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Musculoskeletal responses to exercise plus nutrition in men with prostate cancer on androgen deprivation: A 12-month RCT

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ABSTRACT

Purpose: Androgen deprivation therapy (ADT) for prostate cancer (PCa) has multiple adverse effects on musculoskeletal health. This 12-month randomised controlled trial aimed to assess the effects of multi-component exercise training combined with whey protein, calcium and vitamin D supplementation on bone mineral density (BMD), structure and strength, body composition, muscle strength and physical function in ADT-treated men.

Methods: Seventy ADT-treated men were randomised to exercise plus supplementation (Ex+Suppl; n=34) or usual care (Control; n=36). Ex+Suppl involved thrice weekly progressive resistance training plus weight-bearing impact exercise with daily multi-nutrient supplementation. Primary outcomes were DXA hip and spine areal BMD. Secondary outcomes included: tibia and radius pQCT volumetric BMD, bone structure and strength; DXA body composition; pQCT muscle and fat cross-sectional area and muscle density; muscle strength and physical function.

Results: Sixty men (86%) completed the study. Mean exercise and supplement adherence were 56% and 77%, respectively. There were no effects of the intervention on bone or body composition outcomes. Ex+Suppl improved leg muscle strength (net difference [95% CI] 14.5% [-0.2, 29.2], P=0.007) and dynamic mobility (four-square-step test time, -9.3% [-17.3, -1.3], P=0.014) relative to controls. Per-protocol analysis of adherent participants (≥66% exercise, ≥80% supplement) showed Ex+Suppl preserved femoral neck aBMD (1.9% [0.1, 3.8], P=0.026) and improved total body lean mass (1.0 kg [-0.23, 2.22], P=0.044) relative to controls.

Conclusion: Exercise training combined with multi-nutrient supplementation had limited effect on ameliorating the adverse musculoskeletal consequences of ADT, likely related to the modest intervention adherence.

Key Words: Exercise, Nutrition, Cancer, Bone, Muscle, Androgen Deprivation Therapy

INTRODUCTION

Androgen deprivation therapy (ADT) is commonly used to treat advanced or metastatic prostate cancer (PCa) and is shown to improve survival in appropriately selected patients (1), but is associated with multiple adverse effects, particularly regarding musculoskeletal health (1, 2). Within the first year of treatment, 1-5% losses in hip and spine areal bone mineral density (aBMD) (3, 4), a 6-13% deterioration in cortical bone structure and vBMD and a 2-4% reduction in trabecular vBMD (5), a 2-4% decline in lean mass and a 7-14% increase in fat mass along with impaired muscle strength and physical function have been reported (3, 6). Clinically, these marked musculoskeletal changes likely contribute to the reported 39-46% increased fracture risk in ADT-treated men (7, 8).

Exercise training is widely recommended to combat the adverse effects of ADT (4, 9), with aerobic and/or progressive resistance training (PRT) shown to effectively reduce fat mass gains and improve aerobic fitness, fatigue, muscle mass, strength, function and quality of life in ADT-treated men (2, 9). However, the effects of exercise on bone health are largely inconclusive. While some interventions have demonstrated that PRT and impact exercise can attenuate hip and spine aBMD loss in ADT-treated men (10, 11), most report negligible skeletal effects (12-15). Few studies have assessed the effects of exercise on other determinants of bone strength beyond aBMD in ADT-treated men, including cortical and trabecular bone density and cortical bone structure. This is important because changes in these skeletal determinants can influence bone strength without measurable changes in aBMD (16).

Calcium and vitamin D supplementation are recommended in clinical care guidelines for ADT patients to mitigate bone loss (17), but few intervention trials have investigated their effects on bone health or fracture risk in ADT-treated men. In healthy older adults, daily

calcium plus vitamin D supplementation has been shown to modestly improve or attenuate bone loss and reduce fracture risk (18, 19). Increased dietary protein intake and vitamin D in combination with exercise, particularly PRT, are recommended to prevent age-related muscle loss in older adults (20). Indeed, there is evidence that supplementation with whey protein or a multi-nutrient supplement containing protein with vitamin D can enhance the effects of PRT on muscle mass and strength in older men and women (21, 22). Given that exercise alone has not been shown to consistently mitigate bone or muscle loss in ADT-treated men, interventions combining exercise with nutritional support specifically targeted at both bone and muscle may provide the greatest benefits.

The primary aim of this 12-month RCT was to investigate whether a community-based, multi-component exercise program combined with a protein, calcium and vitamin D enriched supplement could improve hip and lumbar spine (LS) aBMD in ADT-treated men. It was hypothesised that the intervention would attenuate the expected decline in aBMD, relative to controls. Secondary aims were to investigate the effects of the intervention on pQCT assessed cortical and trabecular vBMD, bone structure and strength at the distal and proximal tibia and radius, as well as body composition, muscle strength and physical function.

METHODS

Study Design

This was a two-arm, 12-month RCT in which 70 men with PCa treated with ADT were randomised to either multi-component exercise training combined with multi-nutrient supplementation (Ex+Suppl) or a usual care control (CON) group. The study protocol has been described previously (23). Briefly, participants were randomised 1:1 following baseline assessment, stratified by age (<65 or ≥65 years) and BMI (<30 and ≥30 kg/m^2) using a computer-generated random number sequence, by an independent researcher into one of the

two groups. Outcomes were assessed at baseline, six and 12 months. The study was approved by the Deakin University Human Research Ethics Committee, Alfred Health and Peter MacCallum Cancer Centre, and registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12614000317695).

Participants

Men aged 50-85 years with PCa treated with ADT were recruited between April 2014 and November 2017 via clinician referral, PCa support groups and local newspaper advertisements throughout Victoria, Australia. Eligible participants were men with histologically diagnosed PCa currently being treated with pharmacological ADT for longer than 12 weeks. Participants were excluded if they could not complete surveys in the English language, had any disorder(s) known to affect bone, calcium or vitamin D metabolism (other than hypogonadism), were currently receiving pharmacological intervention known to affect bone metabolism (other than ADT), had supplemented with protein, calcium (>600 mg/day) or vitamin D (>1000 IU/day) in the past three months, had undertaken PRT (>1 session/week) or regular weight-bearing impact exercise (>150 min/week) in the past three months, were current smokers, weighed >159 kg or had any absolute contraindications to exercise testing (24). All eligible participants obtained medical approval from their physician and gave written informed consent prior to participation. The study was conducted in accordance with the Declaration of Helsinki.

Intervention

Exercise training program

A detailed description of the exercise program has been previously reported (23). Briefly, participants were prescribed two gym-based sessions and one home-based session per week. Each gym-based session (~60 minutes) consisted of 5-10 minutes of aerobic training (stationary cycling, treadmill walking, rowing) as part of the warm-up, 5-6 PRT exercises

(two sets, 8-12 repetitions at moderate to hard intensity) predominantly targeting the hip and spine using machine and free weights, three weight-bearing impact exercises (three sets, 10-20 repetitions) predominantly targeting the lower-limb (e.g. jumping, hopping, step-ups), two challenging balance/functional exercises (two sets of 30-60 seconds or a given number of repetitions) and two core stability exercises (two sets, 10-15 repetitions). Progressive overload was applied to PRT by increasing the resistance, and to impact exercises by increasing the height of jumps, adding additional weight, increasing the rate of impact-loading or adding multi-directional movement patterns. During the first six months, two weekly gym-based sessions were supervised by an accredited exercise physiologist in a community-based health and fitness facility. For the final six months, one weekly gym-based session was supervised. The home-based exercise program (20-60 minutes) followed a similar structure and exercises to the gym-based sessions but used body weight and resistance bands. Participants first practiced the home exercises in the gym and were provided with instructions and an exercise card to complete at home. All exercise programs were individually tailored with modifications made based on factors such as bone metastases or comorbid conditions.

Multi-nutrient nutritional supplement

The multi-nutrient supplement consisted of a whey protein-, calcium- and vitamin D-enriched drink (powder mixed with 150ml of water) combined with a single vitamin D tablet. Each sachet contained approximately 440kJ energy, 25g whey-protein concentrate 80% (WPC80), containing approximately 2.4g leucine, 1200mg calcium carbonate and 1000IU vitamin D (Omniblend, Campbellfield, Victoria, Australia). The vitamin D tablet contained 1000IU (Ostelin, Macquarie Park, NSW, Australia). Participants were asked to take one sachet every morning, either before breakfast on non-training days or within 1–2 hours of exercise on

training days. Participants were advised to consume the supplement in addition to their regular diet.

Usual Care Control Group

Participants allocated to usual care received ongoing care from their physician/specialist and a single 1000IU vitamin D tablet per day.

Outcome Measures

Areal BMD

Lumbar spine (L1-L4) and proximal femur (femoral neck [FN] and total hip) aBMD (g/cm^2) were assessed using DXA (Lunar iDXA, GE Lunar Corp., Madison, WI, USA). The prevalence of osteoporosis (T-score ≤-2.5) or osteopenia (T-score between -2.5 and -1.0) was based on the World Health Organization criteria (25) from the lowest T-score at any site. The short-term coefficient of variation (CV) for aBMD ranged from 0.6-1.0% within our laboratory.

Volumetric BMD, bone structure and strength

Proximal (66%) and distal (4%) sites of the non-dominant radius and dominant tibia were scanned using pQCT (XCT 3000, Stratec Medizintechnik GmbH, Pforzheim, Germany). Cortical volumetric BMD (mg/cm^3), bone structure (total, cortical and medullary area [mm^2]) and strength (density-weighted polar cross-sectional moment of inertia [I_{polar}, mg/cm]) at proximal sites, as well as trabecular vBMD (mg/cm^3) and strength (bone strength index [BSI, mg^2/mm^4]) at distal sites were assessed. The slice thickness was 1mm and voxel size was 0.5mm at a scanning speed of 20mm/s. pQCT images were analysed in the Fiji image analysis platform (26) using the BoneJ plugin (27) as previously reported (28). Distal radius and tibia (4%) total bone area were analysed based on thresholding at $169mg/cm^3$. Trabecular density was determined by peeling single layers of pixels until 45% of the total bone area

remained. BSI was calculated as total area multiplied by the square of total vBMD (29). For the 66% proximal radius and tibia, the periosteal surface was determined based on a threshold of 280mg/cm^3, and cortical bone a threshold of 550mg/cm^3. Medullary area was calculated by subtracting cortical area from total area. I_{polar} was determined using the bone threshold of 480mg/cm^3 (30). Scans were excluded according to the visual inspection rating scale of participant movement (31, 32). Short-term CVs were 0.9-2.2% for the 4% radius, 0.7-2.5% for the 4% tibia and 0.6-1.8% for the 66% tibia outcomes (33).

Body composition

Total and regional (arms, legs, trunk and appendicular) lean mass and fat mass were assessed by DXA as described above. The short-term CV for lean and fat mass ranged from 1.0-1.7%. Muscle and subcutaneous fat cross-sectional area (CSA) and muscle density (as a measure of intermuscular adiposity) at the proximal (66%) radius and tibia were assessed using pQCT. Thresholds of -40 to +40 mg/cm^3 hydroxyapatite density were used for estimating subcutaneous fat CSA. Muscle CSA was estimated by subtracting the total bone CSA and subcutaneous fat CSA from the total area of the 66% tibia or radius. The following CVs have been reported for muscle CSA (radius, 2.1-5.3%; tibia, 2.5-3.7%), muscle density (radius, 1.4-3.2%; tibia 0.7-3.2%) and subcutaneous fat CSA (radius, 2.4-3.2%; tibia, 6.0-6.3%) (34).

Muscle strength and function

As reported in detail previously (23), maximum muscle strength of the lower body (leg press), chest (chest press) and back (seated row) was assessed using three-repetition maximum (3-RM) protocols. Maximal grip strength was assessed using a digital grip-strength dynamometer (Jamar Plus Digital, Lafayette Instrument Company, IN, USA). Physical function was assessed via the 30-second sit-to-stand test, timed-up-and-go (TUG) test with a cognitive task (counting backwards by 3 from a random number), four-square step test

193 (FSST), Berg Balance Scale, 4-m usual walk (to assess gait speed) and 400-m walk. Detailed
194 methodology for each test has been described previously (23).

195 *Demographic, health and lifestyle information*

196 A questionnaire was used to obtain background demographic, clinical and lifestyle
197 information from participants, including cultural background, PCa and ADT use details,
198 medical conditions (past and current), prescription and non-prescription medication use (type
199 and dose) and history of falls in the previous 12 months and fractures since the age of 45.

200 *Anthropometry, physical activity and diet*

201 Height and weight were assessed using a portable stadiometer (SECA, Hamburg, Germany)
202 and scales (A&D, Tokyo, Japan), respectively. Body mass index (BMI) was calculated as
203 body mass (kg) divided by height (m) squared (kg/m^2). The Community Healthy Activities
204 Model Programme for Seniors (CHAMPS) physical activity questionnaire was used to assess
205 habitual physical activity levels (35). Diet was assessed using a 24-hour food recall and
206 analysed using Australia-specific dietary analysis software (FoodWorks, Xyris software,
207 Highgate Hills, Australia).

208 *Adherence*

209 Exercise adherence was assessed using exercise cards for gym-based sessions or self-reported
210 training diaries for home-based sessions. Supplement adherence was assessed by counting
211 sachets and vitamin D capsules returned at six and 12 months and cross-checked against
212 supplement calendars completed by participants.

213 *Adverse events*

214 Adverse events, defined as any unfavourable or unintended health-related event or issue that
215 developed or worsened during the study period as a result of the intervention, were recorded
216 at exercise sessions for the Ex+Suppl group and at follow-up testing sessions for controls.

Blood biomarkers

Fasted, resting morning blood samples were collected at a commercial pathology clinic, with serum aliquots stored at -80°C. Blood samples were assessed immediately for total prostate specific antigen (PSA) and high-sensitivity C-reactive protein (CRP) using standard techniques. Serum 25-hydroxyvitamin D [25(OH)D] was assessed using a LIAISON® 25OH-Vitamin D assay (DiaSorin, Stillwater, MN, USA) and serum insulin-like growth factor 1 (IGF-1) using a LIAISON® IGF-1 one-step sandwich chemiluminescense immunoassay (DiaSorin, Saluggia, VC, Italy). All samples were analysed in duplicate at Monash Health (Monash Medical Centre, Clayton, VIC, Australia) at the completion of the study.

Sample Size Calculations

Based on previous research (5, 36), it was estimated that 29 participants per group would provide 90% power ($P<0.05$, two-tailed) to detect a net difference of 3.5-4.0% (assuming a SD of 4.0) in the primary outcomes of proximal femur and LS aBMD. For secondary pQCT bone structure outcomes, it was estimated that 39 participants in each group would provide 90% power ($P<0.05$, two-tailed) to detect a 50% reduction in the previously reported 11.5-12.5% annual losses in radial and tibia cortical area (assuming a SD of 8.0) (5). Assuming a 30% dropout, we aimed to recruit and randomise 51 participants per group.

Statistical Analysis

Data were analysed using Stata statistical software (Version 15.0, Stata, College Station, TX, USA). Primary analyses were completed using an intention-to-treat approach. Per protocol analyses were also completed including participants with ≥66% exercise adherence and ≥80% nutritional supplement adherence. All data were screened for outliers and assessed for normality by visual inspection of histograms of the residuals. Linear mixed-effects models with random effects (participants) were used to assess within-group changes over time and

group-by-time interactions (both fixed effects) at six and 12 months. Generalised linear mixed models (GLMM) with a gamma distribution and log-link were used for variables that were non-normally distributed. Baseline measures are presented as means ± SD for continuous data or frequency and percentage for categorical data, unless specified otherwise. Mean change in outcomes with 95% confidence interval are presented as either absolute change or as percentage change from baseline. Net differences between groups for the change from baseline to six and 12 months were calculated as the change within the control group subtracted from the change within the intervention group. For non-normally distributed data that was assessed using GLMMs, the data was log transformed so that the percentage change could be calculated as the absolute change in natural log transformed values multiplied by 100 (37). No data imputation was made for missing data as the linear mixed models can handle missing data with maximum likelihood estimation. An alpha level of 0.05 was used to determine statistical significance.

RESULTS

Participant characteristics

In total, 214 men expressed interest in the study from which 70 were randomised (Figure 1). Recruitment ceased after 43 months, prior to reaching our target of 102 men, due to funding constraints given a slow recruitment rate. As shown in Table 1, on average the men were aged 71 years, with 53% and 30% classified as overweight and obese, respectively, 89% reporting the presence of co-morbidities (mean number 2.6), and 50% and 6% classified as having osteopenia and osteoporosis, respectively. Median time since PCa diagnosis was 3.3 years and median duration of ADT use was 12 months. Overall, 64% of men were classified as having advanced PCa and 29% as having bone metastases, with 49% reported having a previous prostatectomy, 69% previous radiotherapy and 16% previous chemotherapy.

Attrition and adherence

Sixty (86%) men completed the study (Ex+Suppl, n=31; Control, n=29). One participant in Ex+Suppl did not commence the exercise program due to a perceived lack of time, while five men discontinued training (four within three months, one after nine months) due to health issues unrelated to the study (n=3), perceived lack of time (n=1) or personal reasons (n=1). Four of these six men continued taking the nutritional supplement for the duration of the study, and five of the six agreed to attend follow-up testing sessions. Mean ± SD exercise adherence was 56% ± 30% (supervised 65% ± 25%; unsupervised 49% ± 38%). Mean multi-nutrient supplement adherence was 77% ± 30%.

Safety, tolerability and adverse events

There were no serious adverse events related to the intervention. There were 21 musculoskeletal complaints reported by 14 (41%) participants in Ex+Suppl. Most complaints (n=19) were minor requiring no treatment and led to between one and four missed or modified sessions. Two participants experienced exacerbation of existing knee injuries and trained with a modified program for six weeks. Additionally, three participants stopped taking the nutritional supplement within the first six months due to gastrointestinal complaints that they attributed to the supplement.

Prostate cancer treatment

At baseline, median ADT duration was five months higher in the control compared to Ex+Suppl group (Table 1). Eight men (1 Ex+Suppl; 7 CON) discontinued ADT treatment during the first 6 months of the intervention and a further eight (4 Ex+Suppl; 4 CON) discontinued treatment between 6 and 12 months. The total number of men in each group that discontinued ADT (5 Ex+Suppl; 11 CON) did not differ statistically (P=0.114). During the study period, four participants (all Ex+Suppl) commenced radiation therapy, six participants (5 Ex+Suppl; 1 CON) commenced chemotherapy, and seven participants (4 Ex+Suppl; 3

CON) were prescribed adjuvant anti-androgen medication, to be taken concomitantly with existing gonadotropin-releasing hormone agonists. The results were unchanged when ADT duration, whether participants discontinued ADT, had bone metastasis at baseline, commenced radiation therapy, commenced chemotherapy or were prescribed anti-androgen medication during the study, were included as covariates in the analyses. Thus the unadjusted results are presented below.

Diet and physical activity

Baseline mean dietary calcium intake was 841 mg/d, with 51 (73%) men classified as having intakes below the Australian Recommended Dietary Intake (RDI). There were no significant between-group differences over time or within-group changes in habitual physical activity and daily energy, carbohydrate, protein, fat or calcium intake (excluding the supplement) (Supplementary Table 1), except for an increase in habitual physical activity within the control group at 12 months (mean change, 453 kJ/day [95% CI 70, 835], P=0.040).

Blood biomarkers

Mean baseline serum 25(OH)D levels were 69.8 nmol/L, with 12 (17%) men having insufficient vitamin D levels (<50 nmol/L). Ex+Suppl had a greater increase in serum 25(OH)D compared to controls after six months (net difference 12.4 nmol/L [95% CI 8.9, 19.9], P=0.001), but not 12 months (Supplementary Table 2). There were no significant between-group effects or within-group changes in serum IGF-1, hs-CRP or PSA after six or 12 months (Supplementary Tables 2-3).

DXA areal BMD

There were no significant effects of the intervention on LS or proximal femur aBMD (Table 2), with both groups experiencing a significant 1.1% to 1.9% loss in FN and total hip aBMD after 12 months.

315 **pQCT volumetric BMD, bone structure and strength**

316 There were no significant effects of the intervention on distal (4%) tibia or radius trabecular
317 vBMD or BSI after six or 12 months (Table 3), with both groups experiencing similar losses
318 in distal tibia (3.8-4.5%) and radius (9.2-10.6%) BSI, and distal radius (2.7-2.9%) trabecular
319 vBMD after 12 months. There were also no significant intervention effects on proximal
320 (66%) tibia or radius cortical vBMD, bone structure or I_{polar} after six or 12 months, except for
321 a 1.4% net benefit of Ex+Suppl on proximal radius cortical vBMD after six months
322 (P=0.035). Tibia and radius cortical area declined similarly in each group after 12 months
323 with no change in total bone area, indicating that cortical bone loss was due to increased
324 endocortical resorption.

325 **Body composition**

326 There were no significant between-group effects on weight or any DXA or pQCT body
327 composition measure after six or 12 months (Table 4 and Supplementary Table 4), except
328 that leg fat mass increased in Ex+Suppl compared to controls at 12 months (net difference
329 0.34kg [95% CI -0.06, 0.74], P=0.018), proximal tibia and radius subcutaneous fat CSA
330 increased in Ex+Suppl compared to controls at 12 months (net differences 9.8% [95% CI 0.8,
331 18.8], P=0.030 and 9.0% [95% CI 1.4, 16.7], P=0.004, respectively), and proximal radius
332 muscle density decreased in Ex+Suppl compared to controls at 12 months (net difference -
333 1.7% [95% CI -3.3, -0.2], P=0.012).

334 **Muscle strength and function**

335 Lower body muscle strength (leg press) improved in Ex+Suppl compared to controls at six
336 months (net difference 11.0% [95% CI 0.1, 21.9], P=0.048) and 12 months (net difference
337 14.5% [95% CI -0.2, 29.2], P=0.007) (Table 5). Chest press muscle strength increased in
338 Ex+Suppl compared to controls at six months (net difference 10.7% [95% CI 0.2, 21.1],
339 P=0.024), but not at 12 months. There was no effect of the intervention on back (seated row)

or grip strength or any measure of physical function (Table 5), except that FSST performance improved in Ex+Suppl compared to controls at six months (net difference -10.3%, (95% CI -17.1, -3.4), P=0.003) and 12 months (net difference -9.3% [95% CI -17.3, -1.3], P=0.014).

Per protocol analysis

All results for the per-protocol analysis (exercise adherence ≥66% and supplement adherence ≥80% [n=11]) remained unchanged, except for the following (Supplementary Tables 5-8): 1) there was a net beneficial effect of Ex+Suppl relative to controls on FN aBMD at 12 months (net difference 1.9% [95% CI 0.1, 3.8], P=0.026), which was driven by a significant loss in controls (-1.8% [95% CI -2.9, -0.7], P<0.001); 2) there was no effect of Ex+Suppl on proximal radius cortical vBMD; 3) total body lean mass increased in Ex+Suppl compared to controls at six months (net difference 1.2kg [95% CI 0.2, 2.1], P=0.021), which persisted after 12 months (net difference 1.0kg [95% CI -0.2, 2.2], P=0.044) (similar findings were observed for leg lean mass); and 4) weight increased in Ex+Suppl compared to controls after 12 months (net difference 1.9kg [95% CI -0.4, 4.1], P=0.039).

DISCUSSION

The main findings from this 12-month RCT was that a multi-component exercise program with a daily protein, calcium and vitamin D enriched supplement was largely ineffective for improving or maintaining bone density, structure or strength, body composition or physical function compared to usual care in men with prostate cancer treated with ADT. There was evidence to support a beneficial effect on FN aBMD and lean mass among men who were adherent to the intervention (exercise adherence ≥66% and supplement adherence ≥80%), but these findings must be interpreted with caution due to the small number of men (n=11) that achieved this level of adherence.

The lack of any significant effect of our intervention on aBMD measures is largely consistent with several previous 12-month interventions that have reported no or limited benefits of exercise (all incorporating PRT) alone on LS and proximal femur aBMD in ADT-treated men (10, 12-15). While one three-arm, 12-month RCT in 154 ADT-treated men reported that PRT plus impact exercise, but not PRT plus aerobic training, attenuated LS aBMD loss relative to controls (–0.6% versus –1.8%, P=0.035), there were no long-term exercise benefits on proximal femur aBMD after 12 months (10). Similarly, the lack of effect on tibia or radius vBMD, bone structure or strength in our study is consistent with the only other known exercise RCT in ADT-treated men that used pQCT (12). Cormie and colleagues (12) reported no effect of three months of PRT and aerobic training on distal tibia total vBMD in 63 men commencing ADT, although a limitation of this study is the short duration which is insufficient to capture true physiological changes in bone given the typical bone remodelling cycle lasts approximately six months. However, several longer-term trials (8-18 months) in healthy older men have reported inconsistent findings regarding the effects of PRT and impact exercise training on (p)QCT-derived bone measures (38, 39). Collectively, findings from our trial and previous interventions suggest that there is currently little evidence to support multi-component exercise programs as an approach to attenuate ADT-related bone loss in men with PCa, particularly at the proximal femur.

A number of factors likely explain the lack of effect of our multi-faceted exercise and nutrition intervention on bone outcomes, despite our exercise program being modelled on the successful *Osteo-cise: Strong Bones for Life* community-based exercise program that significantly improved LS and FN aBMD by 1.0-1.1% in healthy older adults (36). Modest adherence to the exercise training in our study (mean 56% over 12 months) is likely a key reason, which is partly supported by our per-protocol analyses that revealed a significant positive effect (net 1.9% benefit) of the intervention on FN aBMD relative to controls.

However, these findings must be interpreted with caution given the relatively small number (n=11) of men from the intervention group that were included in the per-protocol analysis. There were also no intervention effects on other bone outcomes in the per-protocol analysis, suggesting that factors beyond just adherence contributed to the lack of effect on bone. For instance, modifications made for some participants due to PCa related factors, such as bone metastases and adverse effects associated with additional PCa treatments, limited the intensity and/or dose of exercise training or the specificity of the program to target clinically relevant skeletal sites. It is also possible that hypogonadism induced by ADT may have blunted the osteogenic response to exercise training. Testosterone suppression with ADT can lead to low estrogen levels, which is suggested to influence the minimal effective strain threshold required for bone adaptation and therefore the anabolic response of bone to loading (40). Consequently, a greater mechanical stimulus (strain) may be required to overcome this and elicit osteogenic adaptations in men with hypogonadism induced by ADT. Finally, men in the current study generally had sufficient dietary protein intakes, and calcium intakes were within the current Australian estimated average requirements, and vitamin D levels were replete, which may have limited potential additional exercise-related benefits of the nutritional supplement on bone (or muscle) outcomes.

The lack of any intervention effects on bone may also relate to negligible effects of the intervention on muscle-related outcomes, including lean mass, muscle CSA and muscle strength. The 0.5 kg non-significant net intervention related benefit to total body lean mass in our study was less than the significant 0.8 kg net benefits reported in two previous three to six month PRT and aerobic exercise interventions in ADT-treated men (41, 42), however several other PRT-related trials over three to 12 months in ADT-treated men also reported non-significant 0.3 to 0.7 kg net benefits to lean mass relative to controls (10, 12, 13, 43). The heterogeneity in reported skeletal muscle responses to PRT-related training in ADT-treated

men may be attributed to a number of factors, including differences in training intensity and frequency, the inclusion of aerobic training which has been hypothesized to influence hypertrophic adaptations, and the timing of commencing exercise relative to the initiation of ADT (44). As with the bone outcomes, modest adherence to the intervention also likely contributed to the lack of marked muscle benefits. Indeed, our per-protocol analyses showed a net 1.0 to 1.2 kg intervention related benefit to total body lean mass after six and 12 months. However, there were no effects on pQCT assessed muscle CSA of the forearm or lower leg. Collectively, these findings may relate to the multi-component nature of our exercise program in which PRT was one of four key training elements and a greater dose or volume of PRT may be required to elicit skeletal muscle gains. This is supported by a meta-analysis reporting higher volume PRT programs were associated with the greatest benefits in lean mass among older adults (45). Furthermore, a meta-analysis of seven exercise RCTs in ADT-treated men found that low- to moderate-intensity PRT and aerobic training had no effect on lean mass, despite increasing muscle strength (44). It is also possible that the dose of whey protein provided (25g/d) in the nutritional supplement in our study may have been insufficient to enhance skeletal muscle adaptations in combination with the exercise program as there is some evidence from acute feeding studies that protein doses (whey or milk protein) of 30-40g post-exercise are required to maximally stimulate muscle protein synthesis (46, 47). However, there are mixed findings from meta-analyses of RCTs examining whether protein supplementation can enhance the effects of exercise (resistance training) on muscle mass or strength in older adults (48-50). As a result, there is no universal consensus on the optimal dose (or type or timing) of protein needed to enhance the effects of exercise on muscle mass and strength in older adults or cancer survivors (51, 52).

Previous exercise studies in ADT-treated men have reported improved upper and lower body strength (10, 12, 41, 53), chair rise performance, gait speed and balance (12, 13, 41, 54). In

our study, leg press muscle strength and dynamic balance assessed by the FSST, were the only outcomes that improved following exercise relative to controls. While it is possible that the lack of intervention effects on lean mass or muscle CSA contributed to the limited effects on other measures of muscle strength and physical function, the positive effects observed on the above outcomes supports the training principle of specificity as the exercise program focussed on lower body resistance exercises and challenging balance and mobility exercises. Nevertheless, it should be recognised that our net benefits to muscle strength (15%) and dynamic mobility (9%) were relatively modest, which may be likely due to the men included in the study being relatively well functioning at baseline.

Previous exercise interventions in ADT-treated men have reported either reduced fat mass (12, 42) or no changes over time relative to control groups (10, 13, 41), but no studies have examined the combined effects of exercise with nutritional supplementation. In older overweight/obese adults, there is evidence to support reduced fat mass and weight loss with whey protein supplementation alone or in combination with exercise (55, 56). Therefore the observed, albeit non-significant, 0.9 to 1.0 kg net increases in fat mass and body weight (and greater gains in forearm and lower leg subcutaneous fat CSA) in Ex+Suppl relative to controls after 12 months in our study were unexpected. While this could relate to the additional 440 kJ per day consumed from the supplement, all results remained unchanged when energy (kJ) from the nutritional supplement (adjusted for supplement adherence) was factored into the daily dietary energy intake results. Although the observed net gain in fat mass in our study appears to contrast with findings from several previous exercise interventions in ADT-treated men (10, 12, 13, 41, 42), similar magnitude 0.9 to 1.1 kg within group increases have been reported following six to 12 month exercise interventions conducted in ADT-treated men (10, 14). It is important to note that men allocated to the intervention in our study were advised that the supplement was not to be taken as a meal

replacement. Subsequent dietary analyses indicate that this occurred as mean habitual dietary intakes (excluding the supplement) were no different between groups at any timepoint. Given that weight and fat gain are common side-effects of ADT, further studies are needed to evaluate the effects of nutritional supplementation with exercise on body composition in ADT-treated men.

A strength of this study is that it is the first to investigate the effects of multi-component exercise training combined with targeted nutritional supplementation on a wide battery of musculoskeletal health outcomes known to be adversely affected by ADT. This provided a comprehensive assessment of the effects of our intervention on a battery of common fracture risk factors. However, there are several limitations. Firstly, due to the lack of a factorial 2x2 study design we cannot address the question of whether the combination of exercise with nutritional supplementation is more effective (additive or synergistic) than either approach alone. Secondly, we did not reach our target sample size which likely limited the statistical power to detect possible between group differences in some bone outcomes, particularly bone structure and strength estimates. Thirdly, intervention adherence was relatively modest and our per protocol analyses were limited by a small number of men who met pre-specified cut points for both exercise and supplement adherence. Furthermore, we could not access either tumor characteristics or cancer recurrence data, so the intervention's effect on these clinical outcomes could not be evaluated. Additionally, compared to more precise objective physical activity assessment, the subjective physical activity measurement tool used in this study may have limited our ability to capture differences and changes in habitual physical activity throughout the intervention. Finally, volunteer bias may limit the generalisability of the results as it is possible that participants capable of completing the intervention volunteered for the study knowing they could be allocated to a 12-month exercise and nutritional supplementation intervention.

In conclusion, we have demonstrated that a 12-month multi-component exercise program combined with a daily protein, calcium and vitamin D enriched supplement was largely ineffective for improving or maintaining bone density, structure or strength, body composition or muscle function in men with PCa treated with ADT compared to usual care. This is likely related to the modest intervention adherence as there was some evidence that the intervention was effective for improving FN aBMD and total body lean mass among highly adherent participants. Further research is therefore required to identify strategies to promote long-term exercise adherence for this cohort of men.

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Author contributions: Study design: PJO, RMD, PML, SFF. Study conduct: JDV, PJO, NLM, SJF. Data collection: JDV, PJO, NLM, SJF. Data analysis: JDV, TR, PJO. Data interpretation: JDV, RMD. Drafting manuscript: JDV. Revising manuscript content: All. Approving final version of manuscript: All. JDV takes responsibility for the integrity of the data analysis.

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Figure legends:

Figure 1. Participant flow through the study.

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