REVIEW ARTICLE

A Review on Sarcopenia, Cachexia, and Aging

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Abstract

Sarcopenia and cachexia are two crucial geriatric problems that largely pass unrecognized, and their presence is a harbinger of a bad outcome. With the growing older of the human body, there is a gradual loss of muscle tissue and an increase in fat mass, leading to increased abdominal circumference. Sarcopenia is described as the progressive and generalized loss of skeletal muscle mass, strength, and physical function, leading to reduced workout capacity. It needs to be differentiated from cachexia, wherein the weight loss is because of an underlying sickness like cancer, chronic obstructive pulmonary disease (COPD), and immunodeficiency disorder, leading to loss of fat and muscle tissues, and starvation, which is a reversible situation on proper nutrient supplementation. Skeletal muscle tissue loss due to sarcopenia is resistant to dietary vitamin supplements. Even with many commonalities between these two situations, these are considered separate clinical entities.

Aging may be described as the time-associated deterioration of the physiological functions critical for survival and fertility. The traits of growing older—as distinguished from ailments of growing old (together with cancer and coronary artery disease)—affect all the humans of a species. A massive loss of muscle tissue and strength (sarcopenia), a reduced regenerative capacity, and a compromised physical performance are hallmarks of aging skeletal muscle. It is prudent to outline the distinction between the two conditions within the aging population so that a therapeutic method may be targeted toward the skeletal muscle loss and strength in aged humans. The treatment consists of appetite stimulants, dietary and nutritional supplementation, tailored exercise, and anti-inflammatory drugs. Megestrol acetate, an appetite stimulant, and dronabinol (Marinol), a narcotic drug used to treat nausea and vomiting in patients with cachexia.

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Introduction

There is a rising percentage of the geriatric population as a result of better medical facilities, such as early diagnosis and treatment by advanced technologies, although the problem of polypharmacy and multiple comorbidities in elderly people is still causing a problem for the treating physician. Skeletal muscle mass is useful in locomotion, metabolism of glucose, and synthesis of protein.[1]

Slow weight reduction is common among older human beings. If there is a loss of 10% or more of body weight between age 50 and old age, it is associated with a 60% increase in mortality compared to those with stable weight.[2] With the aging of the human body, there is a gradual loss of muscle tissue and an increase in fat mass, leading to expanded abdominal circumference. This aging-associated loss of muscles and strength is known as sarcopenia. Sarcopenia is characterized by declining muscle mass, strength, and physical function.[3] It must be differentiated from cachexia, wherein the weight reduction is due to an underlying disease, leading to loss of fat and muscles, and starvation, which is a reversible condition on proper nutrient supplementation. Skeletal muscle mass loss due to sarcopenia is resistant to nutritional supplementation. Failure to differentiate these conditions often causes frustration among the treating geriatric physicians.

Ancient Elements

As lifespan increased at the beginning toward people who we consider long-lived, the genetics of aging might also become increasingly important. Operational definition of sarcopenia includes: (1) probable sarcopenia is low muscle strength (LMS); (2) confirmed sarcopenia is LMS with low muscle quantity or quality; (3) severe sarcopenia is LMS, low muscle quantity or quality with low physical performance (LPP).[4]

Cachexia

Cachexia has been described as a lack of lean tissue mass, involving a weight reduction of >5% of body weight in 12 months or less within the presence of persistent inflammation, or as a body mass index (BMI) <20 kg/m^2. In addition, three criteria out of the following five are required: reduced muscle power, anorexia, reduced fat-free mass index, fatigue, and increase of inflammatory markers such as C-reactive protein (CRP) or interleukin-6 (IL-6), as well as low hemoglobin or hypoalbuminemia.[5] Cachexia can occur in most major illnesses, including infections, cancer, heart disease, chronic kidney disease, chronic obstructive pulmonary disease (COPD), and stroke.

Aging

Aging is defined as a time-associated reduction in the physiological skills that are vital for life. Aging is completely different from the diseases of the elderly (which include most cancers and coronary heart disease), as aging affects all human beings of a species. An enormous reduction in the muscles and strength (sarcopenia), which is associated with reduced regenerative capabilities of muscles and a decrease in overall performance of the body, is characteristically seen during aging.[6] These changes are normally accompanied by impaired muscle metabolism, including mitochondrial disorder and insulin resistance. To decelerate aging, physical exercise is a major counterpoint to age-related reduction in muscle mass, muscle strength, regenerative potential, and muscle metabolism. Exercise and physical activity definitely retard aging at some point and therefore need to be emphasized as part of a lifestyle vital to healthy aging. With advancing aging, motor neurons lose their ability to regenerate, and denervation of some muscle fibers also leads to loss of function.

Pathophysiology of Sarcopenia

There are two types of skeletal muscle fibers: type I fibers are usually resistant to fatigue because of densely packed mitochondria, a rich capillary network, and myoglobin material, while type II fibers are relatively susceptible to fatigue because of higher glycolytic capacity and lower oxidative capacity; however, at the same time, they may carry out excessive-intensity exercising hobby.[7] In sarcopenia,

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there is a decline in length and range of type II muscle fibers associated with infiltration of fatty tissues in the muscle fibers. Sarcopenia is also characterized by reduced functional capacity of the satellite cells, which are primarily involved in the restoration and update of damaging muscle fibers.

Many causes for sarcopenia have been proposed, including factors spanning muscle-specific processes and systemic mediators concerning numerous domains (e.g., inflammation and amino acid dysmetabolism), neurodegenerative processes (α motor neuron), and decreased production of anabolic hormones. Mitochondrial disorder describes the mechanism of aging and sarcopenia. Skeletal muscle tissues have strong reliance on oxidative metabolism, which results in the production of reactive oxygen species (ROS) in mitochondria, triggered by breaks in telomere regions.

Mitochondrial Dynamics

Exchange of matrix content and proteins between individual mitochondria takes place through the process of fusion and fission. Alteration of these processes hampers mitochondrial functioning in terms of respiration potential, coupling, ROS production, and apoptotic sensitivity. Excessively fragmented mitochondria generally tend to exhibit decreased respiration chain potential, increased ROS production, and increased susceptibility to the release cascades, which will ultimately cause apoptosis.[8] Dysfunctional mitochondria are removed by means of the process of mitophagy, in which a fragmented mitochondrion becomes encapsulated with a double membrane and forms an autophagosome, which ultimately fuses with a lysosome and undergoes hydrolytic lysis.

As age progresses, there is an increase in oxidative damage and reduced antioxidant defense, which results in mitochondrial damage at the neuromuscular junction (NMJ). Neurotransmitter-containing synaptic vesicles are also reduced in number, which slows down transport across the axon. Mitophagy-associated clearance of damaged mitochondria is also reduced, which leads to accumulation of abnormal proteins and mutated mitochondrial DNA. These respiratory-deficient mitochondria lead to a reduction in neuromuscular transmission, decreased capability of the mitochondrial membrane, and release of cytochrome c-like proapoptotic factors.[9]

Lower Motor Neuron

As the age advances, there is a reduction in motor neurons of the spinal cord and transmission across the NMJ, which leads to a reduction in the strength of muscles and their power. Loss of motor neurons also leads to lateral sprouting of neighboring neurons to innervate muscle fibers, which results in metabolic overburden and hypertrophy of the motor neurons and makes the nerve fibers prone to overload-associated degeneration.[10]

Sarcopenia and Hormones

Insulin-like growth factor I (IGF-I) is an essential component to increase the muscle mass and strength; it also reduces the degenerative capacity, which leads to enhanced proliferation of satellite cells of muscle fibers. For this purpose, IGF-I may recently be used as an important health biomarker. IGF-I is also related to aerobics and measurements of muscle endurance.[11]

Adjustments within the growth hormone (GH)/IGF-I level cause a decrease within the levels of protein anabolism in skeletal muscle cells and accordingly have a key role in the reduction of skeletal muscles. As age increases, testosterone levels decline, leading to loss of muscle mass and weakening of bone strength, increasing the risk of fracture. Still, patients suffering from loss of muscle mass cannot benefit from GH or testosterone injections, where they are likely to increase the muscle mass because of their side-effect profile.[12]

Increasing age was found to be associated with a state of hypercortisolism, which causes an increase in visceral fat accumulation. A low level of vitamin D is associated with decreased muscle strength. In elderly people, because of insulin resistance, they lack anabolic action, viz., protein synthesis driven *via* insulin, therefore leading to loss of muscle mass. Inflammatory markers and sarcopenia: IL-6, CRP, and tumor necrosis factor (TNF)-α—these inflammatory markers consistently show a negative association with muscle mass, strength, and physical function. Due to a sedentary life in the elderly population, visceral fat increases, which has more glucocorticoid and androgen receptors as compared to subcutaneous fat; therefore, it is hormonally more active. Visceral fat directly correlates with the level of TNF-α and IL-6, which leads to a reduction of skeletal muscle mass. Moreover, high-intensity exercise has shown reduced levels of IL-6 and improvement of muscle mass and performance.[13]

Interrelation between Exercise, Myokines, and Sarcopenia

Exercise causes the release of cytokines or signaling peptides called myokines, and it also maintains a positive balance between anti- and proinflammatory mediators. Myokines are necessary for whole-body homeostasis and metabolic, cardiovascular, kidney, bone, and hepatic tissue.[14] Myostatin is a negative regulator of skeletal muscle mass; it acts *via* activation of small mothers against decapentaplegic (SMAD) proteins, which results in transcription of catabolic genes and also activates satellite cells and the ubiquitin–proteasome system (UPS).[15]

Follistatin is secreted by the liver and increases with exercise. It binds with myostatin and inhibits it. Decorin also counter-regulates myostatin. Musclin is also released by exercise and is expressed in bone; it inhibits cardiac remodeling after myocardial infarction and modulates muscle mass. Apelin is a positive regulator of mitochondriogenesis, stimulates regenerative properties, and thereby exerts a positive effect on muscle mass. Myonectin turns on protein kinase B (AKT), insulin receptor substrate 1 (IRS-1), and mechanistic target of rapamycin (mTOR), consequently downregulates transcription of autophagy genes, and still has an aerobic shielding effect. Brain-derived neurotrophic factor (BDNF) plays a crucial role in regulating the increase, survival, and preservation of neurons and decreases adipose tissue bulk.[16]

Sarcopenia Obesity

It is a multifactorial syndrome that is characterized by the cooccurrence of obesity and sarcopenia. Physical inactivity is the most important risk factor for obesity. With advancing age, there is an increase in fat mass and a reduction in muscle mass. Specifically, visceral fat and intramuscular fat tend to increase and lead to intramuscular fat infiltration, leading to a decrease in muscle strength. Visceral fat also increases the proinflammatory adipokines, which have a catabolic effect on muscle fibers.[17]

Aging Pathophysiology

It is a point of debate whether detrimental effects on muscle physiology are related to age or are a consequence of lifestyle and ailment. Primary aging is related to adjustments in morphological and physiological aspects that occur independent of lifestyle, environmental impacts, or sickness. Changes regarding interactions of aging with environmental factors and sickness are considered secondary aging. Aging is associated with decreases in muscular tissues, muscle strength, and regenerative potential. A high body fat content reduces the muscle mass and strength and is related to insulin resistance, mitochondrial dysfunction, and defective potential of regeneration.

Etiological elements in sarcopenia include enhanced fatty tissues in muscle, insulin resistance, lack of alpha motor neurons, reduced dietary consumption of protein, high IL-6, reduced estrogen or androgen levels, a physical state of no activity, and many others. These modifications are possibly linked to age-related adjustments in the central nervous system and peripheral nervous systems and lead to a reduction in the motoneurons and degradation of NMJ.[18] With aging, there is denervation of single motor nerve fibers (typically fast). After denervation, there is always reinnervation of the remaining motoneurons (usually slow). This reinnervation of muscle fibers leads to conversion and grouping of fiber type.

Clinical Aspects of Sarcopenia

The most common symptom of sarcopenia is muscle weakness. Other symptoms may include recurrent injuries and fractures due to muscular imbalance, difficulties in ascending stairs, getting from a chair, decreased levels of protein-related hormones, and vitamin D value in blood (<50 nmol/L) (Fig. 1).[19]

Screening of Patients with Sarcopenia

Screening helps in the early identification of conditions and early detection of patients at risk for muscle decline[20]:

- SARC-F is the most confirmed and adapted screening survey for sarcopenia and has very high specificity to expect sarcopenia. The SARC-F questionnaire consists of self-reporting of strength, help with walking, rise from a chair, climbing stairs, and falls. High scores are associated with deficits in everyday living activities.
- Anthropometric measures—BMI, mid-upper arm muscle circumference (MUAMC/MAMC), and calf circumference (CC). Low muscular tissues may be classified as MUAMC/MAMC <21.1 cm in men and 19.2 cm in women. The cutoff point for measurement of CC of <34 cm in men and 33 cm in women is considered low muscle tissues.
- Muscle strength and performance—hand grip power, chair stand test (chair upward push test), gait pace, timed-up-and-go (TUG) test, and short physical performance battery (SPPB).
- Combined tools—the Ishii screening tool, which includes age, grip energy, and CC, stratified for sex. It has high sensitivity (75.5% for men and 84.9% for women) compared to SARC-F and specificity (92.2%) comparable to SARC-F (93.7%). In evaluation to the SARC-F, the Ishii screening tool gives a more objective risk evaluation of the probability of being sarcopenic. Different combined tools use the presence of two criteria to discover sarcopenia, particularly decreased muscle mass and decreased muscle functionality.

Other combined tools include MSRA-7, MSRA-5, and the finger circle test.

Diagnostic Tools

Tools used for diagnosis of sarcopenia are computed tomography (CT), magnetic resonance imaging (MRI), ultrasound, dual-energy X-ray absorptiometry (DEXA), bioelectrical impedance analysis (BIA), muscle biopsy, and other serological markers. Advantages and limitations for various diagnostic tools are tabulated in Table 1.

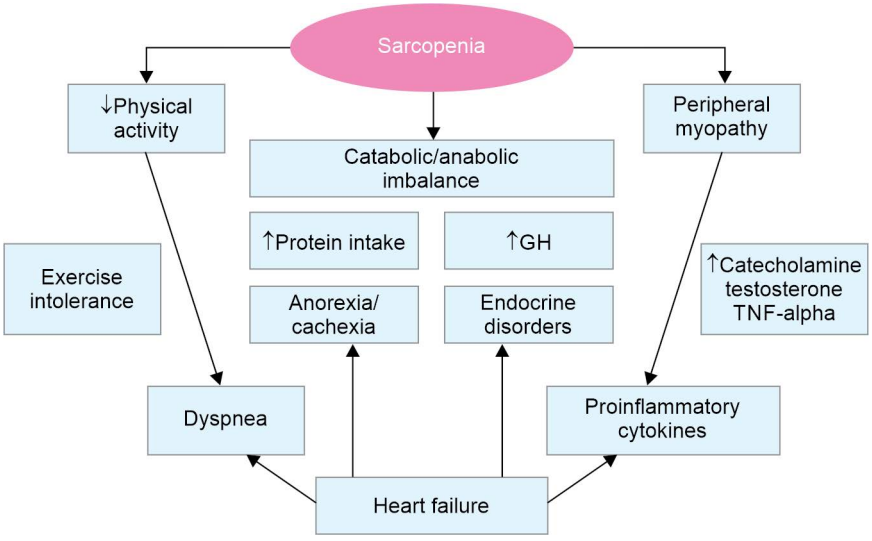

Fig. 1: Clinical aspects of sarcopenia

Diagnostic Criteria

There is no specific test to diagnose sarcopenia, nor is there a gold-standard method for determining whether a patient is sarcopenic.

Three main components used for the diagnosis of sarcopenia are:

- An evaluation of muscle mass: the skeletal muscle index (SMI) was recorded by usage of DEXA. The SMI was calculated as appendicular skeletal lean mass (ALM; the sum of the muscle tissues in both legs and arms) divided by height squared.
- An assessment of muscle power: the handgrip power was evaluated by using a handheld dynamometer. Individuals needed to squeeze the device as hard as they could three times in each hand.
- An assessment of physical ability: the SPPB test was used to assess physical performance. It consisted of three separate assessments—balance, 4 m gait velocity, and chair stand test. A rating between 0 and 4 was assigned for each component (with a maximum of 12 points).[22] The European Working Group on Sarcopenia in Older People (EWGSOP) criteria 2019 for defining sarcopenia and assessment criteria for cachexia are mentioned in Tables 2 and 3. Sarcopenia must be differentiated from cachexia on a clinical and physiological basis. The comparative differences between sarcopenia and cachexia are mentioned in Table 4.

Sarcopenia is defined as low appendicular skeletal muscle mass (ASMM) with reduced strength of muscles or reduced physical performance, while severe sarcopenia is defined as low ASMM with reduced strength of muscles and reduced physical performance.

Assessment of cachexia includes:

- Primary criteria: at least 5% weight loss within 3–6 months for cancer or within 12 months for other chronic disease, or low BMI <20 kg/m^2.
- Secondary criteria: reduced muscle strength, fatigue, reduced appetite, low fat-free mass index, anemia, hypoalbuminemia, and increased inflammatory markers.[20] Cachexia includes the primary criterion and three secondary criteria.

Preventive and Treatment Strategies for Sarcopenia

Preventive strategies targeted at exercise and nutritional interventions are the most effective targets for prevention of sarcopenia and can slow the progression to sarcopenia, improve physical performance, and prevent future loss (Table 5). The newer pharmacologic

Table 1: Advantages and limitations for various diagnostic tools for sarcopenia[21]

Diagnostic tools	*Assessment*	*Advantages*	*Limitations*
CT	SMA (skeletal muscle area per centimeter square) SMI (cm^2/m^2) MRA (muscle radiation attenuation, HU)	Gold standard for precise measurement of muscle mass	High cost, high radiation exposure
MRI	Muscle mass (DTI) Water/fat composition of a muscle Fiber type composition of muscle (31P-MRS)	Gives cross-sectional analysis of muscle quantity and quality and unique insight into the metabolic quality of the muscle	High cost and low availability contraindication—implants results in exclusion of participants
DEXA scan	• SMI • ASMM	High reproducibility for body composition Low radiation exposure, highly acceptable	Even this low dose radiation needs to be considered as a limiting factor for routine assessment of body composition, high cost, and low availability
Ultrasound	Skeletal muscle architecture and texture: • Thickness • Cross-sectional area • Fascicle length • Pinnation angle	Portable, low costs and risk, and no ionizing radiation is used	Few validation studies have been made and the heterogeneity of methodology and references limits accurate interpretation
Muscle biopsy	Type of muscle fiber: type I—being slow twitch fibers and types IIA and IIB, respectively fast twitch oxidative and fast twitch glycolytic fibers	Gives valuable data on muscle quality	The invasive technique poses burden for patients, risk of infection, requires additional infrastructure and knowledge in obtaining, processing, and interpretation of the data
BIA	Skeletal muscle mass	Noninvasive, fast, and easy-to-use method for estimating body composition, with moderate acquisition and low maintenance costs, commonly used in clinical practice BIA is validated and useful for determining the body composition at a distinct point of time as well as for monitoring the change of body composition over a longer period of time	Limitations in obese and cachectic patients due to disproportion of body mass and body conductivity and a greater variety of intra- and extracellular water
Laboratory assessment	Serum albumin, creatinine kinase, myoglobin, urine or creatinine dilution test, amino acids and micronutrients		No specific recommendations, references, or cutoff values available for any specific biomarker in order to assess muscle mass or quality

Table 2: EWGSOP criteria 2019 for defining sarcopenia[23]

Variable	*Assessment*	*Reference range*
Muscle mass	DEXA	SMI = ASMM or appendicular muscle mass/height per meter square [2 standard deviations (SD) below mean of young adults] Men: <20 kg or 7.26 kg/m^2; women: <15 kg or 5.5 kg/m^2
Muscle strength	Handgrip strength	Men: <27 kg; women: <16 kg
	Chair stand test	>15 seconds for five rises
Physical performance	SPPB	<8 point score
	Gait speed	<0.8 m/second
	TUG test	>20 seconds
	400 m walk test	>6 minutes/noncompletion

Sarcopenia = low ASM + LMS or LPP; Severe sarcopenia = low ASM + LMS and LPP

approach for treatment of sarcopenia is mentioned in Table 6.

Dietary Strategies

Dietary strategies include adequate protein intake (1–1.5 gm/kg/day), nutrition-rich diet like soybeans, whey, cowpea, lentils, and vitamin D supplementation (50,000 IU per week) (Table 4). Administration of leucine stimulates the synthesis of muscle protein and inhibits the degradation of protein. As per study record, increasing the contents of leucine in the meal accelerates the postprandial muscle protein synthesis *in vivo* in aged men. Calorie restriction (CR) mimetics are bioactive substances obtained from plant sources, herbs, and spices, which mimic the substantial antiaging effects. These CR mimetics include resveratrol, quercetin, epigallocatechin-3-gallate, and nootkatone. Due to insufficient data on antioxidants, currently there is no scientific rationale for using antioxidants in patients with sarcopenia.[24]

Exercise

To increase muscle strength and improve muscle function, resistance and aerobic exercise are both useful:

- Aerobic exercise: The anabolic response to amino acids and glucose is increased by aerobic exercise in healthy adults, which is useful to prevent muscle loss during aging. Studies have shown that aerobic exercise

Table 3: Assessment criteria for cachexia[20]

Primary criterion	*Other criteria*
Weight loss of at least 5% in 3–6 months for cancer or in 12 months for other chronic illness OR Low BMI <20 kg/m^2 (in absence of data on weight history)	• LMS • Fatigue • Anorexia • Low fat-free mass index • Abnormal biochemistry (anemia, low serum albumin, and increased inflammatory markers)

CACHEXIA = primary criterion + three of other criteria

helps in the reduction of oxidative damage to skeletal muscle and mitochondrial proteins.

- Resistance exercise: Resistance exercise increases muscle protein synthesis and causes hyperplasia of type 1 and type 2 muscle fibers.

Progressive resistance exercise is considered the best exercise for the prevention of sarcopenia. In this, the participant exercises their muscles against resistance at least 2–3 times a week for 8–12 weeks. Studies have shown that after PRE, participants showed a gain in whole-body muscle mass, as well as strength and gait speed.

Table 4: Differences between sarcopenia and cachexia[2]

	Sarcopenia	*Cachexia*
Definition	Muscle mass <2 SD of young healthy population, decreased muscle function	Weight loss >5% in 6 months
Mechanism	Aging	Pathologic
Comorbid condition	+/–	+++
Functional limitation	++	+++
Inflammation	–	++
Protein degradation	–/+	+++
Resting energy expenditure	Decreased	Increased
Anorexia	+	++
Muscle protein synthesis	Increased	Increased
Muscle mass, strength, and function	Decreased	Decreased
Fat mass	Increased	Decreased
Basal metabolic rate and total energy expenditure	Decreased	Increased
Insulin resistance	Increased	Increased

Table 5: Dietary strategies for management of sarcopenia[24]

Dietary strategies	*Recommendations*
Protein	The total protein intake should be 1–1.5 gm/kg/day
Vitamin D supplementation	Doses of 50,000 IU of vitamin D a week are safe
Branched chain amino acids—leucine	Leucine administration stimulates muscle protein synthesis and inhibits protein degradation *via* insulin-structured and insulin-unbiased pathways. Recent research record that growing the leucine content of a meal to a stage exceeding 3 gm, increases rate of postprandial muscle protein synthesis *in vivo* in aged men, thereby normalizing the blunted reaction of muscle protein synthesis to meals ingestion
CRs and CR mimetics	
• Resveratrol (found in grapes and red wine) • Quercetin (found in apples, onions, and berries) • Epigallocatechin-3-gallate (found in green tea) • Nootkatone (found in grapefruit)	Reduction in total calorie intake, of about 20% (mild) and 50% (severe) and without malnutrition CR mimetics are bioactive substances from plant sources, herbs, and spices which mimic the substantial antiaging effects that CR has on many laboratory animals and humans

Angiotensin-converting Enzyme Inhibitor and Sarcopenia

Angiotensin-converting enzyme inhibitor (ACE-i) improves endothelial function and angiogenesis and reduces inflammation by improving mitochondrial function, enhancing IGF-I levels, promoting skeletal muscle glucose uptake, and suppressing proinflammatory cytokine levels such as IL-6.

Treatment of Cachexia

There are no specific guidelines for the management of cachexia. The treatment includes appetite stimulants, dietary and nutritional supplementation, adapted exercise, and anti-inflammatory drugs. Megestrol acetate, an appetite stimulant, and dronabinol (Marinol), a narcotic drug used to treat nausea and vomiting in patients with cachexia.

Patient-centered approach for management of sarcopenia includes early identification by SARC-F screening test and intervention by way of exercise.[25] Primary treatment for cachexia includes exercise and adequate intake of protein diet for all chronic hospitalized patients with aggressive resistance exercise. Secondary treatment for cachexia includes resistance exercise, low protein intake, leucine, methyl hydroxy butyrate, and vitamin D3 supplementation as per requirements. Tertiary treatment for cachexia includes physical therapy, occupational therapy, speech therapy for dysphagia, providing adequate protein diet, and treatment of underlying disease.

Conclusion

As the population is rising, the prevalence of patients with sarcopenia will also rise, leading to more dependency both physical and emotional. The population who are at high risk should be screened for sarcopenia as it prompts early diagnosis and early management. Isolated LMS is defined as probable sarcopenia, while LMS associated with low muscle quantity or quality is called confirmed sarcopenia. When confirmed sarcopenia is combined with LPP, then it is called severe sarcopenia. Increasing awareness among patients and healthcare providers, early detection, and intervention can delay the progression to sarcopenia. Many mechanisms have been proposed for sarcopenia, including mitochondrial dysfunction in skeletal muscles, systemic inflammation, defective amino acid metabolism, neurodegenerative process (α motor neuron), and decreased anabolic hormones. The fields of muscle aging and exercise physiology have synergized

Table 6: Newer pharmacologic approach for treatment of sarcopenia the road to future[26]

Drug name	*Target*	*Remark*
Brimagrumab	Activin receptor type 2B	Thigh muscle volume increased by week 2 and was sustained throughout the treatment period (June 2017, phase 2)
Trevogrumab (antibody)	Myostatin	Primary end point of phase 2: percent change in total lean body mass
Sarconeos (natural active ingredients)	Proto-oncogene protein c-MAS-1, MAS receptor	Meaningful activity in animal models of muscular dystrophies. Good tolerability profile and no serious adverse events (phase 1)
ARM-210 (small molecule)	Ryanodine receptor	Treatment of Becker and limb-girdle muscular dystrophies as well as cachexia
TEI-SARM2	Androgen receptor	Selective androgen receptor modulator
AAV (gene therapy)	Myostatin	Obtained from a natural source and has potential in the modulation of myostatin expression
Peptide of follistatin	Furin, Janus kinase 3, myostatin	Discovery of a myostatin inhibitor therapeutic for the treatment of sarcopenia
ATA 842 (antibody)	Myostatin, activin	ATA 842 demonstrated increased muscle mass and muscle strength in the treatment of young and old mice for 4 weeks
AVGN7 (gene therapy)	Activin receptors	Gene expression inhibitors. *AVGN7* contains a gene called *SMAD7*, which stops gene expression for muscle wasting

to provide vital insights into primary results of aging on muscle and how aging-associated modifications can be attenuated or prevented by way of exercising. Dietary factors and exercise have a major role in prevention and treatment of sarcopenia. However, more trials should be done on drugs targeting the molecular pathway for better and specific treatment strategies.

Author Contributions

Dr C Nawal and Dr RS Chejara contributed to the concept and design of this expert opinion document. The manuscript draft was developed by Dr A Singh and critically reviewed by all the authors. The manuscript was edited and modified by Dr G Rankawat. All authors have approved the final draft of the manuscript.

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