Persisting adverse body composition changes 2 years after cessation of androgen deprivation therapy for localised prostate cancer

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Abstract

Objective: Hypogonadism from androgen deprivation therapy (ADT) for prostate cancer causes adverse body composition changes associated with insulin resistance and decreased quality of life (QoL). Our objective was to assess whether adverse body composition changes improve after cessation of ADT.

Design: Prospective case–control study in a tertiary referral hospital. Thirty-four men newly commencing ADT (cases, median age: 67.6 years (interquartile range: 64.6–72.0)) and 29 age-matched (70.6 years (65.3–72.9)) prostate cancer controls not on ADT were assessed 2 years after cessation of ADT (median: 4.4 years).

Methods: Serum testosterone, body composition, handgrip strength, frailty and QoL were measured. Using a mixed model, the mean adjusted differences (MADs (95% CI)) between groups from baseline to study end are reported.

Results: Twenty-seven cases and 19 controls completed the study. Median duration of ADT was 2.3 years (interquartile range: 1.8–3.1). Two years after cessation of ADT, total testosterone remained lower (MAD: -3.4 nmol/L (-6.3 to -0.5), $P < 0.022$), fat mass (2214 g (490–3933), $P = 0.025$) and insulin resistance (homeostasis model assessment of insulin resistance: 0.69 (0.31–1.07), $P < 0.001$) remained higher in cases, whereas lean mass (-1450 g (-2259 to -640), $P < 0.001$) and physical component of QoL remained lower than controls (-11.9 (-16.4 to -7.4), $P < 0.001$).

Conclusion: Two years after ADT cessation, metabolically adverse changes in body composition, increased insulin resistance and reduced QoL persisted. This may be related to incomplete testosterone recovery. Persisting adverse effects need to be considered in the risk to benefit assessment of ADT and proactive mitigation should continue after cessation of treatment.

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Introduction

Androgen deprivation therapy (ADT) is a highly effective treatment for high-risk prostate cancer (1), however, significantly affects quality of life (QoL) due to a number of adverse effects arising from profound hypogonadism, including marked changes in body composition, hot flushes, tiredness and mood disturbance (2). Body composition changes with gain in fat mass, loss of lean

mass and bone mass occur most rapidly in the first 6 months of treatment and are associated with increased insulin resistance, loss of muscle strength and function and increased frailty (3, 4). It is uncertain whether these adverse changes improve following cessation of ADT.

Treatment for localised high-risk prostate cancer with ADT is typically given for 2–3 years in combination

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with radiotherapy. Within the first 12 months, fat mass increases by 10–15% and muscle mass decreases by 3–4% (5). In a prospective study, 12 months after ADT initiation, men receiving ADT gained 3.5 kg of fat mass and lost 1.5 kg of lean mass compared to prostate cancer controls not receiving ADT (4). This was associated with a significant increase in insulin resistance, measured by the updated homeostasis model assessment of insulin resistance (HOMA2-IR). Increased insulin resistance was primarily related to the gain in fat mass (4). ADT-associated increases in insulin resistance have also been reported in uncontrolled observational studies (3, 6). Large population-based studies have associated ADT with increased risks of the metabolic syndrome, largely driven by men meeting hyperglycaemia, waist circumference and elevated triglycerides criteria, rather than the hypertension or HDL criteria. ADT has also been associated with increased risks of diabetes ranging from 16 to 44%, and possibly, of cardiovascular events (7).

Computerised musculoskeletal modelling combined with 3D gait analysis demonstrated a selective loss of muscle function during ADT, which leads to functional deficits evident during normal walking (8). In association with these objective deficits, self-reported QoL decreases significantly, particularly with respect to physical and sexual domains (5, 9). Whether adverse effects of ADT persist after cessation of treatment is of major relevance, given the overall low prostate cancer-specific mortality in such men (10) and impact on QoL as well as cardiovascular mortality, particularly as these individuals typically have high baseline prevalence of obesity and cardiovascular risk factors (11). Minimising long-term morbidity associated with treatment is imperative. Very little is known about these changes once ADT is ceased and whether these changes can in fact be improved or reversed (12).

Using a controlled prospective design, we aimed to determine first, whether gains in fat mass and loss of muscle mass improve after cessation of ADT, and secondly, to assess insulin resistance, frailty, handgrip strength and QoL. We hypothesised that ADT-associated adverse effects would not recover, even 2 years after cessation of treatment.

Subjects and methods

Study participants

We conducted a prospective case–control study of men newly commencing long-term ADT for localised prostate cancer and age- and radiotherapy-matched prostate

cancer controls at a tertiary referral hospital (Austin Health, Melbourne, Australia). The study was approved by the Human Research Ethics Committee, Austin Health (H2011/04224), and all participants provided written informed consent.

From an outpatient clinic for men with non-metastatic prostate cancer at a tertiary referral hospital, we recruited men newly commencing long-term ADT ($n=34$) and age- and radiotherapy-matched prostate cancer controls ($n=29$) who did not receive ADT during the follow-up period. Detailed inclusion and exclusion criteria as well as changes in muscle function and body composition 12 months after ADT initiation have been reported previously (4, 8). Briefly, ADT-naïve, ambulatory men unrestricted in their physical activities with normal performance status (Eastern Co-operative Oncology Group performance status 0) and independently living in the community were eligible to participate in the study. Men had no evidence of metastases on staging investigations at entry to the study. Groups were matched for age, BMI, medical comorbidities, radiotherapy treatment and baseline testosterone level. Men were excluded if they had evidence of androgen deficiency (baseline total testosterone (TT) <10 nmol/L), neuromuscular disease, limitation in their exercise tolerance, active cardiac, respiratory or joint disease or if they required a walking aid.

We now present results 2 years after cessation of ADT to assess fat mass, lean mass, insulin resistance as estimated from the updated HOMA2-IR (13), serum testosterone, frailty and QoL. Cases who were continuing to receive ADT or controls who had commenced ADT during the follow-up period were excluded.

Outcome measures

All outcome measures including body composition, biochemistry, QoL, frailty score and handgrip strength were taken at 0 and 12 months during treatment and 2 years post ADT. Handgrip strength (kg) (Jamar Hand Dynamometer; S.I. Instruments, Adelaide, Australia) was measured in the dominant hand. Frailty score as described by Fried (14) was considered as a categorical value where 0 was defined as not frail, and scores 1–5 were considered pre-frail or frail.

Body composition

Body composition was measured by dual-energy X-ray absorptiometry (Prodigy version 7.51; GE Lunar, Madison,

WI, USA). The coefficient of variation was less than 2% for repeated scans (15), and all scans were performed by the same technician.

Biochemical assays

All participants had morning fasting biochemistry performed. Serum TT was determined using an electrochemiluminescence immunoassay (Cobas C8000, Roche Diagnostics) with a minimum detection limit of 0.4 nmol/L and an inter-assay variation of 5.0–6.9%. The reference range for the TT assay was 10.0–27.6 nmol/L, derived from an independent reference panel of 124 healthy young men who had simultaneous testosterone measurements by both immunoassay and gas chromatography/mass spectrometry (16). C-peptide was measured by electrochemiluminescence immunoassay (Cobas C8000, Roche Diagnostics). Fasting plasma glucose was measured using hexokinase photometric assay (Cobas C8000, Roche Diagnostics) with inter-assay variation of 1.5%. Insulin resistance was estimated from fasting glucose and c-peptide using the updated HOMA2-IR (13).

Quality of life

QoL was measured by the 12-item Short-Form QoL Survey, version 2 (SF-12), which generates a physical and mental component score and the Aging Males' Symptoms (AMS) Scale as previously described (9, 17).

Statistical analysis

Data were not normally distributed and are presented as median and interquartile range (IQR). Comparisons of baseline characteristics between groups were made using Wilcoxon rank-sum test for continuous variables or chi-square test for frequencies substituted with Fisher's exact test in case of low numbers. Follow-up measurements over time were assessed with a linear mixed model of the factorial time point $\times$ group interaction, incorporating baseline values as a fixed covariate and repeated measures by subject as random effects. For continuous outcomes, we show the adjusted means in the figures and report the mean adjusted difference (MAD) plus profiled 95% CI between the groups at study commencement and study end 2 years post ADT cessation. *P* values for *post hoc* group comparisons were adjusted by Holm's method. A robust linear mixed model was used for lean mass, where a small proportion of outliers were present. For binary outcomes,

a generalised linear mixed model with a binomial link function was used and odds ratios (OR) are reported for group differences. This approach accounts for missing values (missing at random (MAR)), implements the intention-to-treat principle and it is also robust against regression to the mean. Two-sided *P* values <0.05 were considered significant. Statistical analyses were performed using R statistical package (version 3.4.2 for Mac) together with lme 4 1.1-14, robustlmm 2.1-3, effects 4.0-0 and phia 0.2-1 (18, 19, 20).

Results

Participant characteristics

Of 34 initial participants in the ADT group (cases) and 29 in the control group, 27 cases and 19 control participants completed the assessment 2 years post cessation of ADT. Reasons for non-completion included continuing ADT (cases $n=2$), death (cases $n=3$; metastatic prostate cancer $n=1$, pancreatic cancer $n=1$ and dementia $n=1$) or inability to attend a study visit (cases $n=2$, controls $n=10$). Median duration of ADT was 2.3 years (IQR 1.8–3.1). ADT men were assessed 2 years after cessation of ADT, at median 4.4 years (4.0–5.1) and controls were assessed at 4.1 years (4.0–4.2) from study entry, which was not significantly different ($P=0.147$).

Baseline characteristics of study participants have been reported (8) and are summarised in Table 1. Both groups were matched for age, radiotherapy status and medical comorbidities (8). Inevitably, the two groups differed in their prostate cancer characteristics, consistent with indications for ADT treatment; the ADT group had high-risk prostate cancer, whereas controls had intermediate-risk disease (Gleason 9 (8, 9) vs 7 (7, 7), $P<0.001$). This different risk is solely based on the Gleason score and was not expected to influence body composition.

Total testosterone

As reported (8), TT levels were castrate throughout ADT, however, controls maintained eugonadal testosterone levels. Two years after cessation of ADT, TT remained lower in cases compared to controls with MAD -3.4 nmol/L (95% CI: -6.3 to -0.5), $P=0.022$ (Fig. 1 and Table 2). Two years after cessation of ADT, 48% of men in the ADT group had TT levels below the assay reference range (10 nmol/L).

Table 1 Baseline characteristics of the study participants. Data presented are median (interquartile range) or proportions (%). *P* values <0.05 were considered statistically significant between groups (Wilcoxon-sum rank test or chi-square for frequencies). Prostate cancer Gleason score <7=low-moderate risk, 7=intermediate risk, 8–10=high-risk prostate cancer.

Baseline characteristic	ADT group (n=34)	Controls (n=29)	<i>P</i> value
Age (years)	67.6 (64.6–72.0)	70.6 (65.3–72.9)	0.48
BMI (kg/m ²)	27.8 (25.4–31.5)	27.2 (26.0–31.8)	0.75
Prostate cancer Gleason score	9 (8–9)	7 (7–7)	<0.001
Concurrent radiotherapy treatment	94.1%	89.7%	0.51
Total testosterone (nmol/L)	14.1 (10.2–17.6)	15.0 (11.1–16.9)	0.91
PSA (µg/L)	3.62 (0.21–18.7)	0.05 (0.03–0.28)	<0.001
Haemoglobin (g/L)	149 (140–157)	150 (142–155)	0.66
Medical comorbidities			
Ischaemic heart disease	17.6%	17.2%	1.00
Diabetes mellitus	14.7%	17.2%	1.00
Liver disease	0%	0%	1.00
Chronic kidney disease	0%	0%	1.00
Hypertension	58.8%	58.6%	1.00

Adapted from (8). ADT, androgen deprivation therapy; PSA, prostate specific antigen.

Fat mass and insulin resistance

Two years after cessation of ADT, fat mass (MAD: 2214 g (490–3933), *P*=0.025) and insulin resistance (HOMA2-IR MAD: 0.69 (0.31–1.07), *P*<0.001) remained higher in cases compared to controls (Figs 2 and 3). BMI (MAD: 0.7 kg/m² (0.0–1.4), *P*=0.15) and waist circumference (MAD: –0.2 cm (–2.8 to 2.5), *P*=0.91) were not significantly different from controls.

Lean mass, muscle strength and frailty

After initial decrease on ADT, at 2 years post ADT, lean mass remained reduced compared to controls with a robust MAD: –1450 g (–2259 to –640), *P*<0.001. After initial decrease, handgrip strength (*P*=0.97) and frailty (*P*=0.76) were no longer different to controls 2 years post ADT.

Quality of life

Self-reported physical component of QoL (SF-12) remained worse than controls (MAD: –11.9 (–16.4

Figure 1

Serum TT levels. Solid lines represent the ADT group and dashed lines represent the control group. Adjusted means and 95% CIs for the two groups were derived using a mixed model (see 'Methods' section) and are shown at three visits (or time points), that is at baseline, 12 months after commencement of ADT and 2 years after cessation of ADT. The MAD (95% CI) and corresponding *P* value is reported. ADT, androgen deprivation therapy; CI, confidence interval; MAD, mean adjusted difference.

to –7.4), *P*<0.001) after cessation of ADT, a clinically meaningful difference far greater than the minimally important difference of three points (Fig. 4). There were no significant differences in mental component of QoL. During ADT, AMS score increased reflecting worse QoL, which was related to an increase in hot flushes (9). Two years after cessation of ADT, AMS was also no longer different to controls likely related to an improvement in hot flushes (MAD: 3.3 (–0.8 to 7.6), *P*=0.12).

Two years after cessation of ADT, fat mass was not different in individuals who had recovered their testosterone levels to the assay reference range (>10 nmol/L), compared to those individuals that did not recover their testosterone, (MAD: 706 g (–704 to 2116), *P*=0.33). In addition, two years after cessation of ADT, participants recovering their testosterone to the normal range, compared to those who did not, had no difference in lean mass (MAD: 311 g (–128 to 750), *P*=0.16), HOMA2-IR (MAD: 0.03 (–0.26 to 0.32),

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Table 2 Changes in clinical values 2 years after cessation of ADT compared to baseline between groups. Baseline refers to study commencement at initiation of ADT. Post-ADT refers to 2 years after cessation of ADT at median of 4.4 years (4.0–5.1) for the ADT group and 4.1 years (4.0–4.2) for the control group. Median and (interquartile range) are reported. The MAD and 95% confidence interval refers to the difference between the two groups at the initial and final visit (or at the two time points). ADT, androgen deprivation therapy; MAD, mean adjusted difference.

Clinical value	ADT group (n=27)	Controls (n=19)	Mean adjusted difference (95% CI)	P value
BMI (kg/m ²)				
Baseline	28.1 (25.4–31.6)	27.2 (26.0–31.8)		
Post-ADT	30.9 (26.2–33.9)	28.0 (25.5–31.3)	0.7 (0.0–1.4)	0.148
Waist circumference (cm)				
Baseline	103 (96–111)	100 (96–108)		
Post-ADT	109 (96.2–118)	104 (100–110)	–0.2 (–2.8 to 2.5)	0.908
Total testosterone (nmol/L)				
Baseline	13.9 (9.25–17.6)	15.0 (11.1–16.9)		
Post-ADT	10.2 (3.95–15.4)	15.6 (11.2–16.4)	–3.4 (–6.3 to –0.5)	0.022
Calculated free testosterone (pmol/L)				
Baseline	217 (137–274)	234 (199–314)		
Post-ADT	177 (66.5–250)	237 (184–258)	–29 (–80 to 22)	0.27
Sex hormone binding globulin (nmol/L)				
Baseline	45 (37–56)	44 (33–49)		
Post-ADT	45 (38–74)	50 (44–60)	–3.3 (–8.8 to 2.3)	0.77
Luteinising hormone (LH) (IU/L)				
Baseline	5.0 (3.2–8.0)	5.9 (4.6–8.3)		
Post-ADT	12.6 (8.8–16.3)	7.0 (4.8–10.2)	5.9 (0.9–10.9)	0.023
Haemoglobin (g/L)				
Baseline	148 (140–156)	150 (142–155)		
Post-ADT	143 (132–152)	146 (143–154)	–5.4 (–11.1 to 0.1)	0.068
Fat mass (g)				
Baseline	26 858 (19 261–33 028)	23 856 (20 396–29 710)		
Post-ADT	33 334 (20 162–40 824)	28 205 (20 806–30 954)	2214 (490–3933)	0.025
Lean mass (g)				
Baseline	54 753 (50 318–60 820)	55 302 (51 380–60 935)		
Post-ADT	53 502 (49 191–58 030)	55 517 (52 138–59 775)	–1450 (–2259 to –640)	<0.001
HOMA2-IR				
Baseline	2.28 (1.65–2.77)	1.89 (1.40–2.76)		
Post-ADT	2.26 (1.80–3.80)	1.86 (1.48–2.64)	0.69 (0.31–1.07)	<0.001
Frailty*				
Baseline	15 (30%)	11 (37.9%)		
Post-ADT	9 (36%)	10 (52.6%)	OR 1.86 (0.2–21)	0.759
Dominant handgrip strength (kg)				
Baseline	40 (35–44)	40 (34–45)		
Post-ADT	36 (32–44)	38 (32–43)	0.1 (–2.9 to 3.0)	0.970
Short-Form 12 mental component score				
Baseline	56.9 (51.8–61.1)	55.5 (53.0–57.5)		
Post-ADT	58.5 (52.5–62.3)	55.8 (45.8–57.8)	4.0 (–1.0 to 9.0)	0.237
Short-Form 12 physical component score				
Baseline	51.7 (45.7–55.2)	50.4 (44.5–56.3)		
Post-ADT	45.2 (32.5–49.7)	55.5 (48.3–57.6)	–11.9 (–16.4 to –7.4)	<0.001
Aging Male's Symptoms total score				
Baseline	32 (26–39)	32 (28–41)		
Post-ADT	35 (31–39)	34 (30–48)	3.3 (–0.8 to 7.6)	0.121

*Frailty was considered as a categorical variable and results represent those classified as pre-frail or frail (proportion scoring greater than 0). Odds ratios are correspondingly reported.

$P=0.85$), grip strength (MAD: 1.31 g (–0.58 to 3.21), $P=0.18$), frailty score (MAD: 0.55 (0.1–3.2), $P=0.51$), physical component of QoL (SF-12) (MAD: 5.31 (–4.11 to 14.7), $P=0.28$) or AMS score (MAD: –0.11 (–2.89 to 2.66), $P=0.94$).

Discussion

In this prospective controlled study, we report that among men with localised, non-metastatic prostate cancer treated with adjuvant ADT, the objective and self-reported

Figure 2

Fat mass. Solid lines represent the ADT group and dashed lines represent the control group. Adjusted means and 95% CIs for the two groups are plotted at baseline, 12 months after commencement of ADT, and 2 years after cessation of ADT. As a summary result of the adjusted between-group difference from baseline to 2 years post ADT, MAD (95% CI) and corresponding *P* value is reported. ADT, androgen deprivation therapy; CI, confidence interval; MAD, mean adjusted difference.

adverse effects of this treatment persist even 2 years after ADT cessation. Compared to carefully matched controls over 4 years, men who had previously received ADT had persistent adiposity and increased insulin resistance, while lean mass and physical QoL remained lower compared to controls over time. Incomplete gonadal axis recovery with persistent hypogonadism may be in part responsible for these findings. Given the excellent long-term prognosis of localised prostate cancer, and potential prolonged aggravation of cardiovascular mortality risk, even several years after cessation of ADT, these findings are concerning.

Surprisingly, persistence of adverse effects has previously only been assessed in one uncontrolled study, which reported persisting changes in body composition after short term (9 months) of ADT (12). Inclusion of a matched control group is particularly important especially in a longer-term study, given that ageing in itself may lead to changes similar to those caused by ADT.

Body composition

Two years after ADT cessation, metabolically adverse changes in body composition persisted, which may

Figure 3

Insulin resistance. Solid lines represent the ADT group and dashed lines represent the control group. Adjusted means and 95% CIs for the two groups are plotted at baseline, 12 months after commencement of ADT and 2 years after cessation of ADT. As a summary result of the adjusted between-group difference from baseline to 2 years post ADT, MAD (95% CI) and corresponding *P* value is reported. ADT, androgen deprivation therapy; CI, confidence interval; HOMA2-IR, homeostasis model assessment of insulin resistance; MAD, mean adjusted difference.

be related to elevated fat mass and reduced lean mass compared to controls. Whether the change in insulin resistance observed, based on HOMA-IR rather than gold standard glucose clamp technology, is clinically relevant is not certain. However, insulin resistance is an independent risk factor for cardiovascular events (21), which is a major cause of mortality in men with non-metastatic prostate cancer, and interestingly, HOMA2-IR levels above 1.9 have been associated with endothelial dysfunction (22).

From a practical clinical perspective, it is important to note that body weight was not different and relying on weight that is routinely available may underestimate deleterious body composition that may mediate adverse changes in metabolism and physical performance.

Muscle strength and frailty

Despite the incomplete recovery of body composition, some improvements in functioning were observed. After initial decrease during ADT, muscle strength as measured by handgrip and frailty score were no longer different

Figure 4

SF-12 Physical Component of Quality of Life. Solid lines represent the ADT group and dashed lines represent the control group. Adjusted means and 95% CIs for the two groups are plotted at baseline, 12 months after commencement of ADT and 2 years after cessation of ADT. As a summary result of the adjusted between-group difference from baseline to 2 years post-ADT, MAD (95% CI) and corresponding *P* value is reported. ADT, androgen deprivation therapy; CI, confidence interval; MAD, mean adjusted difference.

to controls 2 years after cessation of ADT. These bedside clinical tests however may not be sensitive enough to detect deficits attributable to ADT (8) as continual decrements were observed in physical aspects of QoL.

Quality of life

QoL is almost certainly the most important aspect of cancer survivorship and although some benefit was observed on the AMS score, physical aspects of QoL continued to decrease significantly after cessation of ADT and was markedly lower than controls (–12 points). Given that in the first 12 months of treatment, a difference of only –3.6 points between the ADT group and controls was seen (9), the 12-point difference we observed is alarming and far greater than published minimally important differences of 2–3 points (23), which is already associated with 20% increase in mortality and 16% higher risk of hospitalisation in the subsequent year (24). Further studies assessing contributing factors to the continual decline in physical aspects of QoL are required.

Possible mechanisms underlying the persistent adverse effects after ADT cessation

Given that the adverse effects of ADT are a direct consequence of the severe hypogonadism, we postulate that the persisting adverse effects reported here are, at least in part, due to an incomplete recovery of the endogenous hypothalamic–pituitary–testicular axis. Even 2 years following ADT cessation, despite increased luteinising hormone levels, the ADT group had lower testosterone levels compared to controls and values remained below the reference limit in 50%. The prolonged duration of time that men remain hypogonadal after ADT cessation may not be appreciated by patients and clinicians and may contribute to observations that intermittent ADT may not always mitigate treatment-associated adverse effects (25). While our study is, to our knowledge, the first to report post-ADT testosterone levels in a controlled setting, uncontrolled studies have suggested that testosterone recovery can take beyond 5 years (26).

The mechanism behind the persisting body composition changes in the setting of low testosterone is unknown. The increase in fat mass may be related to factors other than direct effects of low testosterone including changes in energy regulation or set point changes in the hypothalamic–pituitary–thyroid axis (27), decreased physical activity or mood effects that can occur with treatment of prostate cancer. However, it is clear from obesity literature that adiposity, once gained, as occurs in an accelerated fashion with ADT, is difficult to shed due to a shift in the body's homeostatic set point and counter-regulatory hormones, which promote fat regain (28). Even with recovery of TT levels, it is therefore doubtful that fat gained as a result of ADT would return to control levels. Much less is known about potential mechanisms behind the persisting changes in lean mass but reduced motivation and reduced physical activity may play a role in persisting muscle loss during ADT, although this requires further study. It is important to note that a recently updated meta-analysis of 15 studies including 1135 patients has reported that exercise mitigates ADT-associated increases in body fat and improves muscle strength and fatigue, although changes in lean body mass were not significant (29).

Strengths and limitations

The unique strengths of this study include the inclusion of an age-, radiotherapy- and comorbidity-matched control group, the relatively long follow-up after ADT

cessation, and the assessment of both objective and self-reported ADT-associated adverse effects. The main limitations include a relatively small sample size, with a number of dropouts over the 4-year duration of our study. In addition, functional assessments were limited to handgrip strength and frailty scores, measures that may lack sensitivity to capture ADT-associated decrements in physical performance (8), and QoL was assessed by self report. Insulin resistance was estimated by the HOMA2-IR rather than that determined by gold standard glucose clamp studies. However, HOMA2-IR uses a computer-based model to determine insulin resistance and accounts for variations in hepatic and peripheral glucose resistance. In contrast to the simpler HOMA1 equation is valid for currently available insulin assays (30). Finally, testosterone levels were measured by immunoassay, rather than by liquid chromatography/tandem mass spectrometry (LCMS/MS). However, the quality controlled immunoassay routinely used in our hospital for clinical decision making has previously been validated against LCMS/MS technology (16).

In conclusion, ADT can adversely impact body composition, insulin resistance and QoL for at least 2 years after cessation of treatment, which is likely related to incomplete testosterone recovery. Given excellent survival rates after treatment of high-risk prostate cancer, characterisation of effects of ADT after treatment cessation has clinical relevance not only for the overall risk–benefit ratio of ADT, but also underscores the importance of ongoing monitoring for and proactive mitigation of potential persisting adverse consequences of ADT even years after cessation of treatment. While these findings require confirmation in larger studies and further research into effective strategies to mitigate ADT-associated adverse effects are needed, men previously treated with ADT should be considered a vulnerable population that require ongoing management with emphasis on lifestyle measures and medical therapy to optimise cardiometabolic risk, physical functioning and overall QoL.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

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Author contribution statement

M G, J D Z and A S C designed the research study. M G acquired the funding for the research study. M G and J D Z supervised the overall research project. A S C recruited all participants. A S C, A J T and S V M conducted all experiments and acquired the data. A S C and R H performed statistical analysis of the results. A S C wrote the original draft of the manuscript. All co-authors revised and approved the current manuscript.

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