletal muscle strength	Grip strength Chair stand test (chair rise test)	Grip strength Chair stand test (5-times sit-to-stand)	Roberts *et al.* (2011) [41] American Academy of Orthotists & Prosthetists https://www.youtube.com/watch?v=_jPl-IuRJ5A
Skeletal muscle mass orSkeletal muscle quality	Appendicular skeletal muscle mass (ASMM) by Dual-energy X-ray absorptiometry (DXA)*	ASMM by DXA	Schweitzer (2015) [42] Mitsiopoulos (1998) [43]
	Whole-body skeletal muscle mass (SMM) or ASMM predicted by Bioelectrical impedance analysis (BIA)*	Whole-body SMM or ASMM by Magnetic Resonance Imaging (MRI, total body protocol)	Shen (2004) [44] Sergi (2017) [45] Maden-Wilkinson (2013) [46] Heymsfield (1990) [47] Kim (2002) [48] Yamada (2017) [49]
		Mid-thigh muscle cross-sectional area by Computed Tomography (CT) or MRI	Lee (2004) [50]
	Lumbar muscle cross-sectional area by CT or MRI	Lumbar muscle cross-sectional area by CT or MRI	Van der Werf (2018) [51] Derstine (2018) [52]
		Muscle quality by mid-thigh or total body muscle quality by muscle biopsy, CT, MRI or Magnetic resonance Spectroscopy (MRS)	Goodpaster (2000) [53] Reinders (2016) [54] Grimm (2018) [55] Distefano (2018) [56] Ruan (2007) [57]
Physical performance	Gait speed	Gait speed	NIH Toolbox 4 Meter Walk Gait Speed Test https://www.nia.nih.gov/research/labs/leps/short-physical-performance-battery-sppb https://www.youtube.com/watch?v=xLSeK_NXUN0
	Short physical performance battery (SPPB)	SPPB	Short Physical Performance Battery Protocol https://research.ndorms.ox.ac.uk/prove/documents/assessors/outcomeMeasures/SPPB_Protocol.pdf NIH Toolbox https://www.nia.nih.gov/research/labs/leps/short-physical-performance-battery-sppb
	Timed-up-and-go test (TUG) 400-meter walk or long-distance corridor walk (400-m walk)	TUG 400-m walk	Mathias (1986) [40] Newman (2006) [41]

*Sometimes divided by height^2 or BMI to adjust for body size.

Chapter 5

General Summary

Sarcopenia can be defined as a muscle disease involving muscle failure, rooted in adverse muscle changes that occur across a lifetime, and is further defined by low measures for three parameters: muscle strength, muscle quantity/quality, and physical performance as an indicator of severity. Sarcopenia is recognized as a disease state and was assigned an ICD-10 code in 2016. Having a standardized operational and clinically applicable definition is important, not only for research purposes, but to develop prevention and treatment strategies. The development of definitions and guidelines to diagnose and treat sarcopenia has helped improve understanding of this condition. The lack of census regarding definition and diagnosis is hindering addressing sarcopenia in an aging population.

The ICD-10 code for sarcopenia was established in 2016. Though sarcopenia is a relatively common condition, diagnosis and treatment of this condition is not common. Sarcopenia has been overlooked and undertreated in mainstream practice. Patients with symptoms of sarcopenia are often diagnosed with generalized weakness. Sarcopenia has significant impact on the physical, emotional, and social aspects of patients' lives. The condition may be under recognized or treated; new approaches are needed to address the challenges that patients living with sarcopenia experience. The creation of a sarcopenia toolkit could help guide diagnosis and treatment of sarcopenia. The goal of the toolkit is to translate research into practice. If the condition is correctly diagnosed

and treated using the ICD-10 code, more data will be collected, and could help drive further research.

Challenges

Inconsistencies in sarcopenia definitions and/or which measures are studied make it difficult to draw conclusions from the available research. There is a widely accepted definition that has been put forth by The European Working Group on Sarcopenia in Older People (EWGSOP), but it is a work in progress and was last updated in 2018. There are definitions put forth by other organizations, such as, The Society of Sarcopenia, International Working Group on Sarcopenia (IWGS), the Asian Working Group for Sarcopenia (AWGS), and the Foundation for the National Institutes of Health (FNIH). The definitions are similar but differ in key points. If consensus is reached it will drive better treatment for sarcopenia and more opportunities for further research.

There is also not consensus in what constitutes a sarcopenia diagnosis. Criteria for diagnosis varies; most recommendations focus on measures of muscle strength, mobility, and lean mass, but measurements and cut-off points differ. These differences make it difficult to make recommendations to operationalize a process for diagnosis and treatment in the clinical setting.

The toolkit was created by the author, a registered dietitian. There is overlap between the knowledge registered dietitians possess and that of other disciplines, such as physical therapy. Sarcopenia is a muscle disease. This toolkit could be greatly enriched by added collaboration with a physical therapist

or similar discipline. This toolkit is in hard-copy form. Collaboration with a web designer or web developer would also further enrich the toolkit by transforming it into an electronic web-based resource. The lack of utilization of a multi-disciplinary team is a definite challenge in creation of this toolkit.

Practical Application of the toolkit

This toolkit provides a PowerPoint for healthcare professional education. It touches on: definition, prevalence, cost both financial and human, use of the ICD-10 code, etiology, diagnosis, and treatment of sarcopenia. There are handouts that can be used for patient education. There is a resource page that further provides education and options for diagnosis and treatment of sarcopenia. There is not consensus regarding diagnosis and treatment, but the toolkit provides options that could be customized for clinical use. In particular, the tools provided to facilitate screening patients for sarcopenia may assist in referring patients to other disciplines that can provide relevant treatment. By providing education, clinicians could utilize strategies that are appropriate for their patients, based on the resources and personnel available. Best practice for addressing sarcopenia involves a multidisciplinary team to address medical, physical, and nutritional needs.

Future research necessary to advance diagnosis and treatment of sarcopenia

Research regarding the etiology of sarcopenia should continue so influences operating to cause and worsen the condition can be addressed in practice. There currently are no approved pharmacological treatments for

sarcopenia at this time. As knowledge is expanded regarding etiology, pharmacological treatments can be better explored. Exercise-based and nutritional treatments will also be refined as more research is conducted.

To move forward, consensus must be reached regarding diagnosis and treatment of sarcopenia. A clear operationalized definition with diagnostic criteria that addresses differences in sex and ethnicity is crucial. Diagnostic cut-off points are arbitrary; establishment of clear criteria is vital to advancing diagnosis and treatment. Diagnostic tests must be accurate, affordable, and relevant to clinical use. Recent research findings have answered many questions, but also raised more for researchers to address in the future. A clear definition of sarcopenia, as well as clear diagnostic criteria, are necessary to guide both clinical practice and research design for the future.