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EXERCISE AND BONE METASTASES

Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, Chee R, Peddle-Mcintyre CJ, Hart NH, Baumann FT, Denham J, Baker M, Newton, RU. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sports Exerc. 2018; 50(3):393–99.

According to the World Health Organization, cancer is the fifth leading cause of death globally. Of an estimated 1.2 million cases of cancer diagnosed annually, within the United States (~138,000 new cases per year in Australia), 50% will likely result in metastatic bone disease (MBD). Metastatic bone disease manifests from many different types of cancer with lesion formations occurring in the spine, pelvis, femur, and/or humerus, leading to signs and symptoms including: (1) bone pain, (2) weakness of the limbs, (3) incontinence, and/or (4) hypercalcemia**.** Many people diagnosed with MBD will have decreased physical function, reduced quality of life, and increased risk of mortality. Of the types of cancer, prostate cancer (PC) is most strongly correlated with MBD. There is an 80% risk of bone metastasis occurring in advanced PC, with a documented 30% 5-year survival rate in men.

Current recommendations state that the presence of MBD in persons with prostate cancer (PC+MBD) is considered a relative contraindication to exercise (2). This is due to exercise potentially increasing the risk of bone fracture, spinal cord/nerve compression, or exacerbation of bone pain at the site of MBD lesions. Limiting or eliminating exercise also contradicts current oncology recommendations that encourage persons with cancer, including those who have MBD, to avoid becoming physically inactive. There is little research demonstrating the efficacy and safety of well-rounded exercise programs in people with PC+MBD or exercise's effects on the risk of skeletal complications.

MANUSCRIPT REVIEW

The aim of this study was to determine the efficacy and safety of a comprehensive, supervised exercise program (cardiorespiratory, resistance training, or static flexibility modes) on physical function in men diagnosed with PC+MBD. The authors of this study hypothesized that well-rounded exercise programming over a 12-week duration would result in favorable outcomes for people with PC+MBD and could provide new insight to exercise programming.

A total of 103 participants were screened in Australia between 2012 and 2015 for this 2-armed, prospective, randomized control study. Fifty-seven participants met the following inclusion criteria: (1) bone metastasis confirmed via scan, (2) no acute illness, and (3) no significant bone pain as reported by the oncologist. Exclusion criteria were: (1) presence of cardiovascular, neurologic, or musculoskeletal disease that would limit exercise and (2) participation in structured cardiorespiratory or resistance-based exercise two or more times per week in the past 3 months.

Participants were randomly assigned to either an exercise group or control group followed by 12 weeks of an exercise program or standard care without increasing physical activity, respectively. Both groups underwent pre-post testing that included completion of the Physical Function Subscale of the Medical Outcomes Study Short-Form 36 Questionnaire (SF-36), physical function testing (timed-up-and-go, usual and fast 6 m walk, and 400 m walk tests), strength testing (1-repetition maximum leg extension and bench press), balance assessment (sensory organization test), body composition assessment (Dual X-ray Absorptiometry Scan), and fatigue assessment (Functional Assessment of Chronic Illness Therapy—Fatigue Questionnaire). Exercise program safety measures included recording skeletal complications in accordance with the Common Terminology Criteria of the National Cancer Institute and bone pain in accordance with The Functional Assessment of Cancer Therapy—Bone Pain (1). Those participants who had known MBD of the humerus and femur were excluded from the 1-repetition maximum leg extension and bench press test, respectively, to prevent overloading of those lesion sites. The 12-week, supervised, exercise program consisted of three 60-min sessions per week^{-1} of cardiorespiratory exercise (20–30 min of treadmill walking and stationary cycling/rowing at 60–85% max heart rate), resistance training (three sets of 10–12 repetitions [2:2 second concentric : eccentric phase] for all major muscle groups, with a 5–10% progression of weight once twelve repetitions were achieved), and static flexibility training (2–4 sets of 30–60 s holds for major joints).

Metastatic bone disease lesions were located in the pelvis (75.4% of participants), femur (40.4%), torso/spine (66.7%), lumbar spine (43.9%), and humerus (24.6%). Eight participants withdrew (n = 5 exercise group and n = 3 control group) due to increased bone pain, at-home falls, lack of time, and health deterioration. There were no differences in

participant characteristics. There was a significant difference in SF-36 scores for the exercise group only, following 12 weeks of exercise suggesting improvement in self-reported physical function with this group. The exercise group also improved on the 1-repetition maximum leg extension as compared to the control group. There were no differences between groups at postmeasures regarding physical function, balance, lean body mass, fat mass, or fatigue. At the conclusion of the exercise program, there were no occurrences of skeletal complications, and there was a reported 89% adherence rate. For the completers, there was no difference between premeasures and postmeasures for bone pain.

CLINICAL IMPLICATIONS

This innovative study provides important findings regarding the use of exercise to manage PC+MBD that could help to prevent skeletal injury, increase physical function, and improve quality of life. Furthermore, this study indicates that moderately conservative exercise programming, supervised by a clinical exercise physiologist, is safe for people with PC+MBD. These findings provide a potential additional option for treatment and management of a disease in a population that has historically been limited from exercise due to relative contraindications.

Study limitations include the observation that self-reported/subjective perception of physical function improved, while there were no changes of objective physical function or balance testing. This could be due to a portion of the participants being excluded from some tests to avoid skeletal overload of lesion sites, thus reducing statistical power. The findings of this study apply to a highly supervised and conservative exercise program for people with PC+MBD. It may be possible that more aggressive exercise intensities, when deemed appropriate, could lead to greater improvements. Other types of cancer that include MBD might respond differently to exercise programming due to the differences in cellular pathology of tissue and organs associated with the specific type of cancer. Future research is required to build on the findings of this study and should be expanded to other types of cancer.

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RESISTANCE TRAINING IN PARKINSON'S DISEASE

Kanegusuku K, Silva-Batista C, Pecanha T, Nieuwboer A, Silva ND, Costa, LA, de Mello MT, Piemonte ME, Ugrinowitsch C. Effects of Progressive Resistance Training on Cardiovascular Autonomic Regulation in Patients with Parkinson's Disease: A Randomized Controlled Trial. Arch Phys Med Rehabil. 2017;98:2134–41.

Parkinson's disease (PD) is a progressive neurodegenerative disease that results from destruction of dopamine-producing nerve cells in the midbrain, specifically the substantia nigra pars compacta. Second only to Alzheimer's disease, PD is one of the most common neurologic diseases with onset typically occurring in older adults (aged >55 y). Motor dysfunction is a primary manifestation of PD and presents clinically as bradykinesia (slowness of movement), postural instability, muscular rigidity, and tremor at rest. Due to disease-related neurodegeneration in other areas of the brain, autonomic dysfunction is also common in many cases of PD and can result in increased risk of cardiovascular events, complications, and mortality, as well as reduced quality of life. Disruptions associated with autonomic dysfunction present clinically as reduced heart rate variability, diminished cardiovascular responses to autonomic stress, and orthostatic hypotension, which are all well documented in PD and should be considered when performing exercise testing or prescription.

Progressive resistance training (PRT) is one mode of exercise that can be used to manage motor impairments associated with PD by improving muscular strength and endurance, physical function, balance, and gait. Currently, it is unknown if PRT can also improve nonmotor symptoms of

PD such as autonomic dysfunction. Progressive resistance training has been shown to improve autonomic modulation in other disease populations that experience autonomic dysfunction, such as chronic heart failure and fibromyalgia (1,2).

MANUSCRIPT REVIEW

The aim of this study was to determine the effects of 12 weeks of PRT on autonomic modulation and cardiovascular responses associated with autonomic stress in people with moderate PD. As part of a prospective, nonblinded, randomized, controlled study, a total of 30 men and women diagnosed with PD were recruited from the Brazil Parkinson Association and met inclusion criteria. These participants were randomized into 2 groups (n = 15 in the PD exercise training group and n = 15 in the PD control group). For comparison of autonomic function, an additional 16 age-and-sex matched healthy controls, with no known neurologic disease, were recruited and met inclusion criteria. Inclusion criteria were (1) over the age of 50 y, (2) diagnosed with PD, and (3) moderate disease, defined as Stage 2–3 on the Hoehn and Yahr Disease Severity Scale (excluding the healthy control group). Exclusion criteria were (1) presence of other neurologic, musculoskeletal, or cardiovascular diseases, (2) use of hypertension medication or resting blood pressure ≥140/90 mmHg, (3) cardiovascular medications that could disrupt autonomic function, (4) change in PD medications during the study, and/or (5) currently engaging in consistent physical activity.

All participants underwent pre-post testing separated by a 12-week duration of either PRT or standard care. Autonomic nervous function testing included electrocardiogram measures of the R-R interval, respiratory movements via respiratory belt assessment, and spectral analysis of the low-frequency (LF_{R-R}) and high-frequency (HF_{R-R}) components of the R-R interval (i.e., heart rate variability). LF_{R-R} and HF_{R-R} were used as the chief markers of sympathetic and parasympathetic modulation, respectively. The LF : HF ratio was also calculated to assess sympathovagal balance. Cardiovascular responses to autonomic stress testing included spectral analysis and blood pressure measures at three provocations including: (1) deep breathing (6 br·min^{-1}), (2) Valsalva maneuver, and (3) change in position (sit-to-stand). One-repetition maximum strength testing was completed for both groups on a standard seated leg press. The PD training group underwent a PRT program that progressed from 2 to 4 sets and 6–12 repetitions with 2-week volume adjustments focusing on muscular strength development. The training protocols included five resistance-training exercises of the upper and lower body. The healthy control group only performed autonomic and cardiovascular stress testing at the pretraining session.

Participant characteristics between groups (i.e., sex, age, disease duration, and body composition) were not significantly different. Autonomic modulation outcomes revealed no significant differences with pre-post measure of HF_{R-R} or LF : HF with both the PD training and control groups. For the PD training group only, LF_{R-R} decreased significantly following 12 weeks of PRT, suggesting an improved sympathetic modulation. When compared to the healthy control group at postmeasures, there were no significant differences for HF_{R-R}, LF_{R-R}, and LF : HF ratio detected for the PD training group. The PD control group had significantly higher LF_{R-R} and LF : HF ratio and lower HF_{R-R} when compared to the healthy control group. Regarding cardiovascular responses to autonomic stress testing, there were no significant differences from pre-post measures with any of the spectral analysis measures and R-R interval responses for both the PD training and control groups. Only the PD training group showed significant improvements in systolic blood pressure fall following the sit-to-stand test. When compared to the healthy control group, the PD training group had similar values for spectral analysis and blood pressure, and the PD control group had significantly greater systolic blood pressure reduction as compared to both the PD training and healthy control groups. As expected, the PD training group had significant increases with the 1-repetition maximum strength testing when comparing pretest to posttest measures.

CLINICAL IMPLICATIONS

The authors of this study concluded that 12 weeks of PRT may result in improved cardiac sympathetic modulation and orthostatic stress in persons with moderate PD. There are several limitations associated with this study, resulting in caution with interpreting the outcomes. Results of this study can only be applied to people with PD who are classified with moderate disease (Hoehn and Yahr Stage 2–3) effects and who do not have hypertension. This excludes mild and advanced cases of PD as well as people who also have hypertension or are prescribed with hypertension medication(s). There are many different combinations of PD prescribed medications that can result in a variety of adverse side effects causing different outcomes with autonomic impairment not experienced by the participants in this study. Although the spectral analysis techniques, variables of measurement, and interpretation used in this study are recommended by the Task Force for Heart Rate Variability Analysis, controversy on these methodologies currently exists within the literature. Finally, the outcomes of this study only focused on a specific PRT program, which is not standardized for all PD-related exercise programs.

Considering the novelty of this study, the findings are promising regarding the benefits of resistance training as a method of managing the effects of PD. In addition to improving muscular strength in people with PD, PRT may also serve as a nonpharmacologic method to improve autonomic impairment that is a common nonmotor effect. Improved autonomic dysfunction can lead to reduced cardiovascular risk, a reduced occurrence of orthostatic hypertension, and improved quality of life in persons with PD. Future research is needed to gain a better understanding of the effects of PRT on autonomic dysfunction in persons with PD.

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