Exercise Mode Specificity for Preserving Spine and Hip Bone Mineral Density in Prostate Cancer Patients

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ABSTRACT

NEWTON, R. U., D. A. GALVÃO, N. SPRY, D. JOSEPH, S. K. CHAMBERS, R. A. GARDINER, B. A. WALL, K. A. BOLAM, and D. R. TAAFFE. Exercise Mode Specificity for Preserving Spine and Hip Bone Mineral Density in Prostate Cancer Patients. *Med. Sci. Sports Exerc.*, Vol. 51, No. 4, pp. 607–614, 2019. **Purpose**: Androgen deprivation therapy (ADT) in men with prostate cancer (PCa) is associated with an array of adverse effects, including reduced bone mineral density (BMD) predisposing patients to increased fracture risk. Our purpose was to examine the effects of targeted exercise modes on BMD in men with PCa undergoing ADT. **Methods**: Between 2009 and 2012, 154 PCa patients 43–90 yr old on ADT were randomized to exercise targeting the musculoskeletal system (impact loading + resistance training [ImpRes], $n = 57$) supervised for 12 months, cardiovascular and muscular systems (aerobic + resistance training, $n = 50$) supervised for 6 months followed by a 6-month home-based program, or delayed aerobic exercise (DelAer, $n = 47$) received exercise information for 6 months followed by 6 months of supervised aerobic exercise (stationary cycling). End points were lumbar spine, hip and whole-body BMD measured by dual-energy x-ray absorptiometry with secondary end points of lean and fat mass, appendicular skeletal muscle mass, and neuromuscular strength. ANOVA was used to compare the exercise groups with DelAer at 6 and 12 months. **Results**: There was a between-group difference in BMD for ImpRes and DelAer at the spine (6 months, $P = 0.039$; 12 months, $P = 0.035$) and femoral neck (6 months, $P = 0.050$), with decline attenuated in ImpRes (~−1.0% vs ~−2.0%). Compared with DelAer, ImpRes increased appendicular skeletal muscle at 6 months (0.3 kg, $P = 0.045$) and improved muscle strength at 6 and 12 months ($P \leq 0.012$) by 9%–34%. A limitation was inclusion of well-functioning patients. **Conclusion**: Combined impact loading and resistance exercise attenuates bone loss at the spine and enhances overall musculoskeletal function in PCa patients undergoing ADT. **Key Words:** BONE, ANDROGEN DEPRIVATION THERAPY, RESISTANCE, IMPACT, EXERCISE

Androgen deprivation therapy (ADT) in men with localized and metastatic prostate cancer (PCa) is accompanied by an array of adverse effects compromising multiple body systems and quality of life (1). The musculoskeletal-related effects are severe with a reduction in bone mass (2) leading to osteoporosis and increased risk for fracture (3,4) and reduced muscle mass (2) and strength (5,6) leading to poorer physical function (6) and increased risk of falls (7). Pharmacological agents, primarily in the form of bisphosphonates, are effective for increasing bone mineral density (BMD), although less clear is the effect on reducing fractures (8). Moreover, given the cost of pharmacological interventions, the potential for side effects (9), and the fact that they do not address other adverse effects of ADT that contribute to falls and fragility fracture, alternative strategies are needed to counter the deleterious influence of ADT on the musculoskeletal system.

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We (10,11) and others (12,13) have demonstrated beneficial effects of exercise as a countermeasure to several ADT adverse effects; however, until recently (14,15), little if any work had been undertaken to identify specific exercise modes and dosage most effective for arresting BMD loss. Moreover, undertaking standard exercise recommendations for cancer populations (16,17) is unlikely to be the most appropriate to preserve or increase BMD in PCa patients undergoing ADT (18), as the exercise prescription is not specific to skeletal loading and as such bone preservation or accrual. Here we report for the first time the efficacy of a yearlong randomized controlled trial (RCT) of different exercise modes, including targeted musculoskeletal loading on primary end points of regional and whole-body BMD in men with PCa on ADT.

METHODS

Patients. Two-hundred and sixty-five patients with PCa were screened for participation from 2009 to 2012 in Perth, Western Australia, and their progress through the study is shown in Figure 1. Inclusion criteria were histologically documented localized PCa, minimum ADT exposure >2 months, without prostate-specific antigen (PSA) evidence of disease activity, and anticipated to remain hypogonadal for 12 months (19). Exclusion criteria included bone metastases, musculoskeletal, cardiovascular, or neurological disorders that could inhibit them from exercising, medications known to affect bone metabolism such as bisphosphonates, inability to walk 400 m or undertake exercise, or any resistance training in the previous 3 months. All patients obtained medical clearance from their physician and completed a health history questionnaire. The study was approved by the University Human Research Ethics Committee, and all participants provided written informed consent.

Study design and random assignment. This was a three-armed RCT (19). The primary study end point was regional and whole-body BMD, and we have recently reported the intervention effects on fatigue (20). As previously reported (20), potential participants were identified by their treating urologist/oncologist and referred to the study coordinator. After baseline assessment, patients were randomly allocated to one of three study arms: impact loading + resistance training (ImpRes), aerobic + resistance training (AerRes), or usual care/delayed exercise (DelAer) by computer random assignment and stratified according to time on ADT (< or ≥6 months).

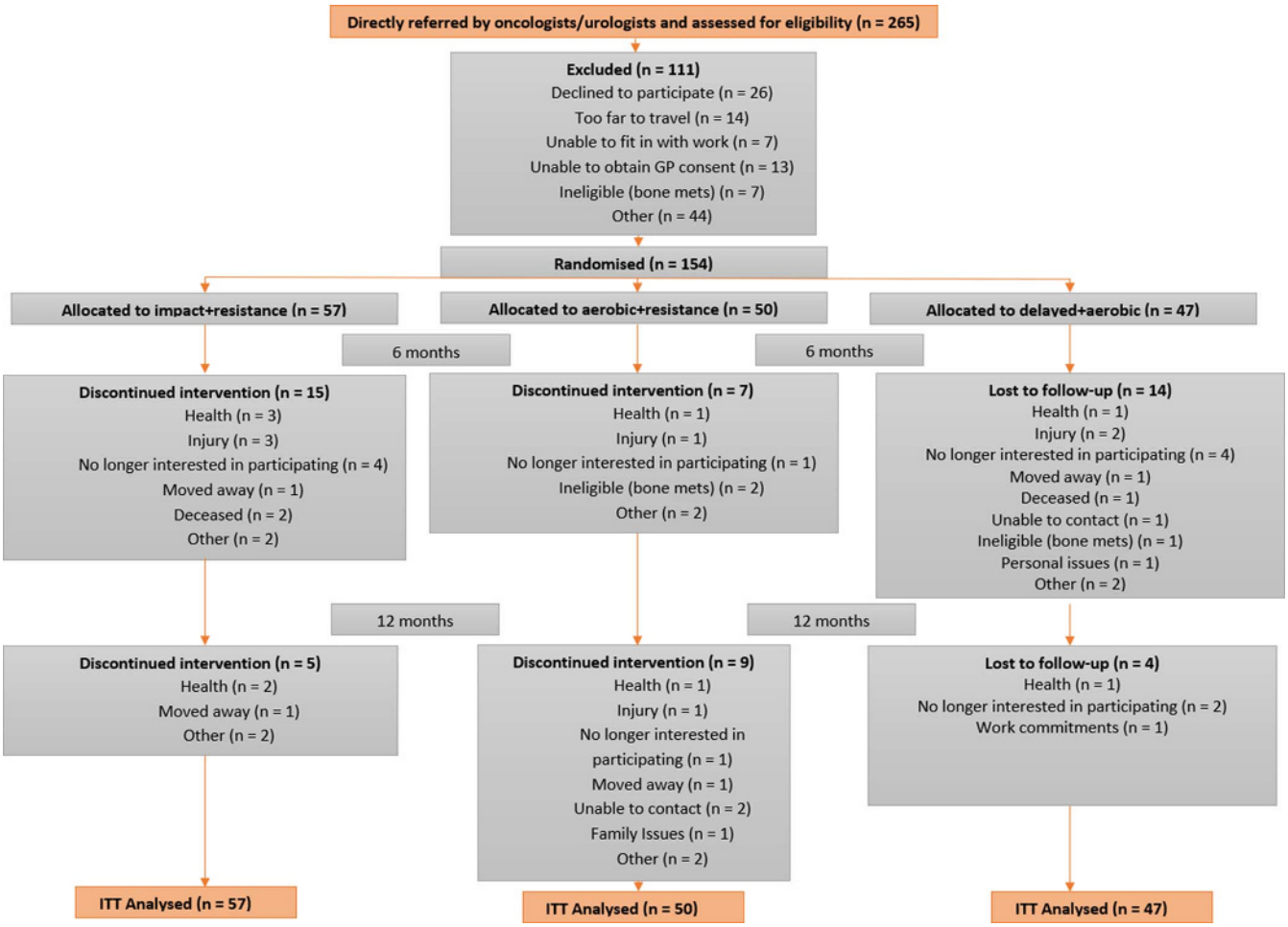

FIGURE 1—CONSORT diagram.

Exercise training program. Detailed information on the exercise training protocol has been published elsewhere (19,20), and the different interventions and setting (clinic or home) across the 6- and 12-month intervention phases is summarized in Figure 2. In brief, training for ImpRes was undertaken twice weekly in an exercise clinic for 12 months under supervision and consisted of small groups of up to 10 patients. The impact-loading component consisted of a series of bounding, skipping, drop jumping, hopping, and leaping activities that produced ground reaction forces of 3–5 times body weight, and was progressive in nature. For the first 12 wk, two rotations were performed of skipping (30 s), bounding over soft hurdles (10 times, 13–16 cm), and drop jumping (10 times, 10–15 cm). In the second 12 wk, hopping on one leg (10 times) was added, and three rotations of all activities were performed. In the third 12-wk period, leaping (10 times) replaced skipping, and for the remainder of the program, four rotations were performed of bounding (19–25 cm), drop jumping (20–25 cm), hopping, and leaping. Resistance training consisted of six principal exercises that targeted the major upper and lower body muscle groups: chest press, seated row, shoulder press, leg press, leg extension, and leg curl, and these exercises were supplemented by the latissimus pull down, biceps curl, triceps extension, and seated calf raise exercises. Patients performed 2–4 sets of each exercise at an intensity of 6- to 12-repetition maximum (RM), with a rest period between sets of 1–2 min. Resistance was increased by 5%–10% for the next set/training session when they exceeded the prescribed RM. In addition to training in the clinic, the ImpRes group undertook home exercise 2 $d \cdot wk^{-1}$ that consisted of two to four rotations of skipping (30 s), hopping, leaping, and drop jumping (all 10 times). Participants were instructed to perform their jumps near a railing or similar supportive structure that they could hold onto in the event they lost their balance.

AerRes underwent supervised exercise in the clinic twice weekly for the initial 6 months followed by home-based training for the second 6 months. The aerobic-based component consisted of 20–30 min of exercise using various modes, which included walking/jogging on a treadmill and cycling or rowing on stationary ergometers with intensity set at 60%–85% of maximal heart rate (HR_{max}) using individual heart rate monitors (Polar Electra Oy, Finland). Intensity of exercise was adjusted so that patients remained within the target HR range. To reduce the possibility of boredom, some intervals in the later stages of the program were included with intensity up to 85% HR_{max}. The resistance program during the initial 6 months was identical with that undertaken in the ImpRes regimen. In addition, patients were encouraged to undertake home-based aerobic activity with the goal to accumulate 150 $min \cdot wk^{-1}$. For the second 6 months, patients were provided with a home-based program that recommended 150 min of aerobic exercise per week and resistance exercise using body weight and resistance bands.

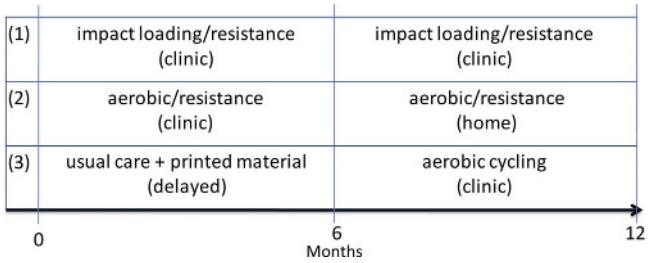

FIGURE 2—Participants were randomized to three groups: (1) ImpRes training in an exercise clinic for 12 months; (2) AerRes training in an exercise clinic for 6 months then 6 months at home; (3) DelAer only receiving printed material about exercise for the first 6 months and then an aerobic cycling program in an exercise clinic for the second 6 months.

DelAer were provided with a printed booklet with information about exercise for the initial 6 months, followed by 6 months of twice weekly supervised exercise on a cycle ergometer at an intensity of ~70% HR_{max} for up to 30–40 min and flexibility exercises in the clinic. During the 12-month study period, ImpRes, AerRes, and DelAer participants were asked to maintain their customary physical activity and dietary patterns.

Primary study end points. Study end points were assessed at baseline, 6 months, and 12 months. The primary study end point was BMD ($g \cdot cm^{-2}$) of the lumbar spine (L2–L4), hip (total hip, femoral neck, and trochanter), and whole body, assessed by dual-energy x-ray absorptiometry (DXA; Hologic Discovery A, Waltham, MA).

Other measures. Body composition (lean mass, fat mass, and appendicular skeletal muscle [ASM]) (21) was assessed by DXA and muscle strength by 1RM method (22). Height and body mass were assessed with body mass index (BMI) calculated as kilograms per square meter. Testosterone, PSA, bone formation markers alkaline phosphatase, and procollagen type 1 N-terminal propeptide, and C-reactive protein levels were measured by an accredited laboratory (Pathwest Diagnostics, Perth, Western Australia). Nutritional status was assessed by using Mini Nutritional Assessment (23) and physical activity by the Godin Leisure-Time Exercise Questionnaire (24).

Statistical analyses and sample size calculation. The sample size estimate (19) was based on projected changes in the primary study end points between the ImpRes and the DelAer groups, with a net difference expected to be ~3.5%, 4.0%, and 2.5% at the hip, lumbar spine, and whole body, respectively. To achieve 90% power at an alpha level of 0.05 (two-tailed), 40 participants per group were required to demonstrate this difference at the end of 12 months. Allowing for attrition of up to 25% resulted in the requirement for ~54 participants per group. Data were analyzed using IBM SPSS version 21 (IBM Corp., Armonk, NY). Normality of the distribution was assessed using the Kolmogorov–Smirnov test and visual inspection of the data. Analyses included standard descriptive statistics, and to examine differences among groups at baseline, the chi-square test for categorical variables and one-way ANOVA or the Kruskal–Wallis test for continuous data, as appropriate, were used. ANOVA values adjusted for the baseline value, BMI, and postsecondary education were used to compare each exercise regimen to DelAer for the primary and secondary end points. A group–time repeated-measures ANOVA was used to examine changes in nutrition status and physical

activity over the course of the study. An intention-to-treat approach was used for all analyzes using maximum likelihood imputation of missing values (expectation maximization). For the analysis of spine BMD, one participant each from ImpRes and DelAer had outlying values and were excluded. All tests were two-tailed, and an alpha level of 0.05 was required for statistical significance.

RESULTS

Patient characteristics. One hundred and fifty-four patients were recruited and randomized to ImpRes (n = 57), AerRes (n = 50), and DelAer (n = 47). There were no significant differences among groups at baseline for clinical characteristics apart from BMI and postsecondary education where BMI was higher in DelAer and postsecondary education was more prevalent in ImpRes (Table 1). In the first 6 months of the study, 36 patients withdrew with an additional 18 by 12 months (Fig. 1). Common reasons for dropout were no longer interested in participating (n = 12), poor health (n = 9), injury (n = 7), and moved away or was not contactable (n = 7). There was no significant change in nutritional status (interaction, P = 0.202) among groups over the 12-month study period; however, there was a significant interaction for physical activity levels among groups (P = 0.047) although no significant within-group differences were detected. However, the general direction of the observed changes was for an increase in physical activity from 6 to 12 months for AerRes, an increase at 6 months but then a return to baseline levels at 12 months for DelAer after home-based training, and a decrease in physical activity at 6 months in DelAer during the nonexercise period with a return to baseline values at 12 months with exercise. There were no differences between groups for PSA, testosterone, and C-reactive protein. Attendance at the supervised sessions was 65% and 69% for ImpRes at 6 and 12 months, respectively, 70% for AerRes at 6 months, and 64% for DelAer for the second 6-month study period.

BMD. There was a significant difference between the ImpRes and the DelAer groups for lumbar spine BMD at 6 months (P = 0.039) and 12 months (P = 0.035) and at the femoral neck at 6 months (P = 0.050), with the decline in BMD at these sites attenuated in the ImpRes group (Table 2). At the spine, the ImpRes loss in BMD was halved compared with DelAer at 6 months (−1.1% vs −2.1%) and 12 months (−0.6% vs −1.8%) (Fig. 3). Similarly, at the femoral neck, 6-month loss was halved in the ImpRes group compared with DelAer (−1.0% vs −2.0%) (Fig. 3); however, there was no difference by 12 months. There were no between-group differences for AerRes and DelAer at the spine, hip, or whole body at either 6 or 12 months. There were no differences between groups for the bone markers alkaline phosphatase or procollagen type 1 N-terminal propeptide.

Other measures and adverse events. ImpRes increased their ASM compared with DelAer over the initial 6 months (P = 0.045) with an adjusted difference of 0.3 kg (Table 3), although this difference was not statistically significant at 12 months (P = 0.094). There was no difference between ImpRes and DelAer in fat mass at 6 or 12 months and no differences between AerRes and DelAer for lean mass, fat mass, or ASM at 6 or 12 months. Further, there was a significant difference (P = 0.012) between ImpRes and DelAer for all muscle strength measures at 6 and 12 months (Table 4). The improvement in muscle strength for ImpRes was 9%–20% and 11%–34% at 6 and 12 months, respectively. Similarly, for AerRes and DelAer, there were significant between-group differences (P = 0.002) for all strength measures at 6 months with strength increasing in AerRes by 5%–20%, but not at 12 months. As

TABLE 1. Baseline characteristics of exercise and control groups.

	Total (n = 154)	ImpRes (n = 57)	AerRes (n = 50)	DelAer (n = 47)	P
Age, yr (SD)	69.0 (9.0)	68.7 (9.3)	69.1 (9.4)	69.1 (8.4)	0.958
Height, cm (SD)	172.7 (6.0)	173.5 (5.8)	172.7 (6.6)	171.6 (5.4)	0.250
Body mass, kg (SD)	85.7 (13.6)	84.6 (11.4)	83.8 (13.5)	89.2 (15.5)	0.106
BMI, $kg \cdot m^{-2}$ (SD)	28.7 (4.1)	28.1 (3.5)	28.0 (3.7)	30.3 (4.8)	**0.008**
Medications ≤3, n (%)	94 (61)	38 (67)	31 (62)	25 (53)	0.369
Comorbidities ≤1, n (%)	137 (89)	53 (93)	45 (90)	39 (83)	0.258
MNA, median (IQR)	27.8 (26.1–29.0)	27.5 (26.0–29.0)	28.0 (26.9–29.1)	28.0 (26.0–29.0)	0.683
SF-36 PF, median (IQR)	50.7 (43.9–54.9)	50.7 (42.4–54.8)	52.8 (45.3–55.1)	50.1 (42.3–54.4)	0.121
Godin index, median (IQR)	18.0 (9.0–33.0)	18.0 (7.0–30.5)	21.0 (12.0–35.0)	18.0 (9.0–35.0)	0.576
Postsecondary education, n (%)	70 (46)	34 (60)	18 (36)	18 (38)	**0.032**
Marital status, n (%)	122 (79)	44 (77)	38 (76)	40 (85)	0.716
Employed, n (%)	56 (36)	22 (39)	16 (32)	18 (38)	0.584
Employed full time, n (%)	38 (25)	14 (25)	11 (22)	13 (28)	0.794
Current smoker, n (%)	9 (6)	3 (5)	3 (6)	3 (6)	0.799
Gleason score, median (IQR)	7.9 (7.3–8.1)	7.9 (7.1–8.0)	8.0 (7.5–8.1)	8.0 (7.0–8.1)	0.895
ADT time, months median (IQR)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	2.0 (2.0–3.5)	0.352
ADT + anti-androgen, n (%)	84 (55)	27 (47)	29 (58)	28 (60)	0.386
Radiation therapy, n (%)	136 (88)	50 (88)	46 (92)	40 (85)	0.564
PSA, $\mu g \cdot L^{-1}$, median (IQR)	0.4 (0.1–1.5)	0.4 (0.0–1.5)	0.4 (0.1–1.2)	0.6 (0.1–1.6)	0.727
Testosterone, $nmol \cdot L^{-1}$, median (IQR)	0.8 (0.0–1.2)	0.0 (0.0–1.4)	0.8 (0.0–1.1)	0.9 (0.0–1.2)	0.944
CRP, $mg \cdot L^{-1}$, median (IQR)	1.4 (0.0–2.7)	1.5 (0.0–2.7)	1.1 (0.0–2.3)	1.8 (0.2–3.4)	0.402
ALP, $U \cdot L^{-1}$, median (IQR)	71.05 (61.0–83.5)	70.5 (62.3–85.5)	70.5 (60.8–84.5)	71.0 (58.0–79.0)	0.655
P1NP, $\mu g \cdot L^{-1}$, median (IQR)	43.0 (34.0–57.5)	39.0 (27.3–59.8)	46.0 (35.0–60.3)	41.0 (31.0–53.0)	0.166

Bold text indicates statistical significance at $P \leq 0.05$.

MNA, Mini-Nutritional Assessment; PF, physical function; AST, androgen suppression therapy; IQR, interquartile range; ALP, alkaline phosphatase; PINP, procollagen type 1 N-terminal propeptide; CRP, C-reactive protein.

TABLE 2. BMD absolute values and change over 6 and 12 months.

	Baseline	6 Months	12 Months	Between-Group Difference, Baseline–6 Months[a]		Between-Group Difference, Baseline–12 Months[a]	
	Mean (SD)	Mean (SD)	Mean (SD)	Adjusted Mean Difference (95% CI)	*P*	Adjusted Mean Difference (95% CI)	*P*
Lumbar BMD ($g \cdot cm^{-2}$)							
ImpRes	1.115 (0.151)	1.103 (0.150)	1.108 (0.149)	0.014 (0.001 to 0.027)	**0.039**	0.014 (0.001 to 0.027)	**0.035**
AerRes	1.125 (0.158)	1.103 (0.162)	1.101 (0.152)	0.004 (−0.009 to 0.017)	0.525	−0.004 (−0.019 to 0.011)	0.617
DelAer	1.140 (0.183)	1.116 (0.173)	1.119 (0.174)				
Total hip BMD ($g \cdot cm^{-2}$)							
ImpRes	1.008 (0.130)	0.992 (0.130)	0.986 (0.134)	0.007 (−0.002 to 0.016)	0.128	0.001 (−0.009 to 0.008)	0.870
AerRes	0.982 (0.111)	0.960 (0,114)	0.952 (0.112)	0.001 (−0.009 to 0.011)	0.807	−0.008 (−0.018 to 0.003)	0.147
DelAer	0.995 (0.169)	0.973 (0.170)	0.972 (0.162)				
Femoral neck BMD ($g \cdot cm^{-2}$)							
ImpRes	0.826 (0.114)	0.818 (0.116)	0.810 (0.122)	0.010 (0.000 to 0.020)	**0.050**	0.005 (−0.004 to 0.015)	0.261
AerRes	0.807 (0.109)	0.788 (0.105)	0.783 (0.106)	−0.003 (−0.014 to 0.008)	0.571	−0.003 (−0.013 to 0.008)	0.621
DelAer	0.814 (0.156)	0.798 (0.155)	0.797 (0.163)				
Trochanter BMD ($g \cdot cm^{-2}$)							
ImpRes	0.782 (0.109)	0.767 (0.112)	0.770 (0.112)	−0.003 (−0.010 to 0.004)	0.449	−0.003 (−0.010 to 0.004)	0.414
AerRes	0.763 (0.096)	0.748 (0.103)	0.746 (0.105)	−0.002 (−0.010 to 0.007)	0.699	−0.005 (−0.015 to 0.005)	0.335
DelAer	0.770 (0.141)	0.757 (0.142)	0.759 (0.138)				
Whole-body BMD ($g \cdot cm^{-2}$)							
ImpRes	1.144 (0.106)	1.130 (0.103)	1.127 (0.106)	0.005 (−0.002 to 0.011)	0.174	0.007 (−0.001 to 0.014)	0.094
AerRes	1.132 (0.099)	1.117 (0.097)	1.112 (0.097)	0.003 (−0.007 to 0.012)	0.614	0.001 (−0.011 to 0.014)	0.831
DelAer	1.141 (0.139)	1.124 (0.135)	1.119 (0.142)				

Bold text indicates statistical significance at $P \leq 0.05$.
[a]Between-group difference for ImpRes compared with DelAer and AerRes compared with DelAer. ANOVA adjusted for baseline, BMI, and postsecondary education.

previously reported (23), there were no adverse events that directly resulted from the exercise interventions.

DISCUSSION

This yearlong RCT comparing different exercise regimens in PCa patients undergoing ADT produced three important findings: 1) only combined impact loading plus resistance exercise attenuated decline in spine and hip BMD, whereas there was no effect of the aerobic plus resistance exercise program; 2) only impact loading plus resistance exercise resulted in an improvement in ASM; and 3) both impact loading plus resistance exercise and aerobic plus resistance exercise improved upper and lower body muscle strength but only while the training programs were supervised. These results indicate that to support the preservation of BMD in men undergoing hormone suppression, a generalized exercise program (e.g., current exercise recommendations for cancer patients) (25,26) is not sufficient and that a targeted regimen that includes impact loading needs to be undertaken for a beneficial effect to be derived. Further, supervised exercise in a clinic setting seems more efficacious than home-based exercise for this patient group.

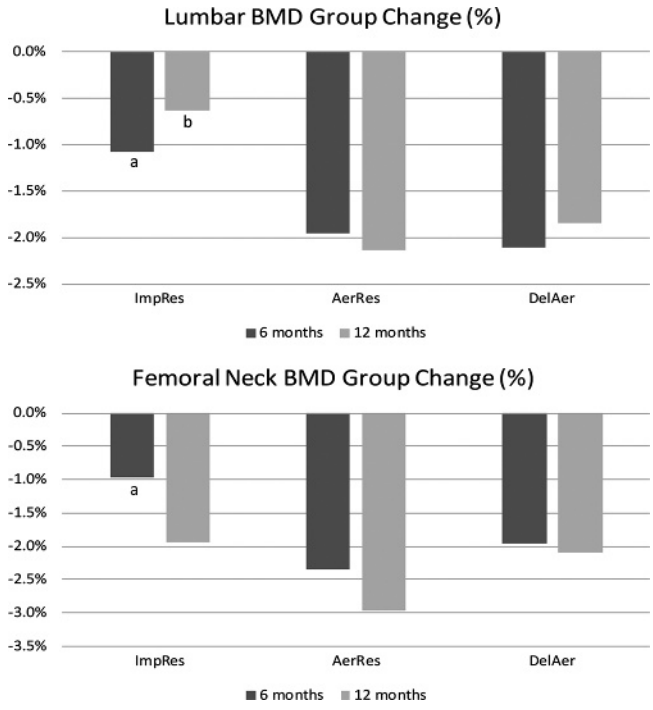

FIGURE 3—Percentage change in group BMD from baseline to 6 and 12 months. [a]Significant difference between ImpRes and DelAer at 6 months. [b]Significant difference between ImpRes and DelAer at 12 months.

We have previously reported exploratory results of the short-term effects of resistance exercise (11) on whole body and regional BMD resulting from 20 wk exercise training in men with PCa on ADT with no effects for BMD. However, BMD was a secondary or additional measure in this early trial, and it was unlikely that changes would have been detected by DXA given that the length of the bone remodeling cycle is approximately 4–6 months (27). In a similar fashion, two other short-term trials reported no effect of aerobic and/or resistance exercise on BMD in men undergoing androgen deprivation with one study only 8 wk in duration with 13 participants (28) and the other 16 wk in duration (29).

Other recent studies of sufficient duration but limited patient numbers have examined other exercise and sports-specific modalities to enhance BMD in patients on ADT. In one study (14), 51 PCa patients on ADT were randomized to either combined impact loading plus resistance exercise or to flexibility training for 1 yr with no difference reported between groups for change at the lumbar spine or hip, but some preservation of BMD at L4 compared with controls. Another study using sport-based intervention of recreational football (soccer) 2–3 times per week (15) reported that total hip and femoral

TABLE 3. Lean mass, ASM, and fat mass absolute values and change over 6 and 12 months.

	Baseline	6 Months	12 Months	Between-Group Difference, Baseline–6 Months[a]		Between-Group Difference Baseline-12 Months[a]	
	Mean (SD)	Mean (SD)	Mean (SD)	Adjusted Mean Difference (95% CI)	*P*	Adjusted Mean Difference (95% CI)	*P*
Lean mass (kg)							
ImpRes	57.9 (6.6)	58.6 (6.6)	59.3 (6.8)	0.3 (−0.4 to 1.0)	0.456	0.3 (−0.3 to 1.0)	0.304
AerRes	58.1 (8.4)	58.8 (7.8)	58.7 (8.3)	0.3 (−0.5 to 1.0)	0.508	−0.5 (−1.2 to 0.3)	0.221
DelAer	59.3 (8.6)	59.5 (7.4)	60.4 (8.6)				
ASM (kg)							
ImpRes	25.0 (3.1)	25.5 (3.3)	25.9 (3.3)	0.3 (0.01 to 0.7)	**0.045**	0.3 (−0.1 to 0.7)	0.094
AerRes	25.2 (4.0)	25.5 (4.1)	25.6 (4.1)	0.1 (−0.3 to 0.4)	0.631	−0.2 (−0.6 to 0.1)	0.214
DelAer	25.3 (3.8)	25.4 (3.9)	25.9 (4.0)				
Fat mass (kg)							
ImpRes	24.0 (6.6)	24.9 (6.2)	25.1 (6.6)	−0.5 (−1.2 to 0.2)	0.155	−0.1 (−0.8 to 0.7)	0.820
AerRes	22.8 (7.4)	23.5 (7.8)	23.7 (8.2)	−0.4 (−1.2 to 0.4)	0.330	−0.1 (−0.9 to 0.8)	0.867
DelAer	27.1 (8.3)	28.2 (8.1)	28.3 (8.5)				

Bold text indicates statistical significance at $P \leq 0.05$.
[a]Between-group difference for ImpRes compared with DelAer and AerRes compared with DelAer. ANOVA adjusted for baseline, BMI, and postsecondary education.

shaft BMD were improved, with gains at the hip of ~1% compared with a loss of ~1% in controls after 32 wk. It seems that the high-impact plus unusual or diverse loading at the hip characterized by the intervention may be particularly osteogenic in this group of patients. Our study extends these preliminary findings considerably by providing novel data using the largest exercise trial undertaken with patients on ADT to date and by examining the effects of different exercise modalities (prescriptions) on BMD end points after 12 months intervention. We found that a combined impact loading plus resistance exercise regimen attenuated decline in spine and hip BMD, whereas there was no effect of the aerobic plus resistance exercise. Interestingly, femoral neck BMD at 12 months was not higher in the impact training group so the benefit was not retained. This is in line with previous research (14) demonstrating that it is difficult to maintain or increase BMD at the hip even with targeted impact exercise. Greater responsiveness of trabecular compared with cortical bone to loading is well established (30,31), and thus further research is needed to determine effective exercise prescriptions to benefit hip BMD, a particularly problematic site for fracture in this population. It could be that compliance to the impact training was lower over the second 6 months despite close supervision and perhaps greater loading progression is required? However, the continued superiority of BMD at the lumbar site for the impact loading group suggests neither was the case. The loading exercises performed in the current study were all unidirectional and did not produce as large a benefit for hip BMD as the previous recreational soccer intervention (15) or earlier work involving change of direction activities (32). It may be that to drive continued benefit, greater diversity of loading magnitude and direction is required at the hip. Regardless, lumbar spine BMD was higher at 6 and 12 months, which is a unique finding and clinically important. Our results have important implications for exercise guidelines and recommendations in the setting of ADT as we provide evidence that current exercise guidelines for cancer patients (16,17) are insufficient to arrest the loss of BMD in PCa patients undertaking ADT and that targeted exercise that includes impact loading is required if BMD is the clinical end point of interest to be preserved.

The clinical importance of our findings can be considerable as the intervention led to no toxicities or adverse events and is likely to be lower cost than commonly used pharmacological therapies. For example, bisphosphonates increase BMD, but evidence is lacking in regard to reducing fractures especially in nonmetastatic PCa (8). Apart from cost and potential treatment toxicity, compliance to bisphosphonates has been reported (33) to range from 17.9% to 78.0% at 12 months, whereas here we report 65% and 68% retention at 12 months in the ImpRes

TABLE 4. Muscle strength absolute values and change over 6 and 12 months.

	Baseline	6 Months	12 Months	Between-Group Difference, Baseline–6 Months[a]		Between-Group Difference, Baseline–12 Months[a]	
	Mean (SD)	Mean (SD)	Mean (SD)	Adjusted Mean Difference (95% CI)	*P*	Adjusted Mean Difference (95% CI)	*P*
Chest press (kg)							
ImpRes	36.1 (11.0)	39.3 (11.8)	42.0 (12.4)	3.4 (1.2 to 5.6)	**0.003**	4.6 (1.8 to 7.4)	**0.001**
AerRes	37.1 (11.7)	39.6 (11.5)	39.0 (11.1)	3.2 (1.2 to 5.1)	**0.002**	1.2 (−1.0 to 3.4)	0.271
DelAer	38.2 (14.5)	37.8 (13.3)	39.1 (13.6)				
Leg press (kg)							
ImpRes	125.9 (51.7)	149.2 (55.0)	159.2 (59.2)	12.7 (2.9 to 22.6)	**0.012**	12.5 (1.0 to 24.0)	**0.034**
AerRes	130.5 (52.1)	156.8 (59.0)	155.8 (57.4)	18.6 (8.1 to 29.0)	**0.001**	7.1 (−3.1 to 17.4)	0.169
DelAer	130.1 (62.0)	138.8 (57.6)	149.5 (67.3)				
Seated row (kg)							
ImpRes	66.7 (13.7)	72.6 (12.5)	76.6 (14.0)	6.1 (3.0 to 9.2)	<**0.001**	7.5 (3.9 to 11.1)	<**0.001**
AerRes	68.9 (14.4)	73.7 (13.3)	71.9 (14.1)	5.5 (2.7 to 8.3)	<**0.001**	1.6 (−1.6 to 4.7)	0.330
DelAer	68.1 (14.5)	67.7 (12.5)	69.9 (13.9)				
Leg extension (kg)							
ImpRes	49.0 (17.7)	58.6 (16.5)	65.3 (14.8)	7.9 (4.1 to 11.6)	<**0.001**	8.7 (5.1 to 12.3)	<**0.001**
AerRes	51.7 (17.6)	61.2 (17.5)	60.1 (17.4)	7.9 (4.0 to 11.8)	<**0.001**	0.0 (−4.0 to 4.0)	0.993
DelAer	47.3 (18.2)	49.7 (17.0)	55.7 (16.8)				

Bold text indicates statistical significance at $P \leq 0.05$.
[a]Between-group difference for ImpRes compared with DelAer and AerRes compared with DelAer. ANOVA adjusted for baseline, BMI, and postsecondary education.

and AerRes groups, respectively. However, it needs to be recognized that undertaking structured and supervised exercise training, although safe and beneficial, involves a financial cost and requires access to exercise professionals and training facilities that may not be readily available to all cancer patients, especially those living in rural and remote settings.

Apart from cost and potential treatment toxicity, pharmacological agents do not address other aspects of musculoskeletal dysfunction resulting from ADT or other adverse effects from hormone suppression such as fatigue and reduced quality of life. We have previously reported from this trial that the three exercise regimens undertaken reduced fatigue and increased vitality (20). Moreover, ILRT resulted in improvements in ASM and muscle strength. In addition, DXA-derived BMD may underestimate the benefits of exercise on bone strength as structural properties not assessed may be enhanced with impact-loading exercise (34). Given that lower extremity muscle strength is an important predictor of falls in older adults (35), it is possible that the enhancement of muscle strength resulting from the ImpRes program could contribute to a reduction in falls, and if a fall takes place, then preserved or improved bone strength may reduce the likelihood of a fracture occurring. The increase in ASM by ImpRes but lack of such effect in the AerRes group, although both groups undertook identical resistance training programs, is noteworthy and potentially the result of the interference effect of aerobic exercise compromising muscle hypertrophy drive of resistance training (36). Alternatively, or in combination, it is possible that the additional muscular loading afforded by the impact exercise may have contributed to muscle growth. Further comparison studies are needed to elucidate these potential complexities which will be important for optimal exercise prescription.

Our study has several strengths and limitations that are worthy of comment. This is the largest RCT to date examining the effect of exercise on bone as the primary outcome with a yearlong intervention sufficient in duration to detect changes in BMD in patients on ADT for PCa. We assessed changes in BMD as well as lean mass and muscle strength to comprehensively address adverse ADT-related effects as these may also contribute to osteogenic responses. The program was intensive in nature with multiple high-impact loading activities undertaken and both the resistance and impact-loading components followed the principle of progressive overload. Moreover, the program was well tolerated and acceptable to the patients and was not associated with any adverse events. However, we assessed BMD by DXA and changes independent of BMD contributing to bone strength may have occurred which were undetected. Future studies incorporating computed tomography (CT) or high-resolution peripheral CT (HR-pQCT) would be able to better address this issue. Patients were volunteers for an exercise trial and as such may not be representative of all patients treated with ADT. Moreover, most patients were in the initial year of their treatment, and results may differ for patients on longer durations of androgen suppression who could be even more responsive to various exercise stimuli (37). Lastly, the study involved a substantial number of comparisons/analyses, and therefore we cannot discount that a few of the significant findings, possibly up to four based on the number of tests undertaken, may be due to chance.

CONCLUSIONS

We found that combined impact loading and resistance exercise in PCa patients undertaking ADT attenuated the decline in spine and hip BMD and improved muscle strength and ASM, whereas aerobic plus resistance exercise only improved muscle strength. However, hip BMD and ASM benefits were not sustained by 12 months and this remains a question of interest. Regardless, impact loading in combination with resistance exercise should be recommended for patients to counter the musculoskeletal effects and in particular bone loss associated with ADT.

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Robert U. Newton, Daniel A. Galvão, and Dennis R. Taaffe had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors had no conflict of interest, including relevant financial interests, activities, relationships, and affiliations to declare relating to this manuscript. The results of the study are presented clearly, honestly, without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

CLINICAL TRIAL REGISTRY: A Phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer; ACTRN12609000200280.

REFERENCES

1. Spry NA, Kristjanson L, Hooton B, et al. Adverse effects to quality of life arising from treatment can recover with intermittent androgen suppression in men with prostate cancer. *Eur J Cancer*. 2006;42(8):1083–92.
2. Galvao DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int*. 2008;102(1):44–7.
3. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *New England Journal of Medicine*. 2005;352(2):154–64.
4. Wang A, Obertova Z, Brown C, et al. Risk of fracture in men with prostate cancer on androgen deprivation therapy: a population-based cohort study in New Zealand. *BMC Cancer*. 2015;15:837.
5. Smith MR, Finkelstein JS, McGovern FJ, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. *J Clin Endocrinol Metabol*. 2002;87(2):599–603.
6. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive

cross-sectional investigation. *Prostate Cancer Prostatic Dis*. 2009; 12(2):198–203.
7. Winters-Stone KM, Moe E, Graff JN, et al. Falls and frailty in prostate cancer survivors: current, past, and never users of androgen deprivation therapy. *J Am Geriatr Soc*. 2017;65(7):1414–9.
8. Alibhai SMH, Zukotynski K, Walker-Dilks C, et al. Bone health and bone-targeted therapies for nonmetastatic prostate cancer: a systematic review and meta-analysis. *Ann Intern Med*. 2017;167(5):341–50.
9. Saylor PJ, Smith MR. Bone health and prostate cancer. *Prostate Cancer Prostatic Dis*. 2010;13(1):20–7.
10. Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU. Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. *J Clin Oncol*. 2010;28(2):340–7.
11. Galvão DA, Nosaka K, Taaffe DR, et al. Resistance training and reduction of treatment side effects in prostate cancer patients. *Med Sci Sports Exerc*. 2006;38(12):2045–52.
12. Bourke L, Gilbert S, Hooper R, et al. Lifestyle changes for improving disease-specific quality of life in sedentary men on long-term androgen-deprivation therapy for advanced prostate cancer: a randomised controlled trial. *Eur Urol*. 2014;65(5):865–72.
13. Segal RJ, Reid RD, Courneya KS, et al. Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. *J Clin Oncol*. 2003;21(9):1653–9.
14. Winters-Stone KM, Dobek JC, Bennett JA, Maddalozzo GF, Ryan CW, Beer TM. Skeletal response to resistance and impact training in prostate cancer survivors. *Med Sci Sports Exerc*. 2014;46(8):1482–8.
15. Uth J, Hornstrup T, Christensen JF, et al. Efficacy of recreational football on bone health, body composition, and physical functioning in men with prostate cancer undergoing androgen deprivation therapy: 32-week follow-up of the FC prostate randomised controlled trial. *Osteoporos Int*. 2016;27(4):1507–18.
16. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):243–74.
17. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409–26.
18. Bolam KA, Galvao DA, Spry N, Newton RU, Taaffe DR. AST-induced bone loss in men with prostate cancer: exercise as a potential countermeasure. *Prostate Cancer Prostatic Dis*. 2012;15(4):329–38.
19. Newton RU, Taaffe DR, Spry N, et al. A phase III clinical trial of exercise modalities on treatment side-effects in men receiving therapy for prostate cancer. *BMC Cancer*. 2009;9:210.
20. Taaffe DR, Newton RU, Spry N, et al. Effects of different exercise modalities on fatigue in prostate cancer patients undergoing androgen deprivation therapy: a year-long randomised controlled trial. *Eur Urol*. 2017;72(2):293–9.
21. Heymsfield SB, Smith R, Aulet M, et al. Appendicular skeletal muscle mass: measurement by dual-photon absorptiometry. *Am J Clin Nutr*. 1990;52(2):214–8.
22. Taaffe DR, Duret C, Wheeler S, Marcus R. Once-weekly resistance exercise improves muscle strength and neuromuscular performance in older adults. *J Am Geriatr Soc*. 1999;47(10):1208–14.
23. Vellas B, Guigoz Y, Garry PJ, et al. The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. *Nutrition*. 1999;15(2):116–22.
24. Galvao DA, Spry N, Denham J, et al. A multicentre year-long randomised controlled trial of exercise training targeting physical functioning in men with prostate cancer previously treated with androgen suppression and radiation from TROG 03.04 RADAR. *Eur Urol*. 2014;65(5):856–64.
25. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc*. 2010;42(7):1409–26.
26. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin*. 2012;62(4):242–74.
27. Clarke B. Normal bone anatomy and physiology. *Clin J Am Soc Nephrol*. 2008;3(3 Suppl):S131–9.
28. Mina DS, Ritvo P, Matthew AG, Rampersad A, Stein H, Cheung AM, et al. Group exercise versus personal training for prostate cancer patients: a pilot randomized trial. *J Cancer Ther*. 2012; 3(2):146–56.
29. Nilsen TS, Raastad T, Skovlund E, et al. Effects of strength training on body composition, physical functioning, and quality of life in prostate cancer patients during androgen deprivation therapy. *Acta Oncol*. 2015;54(10):1805–13.
30. Allison SJ, Poole KE, Treece GM, et al. The influence of high-impact exercise on cortical and trabecular bone mineral content and 3D distribution across the proximal femur in older men: a randomized controlled unilateral intervention. *J Bone Miner Res*. 2015;30(9):1709–16.
31. Hinton PS, Nigh P, Thyfault J. Effectiveness of resistance training or jumping-exercise to increase bone mineral density in men with low bone mass: a 12-month randomized, clinical trial. *Bone*. 2015;79: 203–12.
32. Heinonen A, Kannus P, Sievanen H, et al. Randomised controlled trial of effect of high-impact exercise on selected risk factors for osteoporotic fractures. *Lancet*. 1996;348(9038): 1343–7.
33. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007;18(8):1023–31.
34. Cheng S, Sipila S, Taaffe DR, Puolakka J, Suominen H. Change in bone mass distribution induced by hormone replacement therapy and high-impact physical exercise in post-menopausal women. *Bone*. 2002;31(1):126–35.
35. Moreland JD, Richardson JA, Goldsmith CH, Clase CM. Muscle weakness and falls in older adults: a systematic review and meta-analysis. *J Am Geriatr Soc*. 2004;52(7):1121–9.
36. Wilson JM, Marin PJ, Rhea MR, Wilson SM, Loenneke JP, Anderson JC. Concurrent training: a meta-analysis examining interference of aerobic and resistance exercises. *J Strength Cond Res*. 2012;26(8):2293–307.
37. Taaffe DR, Buffart LM, Newton RU, et al. Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer. *BJU Int*. 2018;121(2):194–202.