Exercise and Cancer Treatment

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Introduction

This year alone an approximate 18.1 million people will be diagnosed with cancer around the world (3). Mortality rates vary and are dependent upon individualistic factors– the type of cancer, plan of care, financial requirements, etc. Physicians are always searching for the newest and most beneficial interventions to utilize alongside traditional methods of treatment (3). Recent research evaluating the role of exercise during cancer treatment is proving quite promising. Amongst healthy individuals, recreational exercise is the healthiest form of rehabilitation available in health sciences; incorporation of exercise into modern forms of cancer treatment may similarly benefit cancer patients. Many biochemical adaptations occur during treatment programs related to chemotherapy and radiation, implementing training protocols during periods of therapy may positively influence mortality outcomes through regular and irregular responses to exercise. According to Dr. Gary Kimmel et al. 2016, sedentarism (routine levels of low activity or movement) can be considered a form of chronic disease because of its correlation to all-cause mortality (9). One of the most common symptoms related to all types of cancer treatment is cachexia, or an irreversible state of weight-loss that cannot be reverted through nutritional means, usually resulting in fatigue and possible malnutrition (5). Symptoms such as cachexia make exercising during treatment extremely difficult, but the ergogenic benefits of this intervention may outweigh the physical and psychological demands required by exercise. The goal of this paper is to analyze exercise and cancer treatment in terms of its effect on biochemical adaptations, adverse symptoms of therapy and psychological functionality. This article will also discuss educational deficits experienced by both physicians and patients, as well as, some outcomes pertinent to exercise prescription in cancer patients.

Molecular Adaptations of Exercise During Cancer Treatment

Cancer is a broad term used to describe an abnormal division of cells that can be either localized or systemic. This gives rise to a wide spectrum of treatment methods available to a person diagnosed with cancer. Most of these adaptations negatively affect the overall health of cancer patients. Exercise provides biochemical consequences of its own that may help mediate some of these adverse molecular variations caused by treatment (7). Radiotherapy, or radiation therapy, is the primary type of treatment used to treat carcinoma but some studies have found

that exercise may have some tumor-intrinsic effects on kinetic formation (growth dynamics; volume, thickness, rate of growth etc.), metastatic potential (ability to spread and grow secondary lesions), metabolism (source of nutrients and where it's diverted to) and immunogenic profile of a tumor (immune response to cancer cells). Pernille Hojman et al. reported a decrease in tumor growth rate through a reduction in tumor cell proliferation of about 10-15% in *in vitro* studies that directly analyzed the rate at which a tumor cell multiplied (5). The same article also found that exercise intensities, moderate bouts of aerobic exercise for 10-12 minutes, consistent with increased levels of catecholamines can limit the formation ability of tumor cells because of downregulation to the Hippo signaling pathway; as many researchers have now discovered, the Hippo pathway is composed of multiple molecules that promote tumorigenesis, tumor migration, and tumor malignancy (5). Exercise may even cause redirection of metabolic energy substrates in tumors, since the rate of metabolism is much higher in tumors than throughout the rest of the body (5). Another relevant adaptation to exercise is elevated levels of leukocytes available in the blood; Richard Simpson et al. concluded that exercise increased mobilization of immune cells like NK cells, CD8+T-cells and γT-cells (8). These immune cells are at their highest potential one hour after exercise in response to a single training bout. The same study was able to determine that NK cells present in the blood after exercise were much less-differentiated, allowing these leukocytes to kill more tumor cells (8). NK cells are not only responsible for direct tumor suppressive actions but they also signal a secondary immune response that stimulate dendritic cells and T cells to the site of the tumor (7,8). The increase of T cell concentration in the tumor is said to be the most important cell for fighting tumor cell division. This chain of immune responses is most likely a result of increased concentrations of epinephrine fueled by exercise (8). Adaptations such as these are pertinent to melanoma and lymphoma patients, an increase in allogenic adoptive transfer immunotherapy may positively affect these treatments. Leukocytosis of this potential may serve as an ancillary treatment option for all types of cancer. This overall increase in leukocytes also increases the overall amount of cells present in the blood plasma, which improves cell isolation (differentiation of healthy cells and cancer cells) capabilities of clinicians. Improved isolation strategies will enhance the quality of cells being transported to tissues during treatment. Further research must focus on the extent at which these revised methods enhance cellular isolation techniques.

Benefits of Exercise on Cancer Treatment

Given the rate of mortality, any possible benefits that can be applied to cancer treatment are extremely relevant. An experiment by Yuan Zhou et al. observed exercises effect on acute leukemia patients undergoing therapy (10). A significant improvement in cardiorespiratory fitness, muscle strength and functional mobility was found in exercise groups but no difference was noticed in fatigue, depression, anxiety or quality of life (10). Improved cardiorespiratory fitness was most likely due to adaptations in oxidative capacity because significant differences were found only in groups participating in 12 minute bouts of exercise. Although muscular atrophy and wasting is associated with most cancer treatments, this study found an increase in muscle strength (standardized mean difference of 0.67) in those regularly engaging in exercise; this could be attributed to increased size of cross-sectional myofibril area, protein synthesis and strength with a decrease in protein break down (4,10). Adversely, a study dedicated primarily to observing cancer related fatigue and exercise intervention on various types of cancer found that exercise did in fact decrease fatigue (11). This was done by Jose F. Meneses-Echavez et al. who created a large meta-analysis of 11 studies (n=1530) that used subjective indexes to analyze improvements of fatigue after exercise. These results were obtained using a combination of aerobic, anaerobic and stretching programs were ideal for maximum benefits (11). This decreased level of fatigue may be associated with an increased energy expenditure due to muscle adaptations on progenitor satellite cell proliferation during initial phases of chemotherapy or radiation (11). Positive effects like the ones expressed by Yuan Zhou et al. and Jose F. Meneses-Echavez et al. are the most applicable to individuals undergoing lung and heart cancer treatment. Depression, fatigue and other symptoms of cancer treatment were observed in a meta-analysis by Prue Cormie et al. 2017 composed of 100 studies in which 24 studies that analyzed fatigue were gathered, and all but two of these experiments showed significant improvements of fatigue in cancer patients participating in exercise (6). Twelve of these studies focused on depressive symptoms and psychological variables associated with cancer treatment and discovered significant improvements in overall mood and mental health in those exercising during their treatment (6). Although improvements in fatigue and depression were noticed among these experiments, no significant change in quality of life was expressed in exercise groups; although one could argue that improvements in fatigue and depression are significant aspects of life quality characterization, so more research regarding this benefit is definitely needed (6).

Exercise and Cancer Cachexia

Cachexia is a direct cause of 20% to 40% of all cancer-related deaths (4). Skeletal muscle is the primary tissue affected by cachexia, resulting in a ≥5% decrease in total body mass in as little as 6 months (4). The metabolic responses to muscle loss of this proportion are catastrophic to homeostasis and effect a wide range of systems including: adipose tissue functionality, inflammation reactions, erythropoiesis, sex hormone production, mitochondrial oxidative metabolism, and liver regulation (4). As a health professional, awareness and monitoring of the effects on the various biological systems is extremely relevant to the development of comorbidities and disease progression during cancer treatment. While skeletal muscles are the most affected tissues, cachectic patients usually possess lipotoxic adipose cells, or lipotoxicity, which occurs because of increased lipolysis and hindered lipid storage that heightens the concentration of circulating free fatty acids. These enhanced levels of free fatty acids in the plasma increases metabolic stress in certain tissues like the skeletal muscle. Systemic inflammation is also present in cachexia, elevated concentrations of pro-inflammatory cytokines like intereleukin-6 (IL-6) and tumor necrosis factor (TNF-α) have been found to induce liver growth, limit muscle protein turnover and attribute to insulin resistance (4). Tumor nutrient allocation has been seen to come from the breakdown of glucose in less metabolically active tissues like skeletal muscle and adipocytes; liver growth occurs because of the increased presence of inflammatory molecules (4). Erythrocyte levels can also be a cause of weight loss in cancer patients, anemia is not an common symptom of treatment and a decrease of blood viscosity may contribute to overall body weight-loss. Cachexia progression often effects sex hormone production directly through musculoskeletal metabolism and regulation. Sex hormones in both men and women play a large role in muscle mass and overall cross-sectional area of the myofibrils, inhibition of this hormone would certainly reduce fat-free mass and muscle index (BMI). Disruptions in mitochondrial biogenesis are seen in certain treatments (i.e. tumor bearing, pulmonary carcinoma) that can impair muscle metabolism and contractile functions (4). Exercise positively affected multiple causes and symptoms of cachexia. Surprisingly, exercise redirected the effects of inflammatory molecules and reduced overall systemic inflammation by activating anti-inflammatory cytokines (i.e. IL-1 receptor agonist, IL-10) while simultaneously decreasing the production of TNF-α (4). By limiting TNF-α concentration, researchers have been able to reduce cachexia related weight loss by decreasing lipolysis and muscle atrophy. Cachectic patients with anemia and reduced concentrations of erythropoietin may also benefit from

exercise, some exercise regimens have improved erythropoietin levels, functional capacities and oxidative thresholds (4). Another common side effect of cachexia is a reduced aggregation of androgen receptors because of hypogonadism (reduced production of sex hormones), which could be partially alleviated in those participating in some form of resistance training (4,5). Furthermore, repeated bouts of eccentric exercise in cachectic patients were shown to improve succinate dehydrogenase enzyme activity, subsequently, benefiting mitochondrial biogenesis and damaged muscles by increasing oxidative capacity (4). Researchers believe that mTOR (vital regulator of protein synthesis) may be interrupted due to treatment effects. This made analysis of muscle protein turnover adaptations relevant. Although, mTOR response to exercise was reported to be normal and the potential nutritional benefits offered after bouts of exercise also applied to cancer patients.

Incorporating Exercise into Cancer Treatment

Before prescription many elements need to be considered, some of the most important being: extent and type of cancer, common side-effects associated with the treatment, feasibility, etc. (3). Many of these circumstances may limit the patients ability or desire to partake in continuous exercise programs. To properly prescribe exercise Dr. Kristin Campbell et al. believes that the responsibility of the oncologist is to first assess current physical activity levels. Depending on activity levels prior to therapy, the oncologist can adjust the frequency, type and time of the activity to fit recommendations of +2 days of resistance activity and +3 days of aerobic activity per week (3). After this is done, an oncologist can then refer patients to the appropriate services. This is only applicable if the patient is ambulatory, otherwise, patients should follow-up or be referred to an outpatient rehabilitative healthcare professional for additional evaluation.

Success of an exercise regimen may be partly due to timing of implementation, Amy Dennett et al. was able to determine that the earlier an exercise program is integrated into cancer treatment, the better the outcome, especially in situations of acute cancer (1). The same article emphasized the importance of developing clinical guidelines to help oncologists advise patients of the most current and effective methods of exercise rehabilitation, staff expertise in exercise-based programs and possible outcomes will only enhance the benefits of exercise (1). Gary T. Kimmel, MD, et al. also agreed that the earlier exercise is implemented, the better the prognosis; the time of diagnoses might be the most stressful and scary moment of a patients' life but maybe

the most teachable moment as well, properly educating the patient and detailing the importance of exercise during the time of diagnosis might break some of the psychological barriers associated with willingness to participate in such a program (3,9). Along with the various difficulties present to cancer related exercise prescription Dr. Kimmel also highlighted a few more variables necessary to consider: accessibility to fitness centers, monitored exercises with achievable goals, and supporting community aspects that provide accountability, positivity, self-modeling and inspiration to help the patient successfully complete the program (9).

In order to improve morbidity rates of cancer using exercise, a call to action is required, a standard care model for designing an exercise program for these patients is of great necessity (9). The American College of Sports Medicine (ACSM) proposed standard care model is composed of three components: patient eligibility, program and custom software specific to exercise in cancer treatment. To determine patient eligibility an oncologist must determine the patients' degree of disability, stage of treatment, co-morbidities and cost of program. When designing the program the key factors to consider are the components (aerobic, anaerobic, flexibility, etc.), structure (evaluation, teaching of program, progression of program, etc.), perpetuality (longevity of the program), home exercise (phone counseling, program oversight, access to useful tools, etc.), clinical staff (knowledge in exercise science, experience in program delivery, etc.), research and scalability (9). For example, evaluating a cancer patient exhibiting controlled dyspnea during treatment, an exercise prescription may be appropriate. An aerobic program designed around improving ventilatory variable with or without respiratory therapy may be applicable. Monitoring ventilation responses and progress will allow you to determine the effectiveness of this protocol and how it could be adjusted or improved. By improving comorbidities or other symptoms related to the treatment, a clinician is able to better focus on the actual mechanisms and effectiveness of the cancer treatment itself.

Conclusions

Exercise should be incorporated into most, if not all, cancer treatment protocols. The positive health effects of exercise are unequivocal and extremely applicable to cancer treatments. The benefits of exercise are vast and provide no harmful side-effects if correctly prescribed. As a health professional, incorporation of an exercise protocol might just be the difference between life and death. With improvements in not only physiological responses but psychological responses as well, exercise should be considered an essential intervention that is integrated into

almost all cancer treatments. As evidence-based strategies are created to accurately prescribe exercise for cancer patients, clinicians should continue to educate themselves of the possible benefits and effects of exercise to improve cancer treatment outcomes.

Additional Elements

Apply It

1. The health benefits associated with exercises during cancer treatment are unequivocal, proper designs for exercise in this population is extremely relevant to people of all ages.
2. Exercise should only be prescribed by a registered oncologist
3. After prescription, constant maintenance and progression must be diligently monitored throughout the course of treatment by a registered oncologist. Consultation with a referred exercise physiologist might benefit the patient.

Bridging the Gap

Even though the positive evidence surrounding exercise and cancer treatment is quite overwhelming, exercise is rarely implemented in a clinical setting. There are many reasons for this gap in care but the primary cause is most likely due to inadvertent ignorance related to exercise prescription. The majority of practicing oncologists have never been taught how to properly implement an exercise program designed to fit the individualized needs of a cancer patient. Given the complexity of cancer treatment in general, simultaneously studying and identifying the various relevant treatment adaptations to exercise is practically impossible with no previous knowledge. Recognition of elicit benefits provided by exercise are still fairly new and under-researched but several articles have been developed to help guide exercise prescription during treatment.

Summary Statement

Exercise prescription should be incorporated into all facets of cancer treatment. The benefits are highly agreed upon and may decrease the rate of mortality experienced in cancer patients. Although treatment methods associated with cancer treatment are improving every day, administering an exercise program might improve treatment success even further.

Pulled Text

Exercise has been established as beneficial throughout the cancer management continuum. Its benefits may exceed or improve those of many routine treatment protocols (9). Exercise is associated with improved outcomes in cancer survivors, including reduced cancer

recurrence and cancer-related mortality (1). Exercise improves functional capacity and patient-reported outcomes across a range of cancer diagnoses (7).

Bio

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