Sports Medicine and Health Science 2 (2020) 186–194

Contents lists available at ScienceDirect

Sports Medicine and Health Science

journal homepage: www.keaipublishing.com/en/journals/sports-medicine-and-health-science/

Review Article

Exercise as a therapy for cancer-induced muscle wasting

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ARTICLE INFO

Keywords:
Physical activity
Anabolic resistance
Inflammation
IL-6
Metabolic dysfunction
Protein turnover

ABSTRACT

Cancer cachexia is a progressive disorder characterized by body weight, fat, and muscle loss. Cachexia induces metabolic disruptions that can be analogous and distinct from those observed in cancer, obscuring both diagnosis and treatment options. Inflammation, hypogonadism, and physical inactivity are widely investigated as systemic mediators of cancer-induced muscle wasting. At the cellular level, dysregulation of protein turnover and energy metabolism can negatively impact muscle mass and function. Exercise is well known for its anti-inflammatory effects and potent stimulation of anabolic signaling. Emerging evidence suggests the potential for exercise to rescue muscle's sensitivity to anabolic stimuli, reduce wasting through protein synthesis modulation, myokine release, and subsequent downregulation of proteolytic factors. To date, there is no recommendation for exercise in the management of cachexia. Given its complex nature, a multimodal approach incorporating exercise offers promising potential for cancer cachexia treatment. This review's primary objective is to summarize the growing body of research examining exercise regulation of cancer cachexia. Furthermore, we will provide evidence for exercise interactions with established systemic and cellular regulators of cancer-induced muscle wasting.

Introduction

Cancer-induced wasting, or cancer cachexia, is a progressive disorder associated with a terminal disease characterized by severe body weight, fat, and skeletal muscle loss.[1] Cachexia is multifactorial and induces nutritional and metabolic abnormalities that can be analogous and distinct from the patient's underlying condition, thus obscuring both diagnosis and treatment options.[2] Cachectic patients may experience poor disease prognosis, increased treatment-related toxicities, fatigue, reduced physical well-being, and overall quality of life. Skeletal muscle comprises 40%–50% of body mass and is maintained through an ongoing balance of protein synthesis and degradation, which are tightly regulated by systemic and local environmental stimuli. Inflammation, hypogonadism, malnutrition, insulin resistance, and sedentary behavior can disrupt muscle energy metabolism and protein turnover during cancer cachexia[3] (see Fig. 1). Suppressed muscle protein synthesis has been reported in preclinical cancer models and cancer patients; however, interventions directed toward increasing protein synthesis (i.e., amino acids, protein administration) alone do not fully counteract cancer-induced wasting. Therefore, a multimodal intervention approach may be necessary.[4–8] The inability to stimulate protein synthesis, termed "anabolic resistance," is observed in models of aging and wasting disorders.[3,9–11] However, mechanisms governing this phenomenon are complex and not yet fully understood.

Regular physical exercise has proven to benefit individuals with chronic diseases by improving muscle metabolic homeostasis and suppressing intrinsic signaling associated with wasting[12–14] (see Fig. 1). According to the 2020 ASCO guidelines,[15] no recommendation can be made for exercise-based interventions in the management and treatment of cachexia due to the lack of clinical trial evidence. However, a promising intervention remains a combination of exercise with other therapies.[16] There has been a rapidly growing interest in understanding how exercise can interact with cancer cachexia's development and progression, with over 450 publications consisting of both literature reviews and original research articles being listed on PubMed related to cancer cachexia and exercise. Amazingly, more than 290 of these have been published since 2015. Preservation of muscle mass and improving physical performance are essential goals of cachexia therapy. The anti-inflammatory nature of exercise and its capacity to induce positive metabolic alterations provide a strong premise for further mechanistic investigations for related to improving the cachectic condition. While cancer cachexia dramatically reduces muscle strength and endurance, the mechanistic underpinnings of these functional changes are not fully understood.[17] Skeletal muscle is highly adaptable and responsive to muscle

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https://doi.org/10.1016/j.smhs.2020.11.004
Received 15 September 2020; Received in revised form 12 November 2020; Accepted 17 November 2020
Available online 3 December 2020
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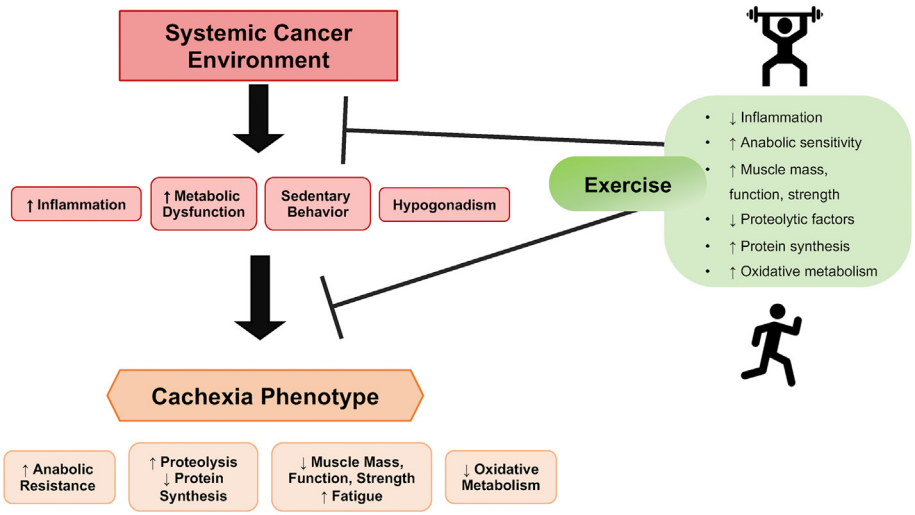

Fig. 1. Exercise Regulation of Cancer-Induced Cachexia. The systemic cancer environment induces whole body alterations including chronic inflammation, metabolic dysfunction, sedentary behavior, hypogonadism, endocrine disruption, insulin resistance, and malnutrition. These systemic factors contribute to the development and progression of the cachectic phenotype. Cachexia can induce a metabolic shift in which skeletal muscle develops resistance to anabolic stimuli (e.g., nutrients, physical activity, growth hormones), altered protein turnover, decreased oxidative metabolism, and an overall loss of muscle mass, strength and function. Regular physical exercise (e.g., walking, running, cycling, resistance training) can benefit patients by improving skeletal muscle function, strength, and metabolic homeostasis, reducing muscle mass loss, and suppressing systemic and cellular signaling associated with cancer-induced wasting.

contraction and loading, which mediate increases in anabolic signaling.[18] Adaptations to physical activity are dependent on exercise mode, intensity, duration, and frequency.[19] Although increased activity is beneficial for cancer patients, prescribing regimens that are well adhered to is difficult. The current recommended dose to elicit health benefits is 150–300 min/week of moderate-intensity aerobic exercise (i.e., walking, running, cycling, swimming) and strength training ~2 days a week. However, these "minimal dose" guidelines relate to disease prevention rather than treatment.[20]

Interestingly, epidemiological studies and clinical trials show that improved prognosis in physically active cancer patients is more closely associated with exercise performed *after* diagnosis as opposed to exercise habits prior.[21–23] Sedentary behavior and muscle disuse can exacerbate disease and treatment-related disruptions. Therefore, even small doses of physical activity or the use of exercise mimetics (i.e., neuromuscular electrical stimulation, pharmacological agents[24,25]) may provide critical physiological benefits to the patient.[26–29] This review will summarize the growing body of research examining how exercise can either prevent or treat cancer cachexia. Furthermore, we will provide evidence and support for how exercise can interact with established systemic and cellular regulators of cancer-induced muscle wasting.

Systemic mediators of cancer-induced muscle wasting

Inflammation

To recognize and treat cancer cachexia, an understanding of its pathophysiology is imperative. Systemic inflammation is a significant contributor to cancer-induced cachexia through the increased production of related pro-inflammatory cytokines, tumor factors, and hormones resulting in metabolic alterations in patients.[30,31] Inflammatory mediators promote activation of wasting related pathways in both adipose tissue and skeletal muscle. Chronic inflammation is prevalent in both clinical and preclinical models of cachexia. For example, mouse models of cachexia have demonstrated elevated interleukin 6 (IL-6), tumor necrosis factor-α (TNF-α), TNF-like inducer of apoptosis (TWEAK), TNF receptor (TNFR)-associated factor 6 (TRAF6), interferon-gamma (INF-γ), and leukemia inhibitory factor (LIF).[31–41] The activated cytokines can act on multiple pathways, including the nuclear factor-κB (NF-κB) pathway, p38 mitogen-activated protein kinase (MAPK) pathway, and the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. These signaling cascades are associated with increased activity of the ubiquitin-proteasome system (UPS), mitochondrial dysfunction, increased oxidative stress, and dysfunctional hypothalamic-pituitary-adrenal (HPA) axis signaling (e.g., cortisol response).[42–46] Despite evidence for the involvement of several inflammatory mediators during cachexia development in preclinical models, we have a limited understanding of how these signaling pathways interact, form regulatory networks, or of their involvement in redundant signaling cascades with different cancers. This complexity appears to be a significant barrier for targeting a single signaling cascade or regulatory process to preserve skeletal muscle mass in the cancer patient.

Hypogonadism

Hypogonadism, a sex hormone deficiency, is often associated with the cachectic condition.[47] However, understanding its role in cancer cachexia and potential interaction with other well studied drivers of cachexia such as inflammation is currently underdeveloped. Estrogens and androgens are established regulators of growth and maturation and affect many adult tissues targeted by cachexia, including bone, skeletal muscle, and adipose tissue.[48] Sex hormones can also regulate processes involving central nervous system function, immune function, and metabolism, which impact cancer cachexia. Hypogonadism can result from normal aging, gonad dysfunction, and many chronic disease states and has been linked to declines in muscle mass and function.[49–52] Cancer is often diagnosed after 65 years of age, and the age-related decline in circulating sex steroids could be a factor contributing to the cachectic environment.[53] Skeletal muscle exhibits sexual dimorphism in overall mass, fiber size, metabolic enzymes, expression of different myosin isoforms, fatiguability, and gene expression.[54–56] Both testosterone and estrogen target skeletal muscle gene expression, metabolism, and protein turnover and can be released in response to muscle contraction.[57,58] Notably, 70% of male patients with cancer cachexia have low testosterone levels.[59,60] In males, low testosterone levels lead to decreased muscle mass and strength, and testosterone replacement therapy effectively attenuates these deficits.[59,61–63] Testosterone increases muscle insulin-like growth factor 1 (IGF-1) and protein synthesis through activation of Akt/mTORC1 signaling[64] and can decrease systemic inflammatory cytokines such as IL-6 and TNF-α in humans.[64–66] The mechanistic role of sex hormones in cancer cachexia's progression and treatment, particularly in females, is not well understood but has been recently reviewed.[67,68] Female sex hormones may contribute to an attenuation of inflammation by inhibiting IL-6 transcription and associated signaling.[32,69] 17 β-Estradiol – the most concentrated form of circulating estrogen – favorably affects skeletal muscle contractility independent of physical activity in preclinical models.[70] Estrogen can also induce IGF-1 signaling.[71–73] Decreased circulating estrogen may alter the cachectic phenotype through dysregulation of protein turnover driven by increased inflammation and autophagy and altered anabolic signaling.[74]

Taken together, hypogonadism during cancer negatively affects survival and patient quality of life.[59] Further research is needed to determine the efficacy and mechanisms of sex hormones' role during cancer cachexia.

Inactivity and disuse

Many cancer patients suffer from chronic fatigue, malnutrition, and limited ability to perform physical activity due to disease progression along with anti-cancer treatment.[17,75,76] Phenotypically, cachexia may appear similar to starvation, however in mice and humans, cachexia often precedes decreases in food intake, and cachexia can occur with or without the presence of anorexia.[77,78] While malnutrition does occur in cancer patients, metabolic disruptions, and altered resting energy expenditure may also be significant contributors to wasting.[79–81] Preclinical models have shown that mice with cachectic phenotypes display low volitional physical activity levels before cachexia development.[82–84] Muscle disuse, similar to disease-induced atrophy (i.e., cachexia), negatively affects metabolism by decreasing protein synthesis, increasing degradation, and promoting resistance to anabolic stimuli (i.e., IGF-1, nutrients, physical activity).[26,85,86] More specifically, skeletal muscle atrophied by disuse exhibits decreased Akt/mTORC1 signaling and suppressed muscle protein synthesis, which is similar to cachexia.[86,87] Prolonged inactivity is also associated with increased reactive oxygen species (ROS), promoting muscle protein breakdown, and has been extensively reviewed.[88] There is a strong rationale for further examination into the impact of disuse and sedentary behavior on cachectic muscle responses to other anabolic therapies.

Cellular regulation of cancer-induced muscle wasting

Increased inflammatory signaling

Cellular mechanisms driving cancer-induced skeletal muscle wasting concentrate on disrupted protein turnover regulation, mitochondrial dysfunction,[89,90] and an emerging area of impaired muscle regeneration.[91] Cellular inflammatory signaling, specifically IL-6 family members, have been widely investigated as regulators of muscle protein turnover in some cancer types.[92] IL-6 is a pleiotropic cytokine involved in processes spanning immune-inflammatory response to skeletal muscle's response to exercise.[40] Cachectic patients demonstrate increased plasma levels of IL-6 compared to non-cachectic patients.[93] IL-6 exerts effects on target cells by forming a heterodimer at the cell surface with glycoprotein 130 (gp130) and the IL-6 receptor,[37,92,94] which activates intracellular signaling involving JAK/STAT and ERK1/2. The cancer environment can promote skeletal muscle STAT3 phosphorylation, and STAT3 inhibition prevents cachexia in some preclinical cancer models.[37,38] Notably, STAT3 also seems to play a part in the blockage of autophagy pathways by altering the beclin-1 complex.[95] In $Apc^{Min/+}$ cachectic mice, activation of these pathways via IL-6 is associated with decreased muscle protein synthesis by mTORC1 signaling and induced muscle protein breakdown.[35,49] Moreover, IL-6 overexpression in pre-cachectic $Apc^{Min/+}$ mice accelerates body weight loss and muscle wasting and can suppress basal protein synthesis in tumor and non-tumor bearing mice.[96] Furthermore, in cultured myotubes, IL-6 suppression of mTORC1 activity is dependent on AMPK activation and independent of STAT3 signaling.[34] Circulating tumor-derived factors can disrupt mitophagy and mitochondrial remodeling.[97] IL-6 has been studied extensively as a potential inflammatory driver for muscle wasting in cancer cachexia. However, the interaction between physical activity and IL-6 signaling requires further study to determine if this regulatory network is a viable therapeutic target for reversing cachexia.

Dysregulation of muscle protein turnover

Disruptions to the homeostatic regulation of muscle protein turnover can have detrimental consequences on cellular metabolism, muscle function, and growth. Muscle atrophy involves the breakdown and net loss of intracellular proteins and organelles, resulting in smaller myofibers. Studies have shown that cancer patients exhibit higher whole-body protein turnover with reduced protein synthesis, and patients with low muscle protein generally present poorer clinical outcomes.[6,98,99] Many factors can disrupt protein turnover and muscle wasting in cancer (for reviews see Refs. 100,101); however, both hypo-anabolism and hyper-catabolism still create a unique challenge to discovering therapeutics. During cachexia, protein breakdown and muscle catabolism can occur even with adequate nutrient intake.[102] Reduced protein synthesis and an impaired response to anabolic stimuli - anabolic resistance - must also be overcome to treat cancer-induced wasting.[3,103,104] The IGF-1/PI3K/Akt/mTORC1 signaling pathway integrates various stimuli to activate protein synthesis and growth-related pathways. Reduced IGF-1 levels occur in preclinical cancer cachexia models and could have a role in the pathophysiology of muscle wasting.[105] Several experimental cachexia models have reported mTORC1 suppression.[34,106,107] Muscle protein degradation in cancer cachexia primarily involves activation of the UPS and autophagy lysosomal systems, which normally function to clean up damaged proteins under physiological conditions, but cause excessive protein degradation in diseased states.[101] Glucocorticoids, cytokines (i.e., TNF-α, NF-κB), activins, myostatin, proteolytic enzymes, ROS, and tumor released factors[108–111] can all regulate muscle protein degradation. Mitochondrial dysfunction can increase myonuclear apoptosis in skeletal muscle, further contributing to cachexia.[112,113] In fact, activation of apoptotic factors such as B cell leukemia/lymphoma 2 (BCL2)-associated X protein (BAX) and presence of DNA fragmentation has been described in wasting muscles from either cancer patients or tumor-bearing mice.[82,114–116] Under atrophic conditions, UPS is responsible for the breakdown of larger myofibrillar proteins, while autophagy contributes to the breakdown of long-lived proteins and organelles.[117] UPS and autophagy activation exacerbate muscle loss in tumor-bearing animals.[101,118,119] A better understanding of cancer-induced mechanisms regulating anabolic plasticity in patients may elucidate valuable treatment options for muscle wasting and improve responsiveness to anabolic therapies.

Muscle metabolic dysfunction

Mitochondrial dysfunction is an established regulator of cancer-induced muscle wasting.[97,120,121] Skeletal muscle plays a critical role in regulating systemic metabolism and displays plasticity to adapt to demands such as nutrient availability, activity, and the systemic environment.[122] Interestingly, nutritional interventions, such as diets high in fat and low in carbohydrates (i.e., ketogenic diet), may reduce tumor growth and improve treatment efficacy by altering cancer cell and systemic metabolism (for review see:[123]). Emphasis has been placed on ketone bodies' anticatabolic effects during inflammation-related muscle atrophy.[124–126] *In vitro*, ketone bodies can attenuate tumor conditioned media induced myotube E3 ligase expression.[127] In C26-tumor-bearing mice, a ketogenic diet partially attenuated muscle and body weight loss.[128] Furthermore, a ketogenic diet can impact the gut microbiome and reduce inflammation[129]; ketone bodies' impact on metabolic dysfunction in cachexia warrants further investigation. Cancer-induced alterations involve increased oxidative stress, decreased mitochondrial biogenesis, and elevated mitophagy. These changes can result in mitochondrial loss and dysfunction,[90] which is evident in tumor-bearing mice before muscle wasting.[130] Skeletal muscle mitochondrial dysfunction also induces functional changes resulting in increased muscle fatigability and weakness.[97] Declines in mitochondrial health with severe wasting are apparent in both oxidative and glycolytic muscle and is associated with increased circulating IL-6.[131] There is a strong premise for examining how the hypogonadal state contributes to cancer-induced mitochondrial dysfunction. Estrogen can regulate muscle mitochondria biogenesis and mitophagy.[70] It is interesting to consider whether an improvement in the

hypogonadal condition could positively impact cachectic muscle mitochondrial dysfunction. Muscle disuse atrophy involves increased oxidative stress and disrupted mitochondrial quality control.[132] Moreover, models of cancer cachexia display disrupted mitochondrial dynamics (see review [97]) and suppressed PGC-1α expression.[107] Data is equivocal regarding PGC-1α in disuse as some studies report increases,[133] decreases,[134] or no change.[135] Interestingly, PGC-1α overexpression does not protect against disuse-induced atrophy but does attenuate E3 ubiquitin ligase expression.[136] Increasing metabolic demand in muscle during exercise exerts positive effects on mitochondrial function and activates genes responsible for mitochondrial biogenesis, while sedentary behavior is associated with decreased mitochondrial health.[137–139] Current data does not fully describe if improved mitochondrial health can overcome anabolic resistance in skeletal muscle.

A role for exercise in the prevention and treatment of cachexia

A role for exercise

Increased physical activity can benefit cancer patients by positively impacting muscle mass, function, and metabolism and decreasing treatment-related toxicity. Physical activity elicits systemic anti-inflammatory effects acting to reduce protein degradation and increase protein synthesis; moreover, training can improve oxidative metabolism and maximize substrate utilization to combat metabolic dysfunction.[140,141] Additionally, ketone bodies, organic compounds derived from lipids, are oxidized during prolonged exercise and utilized as fuel sources.[142] Some types of ketone bodies may function to maintain redox homeostasis in response to metabolic stress, reduce inflammation, and improve exercise performance.[143,144] A single bout of exercise in healthy individuals activates muscle signaling pathways linked to energy metabolism and, when repeated over-time (i.e., training) can elicit beneficial metabolic adaptations.[145,146] Hence, exercise's potential therapeutic role in preventing or treating cancer cachexia should examine both the acute response and chronic adaptations to exercise. However, tumor-derived factors and increased metabolic stress can interfere with muscle mechanical signaling. For example, *in vitro* models using tumor-derived culture media impair the mechanical stretch activation of myotube protein synthesis.[147] Additionally, in severely cachectic mice, the anabolic signaling response to muscle contraction is disrupted.[139] Muscle disuse atrophy and aging, variables to consider with cancer patients, can impair the muscle's response to anabolic stimuli (e.g., amino acids, insulin).[148–150] Understanding physiological skeletal muscle signaling in response to exercise and mechanical stimuli is critical when designing interventions to treat cancer-induced wasting. Interestingly, mechanical stimuli can activate muscle protein synthesis through mTORC1, independent of Akt signaling.[151] Acute bouts of muscle contraction increase mTORC1 signaling and phosphorylation of its downstream effector p70.[152] In fact, increased muscle mass after chronic mechanical stimulation is strongly associated with p70 phosphorylation.[153,154] Mitogen-activated protein kinase (MAPK) signaling cascades, including ERK1/2 and p38, are increased during exercise and myofiber mechanical stretch.[155,156] ERK-dependent mTORC1 activation is involved in muscle mass regulation,[157] but mechanical stimulation can induce mTORC1 signaling independent of ERK, which may involve phosphatidic acid signaling.[158,159] Mechanical activation of protein synthesis pathways combined with other anabolic therapies may provide a means to circumvent anabolic resistance to nutrients and growth factors. In fact, exercise performed with nutritional interventions can improve muscle mass and reduce tumor growth in animal models.[160,161] However, further studies examining muscle sensitivity to different exercise types and nutrition status are needed to elucidate reliable interventions.

In pre-clinical models, exercise performed before severe cachexia development can reduce indices of cachexia and mitigate treatment-related toxicities. Voluntary aerobic exercise in colon-26 (C26) mice can prevent muscle mass loss and improve function by modulating autophagy flux.[21] Moderate treadmill exercise (1 h/d, 6 d/week, 5% grade) attenuates IL-6-dependent cachexia in $Apc^{Min/+}$ mice.[162] Moreover, myokines released during aerobic exercise have shown the potential for cachexia therapy through the downregulation of proteolytic factors.[163] In a mouse model of prostate cancer, long-term voluntary wheel running (20wks) was sufficient to preserve muscle mass and function.[164] In mice, exercise performed before cachectic tumor inoculation can prevent muscle loss and Akt/mTOR suppression.[165] *In vitro* electrical stimulation or mechanical stretch can prevent chemotherapy-induced myotube atrophy.[166] Increased muscle metabolic demand can increase mitochondrial biogenesis. For example, cachectic tumor-bearing mice subjected to an acute bout of low-frequency stimulation display increased activity of genes responsible for biogenesis: PGC1-α, NRF-1, and Tfam.[139] High-frequency electrical stimulation can attenuate cachexia induced muscle loss, improve oxidative capacity, and activate mTOR signaling.[167,168] Cancer cachexia induces muscle ERK1/2 and p38 MAPKs,[169] and ERK signaling inhibition can promote anabolism.[170] For example, inhibition of either ERK1/2 or p38 signaling rescues the mechanical stretch induction of myotube protein synthesis in the presence of LLC media.[147] Resistance exercise increases muscle protein synthesis through mTORC1 and can improve mitochondrial function and muscle mass in tumor-bearing mice (see review[11]). Repeated bouts of eccentric contractions can increase muscle mass and oxidative metabolism in cachectic mice, and these changes coincide with reduced AMPK activity.[3,168] Mechanically stimulated pathways and their regulation in cachexia induced muscle wasting in response to mechanical stimuli require further investigation as they could play a role in mTORC1 mediated protein synthesis and autophagy regulation. Combined exercise and nutritional interventions have shown improvements in patient physical function and quality of life. These multimodal approaches deserve further investigation for the promotion of anabolism and attenuated wasting in cancer patients.

Exercise modulation of oxidative stress during cancer cachexia

Increased pro-inflammatory cytokines and dysfunctional mitochondria contribute to muscle oxidative stress during cachexia.[97] Understanding exercise's role in redox homeostasis modulation is essential, as excessive mitochondrial ROS production can promote tumorigenesis, disrupt cellular processes, and exacerbate declines in skeletal muscle mass and function (see reviews[171,172]). Muscle oxidative stress and mitochondrial dysfunction are observed early in cachexia progression, preceding muscle wasting.[130] Many cachectic cancer patients and cachectic mice cannot perform standard exercise training paradigms.[173] However, preventative therapeutics, such as exercise performed before muscle wasting and fatigue, may offset adverse outcomes by improving oxidative metabolism. Acute exercise promotes ROS production, which may serve as a necessary adaptive response, and chronic exercise training upregulates antioxidant defenses and can reduce inflammation and oxidative stress.[174–177] In C26-tumor-bearing mice, moderate aerobic exercise improved muscle mass and function and was associated with an improved redox balance.[178] Aerobic interval training in tumor-bearing rats did not restore muscle mass but improved muscle function, overall survival, and reduced oxidative stress.[179] Furthermore, in cancer patients, exercise reduced cancer-related fatigue, increased circulating antioxidants, and decreased blood markers of oxidative stress.[180] Recently, the emphasis on oxidative stress during cancer progression has been directed towards understanding and preventing chemotherapeutics' toxic effects.[181] However, we still lack knowledge of whether chemotherapy exacerbates oxidative stress during cancer cachexia progression and if exercise is sufficient to offset this response. Cancer patients may likely benefit from therapies that improve redox homeostasis (e.g., antioxidant supplementation, exercise, exercise mimetics). Whether these combined interventions serve to reinforce muscle antioxidant defenses and reduce oxidative stress remains an open question.

Exercise and muscle anabolic resistance

Unlike healthy muscle, wasting conditions can cause muscle responsiveness to anabolic stimuli to be reduced.[10,85,182] The inability to stimulate protein synthesis in response to anabolic factors (e.g., anabolic resistance) has been observed in aging and cancer. It may play a central role in muscle function decrements during cachexia.[9,11,103,183] Evidence for anabolic resistance has been observed in cancer patients with moderate weight loss and apparent systemic inflammation via impaired glucose uptake in response to insulin[104]. Unfortunately, our current mechanistic understanding of muscle protein turnover does not account for an inherent hour to hour physiological regulation of anabolic stimuli, such as feeding, fasting, and daily physical activity.[84] A recent study reported that the administration of an HDAC inhibitor suppressed muscle IL6/STAT signaling and could improve anabolic sensitivity to androgen based therapy.[184] Combining pharmacological agents and anabolic treatment has the potential to restore muscle responsiveness to these stimuli (i.e., androgens, exercise, nutrients) in cancer patients. In severe cachexia, IL-6/STAT signaling seems to have a role in the initial development of anabolic resistance. Determining mechanisms of anabolic plasticity in cancer patients may elucidate valuable treatment options and improve responsiveness to anabolic therapies. Since nutritional support cannot fully reverse cachexia, the suppressed responsiveness to nutrient supplementation may be related to dysfunctional protein turnover regulation. Cachectic cancer patients exhibit exacerbated whole-body protein turnover rates in response to feeding.[185,186] Interestingly, cachectic pancreatic cancer patients did not increase whole-body protein synthesis after eating like healthy individuals, pointing to impaired anabolic plasticity in cancer.[187] Williams et al. further showed that cachectic colorectal cancer patients did not increase muscle protein synthesis in response to feeding.[188]

Summary

The complex interplay of systemic and cellular disruptions in cancer cachexia has delayed the development of reliable treatment interventions to improve skeletal muscle mass, function, and metabolism. Skeletal muscle is crucial for movement, posture, breathing, and whole-body metabolism; consequently, altered muscle homeostasis intensifies cancer-induced systemic disruptions, worsening disease prognosis. Although exercise is not typically the first line of clinical therapy, its ability to reduce systemic inflammation and promote anabolic processes warrant continued study to treat cancer-induced wasting. Therefore, we reviewed the published research examining exercise and cancer cachexia. Overall, there is evidence that increased physical activity can help attenuate cancer cachexia progression in tumor-bearing mice. To date, there is not a recommended dose of exercise for cachectic cancer patients due to a lack of clinical trials. Results from clinical studies examining exercise are inconclusive (see review[189]), potentially due to poor cachexia diagnostic criteria and heterogeneity in patient cohorts (i.e., cancer type, sex, degree of cachexia, patient age) and variable muscle sample collection sites (i.e., rectus abdominis, quadriceps, diaphragm). Overall, human studies primarily focus on gastrointestinal cancer patients and suggest altered skeletal muscle morphology, increased proteolysis, systemic inflammation, and mitochondrial dysfunction.[31,189] A multimodal treatment approach to cachexia management in cancer patients involving some type of physical activity can positively affect the rate of cachexia progression and functional decline. However, the achievable threshold of physical activity or exercise needed for these positive effects is not well understood. Published studies have demonstrated the ability of exercise to reduce systemic inflammation, reduce muscle mass loss, and improve muscle mitochondrial function. Exercise can stimulate muscle protein synthesis and, in combination with anti-catabolic agents, may have promise for ameliorating cancer-induced anabolic resistance in muscle. Research in clinical settings will provide evidence for the effectiveness of these strategies for improving mortality and quality of life. Well-controlled and characterized exercise studies in cancer patients and complementary mechanistic preclinical cachexia studies should provide further insight into the molecular signaling mechanisms and potential exercise benefits. This knowledge will help delineate the exercise dose that can attenuate cancer cachexia progression.

Submission statement

This manuscript has not been published and is not under consideration for publication elsewhere.

Authors' contributions

All authors listed on the manuscript have made substantial contributions to the literature review and writing.

Conflict of interest

The authors have no conflict of interest to report.

Acknowledgments

This work was supported by National Institutes of Health Grants R01 CA-121249 (National Cancer Institute) and R21 CA-231131 to JAC.

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