Chapter 7

Understanding Cachexia, Sarcopenia, and Physical Exercise in Patients with Cancer

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Abstract

Many patients with cancer experience muscle wasting and weakness. Muscle wasting in patients with cancer can be caused by cachexia and sarcopenia. Both cachexia and sarcopenia involve inflammation and oxidative stress. However, they differ in the underlying mechanisms that lead to muscle wasting. Cachexia involves the release of inflammatory cytokines due to cancer, while sarcopenia involves inflammation due to aging. Physical exercise has shown effectiveness for improving physical function, ability, and quality of life (QOL) in patients with cancer cachexia. On the other hand, no studies have investigated the relationship between physical exercise and sarcopenia in elderly patients with cancer. Previous studies showed effectiveness for improving physical function in elderly patients with cancer. In the future, more studies are required on physical exercise in sarcopenic elderly patients with cancer.

Keywords: cachexia, sarcopenia, physical exercise, quality of life, patients with cancer

1. Introduction

Muscle wasting and weakness are common in many disease states and conditions including aging and cancer [1]. Muscle wasting in advanced cancer is related to age, sex, tumor type, and inflammation [2]. It can be caused by inflammation and malnutrition in patients with cancer [3]. Patients with cancer have problems including anorexia, weight loss, negative nitrogen balance, and skeletal muscle wasting [4]. The loss of muscle and fat tissue due to chronic illness is referred to as cachexia, and the general loss of muscle mass with advancing age is referred to as sarcopenia [5]. Sarcopenia diagnosis requires documentation of low muscle mass along with either low muscle strength or low physical performance [6]. Cachexia and

sarcopenia share some pathological muscle wasting mechanisms characterized by inflammation and oxidative stress [7, 8]. In both cachexia and sarcopenia, muscle loss can lead to frailty and adversely affect various clinical outcomes [9]. Many oncologists and rehabilitation staffs confuse cancer cachexia with simple starvation or physiological processes such as sarcopenia. Since cancer cachexia and sarcopenia can both involve muscle wasting, we speculate that the two conditions can be confused in patients with cancer. However, sarcopenia and cachexia should not be confused in patients with cancer (**Figure 1**). Instead, it should be understood that the loss of skeletal muscle mass occurs in patients with cancer (cachexia) as well as during aging (sarcopenia). Cachexia involves muscle wasting and weakness as a result of cancer-related inflammation, while sarcopenia involves muscle wasting and weakness as a result of age-related inflammation. Thus, the underlying pathological processes leading to muscle wasting and weakness differ between the two conditions.

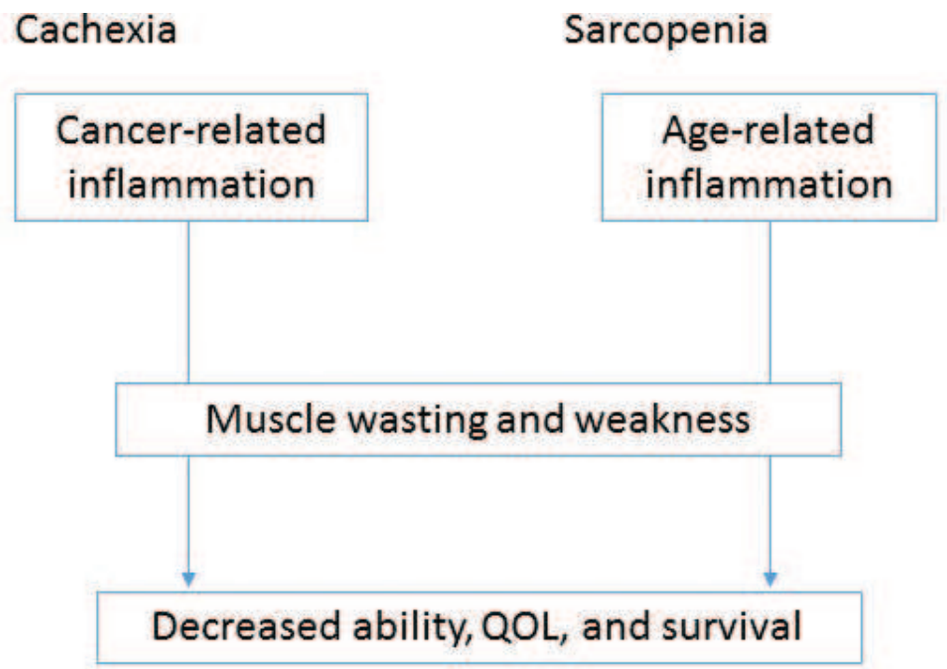

Figure 1. Muscle wasting due to cancer cachexia and sarcopenia.

2. Cachexia

Cachexia is associated with cancer and other chronic diseases, and cachexia patients lose weight and experience a decline in their overall health. The mechanism of cancer cachexia is known to involve inflammatory cytokines such as tumor necrosis factor-alpha and interleukin-6 [10]. Cancer cachexia is a complex syndrome that describes the progressive muscle wasting and weakness observed in many patients with cancer and accounts for at least 20% of cancer deaths [11, 12]. It is caused by numerous complex interactions of tumor and host factors [13, 14], and results in anorexia, wasting syndrome, and subsequent related issues [15].

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It is a multifactorial syndrome defined by an ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support [16]. A panel of experts has also defined consensus criteria for diagnosing cachexia in patients with cancer [16]: (1) weight loss > 5% over the past 6 months (in the absence of simple starvation); (2) BMI < 20 kg/m^2 and any degree of weight loss > 2%; or (3) appendicular skeletal muscle index consistent with sarcopenia (males < 7.26 kg/m^2; females < 5.45 kg/m^2), and any degree of weight loss > 2%. A defining feature of cancer cachexia is the loss of muscle, but fat may also be lost [17]. Weight loss is involuntary, meaning that there is no desire or attempt to lose weight. Cancer cachexia usually worsens over time, and as weight loss increases, cancer cachexia patients also experience difficulties in daily activities.

Cancer cachexia has three clinical stages: precachexia, cachexia, and refractory cachexia [16]. The condition may occur in stages that are defined by differences in food intake, weight loss, and ability to function. In addition to muscle wasting and appetite loss, patients who have cancer anorexia–cachexia have a poor overall quality of life (QOL) and experience fatigue. They find it difficult to perform regular daily activities [18], and experience a significant symptom burden [19, 20]. Patients with cancer cachexia have significant decrease in physical function [21, 22], with low grip strength, and shorter walking distance even when controlling for muscle wasting [23, 24]. Also, cancer cachexia patients demonstrate lower physical activity [25–27]. In the early or mild stage, patients with cancer may only notice a slight loss of appetite. At the moderate stage, patients will notice more weight loss and often eat less than at the early and mild stages. In the severe stage, muscle wasting becomes markedly increased compared to the moderate stage, and the condition may be resistant to normal treatments such as dietary supplementation and nutritional support. Patients with cancer do not experience weight gain. Furthermore, patients may also have great difficulties in performing routine activities [16, 28]. Cachexia can reduce the physical activities of daily living (ADL) in patients with cancer [29]. Many patients with cancer cachexia experience decrease in physical function and ADL after muscle wasting. Thus, in addition to nutritional support, physical exercise may also contribute to improve the physical function in patients with cancer cachexia.

3. Sarcopenia

Sarcopenia, derived from a Greek word meaning "poverty of flesh," is characterized by the triad of progressive loss of skeletal muscle mass, muscle strength, and physical performance [30]. It is defined as age-related muscle wasting; thus, sarcopenia frequently occurs in elderly people. European Working Group on Sarcopenia in Older People (EWGSOP) recommends that the diagnosis of sarcopenia in elderly patients should be based on the presence of both low muscle mass and low muscle function (strength or performance) [6]. EWGSOP uses these characteristics to further classify the condition into the stages of presarcopenia, sarcopenia, and severe sarcopenia [6]. Sarcopenia has emerged as an important prognostic factor in elderly advanced patients with cancer [6]. Modalities used to assess sarcopenia include magnetic resonance imaging, computed tomography, dual-energy X-ray absorptiometry, and

bioelectrical impedance analysis [31]. Sarcopenia is associated with poor performance status, toxicity from chemotherapy, and short time of tumor control [32, 33].

Sarcopenia is now recognized as a multifactorial geriatric syndrome [34, 35], and is a common clinical symptom of elderly patients with cancer [36]. It has been reported to serve as an independent risk factor for poor prognosis indicative of disease and death [37]. It typically co-occurs with cachexia in patients with cancer [38]. However, changes in muscle mass and physical performance may occur before clinically overt cachexia in patients with cancer [35]. In recent years, clinical research on the application of exercise, nutritional support, and drugs, as well as other comprehensive interventions in sarcopenia patients have demonstrated good results [39]. A significant proportion of elderly patients with cancer are at risk of sarcopenia development. However, despite its potential impact on their quality of life [2, 40], limited data are available regarding the factors associated with sarcopenia in elderly patients with cancer, who might have more problems such as malnutrition than non sarcopenic patients.

4. Physical exercise

Physical exercise has the potential to help maintain or slow the loss of physical function [41] as well as sustain and build muscle mass [42]. Aerobic and resistance exercise have been found to better improve upper and lower body strength than usual care in patients with cancer [42]. Aerobic exercise training for skeletal muscles improves wasting in cardiac and cancer cachexia patients [43]. Resistance exercise attenuates muscle wasting associated with a variety of catabolic conditions [44]. Physical exercise has been shown to be effective in improving physical activity levels in cancer survivors [45]. Physical activity intervention significantly improved quality of life for cancer cachexia patients [46, 47]. A systematic review found that physical activity has benefits including improvement in physical activity levels, aerobic fitness, muscle strength, functional quality of life, anxiety, and self-esteem [48] (**Figure 2**).

Physical activity correlated with maximum exercise capacity, weight loss, blood hemoglobin concentration, C-reactive protein, and QOL-related factors of physical functioning and bodily pain in patients with cancer with progressive cachexia [49]. Physical exercise may promote a disruption in the cycle of events leading to cachexia advancement (i.e. muscle tissue loss via anorexigenic proinflammatory cytokines) and, in turn, enhanced functionality and thus, improved QOL in patients with cancer [50]. It has been suggested to counteract sustained disease-related inflammation and the effect of exercise training in cancer cachexia [51]. Furthermore, it has been shown an association with the reduced levels of C-reactive protein in patients with cancer [52].

In patients with cancer, physical exercise represents a function-preserving, anti-inflammatory, and metabolism-modulating strategy with a low cost [53]. It may reverse protein degradation while increasing protein synthesis and lean body mass, thus counteracting the wasting seen in cachexia [54]. It is necessary to develop a better understanding of how to support patients with cancer in starting and maintaining physical activity and exercise programs. It is uncertain whether physical activity during and following cancer treatment has the same benefits

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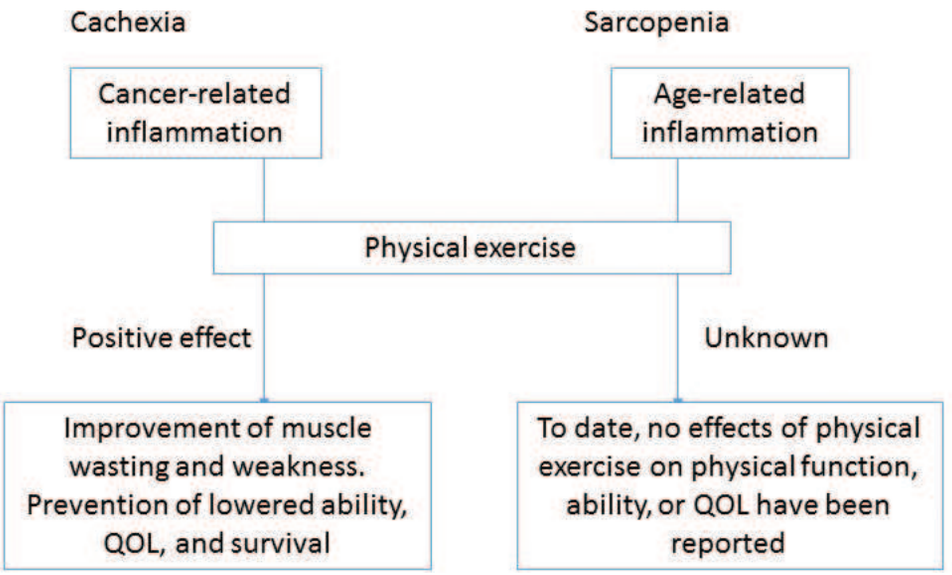

Figure 2. The effectiveness of physical exercise for patients with cancer with cachexia and sarcopenia.

in the weight-stable and weight-losing patients. The question also remains as to whether physical exercise has any health benefit in people with cancer cachexia or those at risk of cancer cachexia. Research investigating physical exercise in patients with cancer undergoing treatment has demonstrated improvements in physical performance, fatigue, and functional quality of life. It is unclear whether these benefits are experienced by patients with cancer cachexia. There is insufficient evidence to establish the safety and effectiveness of physical exercise in cancer cachexia patients, and future trials on exercise and supportive care interventions are required in this population. Aerobic and resistance exercise regimens may have positive effects on decreasing cancer-related fatigue and muscle wasting in patients with cancer cachexia.

To date, no studies have shown a relationship between physical exercise and cancer sarcopenia. In elderly patients with cancer, physical exercise has several benefits including improving immune function [55], hemoglobin and red blood cell count [56], and physical activity [57], not but VO2peak, 1 repetition maximum, functional capacity, anxiety level, or emotional well-being [58]. Physical exercise seems to improve physical function and immune function in elderly patients with cancer [59]. However, it has not shown effectiveness for sarcopenic patients with cancer.

5. Summary and conclusion

Muscle wasting is often encountered in patients with cancer. Both cachexia and sarcopenia lead to muscle wasting in patients with cancer. However, the different mechanisms of muscle wasting in patients with cancer should be recognized. Physical exercise might be effective for improving physical function, physical activity, ADL, and QOL in patients with cancer cachexia. In the future, more studies are required on physical exercise in sarcopenic elderly

patients with cancer. Studies investigating the combined effect of physical exercise and nutritional therapies such as branched chain amino acids in cancer rehabilitation are required to improve patient outcomes in the future.

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