



# Sarcopenia in aging, obesity, and cancer

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**Abstract:** Sarcopenia, defined as loss of muscle mass, strength and physical performance, is a hallmark of aging and is invariably associated with perturbation of amino acid metabolism, increased muscle protein catabolism relative to anabolism, and loss of muscle fibers. Sarcopenia may be associated with general loss of body mass, or it may also occur along with obesity [sarcopenic obesity (SO)]. Although sarcopenia is associated with multiple comorbidities in older adults, its effects may even be more severe in patients with malignant disease where it has been shown to contribute to poor surgical outcomes, increased chemotherapy toxicity associated with both cytotoxic and targeted agents, as well as adversely impacting survival. While development of sarcopenia is a common age-related phenomenon, the associated catabolic processes appear to be promoted by physical inactivity, inadequate nutrition, and systemic low-grade inflammation, as well as intrinsic muscle and molecular changes, including mitochondrial dysfunction and impaired muscle stem cell regenerative capacity. Increased physical activity and adequate protein intake can reduce incidence and severity of sarcopenia in cancer patients, but many older cancer patients do not meet physical activity and nutrition recommendations, and cancer treatment can make it more difficult to make favorable lifestyle changes. Sarcopenia is discussed in terms of its adverse clinical consequences in older subjects and particularly, in older patients with cancer. Contributions of lifestyle, molecular, and cellular factors are likewise reviewed with suggestions for interventions to improve sarcopenia and its comorbid sequelae.

**Keywords:** Sarcopenia; muscle mass; aging; obesity; sarcopenic obesity (SO); cancer

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## Introduction

Sarcopenia is described as a progressive, generalized muscle disorder characterized by loss of muscle mass, decreased muscle strength, and altered muscle composition (1-5). It most commonly occurs in association with aging, but may occur also with inflammatory and degenerative diseases such as rheumatoid arthritis, renal failure and congestive heart failure (1-5). Sarcopenia is commonly associated with adverse outcomes including progressive

frailty, falls, fractures, physical disability and mortality (6). Sarcopenia, is usually characterized by weight loss, but it may also occur in association with obesity, in which case, it is termed sarcopenic obesity (SO). Sarcopenia is even more prevalent in older patients with cancer where it is associated with worse surgical outcomes, increased chemotherapy induced cytotoxicity, and overall worse prognosis. Targeted interventions to reduce the prevalence and severity of sarcopenia and associated comorbidities are clearly needed to improve outcomes in older adults, especially those

undergoing therapy for malignant disorders.

### Sarcopenia pathophysiology

Age-dependent muscle catabolic processes leading to sarcopenia are associated with multiple systemic etiologic processes including altered energy balance, mitochondrial dysfunction, oxidative stress, and immune cell alterations leading to Senescence Associated Secretory Phenotypes (SASP) (7), extracellular matrix alterations (8) and increased fat mass, all contributing to chronic low grade inflammation which can affect all body systems and organs, particularly skeletal muscle. These proinflammatory processes such as SASP, expanded fat mass, altered extracellular matrix all promote inflammatory cytokine secretion stimulating multiple muscle catabolic processes, including upregulation of muscle atrophy f-box protein (MAF-box) and muscle ubiquitin ring finger-1 ligase (MURF-1) resulting in ubiquitination and degradation of muscle protein (9). Chronic low-grade inflammatory markers increased during normal aging process (inflammaging) include CRP, IL-1 $\beta$ , IL-6 and TNF (10,11).

Additionally, oxidative stress consequent to mitochondrial dysfunction can activate caspase 3 release, DNA fragmentation and myofibrillar degradation (12). Circulating F2-isoprostanes produced by reactive oxygen species (ROS) catalyzed by peroxidation of polyunsaturated fatty acids, have been identified as a reliable marker of associated oxidative stress, expanded fat mass and associated metaflammation. T cell P16INK4A has been identified as a marker of senescence and indicative of the SASP, characterized by mitotic arrest and secretion of multiple proinflammatory cytokines (discussed in detail in the accompanying article by Muss *et al.*) (13,14). Each of the above have been shown to contribute individually and collectively to muscle catabolism, suppressed muscle protein synthesis, and increased muscle protein degradation patterns (15).

The elevated inflammatory response and alterations in metabolism related to cancer and cancer treatment lead to further losses of muscle mass (16,17). Moreover, physical inactivity is linked to loss of lean body mass, and receipt of chemotherapy is related to increases in fat mass (18,19), all of which contribute to shifts in lean body/fat mass ratios. While many of these markers are noted to be upregulated during the normal aging process (9,15,20,21), their further increase in association with disease may accelerate the aging process leading to functional decline, age-associated comorbidities including sarcopenia and contribute to inter-individual variation in tolerance and response to cancer therapy (22,23).

In addition to the changes noted above, age related decreases in dehydroepiandrosterone sulfate (DHEAS) and testosterone in both men and women, have been implicated in development of sarcopenia (24,25). Multiple clinical trials employing DHEAS or testosterone supplements, usually in association with exercise, in older individuals have shown beneficial effects in muscle mass, but inconsistent impact on muscle strength and performance. In some of these studies, there was an adverse cardiovascular effect associated with testosterone administration studies (25). Studies are ongoing to improve strategies for improving hormone supplementation to prevent and mitigate development of sarcopenia while avoiding cardiovascular events (25).

### Sarcopenia cell biology

Satellite cells, considered to be muscle progenitor stem cells, are located between the basal lamina and sarcolemma of muscle fibers (26). Along with macrophages, vascular components, and micro-environmental factors, satellite cells participate in muscle regeneration, especially following injury (26). They have been shown to decrease with age and can be depleted in young animals using a genetic mouse model of paired box protein Pax-7 muscle stem cell marker (Pax-7<sup>CreER</sup>-Diphtheria Toxin A). Mice with depleted satellite cells showed impaired regenerative capacity, but no change in age-dependent muscle atrophy compared to controls (27,28). Satellite cells in resting muscle exist in a reversible G<sub>0</sub> phase but can undergo activation in response to injury (29). As mice age, quiescent satellite cells transition to senescent cells, associated with increased expression of P16Ink4a, in which they lose the ability to undergo normal proliferation. They also show increased secretion of proinflammatory cytokines (29). Silencing p16 utilizing an shRNA strategy, resulted in release of satellite cells from the senescence phenotype and restoration of their activation in tissue culture and regenerative capacity upon mouse transfer (29).

Zhang *et al.* (30) investigated the decreased regenerative capacity of muscle stem cells from 24-month-old mice compared to 3-month-old mice and showed lower levels of NAD<sup>+</sup>, TCA cycle and oxidative phosphorylation enzymes, increased phospho-H2AX and increased DNA strand breaks along with reduced ability to replenish muscle stem cells in a mouse model of Duchene muscle dystrophy. All of these abnormalities improved with supplementation of nicotinamide riboside (NR) which also improved endurance. The NR stimulated improvement in muscle stem cell

regeneration was abolished in Sirt 1 knockdown mice. Thus, supplementation with NR to increase NAD<sup>+</sup> levels in association with Sirt 1 restores regenerative capacity to muscle stem cells (30).

Earlier studies have shown that PARP activation due to persistent DNA damage can deplete cellular NAD<sup>+</sup> (31) and that decreased muscle NAD<sup>+</sup> may contribute to mitochondrial dysfunction (32), further suggesting that strategies to target maintenance of NAD<sup>+</sup> levels may contribute to improvement in sarcopenia (33). By preserving NAD<sup>+</sup> pools, PARP inhibitors, commonly used in chemotherapy, can improve mitochondrial metabolism, which may preserve muscle mass (34-40).

### Genetic aspects of sarcopenia

Based on observational studies, especially twin studies, that indicate heritability of muscle mass and muscle strength phenotypes, multiple studies have been initiated to identify genes predisposing to sarcopenia (41). These studies, including genome-wide linkage studies and Candidate Gene Association studies have resulted in a potential association of the vitamin D receptor gene, ciliary neurotrophic factor (CNTF) and its receptors (CNTFR), Myostatin, IGF genes, angiotensin converting enzyme 1, and alpha actinin 3 (41-43). While genes, such as myostatin, are of particular interest because of its ability to interfere with muscle growth, these studies have been overall inconsistent and no clear candidates have been identified (41,42). Moreover, none of these genes appear to account for more than 5% of differences in muscle mass (41).

### Assessment muscle mass and function

A standardized, uniformly accepted definition of sarcopenia has not yet been established. The European Working Group for Sarcopenia in Older People proposed a definition focused on diminished muscle strength as the primary indicator of sarcopenia with low muscle mass as a secondary feature (6). The Working Group further defined “severe” sarcopenia as a combination of decreased muscle strength, low muscle mass, and impaired physical function. However, uptake of this classification of sarcopenia, has been limited by the fact that assessment of muscle strength and function is less regularly obtained in clinical settings, as compared to radiologic assessment of muscle volume.

Further complicating the definition of sarcopenia is the heterogeneity in the imaging modalities used to evaluate

muscle mass, and the lack of clearly established cut points to define low muscle mass. Among the multiple modalities used to measure muscle mass and the different techniques (41) employed for these measurements are computerized tomography (CT), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectric impedance (44-46). More recently being developed is measurement of creatine (methyl-d<sub>3</sub>) dilution in urine (47). Of these techniques, the most commonly used in the clinical setting are CT and DXA scans, with CT being considerably more costly and using more radiation than DXA (48,49). DXA measures appendicular skeletal muscle mass, whereas CT estimates muscle mass by measuring cross-sectional area (48). Assessing body composition using CT scan is accomplished using a cross-sectional CT body slice at the level of L3, which is then used to determine components of body composition and extrapolated to determine total body fat and muscle mass. Disadvantages of using CT scans to assess muscle mass or body fat include the cost and high radiation dose relative to other methods. DXA is also in common use to measure body fat percent and lean body mass. While DXA scanners are common, the cost of a DXA scan is less than for a CT scan, and DXA exposes patients to less radiologic toxicity than CT. However, there are disadvantages of DXA use in the context of measuring muscle mass. In contrast, deuterated creatine (D<sub>3</sub>-Cr) is a promising approach to provide a more direct measure of muscle mass. This technique measures the total body creatine pool size which is 98% located in skeletal muscle. This approach requires an oral dose of a tracer followed by an equilibration period, then a urine sample several days later, in which, the dilution of the D<sub>3</sub>-Cr is used to calculate skeletal muscle mass (50). This technique has great promise, since it measures true muscle mass as opposed to other techniques which actually measure lean body mass or fat free mass. D<sub>3</sub>-Cr measured muscle mass has been shown to correlate with short physical performance battery (SPPB) and mobility limitation in older men (51). While the actual test is easy to administer, use of D<sub>3</sub>-Cr dilution has been limited because of special expertise and equipment required for final measurement and by problems with inter-individual differences which have not yet been resolved (47,52).

Studies of muscle density by radiologic techniques show low muscle attenuation is indicative of fatty infiltration (myosteatosis) and is associated with decreased muscle strength (53-55). Functional tests of muscle strength usually involve hand grip and/or gait speed (45,56). Compared to subjects with normal values, those with abnormally low measurements of these parameters (lower than two standard

deviations or less than 5% of normal) are more likely to experience significant toxicity with chemotoxicity, worse outcomes, and reduced survival (57,58). Additional research is clearly needed to establish the definition of sarcopenia most predictive of adverse outcomes, especially in high-risk populations such as older individuals and individuals undergoing treatment modalities that may have an adverse impact on muscle mass and function, such as chemotherapy.

### Age-related sarcopenia

Age-related loss of muscle mass and function is common in older adults; losses in skeletal muscle mass and strength begin in mid-life and progress linearly with increasing age (59). In otherwise normal adults over age 50, muscle strength declines at 12–14% per decade in association with decreased muscle mass (60–62). Age-related sarcopenia has a multifactorial origin, involving lifestyle factors, hormonal changes, age-dependent biological changes, such as chronic inflammation, mitochondrial abnormalities, and loss of neuromuscular junctions. Sarcopenia can also be accelerated by a number of disease states, and as a response to medications, such as steroids and chemotherapeutic agents. Sarcopenia in older patients is also often accompanied by increases in adiposity, leading to SO (63). Gain of fat mass is associated with upregulation of circulating inflammatory factors and increased oxidative stress, which may further contribute to progression of sarcopenia (63). Recent reports suggest prevalence of sarcopenia in the range of 1–29% in community dwelling individuals, 14–33% among institutionalized patients and as high as 50% in those over 80 years of age (16,64). Several studies have shown a slight preponderance of sarcopenia among men compared to women, but others have not (65–67). For example, a study in Connecticut, of healthy community dwelling adults age >65, showed sarcopenia in 22.6% women and 26.8% in men. In another study performed in Shanghai, women > age 60 showed 8.5% sarcopenia, while men showed 19.2% (66). In contrast, studies performed in Singapore, showed 24.8% sarcopenia in women and 25.4% in men (67). Sarcopenia in older adults has been linked to functional impairment, disability, loss of independence, and mortality (68–70).

While there is great inter-individual variation in the development of sarcopenia, the major contributing lifestyle factors in older adults, appear to be insufficient dietary protein intake and reduced physical activity (71–74). In one cross sectional review of 900 men and women over age 50, 77% had lower than recommended protein intake. Recent

studies of circulating amino acids have shown a seven amino acid signature (methionine, lysine, phenylalanine, threonine and three branch chain amino acids, including leucine, isoleucine and valine) to be negatively associated with sarcopenia (69). In addition, methionine, isoleucine and leucine levels are positively associated with increased muscle function, highlighting the importance of adequate intake of high-quality protein in muscle strength and volume (70–76).

Regular physical exercise has been shown to be protective for many conditions including sarcopenia, cardiovascular disorders, and cancer (77,78). It is noteworthy that protein intake and physical activity appear to be the major anabolic stimuli for muscle protein synthesis and building muscle mass (17,74,79). Resistance exercise has generally been employed to promote increased muscle volume, however, differences among individuals demonstrate that both aerobic and resistance exercises promote synthesis of myokines, such as myostatin and follistatin, with consequent impact on muscle growth (80). In addition, aerobic exercise has been shown to increase muscle vascularity (81,82). Moreover, combined nutrition emphasizing protein content and quality and exercise have been shown to have a synergistic effect to increase muscle mass, strength and function (71–74).

### Sarcopenic obesity

While the image of the older, frail, sarcopenic individual is usually one of low body mass, it is important to emphasize that low muscle mass is not always associated with low BMI. The increasing prevalence of obesity in the population at large, and particularly in older adults, results in its combined occurrence with sarcopenia in a condition identified as SO. Moreover, since obesity has been associated with at least 13 malignancies (83), it is expected that there will be an increased association of SO with many malignancies especially those having been determined to be obesity-associated. Similar to sarcopenia itself, difficulties exist in defining SO due to lack of consensus and specific measurements of sarcopenia. Sarcopenia alone has been described as low weight, low/normal fat mass, low appendicular lean mass, low body mass index, and low/normal waist circumference. In contrast, SO is characterized as normal to high weight, high fat mass, low appendicular lean mass, normal to high body mass and normal to high waist circumference (63).

Depending on technique and criteria used to define sarcopenia, SO has been identified in 0–41% of the older population (63). Some series indicate slightly greater prevalence in men compared to women, while other series

suggest the opposite (63).

From a clinical viewpoint, individuals with SO have been reported to have difficulty with physical function, such as walking and stair climbing and are more prone to develop disability, as compared to individuals without SO (84-86). From a pathophysiologic viewpoint, obesity and sarcopenia have overlapping and probably interacting components. Obesity is a chronic low grade inflammatory disorder (metaflammation) generating altered levels of cytokines and adipokines, including increased IL-6, MCP-1, TNF $\alpha$ , leptin, and decreased adiponectin (87), all of which may contribute to general muscle inflammation (88,89). Obesity also leads to insulin resistance and leptin resistance, each of which can impair muscle metabolism and lead to fatty infiltration of muscle (myosteatosis) (86,90). Obesity also contributes to decreased physical activity, which may further promote sarcopenia. Loss of muscle mass may likewise promote decreased physical activity, further promoting obesity. Whether sarcopenia and obesity are separate but mutually reinforcing processes or part of a single age-associated process remains to be determined. Nonetheless, their combination increases morbidity and mortality. However, both sarcopenia and obesity are the result of potentially modifiable lifestyle factors and thus lifestyle modification needs to be the focus of further basic research and clinical trials.

### **Sarcopenia and treatment toxicity in cancer patients**

Sarcopenia has been linked to treatment toxicity and poor quality of life in mixed-age groups of cancer patients (91). One study looked at the relationship between lean body mass and other measures of muscle volume and toxicity in 151 women with early-stage breast cancer receiving anthracycline and taxane-based chemotherapy regimens and demonstrated that low lean body mass was associated with a higher risk of grade 3/4 toxicities (RR: 1.48,  $P=0.002$ ). Low muscle volume was found to predict for higher rates of hematologic toxicity (RR: 2.2,  $P=0.02$ ), gastrointestinal toxicity (RR: 6.49,  $P=0.02$ ) and hospitalization (RR: 1.91,  $P=0.05$ ) (91). Another study looked at the relationships amongst quality of life, muscle mass, and muscle function in 200 inactive breast cancer patients receiving adjuvant chemotherapy and found that both sarcopenia and dynapenia (poor muscle function compared to age- and sex-based norms) were associated with poor quality of life (92). Sarcopenia has also been associated with toxicity in the setting of advanced breast cancer; a meta-analysis including

four observational studies evaluating the relationship between sarcopenia and outcomes in women with advanced cancer receiving chemotherapy demonstrated that patients with metastatic disease with sarcopenia had a two-fold risk of grade 3-5 toxicity as compared to patients who were not sarcopenic (RR: 2.17, 95% CI: 1.4-3.34,  $P=0.0005$ ) (93).

### **Sarcopenia in older cancer patients**

Studies have demonstrated that cancer and cancer treatment can have a significant impact on body composition, leading to loss of lean muscle mass, often in combination with gains in fat mass. These changes may be especially common and problematic in older individuals with cancer, where cancer progression and treatment effects can lead to increased frailty and loss of independence (22,94). Notably, loss of muscle mass can become an escalating issue in patients, as the elevated inflammatory response related to cancer and aging, as well as alterations in metabolism related to cancer cachexia, lead to on-going loss of muscle mass (16,17). However, there are very limited data prospectively evaluating treatment-related changes in muscle mass and body composition in older cancer patients. One study investigated the association between sarcopenia and decline in physical function in 131 cancer patients  $\geq 65$  years who were initiating chemotherapy for stage I-IV cancers and found that 26.2% of patients had sarcopenia at baseline. Individuals with sarcopenia had a non-significant trend toward increased risk of functional decline during chemotherapy (95).

Although data regarding the impact of cancer treatment on body composition in older cancer patients are lacking, a few small studies have demonstrated that chemotherapy treatment leads to an increase in fat mass, reduction in lean body mass, and decreased strength in mixed-age populations of cancer patients (96). For example, a cross sectional study evaluating muscle function in 225 women with breast cancer and 26 healthy controls demonstrated that patients who received chemotherapy had significantly lower muscle strength in the upper and lower extremities and also experienced muscle fatigue more quickly as compared to age-matched healthy women (96). More information is needed looking at the impact of therapy on body composition in larger groups of cancer survivors.

### **Sarcopenia and treatment toxicity in older cancer patients**

While sarcopenia is associated with multiple comorbidities

in patients with cancer, its effects may be even more severe in older patients with cancer (34). In different series, sarcopenia has been identified before therapeutic intervention in 14% to 74% of cancer patients (34,97-99) where it has been shown to be associated with increased surgical complications, increased chemotherapy toxicity, and poorer outcomes, including poorer survival in multiple malignancies, including lung, breast, colorectal, renal cell, ovarian, hepatocellular cancer, and lymphoma (34,44,58,93,100-104). Older cancer patients with sarcopenia have been shown to experience increased toxicity with multiple chemotherapeutic agents including 5FU, capecitabine, cisplatin, anthracyclines, taxanes, etoposide, and cyclophosphamide (34,99-105). In addition, sarcopenia has been associated with increased toxicity of targeted agents such as sorafenib and sunitinib (106-109). Notably, many of these chemotherapeutic agents cause oxidative stress in muscle, resulting in progressive sarcopenia and increased fat deposition in muscle (34,110). This sets up a vicious cycle in which therapeutic agents induce sarcopenia, and sarcopenia results in increased chemotoxicity. Chemotherapy may also further contribute to sarcopenia through contributing to nausea, which may lead to lower protein intake.

### **Sarcopenia and cancer mortality**

Observational studies also suggest that sarcopenia and SO may be associated with poorer outcomes in cancer patients. A recent analysis looked at the relationship between body composition, evaluated through single-slice CT scan at the L3 vertebral body, and mortality in 3,241 women with early-stage breast cancer (111). Thirty-four percent of patients had sarcopenia, and 6% had both sarcopenia and high total adipose tissue. Women with SO had the highest risk of overall mortality (HR: 1.89, 95% CI: 1.30–2.73). Sarcopenia alone was also linked to higher mortality (HR: 1.41, 95% CI: 1.18–1.69). These data and several other reports were included in a recent meta-analysis by Aleixo and colleagues looking at the relationship between muscle mass and outcomes in women receiving chemotherapy for early-stage (four studies) and advanced (four studies) breast cancer (93). The overall prevalence of sarcopenia reported in these studies was 39.8% (range, 25–66.9%). Sarcopenia, as measured by skeletal muscle index, was associated with poorer overall survival in breast cancer patients (HR: 1.68, 95% CI: 1.09–2.59, 5 studies,  $P=0.02$ ). Notably, in women with advanced disease, time to progression on chemotherapy was 71 days shorter in women

who were sarcopenic versus those who were not ( $P=0.007$ ). However, there is currently limited data evaluating the relationship between sarcopenia or other elements of body composition in older women with breast cancer.

Another study of 3,262 early-stage (stage I–II) patients with colorectal cancer evaluated the relationship of SO and mortality. Women with SO had a 64% higher risk of overall mortality as compared to women with lower adiposity and adequate muscle (HR: 1.64, 95% CI: 1.05–2.57). Additionally, women with sarcopenia alone also had increased mortality as compared to women with adequate muscle and lower adiposity (HR: 1.27, 95% CI: 1.09–1.48) (112).

### **Physical activity, muscle mass, and functional status in older cancer patients**

A number of trials have evaluated the impact of physical activity interventions on muscle strength and mass in older cancer patients. One study demonstrated that a resistance training intervention led to an increase in total body muscle mass, strength and power (all  $P<0.001$ ) in 19 men over age 65 with prostate cancer who were receiving androgen deprivation therapy (ADT) (113). Another study demonstrated that men with prostate cancer over age 65 who were randomized to a resistance training intervention during radiation preserved muscle mass compared with men randomized to aerobic exercise or usual care control (114). Studies have suggested that interventions employing only aerobic exercise have been less successful in maintaining muscle mass in older cancer survivors. For example, a French study randomized 301 cancer patients over the age of 70 who were initiating treatment (surgery, chemotherapy or radiation) to a 12-month telephone-based aerobic physical activity intervention or usual care control (115). After 1 year, there was no difference in SPPB scores between groups ( $P=0.772$ ). Subgroup analyses suggested an improvement in SPPB scores in breast cancer patients randomized to the intervention group at 2 years ( $P=0.006$ ), but falls, hospitalization, institutionalization, and death rates were similar in both groups, suggesting that aerobic training alone was not sufficient to maintain muscle strength and function.

Data regarding the impact of physical activity interventions on muscle mass and function in older breast cancer patients are currently lacking. A few studies have evaluated the impact of physical activity interventions on body composition in mixed-age groups of breast cancer patients and have demonstrated that interventions that

incorporate resistance training exercise lead to increased muscle mass and prevention of clinically significant decline during and after cancer treatment (92,116,117). Aerobic exercise alone, however, has not been shown to result in increased muscle mass or strength, suggesting a critical role for resistance training in building and maintaining muscle mass during cancer treatment (92). In studies of greater than 2,100 women (1,220 newly diagnosed breast cancer, 900 mammographic controls) only 30.5% of women over the age of 65 met American Cancer Society guidelines of 2.5 hours/week combined strenuous and moderate physical activity, underscoring the need for interventions to increase physical activity in this population at risk for sarcopenia (118). Overall, there is a clear need for interventions focused on improving nutrition and increasing physical activity to prevent and reverse sarcopenia.

The question of timing and dose of exercise and diet to address sarcopenia in older adults with cancer remains unanswered. There is compelling evidence that prehabilitation interventions among esophagogastric, colorectal, lung and liver cancer patients result in improved functional outcomes (119-122). Early recovery after surgery (ERAS) protocols also suggest that movement soon after surgery improves function as well, as part of a comprehensive protocol, of which movement is just one part (123-125). The potential to improve body composition, or prevent worsening, by exercise interventions during chemotherapy is an area of active investigation in two ongoing NCI funded R01s (R01 CA206196, R01 CA207753), but neither of these studies focuses on older adults. It is important not to assume that interventions for younger adults will work in older adults with cancer, in whom there may be unique needs regarding sarcopenia and unique barriers to exercise. Exercise trials have documented improved body composition after treatment completion (126,127), but very few have focused specifically on older adults. The potential remains to alter outcomes with exercise and dietary interventions designed to address sarcopenia before, during or after cancer therapy.

As noted above, under Cell Biology, PARP inhibitors can improve mitochondrial function and may preserve muscle mass (34-40). Thus, PARP inhibitors need to be further evaluated for impact on sarcopenia, especially in malignancies where they are already part of the therapeutic armamentarium such as breast, ovarian, pancreas, and some cases of prostate cancer (128-131). Interestingly, dietary supplementation of NAD<sup>+</sup> and/or its precursors is currently undergoing extensive investigation to promote

healthy aging (132,133), although specific information on sarcopenia is not available.

## Conclusions

Sarcopenia is common in older adults with cancer and unfavorably impacts treatment tolerance and long-term outcomes. Sarcopenia can be mitigated through increased physical activity, especially resistance exercise, and adequate protein intake, but studies suggest that many older cancer survivors do not meet nutrition and physical activity goals. There is thus a clear need for a transdisciplinary, mechanistic, and clinical approach involving regenerative cell therapy with targeted metabolic strategies along with pharmacologic, and lifestyle modifications of nutrition and physical activity, including both aerobic and resistance exercise to increase muscle mass and prevent, reverse, and reduce impact of sarcopenia, and improve outcomes in older patients, with and without malignancies.

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