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Narrative Review

Considerations for Exercise Prescription in Patients With Bone Metastases: A Comprehensive Narrative Review

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Abstract

Metastatic disease is a frequent complication of advanced cancer, with bone representing one of the most common sites of metastatic occurrence. Patients with bone metastases receive long-term systemic treatments that have a significant attritional impact on muscle strength, fatigue, and physical functioning. Physical rehabilitation involving exercise and physical activity prescription has a considerable role in counteracting these changes; however, exercise is often perceived as a contraindication in the presence of bone metastases due to concerns about aggravating skeletal related events. This article examines the physical sequelae of bone metastases and outlines the factors for consideration with exercise prescription in metastatic bone disease, including bone health, pain levels, and oncologic treatment. This article includes a comprehensive review of the evidence from trials of exercise prescription in this population, including the efficacy and safety outcomes of exercise interventions. Exercise interventions for patients with bone metastases are associated with positive physical and self-reported outcomes. Studies reviewed reporting adverse events did not find a high fracture incidence with exercise in comparison with control participants, or an association between exercise and fracture risk. The need to individualize exercise prescription and adapt exercises to patient ability were reinforced in all papers reviewed. Exercise prescription to patients with bone metastases does involve complex decision making; however, a number of tools are available that may inform both the assessment of patients and the prescription of exercise.

Introduction

Over the past 20 years, advances in our understanding of tumor biology have led to the development of improved treatment strategies for many cancers. Advances in systemic therapies for cancer have prolonged survival even in those who cannot be cured, and many people now live with advanced stages of cancer for longer periods [1,2]. Metastatic disease is a frequent complication of advanced cancer, with bone representing one of the most common sites of metastatic occurrence [3]. The incidence of bone metastases varies with different primary cancer tumors, ranging from 14% in melanoma to 90% in multiple myeloma. In patients with breast and prostate cancer, the incidence of bone metastases ranges from 65% to 75% [4]. With increased life expectancy of this patient group, the incidences of skeletal metastasis continues to increase, with more than 1.5 million patients worldwide living with bone metastases [5].

It follows therefore that optimizing physical capacity and maintaining independence with activities of daily living in patients with bone metastases for as long as possible is essential to maximize quality of life (QoL) [6]. Patients with bone metastases receive long-term systemic treatments that have a significant attritional impact on muscle strength, fatigue, and physical functioning. Physical rehabilitation involving exercise and physical activity prescription has a considerable role in counteracting these changes, with evidence from systematic reviews of exercise interventions in patient with bone metastases reporting improvements in functional capacity, lower fatigue levels, and increased QoL [7,8].

Despite the known benefits of physical activity for patients living with cancer, exercise prescription in patients with metastatic disease is challenging. Exercise is often perceived as a contraindication in the presence of bone metastases due to concerns about aggravating skeletal-related events (SREs) [9-11]. Recent in-depth

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surveys with health care professionals (medical oncologists, radiation oncologists, palliative care physicians, and specialist physiotherapists) involved in the management of patients with bone metastases in Ireland highlighted concerns that increasing physical activity would increase risk of SREs and aggravate symptom control [12,13]. The consequences of SREs, such as pathologic fractures and extradural spinal cord compression, include severe pain, increased health care costs, reduced QoL, and increased mortality [14]. Among patients, however, interest in physical activity is high. One cross-sectional study of 50 patients living with a high burden of metastatic bone disease reported that 92% were interested in completing exercise programs and felt able to do so [15]. Despite this keen interest, exercise levels in this population are suboptimal, with only 29% of patients with bone metastases meeting the current aerobic exercise guidelines for cancer survivors [16].

This review aims to examine factors for consideration with exercise prescription in metastatic bone disease, review the evidence from trials of exercise prescription in this population, and examine the efficacy and safety outcomes of exercise interventions. The review will examine (1) the physical sequelae of bone metastases; (2) factors to consider with exercise prescription, and (3) a comprehensive review of structured exercise training in patients with metastatic bone disease (Figure 1).

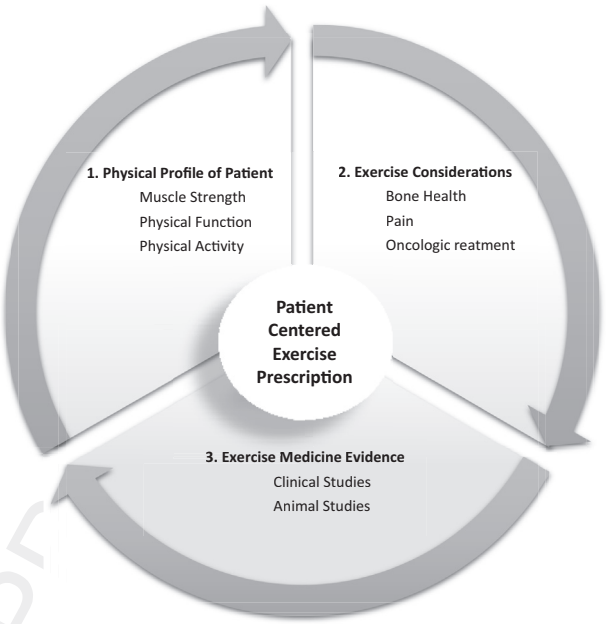

Figure 1. Exercise prescription in metastatic bone disease.

Section One: The Physical Profile of the Patient

Metastatic cancer and its associated treatment have a considerable attritional impact on multiple components of physical performance, including muscle strength, physical function, and physical activity. The following section provides an overview of the unique and multifaceted clinical profile of this patient cohort, thus outlining the challenges to be addressed by exercise rehabilitation

Muscle Strength

Skeletal muscle loss and muscle weakness are a well-described sequela of early-stage cancers [17,18]. Although less is known about skeletal muscle impairment in metastatic bone disease, sarcopenia is associated with treatment toxicity and time-to-tumor progression [19], and therefore addressing muscle loss is of considerable clinical importance. A small number of cohort studies have reported suboptimal muscle strength in patients with metastatic bone disease [20-22]. In one example in metastatic breast cancer (n = 71), both relative and adjusted grip strength (26.6 [6.0] vs 30.2 [6.4] kg, $P = .001$, and 0.38 [0.09] vs 0.46 [0.11] kg.kg^{-1}, $P < .001$, respectively) and leg strength [53.5 23.7] vs 76.0 [27.4] kg, $P < .001$, and 0.76 [0.31] vs 1.15 [0.45] kg.kg^{-1}, $P < .001$) were significant lower than matched healthy controls [23]. Hand grip strength is negatively associated with physical frailty and low scores are predictive of disability in older people [24].

In addition, measures of lower limb muscle function, such as 30-second sit-to-stand (STS) test scores, are impaired in metastatic cohorts, with patients completing approximately one half the number of STS repetitions (11.5 [4]) in comparison with matched controls (22 [7]) [22,25]. In patients with spinal metastases, preintervention data from an exercise study reported baseline STS repetitions as low as 5.1 (1.4) (intervention) and 4.6 (2.0) (control); however, this outcome was amenable to rehabilitation, with the intervention arm increasing to 9.0 (2.6) repetitions after 3 months of isometric spinal strengthening [26]. Of concern, in older healthy cohorts (>60 years old), 30-second STS <15 repetitions is predictive of falls risk and fracture risk and therefore the consequences of the low STS repetition values observed in patients with metastatic bone disease may be considerable [27].

Physical Function

Physical function involves the performance and coordination of various physiological systems, all of which may be impaired as a result of cancer treatment [28,29]. Physical function may be measured with the use of both subjective and objective physical performance measures, which show comparable levels of validity, sensitivity, and responsiveness [30,31]. Functional deficits in patients with metastatic bone disease have been reported by studies using a range of measurement methods.

Subjective measures of physical function are commonly used for patients with metastatic bone