Prevention of the adverse effects of androgen deprivation therapy for prostate cancer using a 12-month home-based progressive resistance training program: a randomised controlled study

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Abstract

Background In men with prostate cancer, androgen deprivation therapy (ADT) has detrimental effects on body composition and quality of life (QOL), which can be ameliorated with exercise interventions including progressive resistance training (PRT). Existing studies focus on reversing established changes using supervised programs. We investigated whether a home-based PRT program, instituted at the start of ADT, could prevent adverse effects over 12-months.

Methods Twenty-five patients scheduled to receive at least 12 months of ADT were assigned to either usual care (UC) (n=12) or PRT (n=13) starting after their first ADT injection. Body composition, body cell mass (BCM; a functional component of lean body mass), insulin sensitivity, QOL and muscle function were measured at 6 weeks, 6- and 12 months. Data were analysed by a linear mixed model.

Results Across the cohort, ADT had a negative impact on body composition, muscle strength, glucose metabolism and QOL. Compared to PRT patients at 12 months, UC patients had greater reductions in BCM by $-1.9 \pm 0.8\%$ ($p = 0.02$) and higher gains in fat mass by $3.1 \pm 1.0\%$ ($p = 0.002$). There was a significant increase in physical activity levels ($p = 0.02$), and QOL in the mental health ($p = 0.01$) and vitality ($p = 0.02$) domains in the PRT compared to the UC group.

Conclusion A home-based PRT program instituted at the start of ADT counteracts detrimental changes in body composition, improves physical activity and mental health over 12 months.

Background

Prostate cancer has the second highest incidence of all cancers amongst men worldwide and is the fifth leading cause of cancer death in men (1). Androgen receptor signalling strongly promotes prostate cancer growth. Thus, androgen deprivation therapy (ADT) with gonadotrophin releasing hormone (GnRH) analogues is a commonly utilised therapy for men with prostate cancer. However, in rendering the patient hypogonadal, ADT is associated with significant adverse metabolic effects. Changes in body composition occur rapidly, with increases of approximately 7–10% in fat mass (FM), and decreases of 2–4% in lean body mass (LBM) after 1 year of ADT (2), with these effects persisting up to two years following cessation (3). Patients also commonly experience a reduction in muscle strength and bone density, development of type 2 diabetes, and a deterioration in quality of life (4).

Physical exercise is currently recognised as an effective strategy to ameliorate many of the adverse effects of ADT (5). Clinical trials have shown both resistance and aerobic exercise improve body composition, metabolic profile, functional capacity, fatigue and health related quality of life (HRQOL) (6). Progressive resistance training (PRT) is an anabolic form of exercise which involves challenging the skeletal muscles with unaccustomed loads. It is well established that PRT is beneficial in the treatment of sarcopaenia in older men and women (7), and is also efficacious in the treatment of ADT-induced adverse effects. However, limitations exist in the current body of literature relating to exercise intervention studies in prostate cancer. Firstly, much of the evidence is derived from interventional studies occurring in patients on stable ADT with an average treatment time of 14 months (8), while the development of adverse effects has been shown to be the most pronounced during the initial months of ADT (9, 10). Only one study by Cormie et al. (8) has examined the use of a supervised exercise program in the prevention of adverse effects when administered at the initiation of ADT. This showed a preservation of appendicular LBM and prevention of gains in whole body FM, when compared to usual care. Secondly, current studies are focused on supervised training programs located in exercise clinics. While compliance rates are superior compared to purely home-based exercise programs (11, 12), fully supervised programs are resource intensive, less accessible and transitioning to community-based programs after a period of close supervision can be confronting for some patients (13, 14). Thus, more evidence is needed regarding the feasibility and efficacy of home-based programs.

The aim of this study was to investigate whether a year long, home-based PRT program, instituted at the start of ADT, would prevent adverse effects of treatment in prostate cancer patients.

Methods

This was a 12-month randomised controlled study of progressive resistance training (PRT) in patients with prostate cancer patients commencing ADT. The detailed recruitment procedures have been described previously (15). In brief, 25 men with prostate cancer scheduled to receive conventional ADT with GnRH analogues were recruited from the Crown Princess Mary Cancer Centre, Westmead Hospital and the Blacktown Cancer and Haematology Centre, Blacktown Hospital, Australia. Inclusion criteria included men aged between 50 and 80 years with histologically confirmed prostate cancer of early or locally advanced stage with ≤ 5 sites of metastases and Eastern Cooperative Oncology Group (ECOG) 0 performance status. Exclusion criteria included concurrent chemotherapy or anti-androgen therapy, previous ADT within the last 12 months, or any musculoskeletal, cardiovascular and/or neurological disorders that could inhibit them from exercising. This

study was approved by the Western Sydney Local Health District Human Research Ethics' Committee. All participants gave written consent. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616001311448).

Experimental Design

A two-armed prospective randomised controlled trial design was implemented. The 25 men were randomised into two arms: PRT (13 men), or usual care (UC) (12 men) using a computer random assignment program. As part of routine care, all participants received non-standardised advice from the treating clinician to participate in regular exercise throughout the intervention period.

PRT intervention

Participants assigned to the PRT group undertook 52 weeks of a home-based PRT program starting soon after their first ADT injection. Resistance training was performed three times per week, with 8–10 exercises targeting the major muscle groups using adjustable dumbbells or body weight loading (calisthenics). Patients performed three sets per exercise with 8–12 repetitions maximum per set. The difficulty and/or the loading of each exercise was advanced with strength adaptation (16). There were three stages of exercises. Stage one: incline push-up, bent over row, biceps curl, triceps extension, side shoulder raise, dumbbell squat, split squat and straight leg deadlift. Stage two involved addition of shoulder press. Stage three: standard push-up, decline push-up, curl to press, chair dips, lunge, side shoulder raise, dumbbell squat, straight leg deadlift. Patients advanced to the next stage after 12 weeks depending on strength and ability determined by the supervising exercise physiologist.

One week of exercise supervision (two sessions) were provided by an accredited exercise physiologist at baseline to instruct patients in proper lifting techniques and loading progressions. Patients then returned for a supervised session every 12 weeks to learn the next stage of exercises, and to ensure proper techniques were being utilised at home. To maximise adherence, online instructional videos and a printed training manual was provided for each exercise, and patients were given monthly reminder phone calls. Adherence to exercise was recorded in a training logbook by patients. Overall activity levels of all participants were monitored by physical activity questionnaires and total step counts for 1 week (via a pedometer) prior to their study visits.

Outcome Measures

Study endpoints were assessed at baseline, 6 weeks, 6 months and 12 months of ADT.

Energy expenditure

Whole-body energy expenditure and substrate oxidation were measured by indirect calorimetry. An open-circuit ventilated hood system (ParvoMedics, Sandy, UT, USA) was used, and calibrated against standard gases before each study. The participants rested on a bed for 30 min before each study. A clear plastic hood was then placed over their heads for a 20-min period. The measurements were taken during two 20-min periods and averaged.

Oral glucose tolerance test

Glucose metabolism was assessed using the oral glucose tolerance test (OGTT). Blood glucose and insulin concentrations were measured at baseline and after a 75 g glucose load at 30, 60, 90- and 120-min. Hepatic insulin resistance (the product of total area under the curve for glucose and insulin during the first 30 min) and muscle insulin sensitivity (the rate of decay of plasma glucose concentration from its peak value to its nadir divided by the mean insulin concentration) were calculated (17). Using the OGTT results, calculations were made of the HOMA-IR, the oral disposition index (18), Matsuda index (index of insulin sensitivity) (19) and overall glucose metabolism was estimated as the incremental glucose area under the curve above fasting over 120 min (18).

Body composition and bone mineral density

LBM and total and regional FM were assessed by dual x-ray absorptiometry (DXA; GE Healthcare Lunar Prodigy Pro) and Bioelectrical Impedance Spectroscopy (BIS) using the ImpediMed Ltd SFB7 analyser (ImpediMed Ltd Qld, Australia) (20). Change in body cell mass (BCM), a functional component of LBM, was estimated by subtracting extracellular water (ECW) from LBM. Vertebral and hip bone mineral density was also measured by DXA at each visit.

Physical activity

A pedometer (G-Sensor 2026) was used to estimate step counts for one week prior to each visit. Patients were asked to complete an exercise diary for one week prior to each visit and to specify the number of hours of light, moderate or intense physical activity. Patients in the PRT group were instructed not to include the intervention in their documented activity, but to only include other types of physical activity.

Physical function

A series of standard tests were used to assess physical function. Maximal strength of the upper and lower body was assessed by an isometric dynamometer (i.e. triceps extension and knee extension) (Chatillon CSD200, JMW Instruments, Chicago, USA) hand-grip strength by a dynamometer (Jamar Plus digital dynamometer). The best performance over 3 trials was recorded. Function lower extremity strength was assessed using the sit-to-stand test (21). The participant is encouraged to complete as many full stands from a chair as possible within 30 sec. The timed get-up-and-go test (TUGT) was used to evaluate dynamic balance and physical performance (22). From a seated position, the participants stood, walked 3 metres, turned around, walked back to the chair, returning to a seated position as quickly as possible (best performance out of three recorded). The Lord sway-meter was used to assess co-ordinated stability, which measures participants' ability to adjust balance in a steady and co-ordinated way while placing them near or at the limits of their base of support. This test uses a 40 cm rod attached to the participant at waist level by a firm belt. Participants are then asked to adjust balance by bending or rotating their body without moving their feet, so that a pen mounted vertically at the end of the rod remains within a convoluted track. A total error score is calculated (23). The postural sway test was used to assess dynamic balance. Participants stood barefoot on the floor or foam surface with open and closed eyes. The test records sway path, maximal anterior-posterior and lateral sway, measured by the Physiological Profile Assessment (PPA) Sway Path Mobile Applications (NeuRa) on an iPad attached to the top of an adjustable height table (24). Aerobic capacity (Submaximal VO_2) was measured by a cycle ergometer (Lode Corival Recumbent Ergometer) and data analysed using LEM software.

Quality of life

HRQOL was assessed at each study visit by the EORTC (European Organisation for Research and Treatment of Cancer) quality of life questionnaires including the QLQ-C30 (used to assess the QOL of cancer patients) and QLQ-PR25 (used to measure disease-specific HRQOL of prostate cancer patients undergoing active treatment). In addition, the Short Form 36 version 2.0 (SF-36v2) physical and psychological health survey was also used.

Blood biomarkers

At each visit, fasting blood samples were taken and stored at -80°C for analysis. All samples for any individual were measured in the same assay run for each analyte. An electrochemiluminescence immunoassay (ECLIA) was used to measure serum SHBG, total testosterone and PSA. The inter-assay CVs for SHBG at 45.7 nmol/L was 2.1%; total testosterone at 0.087 nmol/L, 2.8%; and for total PSA at 1.12 ng/mL, 3.2%. Serum IGFBP-2, IGFBP-3, leptin, adiponectin and decorin were measured by Abcam's human enzyme-linked immunosorbent assay (ELISA). The inter-assay CVs for IGFBP-3 was 5.7%, and for IGFBP-2, leptin, adiponectin and decorin, < 12%. A HMYOMAG-56K MILLIPLEX® MAP Human Myokine Magnetic Bead Panel was used for analysis of brain-derived neurotrophic factor (BDNF) and osteonectin. The inter-assay CVs were < 15% and < 20%, respectively.

Statistical analysis

Sample size calculation was based on a previous study showing improvements in muscle strength following PRT in older adults (25). To achieve 80% power at an alpha level of 0.05 (two tailed), 12 subjects in each group is required to detect a difference in change in lower limb strength (leg curl) of 12 kg.

The statistical analysis consisted of a linear mixed effects model, using a random patient effect to account for baseline and fixed effects for the visit and intervention arm. In this analysis, a difference in time course behaviour between study arms corresponded to an interaction between visit and intervention. Comparisons at specific time points were made using contrasts extracted from the mixed effects model and separately using two-sample t-tests of change in endpoint. Results are expressed as mean $\pm$ S.E.M and a P value < 0.05 was considered significant. Linear regression analysis was used to correlate serum PSA and IGFBP-3 across the time points. All analysis was conducted in R version 3.6.0 (Vienna, Australia), RStudio IDE (Boston, MA) and SPSS statistics v22 (IBM corporation).

Results

Baseline patient characteristics and retention

From May 2015 to December 2016, 12 patients were enrolled in the UC arm and 13 patients in the PRT arm and were followed up for 12 months. At 6 months, one patient in the UC arm was unable to attend follow-up due to hospitalisation (but remained in the study) and one patient in the PRT arm discontinued the study. At 12 months, two patients discontinued the study (one from each arm) and two patients from each arm were excluded from final analysis as ADT

was discontinued for more than 3 months prior to their 12-month visit (one from each arm). Thus, at 12 months, 10 patients remained in each arm for analysis (Figure 1).

Adherence to the home-based PRT program was determined by logbooks. Out of the 13 patients, one patient consistently did not comply with filling in his logbook citing poor literacy as the reason, although he reported full compliance with the PRT program. Logbook analysis showed that from baseline to 6 weeks, patients completed a mean of 2.8 sessions/week; 6 weeks to 6 months, 2.3 sessions/week, and from 6 to 12 months, 2.2 sessions/week. At 12 months, 50% of patients managed to comply with stage 3 exercises; 30% continued with stage 2 and 20% continued with stage 1.

At baseline (table 1), UC and PRT patients were well matched in terms of age, blood pressure, weight, body composition, PSA levels, as well as prostate cancer grade and stage. Testosterone levels were significant higher in the UC group ($p = 0.02$). There were no significant differences between groups in terms of baseline activity level as assessed by pedometer step counts and hours of light, moderate or intense physical activity.

Table 1. Baseline clinical characteristics

Variable	UC (n =12)	PRT (n = 13)	P value
Age (years)	71.8 $\pm$ 1.8	69.3 $\pm$ 2.3	0.14
Weight (kg)	79.9 $\pm$ 2.7	87.2 $\pm$ 4.7	0.03
BMI kg/m ²	28.8 $\pm$ 1.1	29.7 $\pm$ 1.3	0.36
SBP (mmHg)	137 $\pm$ 2	139 $\pm$ 4	0.18
DBP (mmHg)	74 $\pm$ 3	74 $\pm$ 1	0.11
Gleason score	7.6 $\pm$ 0.3	8.2 $\pm$ 0.2	0.42
Cancer staging			
Localized (n)	9	8	0.36
Biochemical recurrence (n)	3	3	
Metastatic (n)	0	2	
Previous radiotherapy (n)	8	5	0.39
Previous ADT (n)	0	2	0.26
Lean body mass (kg)	53.1 $\pm$ 1.2	54.5 $\pm$ 2.2	0.16
LBM (% body weight)	66.5 $\pm$ 1.8	63.2 $\pm$ 2.0	0.68
Fat mass (kg)	24.2 $\pm$ 2.1	29.9 $\pm$ 3.2	0.12
Extracellular water (L)	19.0 $\pm$ 0.6	19.8 $\pm$ 0.9	0.05
BCM (kg)	34.1 $\pm$ 1.0	34.7 $\pm$ 1.3	0.58
Testosterone (nmol/L)	16.1 $\pm$ 1.1	12.5 $\pm$ 0.8	0.02
LH (mIU/mL)	7.0 $\pm$ 0.7	6.3 $\pm$ 0.7	0.70
PSA (ng/mL)	11.9 $\pm$ 2.6	7.7 $\pm$ 1.3	0.08
Step count (number)	40172 $\pm$ 8502	28838 $\pm$ 5377	0.14
Light physical activity (hours)	5.9 $\pm$ 1.6	7.9 $\pm$ 2.5	0.09
Moderate physical activity (hours)	3.9 $\pm$ 1.8	3.3 $\pm$ 1.4	0.93
High physical activity (hours)	0.1 $\pm$ 0.1	0.5 $\pm$ 0.3	0.05

Data are presented as mean $\pm$ S.E.M; P -value is for UC vs PRT group; BMI, body mass index; LBM, lean body mass; BCM, body cell mass; LH, luteinizing hormone; PSA, prostate-specific antigen

Response to ADT across the cohort

Following the administration of ADT, as expected, serum testosterone levels significantly decreased ($p < 0.0001$) by 6 weeks, remaining at castrate levels at 12 months ($p < 0.0001$) (Figure 2A). Similarly, serum PSA levels fell from 9.7 ± 1.5 ng/mL to 0.4 ± 0.1 ng/mL at 12 months (Figure 2B).

Table 2 summarises the effect of ADT on measured indices throughout the follow-up period. At 6 months, there was a significant change in body composition ($p < 0.001$) with a decrease in BCM (BCM %) and increase in FM (FM %) as a percentage of total body mass (TBM).

Similarly, there was a significant increase in fasting glucose ($p < 0.001$), HOMA- IR ($p = 0.01$), as well as hepatic and muscle insulin resistance ($p < 0.01$ and $p = 0.02$, respectively). There was a significant reduction in insulin sensitivity as represented by the Matsuda Index ($p < 0.001$). Bone mineral density also significantly decreased at the lumbar spine ($p = 0.046$) as did muscle strength, with a reduction in right hand grip ($p = 0.003$), left hand grip ($p = 0.04$) and lower limb strength ($p = 0.01$). These changes persisted at 12 months. At study completion, there was a -3.6 ± 0.4 % ($p < 0.001$) decrease in BCM and 3.8 ± 0.5 % ($p < 0.001$) increase in FM. Fasting insulin increased by 6.1 ± 2.1 IU/L ($p < 0.001$). There was a reduction in physical function as reflected by a prolongation in the TUGT by 0.4 ± 0.1 sec ($p = 0.02$) and a decrease in co-ordinated stability ($p < 0.001$). Quality of life also fell with a significant reduction in the QLQ-C30 summary score by -3.6 ± 1.3 ($p = 0.007$).

The effect of ADT on growth factors and adipokines

At 6 weeks, there was a significant reduction in BDNF levels from 8208 ± 1268 pg/mL to 6126 ± 1038 pg/mL ($p = 0.003$) but significance was not maintained at 6 weeks and 6 months (Figure 3A). At 12 months, there was a significant increase in serum adiponectin compared to baseline ($p = 0.006$) (Figure 3C) ($p < 0.001$). There were no significant changes in serum IGFBP-2 and IGF-1 following treatment with ADT. However, there were significant increases in serum leptin ($p < 0.001$) (Figure 3B), IGFBP-3 ($p = 0.02$) (Figure 4A) and the IGF-1: IGFBP-3 ratio at 12 months ($p = 0.02$) (Figure 4B). There was also a negative correlation between serum PSA levels and IGFBP-3 across all time points ($R^2 = 0.07$, $p = 0.01$) (Figure 4C).

The effect of PRT – results of the randomised intervention

Body Composition

The effect of PRT on changes in body composition is shown in Figure 2. At 6 weeks and 6 months, there was a trend towards a greater reduction in LBM % and BCM % in the UC versus the PRT group but this did not reach statistical significance. However, at 12 months there was a preservation of both LBM % by 2.7 ± 0.8 % ($p = 0.001$) and BCM % by 1.9 ± 0.8 % ($p = 0.02$) (Figure 5A) in the PRT versus UC group. Similarly, there was a trend towards a larger gain in FM % at 6 weeks and 6 months in the UC group but this was not statistically significant. At 12 months, patients in the PRT group experienced less of a gain in fat mass, with a -3.1 ± 1.0 % ($p = 0.002$) difference between the two groups (Figure 5B). When assessing regional fat mass, the biggest difference between groups was observed with trunk mass ($p = 0.02$) (Table 3).

Glucose Tolerance and Insulin Resistance

At 6 weeks, there was a decrease in the Matsuda Index in the UC group by -0.3 ± 0.5 ($p = 0.47$) and significant increase in the PRT by 2.2 ± 0.7 ($p = 0.009$) with an overall difference between groups of 2.5 ± 0.8 ($p = 0.004$) (Table 4). However, this significant early difference was not maintained at 6 and 12 months. There were no significant differences between groups in terms of plasma insulin and glucose levels, HOMA-IR, disposition index, or liver and muscle insulin resistance.

Blood biomarkers

PRT did not have any effect on blood pressure, liver function or serum lipids at the various time points. There were no differences between groups in terms of PSA levels, IGF-1, IGF-binding proteins, leptin, adiponectin and other measured biomarkers (Table 5).

BMD and physical function

There were no differences in BMD of the femoral neck or lumbar spine between the UC and PRT groups at each of the time points (Table 6). Similarly, PRT had no significant effect on muscle strength, balance, or submaximal VO_2 (Table 6). However, there was a significant increase in physical activity levels in the PRT group as measured by step count compared to the UC group at 12 months ($p = 0.02$) (Table 6). There were no differences in physical activity levels between groups.

Quality of Life

The effect of PRT on HRQOL is summarised in Table 7. At 6 weeks, there was a reduction in the SF36v2 general health score in the UC group and an increase in the PRT group, with a significant difference of 5.0 ± 2.4 ($p = 0.04$) between the two groups. At 6 months, there were significantly greater reductions in the EORTC QLQ-C30 score for global health status ($p = 0.02$), SF36v2 scores for vitality ($p = 0.02$) and social functioning ($p = 0.03$) in the UC compared to the PRT group. In addition, the EORTC QLQ-C30 score for pain was significantly higher in the UC compared to the PRT group ($p = 0.02$). At 12 months, the SF36v2 scores for vitality and mental health both improved in the PRT group, as opposed to a reduction in the UC group (Figure 6A and 6B).

Intervention safety and adherence

In terms of adverse events, one patient developed right shoulder pain (rotator cuff tendonitis) at the completion of the study, requiring physiotherapy.

Discussion

This randomised controlled trial examined the efficacy of a 12-month home-based PRT program in the prevention of the adverse effects of ADT. Our study was able to demonstrate the detrimental effects of ADT on body composition, insulin resistance, BMD, physical function and quality of life. We showed that the early implementation of a 12-month home-based PRT program at the start of ADT resulted in beneficial effects on body composition and physical activity levels, and clinically meaningful improvements in quality of life.

ADT is well known to decrease LBM and increase FM, resulting in sarcopaenic obesity (26). Across the cohort, we found a significant reduction in BCM (a functional component of LBM) and a significant increase in FM after 12 months of ADT. This was accompanied by a significant increase in insulin resistance and reduction in insulin sensitivity, as measured by the HOMA-IR and Matsuda index, respectively, at 6 and 12 months, similar to previous findings by Smith et al. (27). Likewise, at 6 and 12 months, both muscle and hepatic insulin resistance also increased, which is in keeping with current knowledge regarding the relationship between androgen deficiency and the metabolic syndrome. For example, global deletion of the androgen receptor (AR) in male mice results in impairment of insulin signalling in both skeletal muscle and liver leading to development of insulin resistance (28). We also found reductions in BMD, muscle strength, physical function, coordinated stability and quality of life following 12 months of ADT.

This study showed that a home-based PRT program was able to significantly counteract ADT-induced changes in body composition. PRT was able to offset reductions in LBM by $2.7 \pm 0.8\%$ (1.2 ± 0.2 kg) at 12 months. Similar results were found with BCM, a functional component of LBM. Previous studies investigating PRT in the prostate cancer population are supervised, rather than home-based, and BCM has not been examined previously. A 12-month study conducted by Winters-Stone et al. (29) did not show any differences in LBM between

the PRT and control group. However, Nilsen et al. (30) found a preservation of LBM in the PRT group, with a 2.22 kg difference compared to the control group after 24 weeks. Although our study found a significant effect of PRT on LBM, the magnitude of difference may have been greater with a supervised training program (29).

Our study showed an increase in FM in both the UC and PRT groups but PRT was able to offset a gain in FM by $3.1 \pm 1.0\%$ (2.3 ± 0.8 kg). This is similar to findings by Winters-Stone et al. (29) who found a 1.9 kg difference in FM between the UC and PRT groups after 52 weeks of supervised PRT. Importantly, we found that PRT had the greatest effect on truncal fat mass. Dickerman et al. (31) found that higher visceral fat and waist circumference, a surrogate of central adiposity, were associated with advanced and fatal prostate cancer. Thus, these results provide evidence on the benefits of home-based PRT programs in counteracting ADT-induced negative effects on body composition in the prostate cancer population.

We found an improvement in insulin sensitivity as measured by the Matsuda Index in the PRT group at 6 weeks, however, this difference was not maintained at 6 and 12 months. There is currently a paucity of studies regarding the benefits of PRT on insulin resistance. Fasting insulin levels can be used as a surrogate marker of insulin resistance (32). In an RCT involving a supervised PRT program in patients on long term ADT, Winters-Stone et al. (29) found a non-significant reduction in insulin levels in the PRT group compared to an increase in the control group. In a population of patients with type 2 diabetes, a home-based PRT program was also unable to maintain the glycaemic benefits obtained from supervised gymnasium based PRT (33). Thus, PRT may have initial benefits on glucose metabolism that is difficult to sustain during long-term ADT.

This study showed significant reductions in muscle strength, co-ordinated stability, dynamic balance and lower limb functional performance with long-term ADT. However, we were unable to demonstrate significant differences in muscle strength or physical fitness between the UC and PRT groups. Previous studies involving supervised PRT showed gains in both upper and lower limb strength in prostate cancer patients (12, 30, 34) and Taaffe et al. (12) reported an improvement in physical fitness. In a 6 week home-based exercise program of both aerobic and resistance exercises, Lee et al. (35) found improvements in upper body strength and physical fitness. It is known that home-based programs may have lower adherence, training volume and loading compared to supervised programs (33) which may reduce the potential for strength adaptation or maintenance following initiation of ADT. In our study, patients managed to participate in 2.8 sessions/week from baseline to 6 weeks, decreasing to 2.2 sessions/week in the last 6 months of the study, with 50% able to complete stage 3 exercises. Investigations are needed to identify the underlying reasons for reduced participation over time as disease and treatment-related factors, changing symptomology, and motivational/psychological issues may be contributing.

Our study showed at 12 months that overall physical activity levels as measured by pedometer step counts was higher in the PRT compared to UC group. Physical activity is important in prostate cancer as Phillips et al. found that a higher duration of total, non-vigorous walking activity in prostate cancer survivors was associated with improved HRQOL (36). There is also a correlation between physical activity and reduced mortality in prostate cancer patients (37). Thus, the finding that a home-based PRT program can increase physical activity levels are encouraging, given the insufficient levels of physical activity in the population of men with prostate cancer, with a study by Silva et al. showing that 56.5% of a cohort of men with prostate cancer were inactive based on exercise recommendations by the American College of Sports Medicine (38).

ADT results in a significant decline in bone mass and an increase in fracture risk (39, 40). This study demonstrated a significant decline in BMD at the lumbar spine as early as 6 months of ADT, which was not attenuated by PRT. Only Winters-Stone et al. (29) has reported preservation of BMD at the L4 site in patients in the PRT group versus the control group. Thus, the lack of effect of our home-based PRT program on BMD may be attributed to insufficient duration and impact loading (41).

Psychological distress and anxiety is prevalent amongst men with prostate cancer ranging from 15–27%, and highest in those who have yet to undergo treatment (42). This was reflected in our findings, which showed a significant decline in HRQOL following ADT. However, we also showed that the use of a concurrent home-based PRT program at the start of ADT resulted in significant improvements in HRQOL including vitality and mental component summary (MCS) score which encompasses vitality, social functioning, and emotional well-being (43). This is in line with the effects of supervised PRT programs which showed improvements in fatigue, vitality and mental health (12, 44). These results provide evidence that the mental health benefits of PRT are seen even when implemented in an unsupervised setting.

Across the cohort, ADT affected both growth factors and adipokines. There was no significant change in serum total IGF-1 levels but a significant decrease in IGF-1: IGFBP-3 ratio was found at 6 and 12 months, indicating a reduction in IGF-1 bioactivity. Higher serum IGF-1 levels are associated with tumour progression (45). This study also showed significant increases in serum IGFBP-3 levels at 6- and 12-months following ADT, which has not been previously shown in human studies. IGFBP-3 inhibits prostate cancer growth independent of IGF-1 (46). In-vitro studies of prostate cancer cells show an increase in IGFBP-3 mRNA levels following androgen deprivation, thus facilitating cellular apoptosis (47). We also showed a significant inverse relationship between PSA and IGFBP-3 levels. PSA is a serine protease found in

semen with potent IGFBP-3 protease activity (48). It is postulated that generation of a lower affinity IGFBP-3 fragment by PSA can increase bioactive IGF-1, thereby mediating prostatic growth. Thus, results from our study may suggest a role for serum IGFBP-3, as an adjunct to PSA, in the assessment of treatment response to ADT, although more widescale studies are required.

As expected, serum leptin and adiponectin levels significantly increased following ADT, likely related to an increase in fat mass (49, 50). At 6 weeks following ADT, there was a significant reduction in serum BDNF levels, but significance was not maintained at 6 and 12 months. BDNF is a member of the neurotrophin family of growth factors which support neuronal survival (51). A reduction in BDNF is implicated in the development of depression (51). It is also secreted by prostate cancer cells and have mitogenic effects on the prostatic epithelium (52). Our study showed, for the first time, a reduction in BDNF during ADT initiation in prostate cancer patients. This warrants further investigations, given the potential role of BDNF in the pathogenesis of prostate cancer.

There are limitations to this study. The sample size was relatively small which may have affected the ability to observe differences, particularly in terms of muscle strength and physical function. The large number of outcome measures in relation to the small sample size also raises the possibility of chance findings. Participants were also relatively well functioning individuals who were motivated to undertake home-based exercise and may not be representative of the prostate cancer population at large. Home-based programs also have limitations - particularly in terms of long-term adherence, and ability to achieve maximal intensity and adequate loading for muscle adaptation. However, this study is unique in that it explores the use of isolated PRT at the start of ADT in a home-based setting which has not been investigated previously. Although there is robust data supporting the use of supervised PRT in prostate cancer patients, it is resource intensive and may not be feasible to implement across the whole prostate cancer population. We were able to demonstrate positive outcomes across a 12-month period with a lower resource alternative.

Conclusion

In conclusion, this is the first randomised controlled trial to show that a home-based PRT program instituted at the start of ADT was able to counteract detrimental changes in body composition and improve both physical activity and mental health over a 12-month period. Thus, a home-based PRT program offers clinicians a viable alternative to more resource-intensive supervised programs when instituted at the commencement of ADT and should be recommended following diagnosis of prostate cancer.

List Of Abbreviations

ADT- androgen deprivation therapy

BCM- body cell mass

BDNF- brain-derived neurotrophic factor

FM- fat mass

HRQOL- health related quality of life

IGF-1- insulin-like growth factor 1

IGFBP-3- insulin-like growth factor binding protein 3

LBM- lean body mass

PRT- progressive resistance training

PSA- prostate specific antigen

SHBG- sex hormone binding globulin

TUGT- timed up and go test

UC- usual care

Declaration Of Interest, Funding And Acknowledgements

Ethics approval and consent to participate

This study was approved by the Western Sydney Local Health District Human Research Ethics' Committee. All participants gave written consent. The study was registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12616001311448).

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests

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Author's contributions

All authors have read and approved the manuscript.

TL was responsible for study design, patient recruitment, study visit conduct, patient follow-up, data analysis and wrote the manuscript. BC developed exercise protocol, assisted with exercise training sessions and contributed to manuscript preparation. AH assisted with study design, patient recruitment and manuscript preparation. SL contributed to study design (tests of physical function) and manuscript preparation. HG contributed to study design, patient recruitment and manuscript preparation. SG assisted with exercise training sessions. NR assisted with patient recruitment and study visit conduct. HS and SR assisted with assays and manuscript preparation. GS assisted with statistical analysis and manuscript preparation. MM assisted with study design and manuscript preparation. VB developed research concept, assisted with study conduct, data analysis and contributed to manuscript preparation.

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Tables

Table 2. Effect of ADT on body composition, metabolism and physical function across the cohort

Variables	Baseline (n = 25)	6 weeks (n = 25)	Change from baseline (6 weeks)		6 months (n = 23)	Change from baseline (6 months)		12 months (n = 20)	Change from baseline (12 months)	
				P value			P value			P value
Total mass (kg)	84.4 (3.4)	84.9 (3.4)	0.4 (0.4)	0.37	84.9 (3.4)	0.8 (0.5)	0.07	85.4 (3.3)	1.3 (0.5)	0.008
BCM (%)	42.2 (1.5)	41.9 (1.5)	-0.4 (0.4)	0.34	40.5 (1.4)	-1.9 (0.4)	< 0.001	38.6 (1.2)	-3.6 (0.4)	< 0.001
FM (%)	31.5 (1.8)	31.9 (1.8)	0.5 (0.5)	0.35	33.6 (1.6)	2.4 (0.5)	< 0.001	35.2 (1.3)	3.8 (0.5)	<0.001
Neck of femur BMD (left total)	0.998 (0.03)	1.007 (0.03)	0.01 (0.008)	0.20	1.003 (0.03)	0.006 (0.008)	0.46	0.99 (0.03)	-0.006 (0.009)	0.49
Neck of femur BMD (right total)	0.989 (0.03)	1.012 (0.03)	0.02 (0.009)	0.03	0.999 (0.03)	0.009 (0.009)	0.29	0.991 (0.03)	0.0004 (0.009)	0.97
Lumbar spine BMD	1.329 (0.05)	1.313 (0.05)	-0.004 (0.01)	0.79	1.291 (0.06)	-0.03 (0.01)	0.046	1.28 (0.05)	-0.04 (0.01)	0.004
Fasting glucose (mmol/L)	4.6 (0.1)	4.7 (0.1)	0.1 (0.1)	0.2	5.3 (0.2)	0.7 (0.1)	<0.001	5.3 (0.2)	0.7 (0.1)	<0.001
Fasting insulin (IU/L)	7.9 (1.4)	9.7 (3.6)	1.4 (1.9)	0.47	11.3 (1.5)	4.0 (2.0)	0.05	13.8 (2.3)	6.1 (2.1)	<0.001
Matsuda index	6.0 (0.7)	7.2 (1.0)	1.0 (0.4)	0.03	4.7 (0.6)	-1.6 (0.5)	<0.001	4.5 (0.6)	-1.8 (0.5)	<0.001
HOMA-IR	1.6 (0.3)	2.1 (0.8)	0.4 (0.5)	0.43	2.7 (0.4)	1.2 (0.5)	0.01	3.5 (0.6)	1.9 (0.5)	<0.001
Hepatic insulin resistance	39.4 (7.6)	34.1 (6.9)	-3.9 (6.5)	0.55	56.8 (9.6)	20.1 (6.7)	<0.01	66.6 (14.5)	30.3 (7.0)	<0.001
Muscle insulin resistance	0.6 (0.3)	0.3 (0.2)	-0.2 (0.2)	0.40	1.1 (0.4)	0.5 (0.2)	0.02	1.1 (0.3)	0.5 (0.2)	0.02
Co-ordinated stability (corners)	0.2 (0.1)	0.3 (0.1)	0.04 (0.2)	0.87	0.6 (0.3)	0.4 (0.3)	0.15	1.3 (0.3)	1.0 (0.3)	<0.001
Right hand grip (N)	35.8 (1.5)	35.4 (1.7)	-0.5 (0.6)	0.43	34.1 (1.7)	-2.1 (0.6)	0.003	32.9 (1.6)	-3.3 (0.7)	<0.001
Left hand grip (N)	35.1 (1.6)	35.1 (1.7)	-0.04 (0.6)	0.95	33.4 (1.7)	-1.9 (0.6)	0.04	32.0 (1.7)	-3.3 (0.7)	<0.001
Upper limb strength (N)	146.9 (8.8)	156.5 (9.0)	5.1 (5.8)	0.38	143.1 (8.8)	-4.5 (6.0)	0.45	141.9 (7.8)	-7.0 (6.3)	0.27
Lower limb strength (N)	287.1 (17.6)	277.1 (13.9)	-8.1 (14.1)	0.57	243.5 (14.8)	-38.4 (14.5)	0.01	229.4 (14.5)	-56.5 (15.2)	<0.001
Sit-to-stand test (number)	18 (0.9)	20 (0.9)	1.3 (0.5)	0.39	20 (1.1)	1.2 (0.5)	0.56	19 (1.0)	0.4 (0.5)	0.25
TUGT (sec)	5.6 (0.2)	5.3 (0.1)	-0.3 (0.1)	0.03	5.8 (0.2)	0.2 (0.1)	0.2	5.9 (0.2)	0.4 (0.1)	0.02
QLQ-C30 summary score	89.6 (2.3)	91.2 (2.3)	0.4 (1.2)	0.77	89.5 (2.8)	-1.7 (1.3)	0.2	88.1 (2.5)	-3.6 (1.3)	0.007
Total cholesterol (mmol/L)	4.3 (0.2)	4.6 (0.2)	0.3 (0.1)	0.04	4.7 (0.3)	0.3 (0.1)	0.01	5.0 (0.3)	0.7 (0.1)	<0.001
LDL cholesterol (mmol/L)	2.6 (0.2)	2.7 (0.2)	0.1 (0.1)	0.59	2.7 (0.2)	0.1 (0.1)	0.31	3.0 (0.3)	0.4 (0.1)	<0.001
HDL cholesterol (mmol/L)	1.2 (0.1)	1.3 (0.1)	0.1 (0.04)	0.02	1.3 (0.1)	0.1 (0.04)	0.07	1.4 (0.1)	0.1 (0.05)	0.005
Triglycerides (mmol/L)	1.1 (0.1)	1.2 (0.1)	0.3 (0.1)	0.02	1.4 (0.1)	0.3 (0.1)	0.004	1.4 (0.1)	0.3 (0.1)	0.008

Data are presented as mean $\pm$ S.E.M; *P* value represents change compared to baseline across the cohort at 6 weeks, 6 months and 12 months; BCM, body cell mass; FM, fat mass; BMD, bone mineral density; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 3: Effect of PRT on body composition: absolute values and changes over 6 weeks, 6 months and 12 months

Variables	Baseline		6 weeks		Group difference in mean change over 6 weeks PRT vs UC		6 months		Group difference in mean change over 6 mo PRT vs UC		12 months		Group difference in mean change over 12 mo PRT vs UC	
	UC (n = 12)	PRT (n = 13)	UC (n = 12)	PRT (n = 13)		P value	UC (n = 11)	PRT (n = 12)		P value	UC (n = 10)	PRT (n = 10)		P value
Total mass (kg)	80.3 (2.6)	87.3 (4.6)	80.0 (2.5)	88.4 (4.7)	1.5 (0.9)	0.09	80.7 (2.6)	89.3 (5.1)	0.5 (0.9)	0.60	82.0 (2.7)	88.7 (5.5)	-1.0 (0.9)	0.30
Total LBM (kg)	53.1 (1.2)	54.5 (2.2)	52.1 (1.1)	54.7 (2.1)	1.1 (0.7)	0.09	51.4 (1.0)	53.9 (2.2)	1.0 (0.7)	0.14	50.4 (1.2)	52.8 (2.5)	1.2 (0.7)	0.10
Total LBM (% total mass)	66.5 (1.8)	63.2 (2.0)	65.6 (1.7)	62.8 (2.2)	0.5 (0.8)	0.47	64.1 (1.7)	61.4 (2.2)	1.3 (0.8)	0.11	61.7 (1.4)	60.4 (2.1)	2.7 (0.8)	0.001
Total BCM (kg)	34.1 (1.0)	34.7 (1.3)	33.3 (1.0)	34.9 (1.3)	1.0 (0.6)	0.11	32.6 (1.0)	34.1 (1.4)	1.0 (0.7)	0.12	31.8 (0.9)	33.1 (1.6)	0.8 (0.7)	0.28
Total BCM (% total mass)	42.8 (1.7)	40.3 (1.7)	41.9 (1.6)	40.4 (1.8)	1.0 (0.8)	0.21	40.7 (1.6)	38.8 (1.9)	1.3 (0.8)	0.10	39.0 (1.4)	37.7 (2.0)	1.9 (0.8)	0.02
Total FM (kg)	24.1 (2.1)	29.9 (3.2)	24.7 (2.0)	30.6 (3.4)	0.2 (0.8)	0.78	26.2 (2.2)	32.3 (3.6)	-0.7 (0.8)	0.35	28.5 (2.1)	32.9 (3.6)	-2.3 (0.8)	0.006
Total FM (% total mass)	30.5 (1.9)	33.9 (2.2)	31.1 (1.9)	34.1 (2.2)	-0.4 (0.9)	0.65	32.9 (1.9)	35.9 (2.3)	-1.1 (0.9)	0.25	34.9 (1.5)	36.1 (1.9)	-3.1 (1.0)	0.002
FM trunk (kg)	14.8 (1.7)	18.2 (1.9)	15.4 (1.7)	18.7 (2.1)	-0.1 (0.7)	0.94	15.8 (1.8)	19.1 (2.2)	-0.8 (0.7)	0.39	16.8 (1.8)	19.0 (1.9)	-1.8 (0.8)	0.02
FM android (kg)	2.9 (0.3)	3.4 (0.4)	2.9 (0.4)	3.6 (0.4)	0.1 (0.2)	0.67	3.0 (0.4)	3.6 (0.4)	-0.1 (0.2)	0.58	3.1 (0.4)	3.5 (0.3)	-0.3 (0.2)	0.15
FM gynoid (kg)	3.5 (0.2)	4.5 (0.4)	3.6 (0.2)	4.6 (0.5)	0.1 (0.2)	0.68	4.0 (0.2)	4.9 (0.5)	-0.1 (0.2)	0.51	4.2 (0.3)	5.2 (0.6)	-0.03 (0.2)	0.87

Data are presented as mean $\pm$ S.E.M; P value represents group differences in mean changes between PRT and UC at 6 weeks, 6 months and 12 months; LBM, lean body mass; BCM, body cell mass; FM, fat mass.

Table 4. Effect of PRT on glucose tolerance and insulin resistance: absolute values and changes over 6 weeks, 6 months and 12 months

Variables	Baseline		6 weeks		Group difference in mean change over 6 weeks PRT vs UC		6 months		Group difference in mean change over 6 mo PRT vs UC		12 months		Group difference in mean change over 12 mo PRT vs UC	
	UC (n = 12)	PRT (n = 13)	UC (n = 12)	PRT (n = 13)		P value	UC (n = 11)	PRT (n = 12)		P value	UC (n = 10)	PRT (n = 10)		P value
Glucose (mmol/L) Baseline	4.7 (0.1)	4.5 (0.1)	4.8 (0.1)	4.6 (0.1)	-0.1 (0.2)	0.73	5.2 (0.2)	5.3 (0.2)	0.2 (0.2)	0.34	5.4 (0.2)	5.3 (0.2)	0.01 (0.2)	0.94
Glucose (mmol/L) 30min	8.3 (0.5)	7.2 (0.4)	7.8 (0.4)	6.7 (0.3)	0.1 (0.5)	0.84	8.7 (0.4)	7.7 (0.4)	0.3 (0.5)	0.56	9.0 (0.5)	7.6 (0.4)	-0.3 (0.5)	0.53
Glucose (mmol/L) 60min	10.3 (0.6)	8.9 (0.5)	9.7 (0.6)	8.7 (0.5)	0.4 (0.6)	0.52	9.5 (0.5)	8.5 (0.6)	0.8 (0.6)	0.22	9.4 (0.7)	8.6 (0.5)	0.4 (0.6)	0.51
Glucose (mmol/L) 90min	10.4 (0.6)	9.5 (0.5)	9.6 (0.7)	9.3 (0.6)	0.6 (0.8)	0.46	9.1 (0.6)	8.2 (0.6)	0.3 (0.8)	0.73	7.4 (0.7)	8.5 (0.5)	1.9 (0.9)	0.05
Glucose (mmol/L) 120min	9.3 (0.5)	9.5 (0.5)	8.8 (0.4)	8.9 (0.5)	-0.1 (0.7)	0.86	7.1 (0.7)	7.5 (0.7)	0.3 (0.8)	0.74	6.7 (0.7)	7.2 (0.5)	0.02 (0.8)	0.97
Insulin (IU/L) Baseline	7.2 (1.9)	7.9 (1.3)	11.3 (5.6)	6.8 (1.4)	-5.2 (3.8)	0.18	12.2 (2.3)	11.2 (1.6)	-1.6 (3.9)	0.68	11.7 (2.3)	15.8 (3.7)	3.2 (4.1)	0.44
Insulin (IU/L) 30min	41.8 (11.2)	36.0 (4.9)	37.3 (7.0)	30.5 (6.7)	-1.0 (10.7)	0.92	62.9 (13.1)	44.7 (6.4)	-14.8 (11.1)	0.19	65.9 (17.9)	56.5 (13.7)	-3.0 (11.6)	0.80
Insulin (IU/L) 60min	58 (14.2)	47.3 (10.1)	56 (13.4)	44.7 (10.5)	-0.6 (13.9)	0.97	79.7 (19.7)	58.6 (10.9)	-9.7 (14.4)	0.50	86.2 (28.2)	66.1 (12.9)	-9.5 (15.1)	0.53
Insulin (IU/L) 90min	79.2 (15.8)	65.5 (9.4)	87.3 (25.0)	44.4 (6.9)	-29.2 (23.9)	0.23	133.1 (40.2)	63.4 (8.7)	-53.7 (24.6)	0.03	73.5 (19.8)	71.5 (14.2)	10.8 (25.8)	0.68
Insulin (IU/L) 120min	78.7 (22.7)	68.5 (14.5)	94.9 (30.8)	46.6 (10.5)	-38.2 (26.6)	0.15	115.6 (41.4)	53.3 (10.2)	-53.6 (27.4)	0.05	57.9 (10.9)	55.1 (12.5)	-2.5 (28.6)	0.93
HOMA-IR	1.5 (0.5)	1.5 (0.3)	2.5 (1.2)	1.4 (0.3)	-1.1 (0.9)	0.25	2.9 (0.6)	2.7 (0.4)	-0.2 (0.9)	0.83	2.9 (0.7)	3.9 (1.0)	0.9 (1.0)	0.34
Hepatic insulin resistance	40.7 (11.3)	32.9 (4.9)	39.2 (9.3)	26.9 (5.6)	-4.4 (13.1)	0.73	67.9 (15.4)	46.3 (6.5)	-14.8 (13.5)	0.28	74.0 (22.7)	62.5 (17.0)	-3.4 (14.2)	0.81
Muscle insulin resistance	0.9 (0.4)	0.1 (0.1)	0.6 (0.3)	0.1 (0.3)	0.3 (0.4)	0.50	1.4 (0.6)	0.6 (0.2)	0.1 (0.4)	0.77	1.3 (0.6)	0.8 (0.2)	0.4 (0.4)	0.38
Matsuda Index	6.2 (0.8)	5.9 (0.7)	5.8 (0.8)	8.1 (1.3)	2.5 (0.8)	0.004	4.3 (0.8)	4.6 (0.6)	0.4 (0.8)	0.64	4.7 (0.8)	4.1 (0.8)	-0.04 (0.9)	0.96
Disposition Index	2.6 (0.6)	3.7 (0.7)	3.0 (0.7)	5.9 (1.9)	1.7 (1.5)	0.25	2.7 (0.5)	3.4 (0.6)	-0.8 (1.50)	0.61	2.9 (0.6)	3.2 (0.9)	-0.3 (1.6)	0.84

Data are presented as mean $\pm$ S.E.M; *P* value represents group differences in mean changes between PRT and UC at 6 weeks, 6 months and 12 months.

Table 5. Effect of PRT on blood pressure and blood biomarkers: absolute values and changes over 6 weeks, 6 months and 12 months

Variables	Baseline		6 weeks		Group difference in mean change over 6 weeks		6 months		Group difference in mean change over 6 mo		12 months		Group difference in mean change over 12 mo	
	UC (n = 12)	PRT (n = 13)	UC (n = 12)	PRT (n = 13)	PRT vs UC	P value	UC (n = 11)	PRT (n = 12)	PRT vs UC	P value	UC (n = 10)	PRT (n = 10)	PRT vs UC	P value
Blood pressure (mmHg)	139 (4)	139 (6)	130 (5)		0.8 (7.8)	0.91	123 (3)	136 (5)	9.6 (8.0)	0.24				
Systolic	74 (6)	74 (1)	73 (3)	132 (5)	2.6 (4.7)	0.59	63 (2)	71 (3)	7.2 (4.9)	0.14	129 (5)	132 (6)	1.4 (8.4)	0.87
Diastolic				76 (2)							71 (4)	65 (2)	-7.4 (5.1)	0.15
Total cholesterol (mmol/L)	4.0 (3.4)	4.4 (0.3)	4.3 (0.4)	4.6 (0.3)	-0.1 (0.3)	0.63	4.6 (0.4)	4.5 (0.4)	-0.5 (0.3)	0.08	5.0 (0.4)	5.0 (0.4)	0.1 (0.3)	0.82
LDL cholesterol (mmol/L)	2.3 (0.3)	2.7 (0.2)	2.3 (0.3)	2.8 (0.2)	0.004 (0.2)	0.98	2.5 (0.3)	2.7 (0.3)	-0.3 (0.2)	0.19	2.9 (0.5)	3.0 (0.3)	-0.03 (0.2)	0.90
HDL cholesterol (mmol/L)	1.3 (0.1)	1.1 (0.1)	1.4 (0.1)	1.2 (0.1)	-0.07 (0.08)	0.41	1.5 (0.2)	1.1 (0.1)	-0.14 (0.09)	0.10	1.4 (0.1)	1.3 (0.1)	0.09 (0.09)	0.33
Triglycerides (mmol/L)	1.0 (0.1)	1.2 (0.1)	1.3 (0.2)	1.4 (0.1)	-0.1 (0.2)	0.60	1.4 (0.2)	1.4 (0.2)	-0.2 (0.2)	0.45	1.3 (0.1)	1.5 (0.2)	0.03 (0.2)	0.90
Urea (mmol/L)	6.3 (0.4)	5.7 (0.3)	6.7 (0.5)	6.6 (0.4)	0.5 (0.5)	0.30	7.0 (0.6)	6.1 (0.3)	-0.4 (0.5)	0.46	6.5 (0.4)	6.5 (0.3)	0.6 (0.5)	0.28
Creatinine (mmol/L)	90.2 (4.6)	83.1 (3.6)	90.1 (4.6)	81.9 (3.4)	-1.1 (2.7)	0.67	89.0 (5.7)	77.6 (3.5)	-5.4 (2.8)	0.06	88.0 (5.0)	83.5 (4.0)	3.4 (2.9)	0.24
ALT (IU/L)	20.2 (1.5)	30.5 (4.8)	28.8 (2.9)	37.5 (5.6)	-1.7 (4.5)	0.71	29.6 (5.4)	35.4 (5.9)	-3.4 (4.6)	0.46	22.1 (2.4)	29.1 (5.0)	-1.0 (4.7)	0.84
AST (IU/L)	23.8 (1.8)	28.5 (2.3)	29.1 (2.0)	31.6 (2.4)	-2.1 (2.7)	0.44	29.6 (3.1)	28.8 (2.4)	-5.8 (2.8)	0.04	25.3 (1.8)	30.3 (2.4)	0.2 (2.9)	0.96
GGT (U/L)	27.5 (3.0)	33.9 (4.5)	33.9 (5.6)	36.3 (6.1)	-4.0 (4.5)	0.38	25.0 (2.5)	27.1 (4.1)	-2.2 (4.6)	0.64	22.6 (2.7)	27.3 (3.6)	3.6 (4.8)	0.46
PSA (ng/mL)	11.9 (2.6)	7.7 (1.3)	4.3 (1.6)	2.9 (1.3)	2.9 (2.3)	0.21	0.2 (0.05)	0.3 (0.1)	4.0 (2.3)	0.09	0.5 (0.4)	0.3 (0.2)	3.9 (2.4)	0.11
Testosterone (nmol/L)	16.1 (1.1)	12.5 (0.8)	0.2 (0.04)	1.3 (1.1)	4.7 (1.3)	<0.001	0.2 (0.04)	0.3 (0.1)	3.7 (1.3)	0.007	0.2 (0.03)	0.2 (0.1)	3.6 (1.4)	0.01
CRP	1.6 (0.5)	6.3 (4.0)	1.6 (0.4)	2.6 (0.9)	-3.4 (2.7)	0.18	1.3 (0.6)	2.4 (0.8)	-3.8 (2.8)	0.17	1.9 (0.6)	4.1 (1.2)	-2.6 (2.9)	0.36
IGF-1 (ng/mL)	19.2 (1.7)	21.8 (1.2)	19.0 (1.7)	20.3 (1.1)	-1.4 (2.3)	0.55	20.9 (2.1)	20.4 (1.4)	-2.5 (2.3)	0.29	20.9 (1.4)	24.4 (2.4)	1.9 (2.4)	0.42
Decorin (ng/mL)	10612.5 (769.3)	10067.7 (816.2)	10325.4 (723.5)	10982.1 (1188.5)	1201.5 (809.4)	0.14	10527.6 (912.8)	10592.6 (1178.1)	765.1 (833.3)	0.36	10765.9 (964.1)	10374.3 (1114.7)	735.9 (873.8)	0.40
Leptin (pg/mL)	3788.1 (613.2)	7406.8 (2183.0)	6132.5 (1122.4)	9114.6 (2345.4)	-636.7 (3021.0)	0.84	11375.5 (3944.6)	11772.0 (2714.1)	-4083.0 (3107.8)	0.19	10492.2 (3040.5)	16367.0 (4578.0)	1499.1 (3255.9)	0.65
Adiponectin ($\times 10^7$)	4.8 (0.6)	4.7 (0.6)	5.0 (0.7)	4.7 (0.6)	0.1 (1.4)	0.93	5.6 (0.8)	5.8 (0.8)	0.9 (1.5)	0.95	8.8 (2.3)	5.2 (0.7)	-3.2 (1.5)	0.04
IGFBP2 (ng/mL)	363.6 (39)	260.2 (32.5)	346.4 (35.5)	269.4 (47.8)	26.4 (44.4)	0.45	358.7 (37)	316.4 (60.6)	-2.0 (34.5)	0.22	386.1 (43.9)	286.7 (43.5)	35.5 (37.3)	0.96
IGFBP3 (ng/mL)	2482.9 (231.2)	3007.6 (246.7)	2932.7 (194.9)	2817.3 (261.6)	-640.1 (-193.7)	0.11	3081 (227.1)	3398.8 (240.6)	101.0 (395.0)	0.63	3318.1 (209.7)	3908.6 (246.1)	405.1 (422.7)	0.80
BDNF (pg/mL)	8793.1 (1994.3)	7668 (1662.6)	6606.3 (1603.5)	5683.4 (1390.1)	202.2 (1373.2)	0.88	8794.0 (1753.0)	6628.1 (1453.1)	-952.6 (1413.9)	0.50	9353.8 (2207.7)	6570.9 (1636.6)	-1962.8 (1458.7)	0.18
Osteonectin (ng/mL)	209.8 (23.5)	216.5 (31.8)	210.9 (22.7)	192.2 (26.5)	-25.4 (18.8)	0.18	216.8 (22.6)	198.8 (29.3)	-27.1 (19.4)	0.17	203.7 (26.5)	212.1 (33.1)	-14.1 (20.0)	0.48

Data are presented as mean $\pm$ S.E.M; *P* value represents group differences in mean changes between PRT and UC at 6 weeks, 6 months and 12 months; LDL, low-density lipoprotein; HDL, high-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; PSA, prostate-specific antigen; CRP, c-reactive protein; IGF-1, insulin-like growth factor 1; IGFBP2, insulin-like growth factor binding protein 2; BDNF, brain-derived neurotrophic factor.

Table 6. Effect of PRT on BMD, activity levels and physical function: absolute values and changes over 6 weeks, 6 months and 12 months

Variables	Baseline		6 weeks		Group difference in mean change at 6 weeks		6 months		Group difference in mean change at 6 mo		12 months		Group difference in mean change at 12 mo	
	UC	PRT	UC	PRT	PRT vs UC	P value	UC	PRT	PRT vs UC	P value	UC	PRT	PRT vs UC	P value
	(n = 12)	(n = 13)	(n = 12)	(n = 13)			(n = 11)	(n = 12)			(n = 10)	(n = 10)		
Step count	40173 (8502)	28838 (5377)	35166 (5647)	36695 (6885)	12864 (7102)	0.08	35661 (7464)	30927 (5818)	7719 (7308)	0.30	27343 (8424)	30303 (6309)	19188 (7805)	0.02
Physical activity (hours)														
Light	5.9 (1.6)	7.9 (2.5)	10.2 (2.7)	9.0 (3.1)	-3.1 (2.9)	0.28	7.8 (1.8)	9.0 (2.2)	-0.6 (2.9)	0.84	7.7 (2.5)	9.9 (2.7)	-0.1 (3.2)	0.98
Moderate	3.9 (1.8)	3.3 (1.4)	5.6 (2.3)	4.2 (1.5)	-0.8 (2.0)	0.69	2.7 (1.7)	3.8 (1.5)	1.5 (2.0)	0.46	5.7 (2.3)	2.8 (1.7)	-0.7 (2.2)	0.74
Heavy	0.1 (0.1)	0.5 (0.3)	0.4 (0.3)	1.5 (1.2)	0.8 (0.8)	0.32	0.3 (0.3)	2.0 (1.0)	1.1 (0.8)	0.17	0.9 (0.6)	1.4 (1.0)	0.3 (0.9)	0.69
BMD (DXA)														
Neck of femur (left total)	1.002 (0.04)	1.03 (0.04)	1.01 (0.04)	1.04 (0.04)	-0.004 (0.02)	0.83	1.0 (0.04)	1.02 (0.04)	-0.004 (0.02)	0.84	1.0 (0.04)	0.992 (0.04)	0.01 (0.02)	0.55
Neck of femur (right total)	1.003 (0.05)	1.003 (0.04)	1.02 (0.04)	1.03 (0.04)	0.01 (0.02)	0.45	1.0 (0.05)	1.02 (0.04)	0.02 (0.02)	0.25	0.99 (0.04)	0.995 (0.04)	0.04 (0.02)	0.10
Spine (total)	1.428 (0.05)	1.22 (0.05)	1.42 (0.05)	1.23 (0.05)	0.02 (0.03)	0.58	1.39 (0.06)	1.21 (0.06)	0.03 (0.03)	0.36	1.36 (0.07)	1.18 (0.06)	0.03 (0.03)	0.34
Physical Function														
Balance														
Total sway floor (EO)	102.1 (15.0)	96.4 (12.3)	100.5 (18.7)	103.0 (11.7)	8.2 (19.2)	0.67	82.5 (8.2)	81.8 (7.8)	0.8 (19.7)	0.97	102.9 (14.7)	100.0 (7.6)	3.4 (20.6)	0.87
Total sway Floor (EC)	123.7 (10.3)	152.6 (13.5)	137.2 (24.7)	146.5 (11.8)	-19.6 (22.5)	0.39	135.2 (10.6)	157.6 (15.1)	-12.2 (23.1)	0.60	129.9 (19.4)	171.8 (17.3)	7.1 (24.1)	0.77
Co-ordinated stability														
Corners	0.3 (0.2)	0.3 (0.2)	0.08 (0.08)	0.5 (0.2)	0.4 (0.5)	0.42	0.7 (0.3)	0.6 (0.4)	-0.2 (0.5)	0.67	0.8 (0.3)	1.7 (0.5)	0.8 (0.5)	0.13
Sides	1.5 (0.8)	2.2 (0.5)	1.3 (0.4)	2.2 (0.6)	0.2 (0.8)	0.84	1.9 (0.5)	1.8 (0.6)	-0.8 (1.3)	0.37	1.9 (0.8)	1.0 (0.3)	-1.7 (0.9)	0.06
Strength														
Right hand (N)	37.9 (1.5)	36.3 (2.6)	36.8 (1.8)	36.3 (2.5)	1.2 (1.3)	0.37	35.6 (1.7)	34.4 (2.6)	1.1 (1.3)	0.41	33.2 (1.7)	32.2 (2.7)	1.8 (1.4)	0.2
Left hand (N)	34.4 (1.4)	37.1 (2.3)	34.5 (1.2)	36.9 (2.5)	-0.3 (1.3)	0.84	33.1 (1.5)	34.8 (2.6)	-0.8 (1.3)	0.57	30.9 (1.6)	32.7 (3.0)	0.2 (1.4)	0.91
Upper limb (N)	156.7 (12.4)	148.8 (9.0)	158.3 (11.7)	157.2 (8.3)	6.8 (11.8)	0.57	151.3 (9.6)	146.3 (12.5)	4.9 (12.2)	0.69	144.6 (11.3)	138.4 (10.0)	1.8 (12.8)	0.89
Lower limb (N)	294.2 (25.6)	294.2 (19.3)	263.9 (20.8)	306.5 (15.3)	42.6 (28.2)	0.14	247.3 (19.2)	258.3 (19.8)	15.6 (28.9)	0.59	239.5 (15.6)	222.0 (23.3.3)	-11.0 (30.3)	0.72
Sit-to-Stand	17 (1.1)	19 (1.4)	18 (1.2)	21 (1.4)	0.9 (1.0)	0.40	19 (1.7)	19 (1.2)	-0.6 (1.0)	0.56	18 (1.5)	18 (1.5)	-1.3 (1.1)	0.25
Timed up and go (s)	5.6 (0.2)	5.5 (0.3)	5.4 (0.2)	5.3 (0.2)	0.2 (0.3)	0.52	6.2 (0.3)	5.5 (0.2)	-0.5 (0.3)	0.11	6.0 (0.3)	5.9 (0.2)	0.1 (0.3)	0.72
VO ₂ max (mL/kg/min)	26.3 (2.4)	27.3 (1.1)	29.1 (2.7)	27.8 (1.8)	-2.3 (2.2)	0.33	28.0 (1.7)	25.2 (1.4)	-1.6 (2.3)	0.60	29.2 (1.8)	29.1 (1.9)	0.9 (2.5)	0.91

Data are presented as mean $\pm$ S.E.M; *P* value is for group differences in mean changes between PRT and UC at 6 weeks, 6 months and 12 months; BMD, bone-mineral density; EO, eyes opened; EC, eyes closed.

Table 7. Effect of PRT on quality of life: absolute values and changes over 6 weeks, 6 months and 12 months

Variables	Baseline		6 weeks		Group difference in mean change at 6 weeks		6 months		Group difference in mean change at 6 mo		12 months		Group difference in mean change at 12 mo	
	UC (n = 12)	PRT (n = 13)	UC (n = 12)	PRT (n = 13)	PRT vs UC	P value	UC (n = 11)	PRT (n = 12)	PRT vs UC	P value	UC (n = 10)	PRT (n = 10)	PRT vs UC	P value
EORTC QLQ-C30														
Physical functioning	91.7 (4.4)	95.9 (1.4)	91.7 (3.3)	95.9 (1.8)	0.01 (3.35)	0.99	88.7 (5.5)	93.3 (2.0)	-0.19 (3.51)	0.96	83.3 (7.5)	92.0 (2.4)	2.83 (3.62)	0.43
Role functioning	90.3 (5.2)	93.6 (4.4)	88.9 (6.3)	96.2 (2.8)	4.0 (6.8)	0.56	86.7 (9.2)	91.7 (3.9)	1.9 (7.1)	0.79	83.3 (6.1)	92.6 (4.0)	4.2 (7.5)	0.57
Emotional functioning	91.0 (6.4)	85.9 (4.4)	93.7 (4.2)	85.9 (3.7)	-2.8 (4.6)	0.55	93.3 (4.1)	87.5 (4.5)	-0.8 (4.8)	0.88	89.2 (5.0)	82.5 (5.9)	-3.0 (4.9)	0.55
Cognitive functioning	86.1 (3.5)	84.0 (4.3)	88.9 (3.1)	85.9 (3.7)	-0.9 (5.7)	0.88	86.7 (4.8)	82.6 (6.0)	-1.1 (6.0)	0.86	85.0 (4.6)	85.0 (2.9)	2.6 (6.1)	0.68
Social functioning	88.9 (5.9)	89.7 (4.0)	93.1 (4.8)	83.3 (5.7)	-10.6 (6.3)	0.10	86.7 (4.8)	91.7 (3.8)	3.2 (6.6)	0.63	85.0 (4.6)	91.7 (4.5)	5.4 (6.8)	0.43
Global health status and quality of life (QOL)	82.0 (3.7)	76.6 (4.3)	78.5 (3.9)	82.0 (4.2)	8.9 (5.0)	0.08	75.0 (5.8)	83.3 (4.2)	12.8 (5.2)	0.02	79.2 (4.2)	80.0 (4.3)	8.5 (5.4)	0.12
EORTC QLQ-C30 symptom scales														
Fatigue	11.1 (3.6)	13.7 (3.6)	18.5 (5.7)	13.7 (2.9)	-7.4 (5.4)	0.17	24.4 (6.6)	22.2 (5.1)	-4.5 (5.6)	0.43	17.8 (4.4)	20.0 (6.2)	-1.2 (5.8)	0.83
Pain	5.6 (3.1)	14.1 (2.6)	8.3 (3.8)	12.8 (4.3)	-4.1 (5.8)	0.48	13.3 (5.4)	6.9 (3.8)	-15.1 (6.0)	0.02	15.0 (4.6)	15.0 (5.2)	-6.5 (6.2)	0.30
Insomnia	11.1 (6.3)	17.9 (4.8)	13.9 (4.9)	20.5 (4.7)	-0.2 (7.4)	0.98	23.3 (10.0)	19.4 (6.4)	-10.6 (7.7)	0.17	13.3 (7.4)	23.3 (5.1)	5.2 (7.9)	0.52
EORTC QLQ-PR25														
Sexual activity	70.8 (6.5)	68.0 (8.1)	79.2 (5.5)	71.8 (6.9)	-4.5 (10.2)	0.66	85.0 (6.3)	87.5 (5.5)	5.6 (10.6)	0.60	91.7 (3.7)	80.0 (6.0)	-10.5 (10.9)	0.34
Urinary symptoms	24.3 (5.9)	19.5 (6.5)	21.5 (4.7)	12.4 (2.9)	-3.3 (7.9)	0.68	30.0 (5.2)	20.5 (3.0)	-3.3 (8.3)	0.69	32.5 (5.1)	16.3 (3.9)	-11.1 (8.5)	0.20
Bowel symptoms	2.1 (1.5)	2.9 (1.6)	2.5 (1.9)	4.5 (1.8)	1.1 (2.7)	0.67	2.5 (1.3)	3.5 (1.2)	0.05 (92.8)	0.99	4.2 (1.9)	2.5 (1.8)	-2.3 (2.9)	0.43
Hormone-related symptoms	5.6 (2.5)	5.6 (1.8)	10.7 (2.3)	10.3 (2.7)	-0.4 (3.8)	0.92	17.8 (2.2)	15.8 (2.4)	-1.2 (4.0)	0.77	14.5 (2.8)	15.0 (3.5)	0.2 (4.1)	0.96
SF36v2 health survey														
Physical functioning	50.7 (2.4)	52.3 (1.1)	50.0 (2.6)	52.1 (1.6)	0.3 (2.6)	0.89	50.1 (2.7)	49.4 (2.4)	-2.1 (2.7)	0.45	49.1 (3.1)	49.7 (2.8)	1.3 (2.8)	0.63
Role- physical	49.7 (2.8)	50.8 (1.4)	51.5 (2.5)	52.7 (4.7)	0.002 (2.1)	0.99	47.7 (3.4)	49.1 (1.7)	1.5 (2.2)	0.51	48.4 (3.0)	49.7 (2.3)	-0.6 (2.3)	0.81
Bodily pain	55.8 (2.1)	53.0 (1.6)	54.7 (2.5)	56.9 (1.7)	5.0 (2.3)	0.03	56.2 (2.4)	53.6 (1.5)	0.3 (2.4)	0.91	53.8 (2.2)	54.2 (2.4)	2.6 (2.5)	0.30
General health	55.0 (2.1)	50.6 (2.2)	54.1 (2.4)	54.7 (2.3)	5.0 (2.4)	0.04	57.4 (2.6)	52.8 (2.0)	1.0 (2.6)	0.69	54.4 (3.5)	51.5 (2.0)	2.7 (2.6)	0.32
Vitality	59.3 (2.0)	55.3 (1.8)	56.6 (3.1)	56.4 (2.3)	3.8 (2.4)	0.11	54.1 (3.2)	54.3 (2.8)	5.8 (2.5)	0.02	54.7 (3.2)	56.2 (1.9)	6.0 (2.5)	0.02
Social functioning	54.8 (1.4)	54.9 (2.1)	51.9 (2.4)	54.6 (1.3)	2.7 (1.9)	0.15	50.8 (2.5)	55.3 (1.1)	4.2 (1.9)	0.03	51.3 (2.6)	53.3 (1.8)	2.1 (2.0)	0.31
Role- emotional	53.8 (1.8)	52.8 (1.8)	54.1 (1.7)	54.8 (0.8)	1.8 (2.2)	0.43	51.3 (2.8)	52.7 (1.3)	2.6 (2.3)	0.28	51.0 (3.1)	51.6 (1.6)	1.9 (2.4)	0.43
Mental health	58.7 (1.2)	54.1 (2.4)	56.3 (1.6)	57.4 (1.6)	2.8 (2.2)	0.21	56.8 (2.0)	56.9 (1.9)	3.7 (2.3)	0.12	57.2 (2.1)	50.8 (2.4)	4.9 (2.4)	0.04
Physical component summary	50.8 (2.4)	51.6 (1.4)	51.1 (2.6)	53.4 (1.7)	1.6 (1.8)	0.40	51.3 (3.0)	49.3 (1.9)	-1.7 (1.9)	0.37	48.1 (3.3)	49.6 (2.1)	-0.1 (2.0)	0.97
Mental component	58.2	54.4	56.2	55.9	3.4 (1.9)	0.08	54.9	56.7	5.7 (2.0)	0.006	55.4	56.3	5.5 (2.1)	0.01

Data are presented as mean $\pm$ S.E.M; *P* value represents group differences in mean changes between PRT and UC at 6 weeks, 6 months and 12 months.

Figures

Figure 1
Consort diagram

Figure 2
Change in serum testosterone and PSA across the cohort post-ADT. (A) Change in serum testosterone at 6 weeks, 6- and 12 months post-ADT (* *p* < 0.001). (B) Change in serum PSA at 6 weeks, 6- and 12 months post-ADT (* *p* < 0.001).

Figure 3

Change in serum growth factors across the cohort post-ADT. (A) Change in BDNF levels at 6 weeks, 6- and 12 months (* $p = 0.003$ at 6 weeks ** $p = 0.39$ at 12 months). (B) Change in leptin levels at 6 weeks, 6- and 12 months (** $p = 0.01$ at 12 months). (C) Change in adiponectin levels at 6 weeks, 6- and 12 months (** $p < 0.0001$ at 12 months).

Figure 4

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ADT effect on serum IGFBP-3 and IGF-1: IGFBP-3 ratio across the cohort. (A) Change in IGFBP-3 levels at 6 weeks, 6- and 12 months (** p < 0.001 at 12 months). (B) Change in IGF1: IGFBP-3 ratio at baseline and 12 months (p = 0.02). (C) Correlation between serum PSA and IGFBP-3 levels (R2 = 0.07, p = 0.01).

Figure 5

The effect of PRT on body composition. (A) Change in body-cell mass (% total body mass) in the UC and PRT groups at 6 weeks, 6- and 12 months (** p = 0.01 at 12 months). (B) Change in fat mass (% total body mass) in the UC and PRT groups at 6 weeks, 6- and 12 months (** p = 0.02 at 12 months).

Figure 6

Improvements across SF-36v2 domains after 12 months of PRT. (A) Change in the SF-36v2 vitality score in the UC and PRT groups at 12 months compared to baseline (p = 0.02). (B) Change in SF-36v2 mental component score in the UC and PRT groups at 12 months compared to baseline (p = 0.01).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [PRTtopreventadverseeffectsofADTCONSORTChecklist.docx](#)