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Exercise to Combat Respiratory Muscle Wasting in Cancer

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Abstract

Cachexia is the term used to describe the progressive loss of muscle mass in association with severe disease. The primary resulting alteration observed in cachexia is a shift in the fundamental balance of muscle protein synthesis and muscle protein degradation. One of the diseases most commonly associated with cachexia is cancer, in which the prevalence rate is 50-80%. Furthermore, cachexia is estimated to be responsible for 20% of cancer deaths. Potentially contributing to this mortality rate is the wasting of the respiratory muscles. Despite this, relatively little research has investigated the impact of cancer cachexia on respiratory muscle wasting and dysfunction. Additionally, exercise provides promise in the implementation of a therapeutic intervention aimed at ameliorating the adverse effects of cancer cachexia.

Keywords: respiratory muscle, cancer, cachexia, exercise.

Though leaves are many, the root is one;
Through all the lying days of my youth
I swayed my leaves and flowers in the sun;
Now I may wither into the truth.

— W. B. Yeats

Severe illness is often accompanied by the loss of muscle. This statement typically does not strike people as particularly remarkable. Most of us know this intuitively. And yet, few have ever heard the term cachexia.

What is Cachexia

Cachexia is the term used to describe the progressive loss of muscle mass in association with severe disease. Intuitively, a period of illness resulting in an individual being bed ridden may cause them to lose weight, muscle, and strength. This does not describe cachexia. Although

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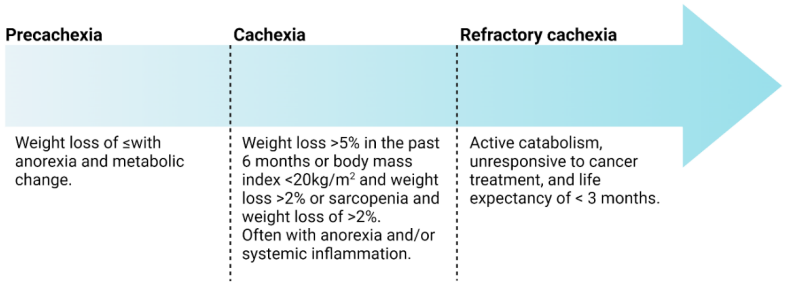

Figure 1: The international framework for defining cancer cachexia (adapted from Fearon et al. 2011[1]).

defined by weight loss (Figure 1), the primary resulting alteration observed in cachexia is a shift in the fundamental balance of muscle protein synthesis and muscle protein degradation. Ultimately, the breakdown of existing muscle is encouraged, whilst the production of new muscle is blocked. This leads to the rapid development of a devastating condition, which can cause fatigue, loss of appetite, and anorexia, in addition to decreased activity level and exercise capacity. As a result, cachexia can compound the adverse effects of disease and drastically impact patient quality of life.

Cachexia is not present in all illness, rather its development is observed in those suffering from particularly severe diseases. Little is known of how or why it originates, whether there is a singular defining change, or a compounding of factors which leads to the imbalance in muscle breakdown and production described. Therefore, it cannot be definitively stated as to why it presents in the diseases it is observed in. However, it may be related to the degree of change imposed by the illness. The more severe the illness, the larger the deviation away from the normal workings of the systems of the body. The larger this change, the more likely one of these systems will begin to operate inappropriately. Needless to say, this abstract speculation is insufficient in detailing the true nature of the condition. A wide array of systemic changes are evident in cachectic individuals. Underlying these changes is a complex inter-connecting web of signalling pathways and mediating factors, each acting to contribute toward the net state of muscle wasting. This diverse mechanistic foundation complicates the description of the condition and prevents identification of the most valid targets for treatment. However, it does imply that considerable systemic changes are necessary for the development of the condition. Indeed, one of the diseases most commonly associated with cachexia is cancer. The prevalence of cachexia in patients differs between cancer types but is as high as 50-80%. Furthermore, cachexia is estimated to be responsible for 20% of cancer deaths. Although uncertainties remain concerning its causes, what can be stated with conviction is that cachexia imparts a considerable burden, with potentially fatal consequences, on populations of cancer patients.

The Respiratory Muscles

Potentially contributing to the cause of death due to cancer cachexia is the wasting of the

respiratory muscles. The diaphragm, along with smaller accessory muscles, is responsible for the action of breathing. Contraction of these muscles leads to the expansion and contraction of the ribcage, resulting in pressure changes in the abdomen, causing air to move in and out of the lungs. These muscles are not immune to the negative effects of cachexia and undergo wasting due to the condition. Where there is muscle wasting there is very often a loss of muscle function. This typically produces two main effects. One, the muscle may not be able to contract as well, meaning it cannot produce as much force as it once could. Two, the muscle may not be able to contract for as long, meaning it fatigues more quickly than it used to. Either one of these changes, or the combination of both, would mean that the muscles responsible for breathing become much less powerful and efficient, compromising their capability to handle increasing stress or a challenge. Therefore, when a challenge does present itself, the muscles of the respiratory system are unable to meet it, and they fail.

Weakness of the respiratory muscles is frequently observed among cancer patients and dysfunction of the respiratory muscles has been identified as a highly relevant issue. Despite this, very little attention has been provided to the study of cachexia with the focal point of interest being respiratory muscle wasting and function. The scarcity of such research is illustrated in the results of our systematic search of the literature, which was designed to collate and interpret the existing research papers concerned with the respiratory system in cancer cachexia. Our comprehensive search strategy identified 346 papers, which was subsequently reduced to only 12 papers following manual screening. Despite the limited depth of knowledge in this area, the findings published thus far support the need for further consideration in this domain. The first evidence of diaphragm wasting in preclinical mouse models of cachexia was reported relatively recently in 2013. Since then, cachexia has been shown to induce atrophy of the diaphragm in addition to reducing the ability of the diaphragm to produce force. Beyond this, recent preliminary evidence suggests that stimulation of the respiratory muscle via the nervous system may be altered, implying that the complexity of respiratory muscle impairment in cachexia is considerably more convoluted than our current understanding.

Therefore, from our systematic review it can be concluded that there is a considerable lack of information surrounding the impact of cancer cachexia on the respiratory musculature. Further research aimed at elucidating this impact may prove to be valuable in identifying valid therapeutic targets which could subsequently inform intervention design for the mitigation of the adverse effects associated with the cachectic condition.

Exercise as Treatment

The nature of cachexia makes it an incredibly difficult condition to treat. Mechanisms known to be involved include inflammation, oxidative stress, and insulin resistance. Although the specific means by which these factors contribute to the development of cachexia is difficult to ascertain, ultimately, they are linked to decreased muscle synthesis and increased muscle degradation. Furthermore, these underlying conditions interact with one another via a wide array of

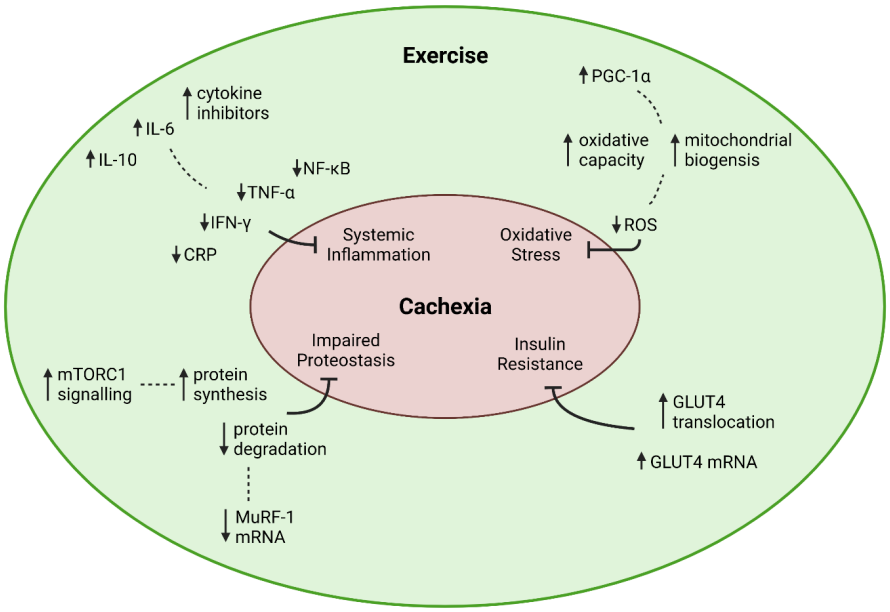

Figure 2: The potential benefits of exercise in cachexia as reported in the literature.

signalling events, greatly enhancing the complexity of the condition. As a result of the wide array of contributing factors and the manner in which they interact with one another, blocking one mechanism does not prevent the condition from developing. Therefore, it is widely acknowledged that any effective therapeutic intervention will likely need to be in the form of a multi-modal approach. The three primary approaches of interest being drug-, nutritional-, and exercise-related. Research thus far surrounding these three modes of therapy has failed to provide a definitive solution to treat cachexia. Although limited benefits may be observed, the condition still prevails. What has been determined is that should an effective therapeutic strategy be developed, more knowledge is needed on the individual elements to be employed. Exercise is an attractive approach for many reasons. It is cheap, practical, and provides very few, if any, contraindications. Additionally, whereas a drug might effectively target a single factor implicated in the production of cachexia (e.g. an antioxidant drug), exercise holds promise as a blanket treatment, affecting many different aspects of the condition (Figure 2). It acts on both sides of the equation, as it has been shown to restore the production of new muscle, in addition to blocking the breakdown of existing muscle. Finally, initial mouse models provide promising evidence supporting the use of exercise as treatment against cancer cachexia. However, there is a distinct lack of research both examining the beneficial impact of exercise toward respiratory muscle, and assessing exercise interventions in humans suffering from cancer cachexia.

Future Research

The prevalence and severity of cancer cachexia identifies it as a condition associated with considerable, and potentially fatal, consequences for populations of cancer patients. Despite a large and continuously growing field of research investigating the condition, a meaningful therapeu-

tic intervention remains to be found. Additionally, the vast majority of this research is focussed on limb muscle, neglecting the impact of the condition on the muscles involved in breathing. This is particularly surprising considering the reported link between respiratory muscle failure and death in cancer sufferers. Our comprehensive search of the literature highlighted the few studies concerned with cancer cachexia and respiratory muscle. The limited results of these studies when considered together identify the consistent presence of diaphragm muscle wasting and dysfunction associated with cancer cachexia. Therefore, this specific area requires much further attention.

My future research will aim at addressing this considerable vacancy in the current literature. As there is so little yet known regarding the nature of muscle wasting in the respiratory muscles in cachexia, the first step will be to characterise this state. This process will essentially entail the asking and answering of many questions through the design and employment of a mouse model of cachexia. How much of the muscle is lost? Does the muscle lose its ability to produce force? Does the muscle fatigue more quickly? In addition, more detailed assessment of the molecular alterations observed will allow potential mechanisms responsible for such changes to be identified. These mechanisms will provide targets for the application of an exercise intervention, facilitating further questions to be posed. For example, if x contributes to respiratory muscle atrophy, and exercise is known to block x, then will exercise block x and thus prevent respiratory muscle atrophy in cancer cachexia? Answering of this question with sufficient certainty would facilitate the ultimate goal of my research, transference of knowledge gained to the clinical setting and implementation of an exercise intervention in patients for the treatment of cancer cachexia. Regardless of whether this final goal is reached, it is my hope that a step is taken, no matter how small, toward the betterment of patient well-being.

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Declarations of Interests

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