Cancer Rehabilitation and Cancer-Related Fatigue

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INTRODUCTION

Cancer-related fatigue (CRF) is one of the most common symptoms experienced by cancer survivors irrespective of type of cancer or type of treatment. It is estimated that 25 to 90% of survivors experience fatigue sometime during the cancer continuum (1). The average prevalence is 48% but is greater with such cancers as pancreatic and breast and greater during treatment (13). The National Comprehensive Cancer Network (NCCN) defines CRF as "a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning." CRF is not related to excessive activity, and the tiredness/exhaustion is not alleviated by rest and, in fact, may worsen the symptoms (6). CRF significantly affects cancer survivors' quality of life and limits personal, social, and occupational activities. Therefore, CRF interventions should be a major component in a comprehensive cancer rehabilitation program.

POTENTIAL MECHANISTIC MODELS OF CRF

The majority of cancer treatments (e.g., surgery, radiation, chemotherapy, stem cell transplantation) have moderate to severe biopsychosocial negative side effects often contributing to CRF. There are many proposed models to explain the mechanisms underlying CRF. These models can be categorized into four groups: 1) energy balance, 2) fatigue as a stress response, 3) neuroendocrine-based regulatory fatigue, and 4) hybrid models (14).

Energy balance abnormalities can result when there is an imbalance between energy intake, metabolism, and energy expenditure. This energy imbalance can result in abnormal mitochondrial function, leading to metabolite depletion and/or metabolite accumulation, which can upset the balance between aerobic and anaerobic pathways. In fact, current thought regarding tumor metabolism is that most tumor cells prefer the conversion of glucose to lactate, favoring the glycolytic pathway (15). The result would be inadequate adenosine triphosphate from aerobic pathways, hindering energy production for aerobic metabolism in other physiological systems. For example, lower cardiac aerobic metabolism could lead to left ventricular dysfunction, reduced cardiac output, and lower oxygen and nutrient delivery.

More recently, Martinez-Outschoorn et al. (25) provided evidence contradicting the view that cancer cells have impaired mitochondrial function and rely metabolically on glycolysis. They have found many cancer subtypes with increased mitochondrial oxidative phosphorylation. This enhanced mitochondrial activity may be connected to cancer aggressiveness. Both viewpoints suggest that the cancer puts a severe burden on the mitochondria, which in turn compromises energy production. Compromised energy production could diminish protein synthesis, leading to cachexia (muscle wasting) and loss of muscular strength and endurance. CRF could also result from insulin sensitivity. Abnormalities that occur with glucose uptake can lead to the enhanced bioactivity of insulin growth factor 1, which increases tumor turnover rate (18).

Fatigue as a stress response proposes that tiredness, fatigue, and exhaustion are behavioral markers on a continuum of adaptation to stressors (14,33). Aistairs (1) stated that CRF is a function of the source of stress, perception of stress, coping mechanisms, and the duration of the stressor, which could lead to energy depletion and exhaustion. The stress response model provides a reason (i.e., coping ability) why some individuals experience severe fatigue and others do not. It also provides an explanation for adaptation between tiredness (formation of an alarm response), fatigue (preservation of resistance), and exhaustion (reduction of ability to endure). There are features that make this model useful, but more recent studies have proposed that tiredness and exhaus-

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tion are not anchors on the fatigue continuum but are separate states with significant clinical meaning (33).

Neuroendocrine-based regulatory fatigue models propose that fatigue is a result of dysfunction in the nervous and endocrine systems, including the hypothalamic-pituitary axis (HPA) and neuroimmune system transmitter secretion and function. Interaction between the immune, nervous, and endocrine systems is related to stress and its effects on immunity. The HPA is the major part of the system that controls internal and external stress responses. Cytokines are chemical messengers that stimulate the HPA when the body is stressed (17). Activation of the immune system may produce fatigue, which is mediated by proinflammatory cytokines. Bower et al. (7) and Collado-Hidalgo et al. (12) investigated proinflammatory cytokines and markers of cytokine activity between fatigued breast cancer survivors and nonfatigued survivors. They found significantly higher levels of interleukin-1 receptor antagonists, soluble tumor necrosis factor receptor type II, and neopterin levels in the fatigued breast cancer survivors compared with nonfatigued survivors 5 yr after diagnosis, suggesting possible mechanisms explaining CRF. Likewise, Shubert et al. (41) completed a review of 18 studies (1,037 participants) to determine if increased cytokine and neopterin levels may be responsible for CRF. They reported significant positive correlations between CRF and cytokine IL-6 ($r=0.12$, $p=0.004$), CRF and cytokine IL-1RA ($r=0.24$, $p=0.0005$), and CRF and neopterin ($r=0.22$, $p=0.0001$).

Cancer and its treatments are associated with many negative side effects. As a result, CRF models that are narrow in focus are limited in their explanations. Hybrid models are more attractive in explaining CRF due to the fact that CRF is a multifaceted syndrome mediated by a number of different factors. Hybrid models are more comprehensive in nature and thus include a variety of explanations for CRF. Olson et al. (34) began the Edmonton Fatigue Framework to study cancer tiredness, fatigue, and exhaustion. After reviewing the literature, the research group proposed that potential declines in cognitive function, sleep quality, nutrition, and muscle endurance reduce individuals' ability to adapt leading to an increase in CRF. Yoon et al. (49) surveyed 1,219 early-stage breast cancer survivors within 6 mo following treatment and found numerous symptoms. These women felt that if they experienced ≥ 3 symptoms, their quality of life was severely compromised. Among these patients, 81% reported CRF, 87% systemic treatment-related side effects, 72% breast complications, 57% sleep difficulties, 55% arm complications, and 50% pain. This study highlights the multifaceted nature of CRF and shows the value of models for CRF that are more comprehensive.

PHYSIOLOGICAL AND PSYCHOLOGICAL POTENTIAL CAUSES OF CRF

The most common cancer treatments of surgery, radiation, and chemotherapy—along with other cancer treatments used to cure or control cancer—affect every system in the body. For example, radiation and chemotherapy destroy cells that are undergoing cell division. Cancer cells that are reproducing uncontrollably are susceptible to destruction, as are normal cells that are reproducing or have continuous turnover of cells (e.g., bone marrow). With the destruction of normal cells in the systems of the body, cancer survivors can struggle to maintain basic physiological functioning and thus experience CRF and reduced quality of life. The negative effects of many specific cancer treatments are quite similar; therefore, system toxicities will be discussed in general.

Cardiovascular System

The cardiovascular system can be negatively affected centrally and peripherally. Chest radiation can induce inflammation of the pericardium, abnormalities in cardiac conduction, and reduced ventricular function. Chemotherapy agents (e.g., Adriamycin) can gradually damage the heart, directly inducing cardiomyopathy and diminished ventricular function. Peripherally, cancer treatments can cause vascular dilation, increased capillary permeability, interstitial edema, decreased blood perfusion, and loss of the number of mature platelets. The damage that occurs within the bone marrow can cause reduced red blood cell counts and lower hemoglobin, leading to lower oxygen-carrying capacity. These negative treatment side effects can greatly reduce cancer patients' quality of life by causing extreme fatigue and constant tiredness (37). Furthermore, several studies have shown that cancer per se may result in cardiac cachexia, which leads to cardiac remodeling and dysfunction.

Pulmonary System

Within the pulmonary system, cancer treatments can cause the formation of scar tissue in the alveoli and abnormal development of pulmonary tissue. This can lead to excessive coughing, dyspnea, and a low-grade fever. In addition, cancer patients have a diminished diffusion capacity and decreased pulmonary compliance. Patients experience shortness of breath, frequent colds, low functional capacity, and extreme fatigue (37).

Immune System

Cancer treatments have a profound negative effect on the immune system. B lymphocytes and T cells are especially susceptible to cell death, as are cells within the bone marrow. White blood cells and granulated white blood cells (neutrophils, basophils, eosinophils) can be destroyed by many cancer treatments. The resulting myelosuppression can enhance patients' susceptibility to infections, colds, and flu-like symptoms (37).

Gastrointestinal System

Intestinal changes that can occur with cancer treatments include a thickening or narrowing of the bowel, ulceration, intestinal fibrosis, vascular edema, distension of the arteries, and increased intestinal motility. Additionally, some of the enzymes of digestion are destroyed along with reductions in intestinal absorption. These negative side effects cause cancer patients to experience malnourishment, loss of appetite,

abdominal pain, constipation or diarrhea, and extreme fatigue (37).

Musculoskeletal Alterations

Cancer treatments disturb muscle integrity, resulting in damage to the sarcolemma, sarcoplasmic reticulum, mitochondrial membranes, myofibrils, and myofilaments. The result is cachexia (muscle wasting), muscle weakness, inflammation, muscle imbalances, and extreme fatigue (37).

Neuroendocrine System

Cancer treatments can induce central nervous system dysfunction. Patients may experience memory loss, numbness (neuropathy) in the feet and hands, blurred vision, hearing loss, loss of balance, and lower motor function (37)—all of which could contribute to CRF. Psychological factors and fatigue appear to be closely linked in cancer patients. The relationship varies from patient to patient and the mechanisms involved are not well understood. Such psychological symptoms as anxiety and depression (21,31), reduced self-efficacy (23), distress (45), and difficulty coping (24) vary according to the stage of cancer and the phase the patients are in along the cancer continuum (diagnosis, treatment, post-treatment) (46).

DIAGNOSIS AND ASSESSMENT OF CRF

The diagnosis/assessment of CRF can be very complex, but the first step in the evaluation of CRF is identifying patients with CRF. There is no single agreed-upon evaluation instrument for CRF. However, because there is widespread CRF among patients, it should become common practice to evaluate CRF during clinical screening.

Many instruments have been developed—none of which are comprehensive. CRF diagnosis should be determined through clinical history, physical examination, relevant biological assessment, information from the family, and the use of self-report standardized measures (9). For example, on a self-report instrument with a 10-point rating scale (zero = no fatigue and 10 = worst fatigue), mild fatigue represents a score of 1 to 3, moderate fatigue as 4 to 6, and severe fatigue as 7 to 10. Using the 10-point scale, research has shown significant decreases in physical functioning at a score of 7 or greater (27,32,35).

A number of effective standardized instruments can be used. There are the Visual Analog Scale (VAS) and the Brief Fatigue Inventory (BFI), which are the easiest and fastest (27,30). More extensive instruments (29) are the Functional Assessment of Cancer Therapy Instrument (FACT-F) (3), the Multidimensional Fatigue Symptom Inventory Short Form (MFSI-SF) (44), and the Piper Fatigue Scale (35). Reassessment of CRF should be done on a consistent basis so the behavior patterns of patients can be established. Cancer patients in treatment should be reassessed daily or following each chemotherapy cycle, while patients post-treatment should be reassessed at regular intervals as established by the health care provider or cancer exercise specialist (32,42). Depending on the severity of CRF, pharmacological (e.g., erythropoietin [28]) or nonpharmacological interventions can be used to reduce CRF.

INTERVENTIONS TO ERADICATE CRF

Currently, there has been no consensus on which pharmacological agents are the most effective at improving CRF. Guidelines from the National Comprehensive Cancer Network (NCCN) recommend treatment for potentially reversible contributors of CRF such as pain, emotional distress, sleep dysfunction, nutritional imbalances, and comorbidities. A meta-analysis of two studies (n=264 patients) investigated the effects of methylphenidate (a psychostimulant) versus placebo on CRF and found that methylphenidate was superior to the placebo (p=0.02) for treating CRF (28). Within the same paper, Minton et al. (28) completed an additional meta-analysis of 10 studies (n=2226 patients), evaluating erythropoietin in patients with anemia during chemotherapy, which showed that erythropoietin was superior to placebo in treating CRF (p=0.008). The authors concluded that there is some evidence that pharmacological agents are effective in treating CRF, but more research is warranted.

CRF is often treated with nonpharmacological interventions. Variables that potentially contribute to CRF and are positively affected by exercise are shown in Table 1. The relationships among these variables may be part of the cause of CRF, and exercise may be an effective means to modify these interactions and relationships. Al-Majid and Gray (2) stated that many studies have examined the effect of exercise on CRF, but few studies have investigated the mechanisms involved with the benefits of exercise and CRF. Therefore, they developed a physiological and psychobehavioral hybrid CRF model that shows the relationship of the beneficial effects of exercise and the reduction of CRF (Figure 1) to be used to guide research and thus the development of exercise protocols that target these mechanisms.

As ascertained by Al-Majid and Gray, the research in exercise and CRF is often inconsistent. McMillan and Newhouse (26) completed a meta-analysis on 16 studies comprising 1,426 participants (exercise = 759; control = 667) that met their criteria. They found a small but significant effect size (standardized mean difference [SMD] 0.26, $p<0.001$) between exercise and control groups, with exercise reducing CRF. They also found that exercise improved functional capacity and musculoskeletal fitness compared with the controls ($p<0.01$). The researchers stated that further research is needed to determine the underlying mechanisms related to the benefits of exercise on CRF.

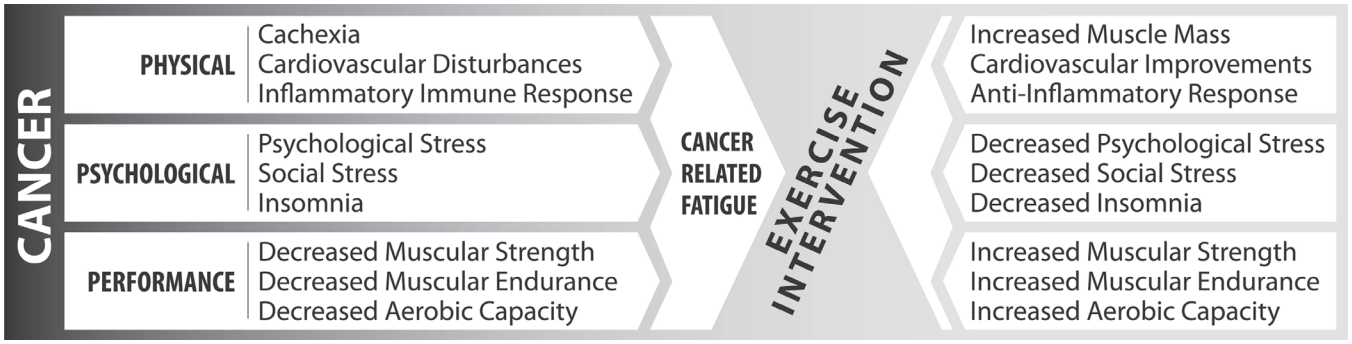
Likewise, Brown et al. (8) completed a meta-analysis on 44 studies consisting of 3,354 participants of varying types of cancer, stages, treatments, and exercise interventions. CRF was diminished in the exercise group (SMD 0.31; 95% confidence interval [CI] = 0.22-0.40) compared with the control group. It also appeared as if the CRF decrease could be generalized across cancer types. The intensity of resistance exercise was proportional to the decrease in CRF. These researchers concluded that moderate intensity resistance exercise was beneficial in reducing CRF.

TABLE 1. Treatment toxicities versus exercise benefits.

Cardiovascular Toxicity • Left ventricular dysfunction • Lower left and right ejection fractions • Abnormal left ventricular contractility • Reduced cardiac output and stroke volume • Reduced oxygen and nutrient delivery • Endothelial dysfunction • Increased myocardial work	**Exercise Benefits** • Strengthens myocardium • Increases cardiac output and stroke volume • Decreases resting heart rate • Lowers exercise heart rate • Improves endothelial function
Pulmonary Toxicity • Decreased total lung capacity • Decreased diffusion capacity • Reduced oxygen and carbon dioxide exchange • Decreased submaximal and maximal exercise oxygen consumption	**Exercise Benefits** • Strengthens intercostal muscles • Improves ventilation and transport of air from the environment to the cell
Gastrointestinal Toxicity • Loss of body nutrients • Loss of body fluids and electrolytes • Alters metabolism	**Exercise Benefits** • Increases uptake of nutrients • Reduces weakness and fatigue • Improves appetite
Musculoskeletal Toxicity • Muscle wasting • Destruction of skeletal muscle tissue • Increased muscle weakness	**Exercise Benefits** • Increases integrity of muscle tissue • Increases muscle protein synthesis • Balances ratio of proinflammatory and anti-inflammatory cytokines • Stimulates the release of hormones that increase muscle cell growth and development • Improves metabolism, which increases the efficiency of energy utilization
Immune and Hematological Toxicity • Myelosuppression • Inhibits bone marrow function • Reduced red blood cell count (anemia) • Reduced oxygen carrying capacity • Disordered coagulation	**Exercise Benefits** • Increases red blood cell production • Increases blood volume • Increases hemoglobin concentration • Improves blood coagulation, fibrinolysis, platelet aggregation
Neurotoxicity • Slows motor function • Decreases coordination	**Exercise Benefits** • Enhances motor unit recruitment • Improves neurochemical availability at the cellular and tissue levels • Improves coordination

Velthuis et al. (48) conducted a meta-analysis on exercise and CRF in randomized controlled trials. Eighteen studies (12 breast cancer, four prostate cancer, two other cancers) met their inclusion criteria. They found that home-based exercise during breast cancer treatment did not significantly reduce CRF; however, supervised aerobic exercise showed a medium, significant reduction in CRF (SMD 0.30; 95% CI = 0.09 to 0.51) compared with no exercise controls. They

FIGURE 1. A biobehavioral model for the study of exercise interventions for cancer-related fatigue.



Adapted from Al-Majid S, Gray DP. A biobehavioral model for the study of exercise interventions in cancer-related fatigue. Biol Res Nurs. 2009;10(4):381-91.

found no significant difference in the reductions in CRF between home-based, supervised aerobic, and resistance exercise programs in patients with prostate cancer.

In summary, studies investigating the effects of exercise on CRF have shown small to medium effect sizes. During cancer treatment, improvements in fatigue ranged from -32 to -39% (43), while following cancer treatments, exercising cancer survivors show decreased fatigue ranging from -33 to -39% (38,39,40).

While the mechanisms of the exercise effects on CRF remain elusive, perhaps some of the mechanisms identified in animal models may contribute to the reduction of CRF in humans. Thus far in the animal model, exercise appears to be beneficial in reducing the toxic effects of cancer treatments through such mechanisms as decreased expression of pro-apoptotic markers (19), attenuated protein carbonyl formation, decreased serum levels of cardiac proteins, reduced lipid peroxidation, elevated antioxidant status (4,5), preserved nitric oxide synthase function, upregulation of heat shock proteins, and/or preservation of the myosin isoform distribution (10,11,20). As stated by Al-Majid and Gray (2), it remains a critical issue for further research to determine the mechanisms involved with the reduction of CRF by exercise. An adequate understanding of these mechanisms could allow for the design of appropriate exercise interventions to specifically address CRF.

Psychosocial therapies comprise educational, supportive, and behavioral interventions. Kangas et al. (22) reviewed 41 randomized controlled trials (n=3620 patients) that tested the efficacy of psychosocial interventions on patients with a variety of cancer types during and after treatment. They found that the effect size (-0.31, $p<0.001$) was near moderate with clinical significance. The interventions were grouped into categories of cognitive behavioral therapy (CBT), supportive-expressive therapy, education/counseling, behavioral/relaxation therapy, massage, and mental restorative treatments. The researchers found that CBT, education/counseling, and supportive/expressive therapy showed the most benefit for the alleviation of CRF. While massage and mental rest therapies also showed some benefit, behavioral interventions (e.g., relaxation) showed minimal benefits.

Goedendorp et al. (16) conducted studies that included physical activity and psychosocial interventions (i.e., CBT) to reduce CRF. They found that during treatment, the CBT group had significantly less CRF than the usual care group. However, there was no difference in CRF between the physical activity group and the usual care group. They concluded that the CBT intervention was effective, while the physical activity intervention was not. It should be noted that the physical activity intervention was two 1 h education sessions 3 mo apart focusing on physical activity. After 1 yr following treatment, the cancer survivors reported less CRF from physical activity alone and physical activity plus CBT compared with the control group. van Weert et al. (47) completed a similar study and found that physical training combined with CBT and physical training alone significantly reduced CRF compared with the control group. Physical training alone was equally effective as or more effective than physical training plus CBT. This group of researchers had cancer patients exercise by using aerobic and strength training exercises based on heart rate, while the Goedendorp study employed physical activity education sessions.

CURRENT EXERCISE RECOMMENDATIONS

There are many factors that contribute to reduced physical functioning; however, fatigue is a major contributor. Upon reviewing the research on exercise and CRF, the following exercise recommendations can be ascertained:

- It is critical to complete assessments of CRF before development of the exercise intervention. There are effective CRF standardized instruments, as stated earlier (3,27,29, 30,35).
- The beneficial effects of exercise on CRF have been found across cancer types, cancer stages, and cancer treatments (8).
- Exercise has been administered during treatment and following treatment with successful reductions in CRF (32,39,40).
- Exercise interventions should be individualized based on CRF status and physical functioning assessments (32,37,38,39,40).
- Aerobic and resistance activities should be included in the exercise interventions (36,38,39).
- Supervised exercise programs appear to be more beneficial for reducing CRF (45).
- Exercise recommendations are the same as age-appropriate guidelines for Americans (36).
- General contraindications for exercise include severe fatigue, anemia, and ataxia. Cancer-specific contraindications include shoulder problems for breast cancer patients, patients with an ostomy as a result of colon cancer, and excessive swelling in the abdomen and lower extremities as a result of gynecologic cancer (32,36).
- Caution should be used during exercise interventions if there are bone metastases, thrombocytopenia, fever or active infection, and any secondary limitations (e.g., cardiopulmonary contraindications) (32).

SUMMARY

CRF is a debilitating sense of physical and emotional tiredness and exhaustion that reduces the quality of life in cancer survivors. There are numerous pharmacological and nonpharmacological interventions that have proven to be beneficial in reducing CRF. Exercise is one of the nonpharmacological interventions that has shown promise in attenuating CRF. Future research should explore exercise interventions that specifically reduce CRF by targeting specific mechanisms. In order to develop appropriate exercise prescriptions against CRF, mechanistic investigations of exercise as a means to attenuate CRF should be conducted.

Keywords: exercise, cancer survivors, quality of life

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