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RESEARCH ARTICLE

AEROBIC EXERCISES VERSUS RESISTANCE EXERCISES ON OSTEOPOROSIS IN PROSTATE CANCER PATIENTS UNDERGOING ANDROGEN DEPRIVATION THERAPY

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ABSTRACT

Background: Most men diagnosed with prostate cancer (PCa) their age are 50 or older treated by androgen deprivation therapy (ADT) treatment has been associated with interconnected adverse effects as decreased bone mineral density (BMD) and a loss in the structure and strength of bone leading to osteoporosis. Exercise has been proposed as a treatment to relieve adverse effects of ADT. **Objective:** This study was conducted to evaluate the effect aerobic exercises versus resisted exercises on osteoporosis in prostate cancer patients undergoing androgen deprivation therapy. **Methods:** Thirty prostate cancer patients suffering from osteoporosis after receiving androgen deprivation therapy,were selected from Oncology department at El Galaa Hospital for Armed Forces. Their age ranged from 50 to 65 years and were subdivided randomly into two equal groups. **Group A (Aerobic exercises group):** This group included 15 PCa patients who received aerobic exercises in the form of cycling on electronic bio in addition to conventional medical care (Calcium and vit D supplements), 3 days per week for 12 consecutive weeks. **Group B (Resisted training group):** This group included 15 PCa patients who received resistance exercises for both lower limbs (hip flexors, abductors and knee flexors, extensors) by free sand bags of different weights in addition to conventional medical care (Calcium and vit D supplements), 3 days per week for 12 consecutive weeks. Dual-energy x-ray absorptiometry (DEXA) was used for estimation of BMD before the treatment and after 12 weeks of treatment for both groups. **Results:** The study showed that there was a statistically significant increase in BMD and T-score mean of spine, femoral neck and total femur post treatment in the resistance exercise group compared to aerobic exercise group, The percent of increase in BMD of spine, left femoral neck and total femur in the group A was 26.02, 18.9 and 19.47% respectively, while that in the group B was 39.55, 41.33 and 39.94% respectively. **Conclusion:** It can be concluded that both aerobic and resistance exercises had fruitful effects in cases of osteoporosis in prostate cancer patients receiving ADT as evidenced by the significant increase in BMD and T-score mean, however higher statistical improvement was reported in the resistance exercise.

INTRODUCTION

The prostate is a gland in the male reproductive system that surrounds the urethra just below the bladderhttps://en.wikipedia.org/wiki/Prostate_cancer#cite_note-6 (1). Prostate cancer (PCa) is cancer of the prostate, most prostate cancers are slow growing, cancerous cells may spread to other areas of the body, particularly the bones and lymph nodes(2) . Most men diagnosed with PCa are age 50 or older,and, as men get older, their risk for osteoporosis also increases (3). Treatment for PCa includes surgery, radiotherapy, androgen deprivationtherapy (ADT) and chemotherapy, which is influenced by the stage and aggressiveness of the cancer [(4)].

The prevalence of osteoporosis in men with PCa on ADT is well documented, with up to 53 % affected by this bone condition [(5)].Although ADT has been shown to improve survival outcomes, treatment-induced hypogonadism has been associated with multiple interconnected adverse effects such as decreased bone mineral density (BMD) and a loss in the structure and strength of bone, a loss in lean tissue mass and muscle cross-sectional area, increase in fat mass and intermuscular adipose tissue and an increased risk of falls and subsequent fractures in this clinical population group [(6)]. Exercise with sufficient bone-loading force such as repetitive weight-bearing, aerobic (walking, aerobics) and resistance training are effective in improving BMD in the general adult population, with a pooled positive effect of 1.8% at the spine.

The effectiveness of weight-bearing exercise on BMD is also seen in adults at risk of osteoporosis [7]. Exercise plays an essential role in the treatment of osteoporosis for improving BMD and reducing bone loss. Wolff's law states that, human and animal bone adapts to new or unusual mechanical stress by altering the bone architecture. Bone tissue will adjust by increasing osteoblast formation in the areas affected by mechanical stress. Conversely, with a lack of mechanical stress, the bone will progressively weaken because of resorption exceeding bone growth. For bone formation to occur, a Minimal Essential Strain (MES) is required. MES is the minimal threshold required for human bone formation. It is estimated that the MES for the human bone is approximately 1/10 of what is required for a fracture. Exercise can provide the necessary essential strain to maintain and promote bone growth [8]. Aerobic exercise plays physical stress on the body and encourage calcium absorption in bone (9). Like muscles bones respond to increase of blood flow and it is thought that the increased circulation prompted by aerobic exercise transports of vital nutrients and minerals such as calcium to bones and like muscle bones weaken if not used (10). Although resistive exercise has been reported to improve muscle strength, power, and endurance, many studies revealed that it also places heavy loads on the skeleton during a training session that increases BMD (11).Resistance training has been highlighted as the most promising intervention to maintain or increase bone mass and density .This is because a variety of muscular loads are applied on the bone during resisted exercise , which generate stimuli and promote an osteogenic response of the bone (12). Little is known about the volume of exercise that is safe for prostate cancer survivors with osteoporosis resulted from ADT and that is effective at maintaining or improving bone health. With the recent increase in the number of PCa survivors and the multiple ways cancer and its treatment may affect the skeleton, there is a need to develop survivorship care plans which include exercise as a means to sustain bone health and reduce comorbidities. Therefore, this study was developed to compare between the therapeutic effect of aerobicexercises and resistance exercises on osteoporosis in prostate cancer patients receiving ADT and to detect which of them is more effective to relief pain and improve their quality of life in a trial to provide the most effective exercise rehabilitation program for osteoporosismanagement,and to avoid oral medications that cannot be tolerated for a long period due to their systemic adverse effects.

MATERIALS AND METHODS

Subjects : Thirty prostate cancer patients suffering from osteoporosis after receiving androgen deprivation therapy were selected from Oncology department at El Galaa Hospital for Armed Forces. Patients were enrolled in the trial if they met the following criteria: Their age ranged from 50 to 65 years, Prostate cancer patients with osteoporosis as a result of androgen deprivation therapy (6 months from receiving ADT), patients who are clinically and medically stable. The exclusion criteria were: Patients with musculoskeletal, cardiovascular/ pulmonary, or neurological disorders that can inhibit them from exercising, Patients with orchiectomy, Patients with physical/mental incapacity to perform study requirements, Patients with chronic kidney disease, Patients with Hypothyroidism, Patients with bone metastatic disease.

Design: This trial was a single-blinded randomized experimental study and was assented by the Ethical Committee of the Faculty of Physical Therapy, Cairo University. The current study was conducted during a period of 3 months starting from 1st April 2021 till 31th June2021.All aspects of the study were disclosed and informed consent was obtained. The patients were randomly assigned into two equal groups via the envelope mode. After patients' agreement to participate in the study, cards with either "aerobic exercise" or "resistance exercise" recorded on them were closed in envelopes; then a blinded physical therapist was asked to select one envelope. According to the selected card, patients were assigned to their corresponding group. Dates for starting the allocated therapy were regulated and the therapy was begun after the first week of randomization. The examiner physical therapist was not included in randomization procedures and was unaware of the therapy allocation. Patients were asked not to disclose their therapy allocation to the physical therapist during assessment. The participants were informed to report any harmful effects throughout the treatment period.

Procedures of the study

Measurement method: Dual-energy x-ray absorptiometry (DEXA)is typically used to diagnose and follow osteoporosis thatperformed on the hip, lumbar spine, and whole-body BMD as these are the most common locations of fractures in people with osteoporosis(13), the patients does not need to prepare before they have a DEXA scan. Patients was informed that they can eat and drink normally on the day of the procedure but to stop calcium supplements around 24 hours before the scan. The scan is painless and relatively quick, taking up to 30 minutes (14). Bone densities are often given to patients as a T score or a Z score. A T score tells the patient what their bone mineral density is in comparison to a young adult of the same gender with peak bone mineral density. A normal T score is -1.0 and above, low bone density is between -1.0 and -2.5, and osteoporosis is -2.5 and lower. A Z score is just a comparison of what a patient's bone mineral density is in comparison to the average bone mineral density of a male or female of their age and weight (13).

Therapeutic procedures: All participants received standard daily supplementation of calcium (1000 mg/day) and vitamin D3 (800 IU/day).

Aerobic exercises for group (A): Biostep cross rowing ergometer (Biodex 950-240 model, made in Holland) was used for aerobic exercises, 3 times/week for 12 weeks. Before the start of training of aerobic exercises, one familiarization session was designed to habituate participants with rowing in the biostep and to ensure that all participants used the correct techniques prior to taking part in the main training sessions. Each training session was 60 minutes commenced with a 10-min warm-up comprising low-level aerobic activities such as treadmill walking, as well as stretching and concluded with a 5-min cool-down period of stretching activities. After familiarization session, the patient started the exercise atinitial intensity of 50- 55% of the maximal heart rate (MHR=220-age) in the first 2weeks, then increased gradually until reaching 55-60 % of MHR in the second 2 weeks, 60-65% in the third 2 weeks and 65-75% in the forth 2 weeks, then increase till reach 80% of MHR by the end of the study (15, 16).

Resistance exercises Group (B):Free sandbags of different weights (Stark model, made in China) were used for lower limbs resistance exercise. Before the start of training of resistance exercises, one familiarization session designed to habituate participants with exercises and to ensure that all participants used the correct techniques prior to taking part in the main training sessions. The exercise requires high loads (70-90% of a maximum repetition) for 8-10 repetitions of 2-3 sets performed, 3 times a week for 45-70 minutes per session. The program in this study included resistance exercises for knee extensors, hip flexors, and abductors of both lower limbs (17)

Statistical analysis: Unpaired t-testwere conducted for comparison of age between groups. Normal distribution of data was checked using the Shapiro-Wilk test for all variables. Levene's test for homogeneity of variances was conducted to test the homogeneity between groups. Unpaired t-test was conducted to compare the mean values of BMD of spine, left femoral neck and total femur between the group A and B. Paired t-test was conducted for comparison between pre and post treatment in each group. The level of significance for all statistical tests was set at $p < 0.05$. All statistical analysis was conducted through the statistical package for social studies (SPSS) version 25 for windows (IBM SPSS, Chicago, IL, USA)(18).

RESULTS

***Subject characteristics*:** Thirty patients with prostate cancer and osteoporosis participated in this study.

Table 1. Mean BMD of spine, left femoral neck and total femur pre and post treatment of the group A and B

	Group A	Group B			
BMD (g/cm²)	mean± SD	mean± SD	MD	t- value	p value
Spine					
Pre treatment	-3.42 ± 0.44	-3.54 ± 0.42	0.12	0.75	0.45
Post treatment	-2.53 ± 0.53	-2.14 ± 0.3	-0.39	-2.48	0.01
MD	-0.89	-1.4			
% of change	26.02	39.55			
t- value	-5.23	-15.15			
	p = 0.001	*p = 0.001*			
Left femoral neck					
Pre treatment	-2.91 ± 0.25	-3 ± 0.42	0.09	0.67	0.5
Post treatment	-2.36 ± 0.45	-1.76 ± 0.34	-0.6	-4.08	0.0001
MD	-0.55	-1.24			
% of change	18.9	41.33			
t- value	-7.72	-13.48			
	p = 0.001	*p = 0.001*			
Total femur					
Pre treatment	-3.39 ± 0.32	-3.38 ± 0.5	-0.01	-0.04	0.96
Post treatment	-2.73 ± 0.31	-2.03 ± 0.36	-0.7	-5.63	0.0001
MD	-0.66	-1.35			
% of change	19.47	39.94			
t- value	-8.87	-12.34			
	p = 0.001	*p = 0.001*			

SD, standard deviation; MD, mean difference; p-value, probability value.

The mean ± standard deviation (SD) age of the group A was 56.4 ± 5.23 years, with maximum value of 65 years and minimum value of 50 years. The mean ± SD age of the group B was 56.93 ± 5.09 years, with maximum value of 65 years and minimum value of 50 years. There was no significance difference between both groups in the mean age values ($p = 0.77$).

Effect of treatment on BMD of spine, left femoral neck and total femur

Within group comparison: There was a significant increase in BMD of spine, left femoral neck and total femur post treatment compared with that pretreatment in the group A and B ($p < 0.001$). The percent of increase in BMD of spine, left femoral neck and total femur in the group A was 26.02, 18.9 and 19.47% respectively, while that in the group B was 39.55, 41.33 and 39.94% respectively (Table 1).

Between groups' comparison: There was no significant difference in BMD of spine, left femoral neck and total femur between both groups pre-treatment ($p > 0.05$). Comparison between groups post treatment revealed a significant increase in BMD of spine, left femoral neck and total femur of the group B compared with that of the group A ($p < 0.01$).

DISCUSSION

ADT is a basic treatment for PCa patients which can prolong survival rate and reduce disease-related morbidity (19) but, treatment has been associated with multiple interconnected adverse effects such as decreased BMD ,a loss in the structure and strength of bone and an increased risk of falls and subsequent fractures in this clinical population[6]. Poor physical function (such as impairment in rising, walking, and balance tasks) is consistently associated with low BMD, bone loss, and hip fractures. Men with PCa receiving ADT should therefore be strongly encouraged to maintain bone health, muscle strength, and physical function through an active lifestyle (20). The results of the present study showed that there was a statistically significant increase in BMD and T-score mean of spine, femoral neck and total femur post treatment in group B treated by resistance exercise compared with that in the group A treated by aerobic exercise. The percent of increase in BMD of spine, left femoral neck and total femur in the group A was 26.02, 18.9 and 19.47% respectively, while that in the group B was 39.55, 41.33 and 39.94% respectively. The possible explanations for the significant improvement in both groups may be due to the general effects of exercise therapy on BMD as the exercise induces an anabolic or homeostatic effect on bone via mechano-transduction. Briefly, fluid movement within the extracellular matrix of bone exerts force on osteocytes and bone lining cells. This subsequently triggers the release of nitric oxide and prostaglandin, which lead to division and differentiation of osteoprogenitor cells. Pre-osteoblasts consequently mature to osteoblast cells and affix to the surface of the matrix to begin the production of new bone. Muscular contractions may also induce this extracellular fluid shear stress within the bone matrix, producing deformations in bone. Similarly, gravitational impacts produce deformations via fluid shear stresses and subsequent mechano-transduction (21).

Nelson *et al*, (22)and Angin and Erden (23), suggested that exercise programs including aerobic exercise, resistance exercises slowing loss of BMD and has positive influence in increasing BMD and quality of life. Regarding to aerobic exercises, Giangregorio and El-Kotob ,(24)stated that aerobic exercise has not only the potential to increase bone density but over more it can improve the physiological variable such as enhancing muscle strength, aerobic power flexibility and balance that in result a decrease in number of falls and so fractures rate. Another study by Blumenthal *et al.* (25)evaluated the effects of exercise training on bone density in older men and women showed that subjects achieved a 10%-15% increase in VO2max after 4 months of exercise training, and 1%-6% further improvement with additional training.

Aerobic fitness was associated with significant increases in BMD in men, but not women, who maintained aerobic exercise for 14 months. In the other hand ,regarding resistance exercise Newton *et al*. (26) evaluated different exercise modes on 154 prostate cancer patients with ADT and recorded a significant difference between groups for lumbar spine BMD (mean change 0.014 g/cm2 , 95% CI 0.001–0.027, p = 0.039) and a positive trend for femoral neck BMD (mean change 0.010 g/cm^2 , 95% CI 0.000– 0.020, p = 0.050), in favor to the resistance and impact-loading exercise group compared to control group and concluded that combination of impact loading and resistance exercises attenuates bone loss at the spine and improves overall musculoskeletal functions in PCa patients receiving ADT. Also, Almstedt *et al*. (27)evaluated the changes in BMD in response to 24 weeks of resistance training in college-age men and women showed that male exercisers were found to increase BMD by 2.7-7.7%, whereas percent change in women ranged from −0.8 to 1.5%, depending on the bone site. Both male and female controls demonstrated about 1% change at any bone site. Results indicate that 24 weeks of resistance training, including squat and deadlift exercises, is effective in increasing BMD in young healthy men. Moreover, a study by Mosti *et al*., (28) showed that after 12 weeks of strength training in patients diagnosed with osteopenia and osteoporosis, 1RM and the rate of force development training group improved and the bone density in the lumbar spine and femoral neck increased for 2.9 and 4.9%, respectively.

A study by Marques *et al*., (29) compared the effects of a resistance training protocol and a moderate-impact aerobic training protocol on bone mineral density and showed that resistance trainingonly group exhibited increases in BMD at the trochanter (2.9%) and total hip (1.5%), and improved body composition. From all the previous studies, it was concluded that strengthening exercise have superior impact on BMD more than aerobic exercise which may be explained by the fact that aerobic exercise intervention is not specifically designed to maximize loading forces to mechanically stress bone and induce changes in BMD (30), and not all exercise modalities are equally osteogenic.

For exercise training to elicit an osteogenic effect, the mechanical load applied to bones should exceed that encountered during daily activities. Weight-bearing impact exercise such as hopping and jumping, and/or progressive resistance exercise, alone or in combination can improve the bone health in adults. Among them, resistance exercise has been highlighted as the most promising intervention to maintain or increase bone mass and density. This is because a variety of muscular loads are applied on the bone during resistance exercise, which generate stimuli and promote an osteogenic response of the bone (31). This study was limited by a small sample size and the absence of patients' quality of life assessment which could provide better statistical analyses. Further researchis recommended with larger sample sizes to evaluate and assure the efficacy of resistance exercises and to examine different intensities, duration, and frequencies to reach the optimal rehabilitation program in osteoporosis management. More studies with different exercise modes are recommended including bone strength assessments like bone microarchitecture, geometry, and turnover. Followup studies are also required to reveal resistance exercises effects in the long run.

Conclusion

It can be concluded that resistance exercises have fruitful effects in cases of osteoporosis in prostate cancer patients receiving androgen deprivation therapy as evidenced by the significant increase in BMD and T-score mean, and hence decrease risk of fractures and enhance physical performance.

Conflict of interest: There is no conflict of interest.

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Abbreviations

(ADT) Androgen deprivation therapy.
(BMD) Bone mineral density.
(DEXA) Dual-energy x-ray absorptiometry.
(MD) Mean difference.
(MES)Minimal Essential Strain.
(P-value)Probability value.
(PCa) Prostate cancer.
(SD)Standard deviation.
(MHR)The maximal heart rate.
(SPSS)The statistical package for social studies.

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