Muscle and bone effects of androgen deprivation therapy: current and emerging therapies

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Abstract

Prostate cancer and treatment with androgen deprivation therapy (ADT) affect significant numbers of the male population. Endocrine effects of ADT are a critical consideration in balancing the benefits and risks of treatment on long-term survival and quality of life. This review highlights the latest advances in androgen manipulation in prostate cancer with an emphasis on the effects of ADT on muscle and bone, which universally affects the health and well-being of men undergoing ADT for prostate cancer. Muscle mass declines with ADT; however, the evidence that this correlates with a decrease in muscle strength or a decrease in physical performance is discordant. Cortical bone decay also occurs in association with an increase in fracture risk, hence optimization of musculoskeletal health in men undergoing ADT is crucial. The role of exercise, and current and emerging anabolic therapies for muscle as well as various new strategies to prevent loss of bone mass in men undergoing ADT are discussed. Future well-designed, prospective, controlled studies are required to elucidate the effects of ADT on physical performance, which are currently lacking, and larger randomized controlled trials are required to test the efficacy of medical therapies and exercise interventions to target proven deficits and to ensure safety in men with prostate cancer.

Key Words
- androgen deprivation
- prostatic neoplasms
- cardiovascular diseases
- osteoporosis
- muscle

Prostate cancer, androgen deprivation, and adverse effects

With one in seven men affected over their lifetime, prostate cancer is the most prevalent solid-organ malignancy in men worldwide. Prostate cancer is exquisitely responsive to androgens, and manipulation of hormones has occurred since the 1940s when first described by Huggins & Hodges (1941a,b). Orchidectomy was the mainstay of treatment of metastatic prostate cancer for decades, until the development of medical castration with luteinizing hormone-releasing hormone (LHRH) agonists in the mid-1980s. Androgen deprivation therapy (ADT) with LHRH agonists is an effective treatment for men with prostate cancer and, currently, is the most common cause of hypogonadism in the western world (Grossmann et al. 2011). A progressive rise in the number of men treated with ADT was observed in the 1990s and 2000s; however, in the last 5 years, a reduction in the rate of inappropriate use of ADT has occurred, probably because of increasing awareness of the adverse side effect profile and risk to benefit ratio of treatment. In the USA, reductions in reimbursement for non-evidence-based indications for ADT may have contributed (Shahinian et al. 2010). Unless otherwise stated, ADT will refer to medical castration with LHRH agonists.

Survival benefits have been demonstrated in multiple randomized trials for the use of long-term (2–3 years) ADT...
in combination with radiotherapy in men with locally advanced prostate cancer (Bolla et al. 2002, 2009, Pilepich et al. 2005, Horwitz et al. 2008). Improvement in overall survival and progression-free survival has also been demonstrated in those with pelvic lymph node disease discovered at prostatectomy, although the evidence for this is more limited (Messing et al. 2006). More recently, it has been shown that shorter durations of ADT (18 months) may not compromise overall survival or disease-free survival compared with 36 months of ADT in a randomized controlled trial (RCT) of 630 men with high-risk prostate cancer receiving adjuvant radiotherapy. If confirmed, this may have profound implications on minimizing long-term side effects (Nabid et al. 2013).

ADT use after prostatectomy to treat biochemical progression (rising prostate-specific antigen (PSA) levels or PSA recurrence) is more controversial. In early, randomized trials of radiotherapy with or without long-term ADT, post-prostatectomy patients with high-risk features were included together with treatment-naïve patients with high-risk prostate cancer, who were to receive radiotherapy and ADT as primary treatment. All men, including the post-prostatectomy group, had a survival benefit (Pilepich et al. 2005). In a preliminary analysis of the SWOG S9921 study investigating the use of goserelin plus bicalutamide for men with high-risk features for recurrence after prostatectomy (extraprostatic extension or Gleason score ≥8), 481 men had an estimated 5-year biochemical failure-free survival of 92.5% and overall survival of 95.9% (Dorff et al. 2011). There was no comparable control group undergoing observation alone. In a retrospective study of 225 node-negative patients with high-risk features after prostatectomy (extracapsular extension, seminal vesical invasion, and/or positive surgical margin), there was improvement in biochemical (hazard ratio (HR) 0.4, \( P=0.02 \)) and clinical (HR 0.2, \( P=0.008 \)) relapse-free survival from combining ADT with radiotherapy, compared with radiotherapy alone (Ost et al. 2012).

More recently, LHRH antagonists such as degarelix have become available to treat advanced prostate cancer with the advantage of rapid lowering of testosterone levels without the acute flare in testosterone levels observed with LHRH agonists. A meta-analysis has indicated improved PSA progression-free survival and overall survival compared with the use of LHRH agonists; however, further longer-term randomized studies are required to compare efficacy and long-term side effect profiles (Klotz et al. 2014).

With the widespread use of ADT in men with non-metastatic high-risk prostate cancer and given the excellent long-term survival of these men, managing long-term endocrine side effects of ADT, such as limiting treatment-related toxic effects on cardiovascular and bone health, is pertinent. Men undergoing ADT almost universally experience constitutional symptoms of hypogonadism with hot flushes, lethargy, and weakness, as well as sexual dysfunction and anemia. Adverse effects on quality of life, cognition, and mood may occur, but these are not well characterized (Casey et al. 2012, Grossmann & Zajac 2012, Jamadar et al. 2012, Mazzola & Mulhall 2012). Significant adverse effects have also been observed on body composition with the loss of muscle and bone mass, and gain in fat. Compounding effects are that, even before starting treatment, men undergoing ADT have a high baseline prevalence of obesity, cardiovascular risk factors, and osteopenia (Cheung et al. 2013).

The recent introduction of novel therapies manipulating androgens and androgen receptor signaling has added to treatment armamentarium and, however, further complicates considerations when balancing risk to benefit profiles (Cannata et al. 2012). Abiraterone, an irreversible and selective inhibitor of cytochrome p-450-17 to suppress adrenal and intratumoral androgen synthesis, and enzalutamide, an androgen receptor antagonist, have both been shown in landmark studies in men with castration-resistant prostate cancer to improve overall survival and progression-free survival (de Bono et al. 2011, Scher et al. 2012). More recently, a novel high-affinity androgen receptor inhibitor ODM-201 showed a favorable safety profile and disease suppression in a phases 1–2 study (Fizazi et al. 2014). Results from these studies confirm that the androgen receptor and androgen receptor signaling play a pivotal role in progressive prostate cancer despite castrate levels of serum testosterone induced by conventional ADT. While these newer agents decrease systemic androgen action to a greater extent than conventional ADT, whether this leads to more profound effects on muscle, bone, and fat has not been investigated in detail. Abiraterone has been shown to cause a decrease in muscle mass, and unexpectedly, also a decrease in visceral fat, the mechanism for which is uncertain (Pezaro et al. 2013). Glucocorticoid co-administration, usually required to prevent abiraterone-associated mineralocorticoid excess, may compound adverse effects on body composition and bone mass. Combination therapies using novel agents are currently undergoing clinical trials in metastatic disease and for primary treatment together with radiotherapy and ADT in earlier stages of disease. If survival can be significantly prolonged, long-term side effects will become increasingly important. It remains to be seen whether these will be more profound
compared with the effects of hypogonadism with conventional LHRH agonists.

This review will focus on the bone and muscle side effects and novel agents in the pipeline for ameliorating such effects.

**Muscle effects of ADT**

Skeletal muscle is an endocrine organ regulated by a number of molecular and signaling pathways. The precise mechanism by which androgen deprivation leads to skeletal muscle atrophy is not well understood, but is a result of an imbalance between muscle atrophy activation and muscle growth factors. Research in recent years has recognized that muscle atrophy is regulated largely by the ubiquitin–proteasome system and the autophagy/lysosomal pathways, whereas muscle growth is predominantly regulated by androgen receptor/β-catenin as well as transforming growth factor beta (TGFβ)/SMAD, and insulin-like growth factor 1/Akt/mammalian target of rapamycin signaling (Fig. 1; Bhasin et al. 2011, Serra et al. 2013).

Understanding the effects of androgen deprivation may have further implications with respect to sarcopenia and frailty in general. A gradual decline in testosterone levels is observed with aging and frailty, which is accelerated by the accumulation of age-related medical comorbidities and obesity. ADT leads to profound hypogonadism with castrate levels of circulating testosterone (and

![Figure 1](http://erc.endocrinology-journals.org) Potential contributors to muscle loss in ADT. +, positive effect; --, negative effect. Sex steroid deficiency resulting from ADT leads to a decline in muscle mass and a gain in fat mass (sarcopenic obesity), as well as a decline in bone mass. Significant crosstalk occurs between fat, muscle, and bone contributing to sarcopenic obesity. Loss of muscle mass may arise from an imbalance between muscle atrophy pathways and muscle growth pathways, and potentially neuronal effects. Emerging therapies, such as myostatin inhibitors and follistatin, target muscle growth pathways and SARMs and may counteract effects of sex steroid deficiency on muscle, bone, and fat.
estradiol (E$_2$)), and, although such levels are not observed in aging men in general, ADT may potentially be considered a unique accelerated model for studying male aging and frailty. The studies of the effects of ADT on muscle mass, muscle strength, and physical performance have yielded variable results and are summarized below. Well-designed, controlled, prospective studies in this area are lacking (Storer et al. 2012). Muscle mass decreases consistently; however, when muscle strength outcomes are assessed, results have not all been concordant. Furthermore, objective measures of physical performance and functioning do not appear to change significantly. Ultimately, it is an individual’s physical functioning, independence, and the risk of falls that is clinically important and it is currently unclear whether loss of muscle mass in ADT makes a difference to these factors.

**Observational studies**

**Muscle mass and body composition** Cross-sectional studies Cross-sectional case–control studies have demonstrated that men undergoing ADT, particularly those undergoing long-term ADT, have greater fat mass and lower lean body mass (LBM) when compared with prostate cancer controls and age-matched healthy controls (Basaria et al. 2002, Clay et al. 2007). Not all controlled studies have yielded consistent results, with no differences observed in fat and lean mass in a group of 48 men treated with ADT compared with 70 healthy age-matched controls (Galvao et al. 2009a). It was unclear as to the mean duration of ADT treatment (>2 months) before entering the study; however, a reduction in muscle strength and functional performance was demonstrated in the ADT compared with the control group, which will be further discussed later.

Longitudinal studies Rapid changes in body composition with decline in fat-free mass and rise in fat mass over 10 weeks were described in an initial report in 1998 of six young healthy men given LHRH agonists (Mauras et al. 1998). Longitudinal studies have shown consistent changes over 36–52 weeks in men undergoing ADT for prostate cancer with significant increases in weight of 1.8–2.4%, increases in fat mass of 9.4–19.3%, and decreases in LBM of 1.9–3.8% (Table 1; Berruti et al. 2002, Smith et al. 2002, Smith 2004, Galvao et al. 2008). The largest reported study (a substudy of the HALT study) analyzed the LBM of 252 men treated with ADT for a median of 20.4 months (Smith et al. 2009a). LBM decreased progressively over 3 years; 1.0% at 1 year, 2.1% at 2 years, and 2.4% at 3 years (all P<0.001). There was a greater rate of decrease in LBM in older men at ≥70 years of age (2.8 vs 0.9%, P=0.035) and a trend toward greater loss in men who had recently commenced ADT within 6 months of study commencement (3.7 vs 2.0%, P=0.0645; Smith et al. 2012). Upon cessation of ADT, the loss of lean mass and gain in fat mass plateaus, however, do not appear to recover despite recovery of eugonadal testosterone levels (Spry et al. 2013). There should be some caution in interpretation given the variable inclusion criteria and the lack of a control group in all of these studies. Thus, the effects of ADT cannot be separated from those of aging itself, which is also associated with decreases in muscle mass and increases in fat mass.

There have only been three longitudinal studies, which included a control group (Table 1). Adverse body composition changes occur maximally over the first 6 months in men newly commencing ADT with little change observed thereafter (Boxer et al. 2005, Greenspan et al. 2005, Levy et al. 2008). Boxer et al. (2005) demonstrated an increase in fat mass of 9.5% with a decrease in LBM of 2% over 6 months in men newly commencing ADT compared with age-matched healthy controls, which is consistent with results from previous studies.

**Muscle strength** Although the majority of studies of body composition show a decrease in muscle mass as measured by dual energy x-ray absorptiometry (DEXA), effects of ADT on muscle strength have been more variable (Table 2). Hand grip strength was significantly lower in men undergoing ADT compared with controls in two case–control studies; however, not all studies have been concordant (Stone et al. 2000, Joly et al. 2006, Soyupek et al. 2008, Alibhai et al. 2010a). Upper limb strength (measured by bench press or seated row) also declines in men undergoing ADT compared with controls in cross-sectional studies (Basaria et al. 2002, Galvao et al. 2009a).

Lower limb strength results have been more variable in cross-sectional studies. No changes have been demonstrated in maximal leg press as reported by Basaria and Galvao; however, Galvao did report a significant decrease in leg extension in the ADT group compared with controls (Basaria et al. 2002, Galvao et al. 2009a). In the same study, muscle endurance (measured by a maximum number of repetitions for chest and leg press) was not significantly different. Notably, these studies were cross-sectional in nature and recruited participants who had been treated with variable durations of ADT. It is possible that changes in muscle strength, similar to muscle mass, occur maximally in the first six months after commencing ADT, which may explain the variable results obtained.
Table 1  Studies reporting body composition changes in men undergoing ADT

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<th>References</th>
<th>Design</th>
<th>No. of subjects</th>
<th>Duration of follow-up</th>
<th>Group characteristics</th>
<th>Bone outcomes</th>
<th>Muscle outcomes</th>
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<tbody>
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<td>Basaria et al. (2002)</td>
<td>Cross-sectional</td>
<td>58</td>
<td>–</td>
<td>Group 1: 20 men receiving LHRH agonists for &gt; 12 months for recurrent or metastatic disease Group 2: 18 men with prostate cancer and not on ADT Group 3: 20 age-matched controls</td>
<td>↓ LS BMD in Group 1, 0.87 ± 0.12 vs Group 2, 1.04 ± 0.16 vs Group 3, 1.13 ± 0.24 g/cm², P &lt; 0.0001, TH BMD, P = 0.49 ↓ Total body BMD in Group 1, 1.00 ± 0.09 vs Group 2, 1.07 ± 0.10 vs Group 3, 1.07 ± 0.09 g/cm², P = 0.03</td>
<td>FM ↑ in Group 1, 32.2 ± 5.4% vs Group 2, 26.2 ± 6.0% vs Group 3, 22.4 ± 4.1%, P &lt; 0.0001</td>
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<tr>
<td>Galvao et al. (2009a)</td>
<td>Cross-sectional</td>
<td>118</td>
<td>–</td>
<td>Group 1: 48 men on LHRH agonists of variable duration with non-metastatic disease Group 2: 70 age-matched healthy controls</td>
<td>↑ TH BMD Group 1, 0.951 ± 0.124 vs Group 2, 0.999 ± 0.113 g/cm², P = 0.034 ↑ Total body BMD Group 1, 1.095 ± 0.110 vs Group 2, 1.147 ± 0.108 g/cm², P = 0.013</td>
<td>FM ↑ not significant Group 1, 22.6 ± 6.3 vs Group 2, 20.4 ± 6.5 kg, P = 0.068</td>
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<td>Smith et al. (2002)</td>
<td>Longitudinal</td>
<td>32</td>
<td>48 weeks</td>
<td>Commencing ADT (LHRH agonists) for locally advanced, lymph node positive or recurrent disease</td>
<td>↓ LS BMD 1.00 ± 0.194 → 0.977 ± 0.182 g/cm², P &lt; 0.002 ↓ TH BMD 0.929 ± 0.136 → 0.923 ± 0.138 g/cm², P &lt; 0.03</td>
<td>↓ Wt 2.4 ± 0.8% (P &lt; 0.005) ↑ FM 9.4 ± 1.7% (P &lt; 0.001) ↓ LBM 2.7 ± 0.5% (P &lt; 0.001)</td>
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<td>Berruti et al. (2002)</td>
<td>Longitudinal</td>
<td>35</td>
<td>12 months</td>
<td>Commencing LHRH agonists for non-metastatic disease</td>
<td>↓ LS BMD 1.00 ± 0.194 → 0.977 ± 0.182 g/cm², P &lt; 0.002 ↓ TH BMD 0.929 ± 0.136 → 0.923 ± 0.138 g/cm², P &lt; 0.03</td>
<td>↓ Wt 1.8 ± 0.5% (P &lt; 0.001) ↑ FM 11.0 ± 1.7% (P &lt; 0.001) ↓ LBM 3.8 ± 0.6% (P &lt; 0.001)</td>
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<td>Smith (2004)</td>
<td>Longitudinal</td>
<td>79</td>
<td>12 months</td>
<td>Commencing ADT (LHRH agonists or bilateral orchidectomy) for non-metastatic disease</td>
<td>↓ LS BMD 3.3 ± 0.4% ↓ TH BMD 1.9 ± 0.3%</td>
<td>↓ Wt 1.0% (95% CI, 0.4–1.5%) at 12 months; P &lt; 0.001, ↓ 1.2% (95% CI, 1.5–2.7%) at 24 months; P &lt; 0.001, ↓ 2.4% (95% CI, 1.6–3.2%) at 36 months; P &lt; 0.001</td>
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<td>Galvao et al. (2008)</td>
<td>Longitudinal</td>
<td>72</td>
<td>36 weeks</td>
<td>Commencing ADT (LHRH agonists) for non-metastatic disease Receiving ADT for a median of 20.4 months</td>
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<tr>
<td>Smith et al. (2012)</td>
<td>Longitudinal</td>
<td>252</td>
<td>36 months</td>
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<td>Preston et al. (2002)</td>
<td>Longitudinal case-control</td>
<td>78</td>
<td>24 months</td>
<td>Group 1: 39 men undergoing ADT for &gt; 6 months (LHRH agonists or bilateral orchidectomy) Group 2: 29 age-matched controls not on ADT</td>
<td>At 24 months:  ( \text{† forearm BMD} ) Group 1, ( -9.4 \pm 1.0% ) vs Group 2, ( -4.4 \pm 0.3% ) (( P&lt;0.0005 ))  ( \text{† FN BMD} ) Group 1, ( -1.9 \pm 0.7% ) vs Group 2, ( +0.6 \pm 0.5% ) (( P=0.0016 )) ( \text{† TH BMD} ) Group 1, ( -1.5 \pm 1.0% ) vs Group 2, ( +0.8 \pm 0.5% ) (( P=0.0018 )) ( \text{† LS BMD} ) Group 1, ( -0.2 \pm 0.8% ) vs Group 2, ( +1.1 \pm 0.6% ) (( P=0.25 ))</td>
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<td>Boxer et al. (2005)</td>
<td>Longitudinal case-control</td>
<td>55</td>
<td>26 weeks</td>
<td>Group 1: 30 men commencing LHRH agonists for localized non-metastatic disease Group 2: 25 age-matched controls</td>
<td>–</td>
<td>FM† in Group 1 at baseline vs 26 weeks, ( 9.5 \pm 0.13% ), ( P&lt;0.001 ); ( \downarrow ) in Group 2 at baseline vs 6 months, ( -3.8 \pm 0.08% ), ( P=0.02 ) LBM ( \downarrow ) in Group 1 at baseline vs 26 weeks, ( 2.1 \pm 0.03% ), ( P&lt;0.001 ), no change in control group</td>
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<td>Greenspan et al. (2005)</td>
<td>Longitudinal case-control</td>
<td>195</td>
<td>12 months</td>
<td>Group 1: 30 subjects undergoing acute ADT for &lt; 6 months Group 2: 50 subjects undergoing chronic ADT for ≥ 6 months Group 3: 72 prostate cancer controls not on ADT Group 4: 43 age-matched healthy controls</td>
<td>Group 1 at 12 months: ( \downarrow ) TH BMD ( -2.5 \pm 0.6% ) (( P&lt;0.05 )) ( \downarrow ) LS BMD ( -4.0 \pm 1.5% ) (( P&lt;0.05 )) ( \downarrow ) Radius BMD ( -2.6 \pm 0.5% ) ( P&lt;0.05 ) Group 2: ( \downarrow ) radius BMD ( -2.0 \pm 0.6% ) (( P&lt;0.05 )) Groups 3 and 4: NS</td>
<td>FM† Group 1, ( 10.4 \pm 1.7% ) (( P&lt;0.05 )). LBM ( \downarrow ) Group 1, – ( 3.5 \pm 0.5% ) ( P&lt;0.05 ) Groups 2, 3, and 4: NS</td>
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<td>Levy et al. (2008)</td>
<td>Longitudinal case-control</td>
<td>48</td>
<td>24 months</td>
<td>Group 1: 23 men on long-term ADT (mean 24.57 months) for non-metastatic disease Group 2: 12 men on short-term ADT (mean 3.83 months) Group 3: 13 men as controls (healthy controls or with prostate cancer not on ADT) not age matched</td>
<td>–</td>
<td>FM across groups: NS FM in Group 1 from baseline to 24 months: NS LBM across groups: NS LBM in Group 1 from baseline to 24 months ( \downarrow ) ( -980.84 \pm 1688.72) g, ( P&lt;0.05 )</td>
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<td>Ziaran et al. (2013)</td>
<td>Longitudinal case-control</td>
<td>183</td>
<td>24 months</td>
<td>Group 1: 95 men commencing ADT for non-metastatic PC Group 2: 88 age- and BMI-matched controls</td>
<td>LS BMD Group 1, ( 0.886 \pm 0.090) vs Group 2, ( 0.985 \pm 0.106) g/cm², ( P=0.001 ) TH BMD Group 1, ( 0.916 \pm 0.172) vs Group 2, ( 0.943 \pm 0.163) g/cm², ( P=0.022 ) FN BMD Group 1, ( 0.668 \pm 0.090) vs Group 2, ( 0.751 \pm 0.084) g/cm², ( P=0.037 )</td>
<td>Group 1 BMI ( 28.93 \pm 2.11) kg/m² vs Group 2 BMI ( 27.91 \pm 2.14) kg/m², ( P=0.03 )</td>
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Data expressed as mean ± s.d. Wt, body weight; FM, whole-body fat mass; FFM, fat free mass; LBM, lean body mass; LS, lumbar spine; TH, total hip; FN, femoral neck; BMD, bone mineral density; NS, not significant.
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<td>58</td>
<td>–</td>
<td>Group 1: 20 men receiving LHRH agonists for &gt; 12 months for recurrent or metastatic disease</td>
<td>Upper body bench press 1 repetition maximum (1REM) – Group 1, 47.6 ± 15.6 vs Group 2, 79.6 ± 35.3 vs Group 3, 61.1 ± 21.4 lb,  ( P = 0.001 )</td>
<td>ADLs: NS</td>
<td>6MWT: NS</td>
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<td>Joly et al. (2006)</td>
<td>Cross-sectional</td>
<td>108</td>
<td>–</td>
<td>Group 1: 57 men undergoing ADT (LHRH agonists), median duration 1.8 years for non-metastatic disease</td>
<td>Grip strength left and right hand: NS</td>
<td>QoL by functional assessment of cancer therapy overall NS. Fatigue subset worse Group 1,  ( P = 0.03 )</td>
<td>TUG: NS</td>
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<td>Clay et al. (2007)</td>
<td>Cross-sectional</td>
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<td>–</td>
<td>Group 1: 25 men with prostate cancer as controls not on ADT</td>
<td>9-Hole Peg test time (arm and hand function): NS</td>
<td>Chair rise time: NS</td>
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<td>Group 2: 13 men on short-term ADT (mean 3.7 months)</td>
<td>4 m gait speed, m/s</td>
<td>Group 3, 0.18 m/s slower than Group 4,  ( P &lt; 0.001 ), no difference in Group 3 vs Group 1 or 2 (Group 1, 1.06 ± 0.13 vs Group 2, 1.04 ± 0.25 vs Group 3, 0.99 ± 0.21 vs Group 4, 1.17 ± 0.26 m/s)</td>
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<td>Group 3: 42 men on long-term ADT (mean 30.7 months)</td>
<td>4 m gait speed, m/s</td>
<td>SPPB lowest in Group 3,  ( P &lt; 0.02 ) (Group 1, 10.4 ± 0.9 vs Group 2, 10.4 ± 1.7 vs Group 3, 9.6 ± 1.7 vs Group 4, 10.3 ± 0.9)</td>
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<td>Group 4: 20 healthy controls – older men, not age matched</td>
<td>4 m gait speed, m/s</td>
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<td>Soyupek et al. (2008)</td>
<td>Cross-sectional</td>
<td>40</td>
<td>–</td>
<td>Group 1: 20 men undergoing ADT for &gt; 1 year for non-metastatic disease</td>
<td>Grip strength – dominant hand Group 1, 27.94 ± 5.82 vs Group 2, 39.17 ± 4.87 kg,  ( P &lt; 0.001 )</td>
<td>Physical Activity Questionnaire (kcal/day): NS 15D QoL questionnaire worse in Group 1, 0.53 ± 0.07 vs 0.81 ± 0.08,  ( P &lt; 0.001 )</td>
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<td>Galvao et al. (2009)</td>
<td>6 m usual walk (s); Group 1, 4.8 ± 0.6 vs Group 2, 4.5 ± 0.6, P = 0.042</td>
<td>Group 1: 48 men on LHRH agonists of variable duration (&gt; 2 months) with non-metastatic disease</td>
<td>Muscle strength (kg): Chest press (kg): Group 1, 32.4 ± 10.5 vs Group 2, 37.5 ± 9.1, P = 0.006</td>
<td>6 m usual walk (s); Group 1, 2.8 ± 1.3 vs Group 2, 2.6 ± 1.4, P = 0.035</td>
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<td>Galvao et al. (2008)</td>
<td>6 m fast walk (s); Group 2, 3.5 ± 0.3, P = 0.013</td>
<td>Group 2: 70 age-matched healthy controls</td>
<td>Seated row (kg): Group 1, 38.7 ± 6.6 vs Group 2, 42.4 ± 6.4, P = 0.018</td>
<td>6 m backward walk (s); Group 2, 2.8 ± 1.5 vs Group 3, 1.6 ± 1.0, P = 0.044</td>
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<td>Bylow et al. (2011)</td>
<td>6 m usual walk (s); Group 1, 4.8 ± 0.6 vs Group 2, 4.5 ± 0.6, P = 0.042</td>
<td>Group 1: 63 men undergoing ADT for biochemical recurrence</td>
<td>Leg extension (kg): Group 1, 49.1 ± 4.1 vs Group 2, 46.0 ± 3.8, P = 0.567</td>
<td>6 m usual walk (s); Group 1, 2.8 ± 1.3 vs Group 2, 2.6 ± 1.4, P = 0.035</td>
</tr>
<tr>
<td>Bylow et al. (2008)</td>
<td>6 m fast walk (s); Group 2, 3.5 ± 0.3, P = 0.013</td>
<td>Group 2: 70 age-matched healthy controls</td>
<td>Leg press (kg): Group 1, 91.0 ± 4.0 vs Group 2, 86.8 ± 3.7, P = 0.567</td>
<td>6 m backward walk (s); Group 2, 2.8 ± 1.5 vs Group 3, 1.6 ± 1.0, P = 0.044</td>
</tr>
<tr>
<td>Levy et al. (2008)</td>
<td>6 m usual walk (s); Group 1, 4.8 ± 0.6 vs Group 2, 4.5 ± 0.6, P = 0.042</td>
<td>Group 1: 71 men with prostatic cancer not on ADT</td>
<td>Chest press (kg): Group 1, 34.8 ± 10.6 vs Group 2, 35.4 ± 10.6, P = 0.625</td>
<td>6 m usual walk (s); Group 1, 2.8 ± 1.3 vs Group 2, 2.6 ± 1.4, P = 0.035</td>
</tr>
<tr>
<td>Stone et al. (2000)</td>
<td>6 m usual walk (s); Group 1, 4.8 ± 0.6 vs Group 2, 4.5 ± 0.6, P = 0.042</td>
<td>Group 2: 70 age-matched healthy controls</td>
<td>Seated row (kg): Group 1, 38.7 ± 6.6 vs Group 2, 42.4 ± 6.4, P = 0.018</td>
<td>6 m backward walk (s); Group 2, 2.8 ± 1.5 vs Group 3, 1.6 ± 1.0, P = 0.044</td>
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<tr>
<td>Levy et al. (2008)</td>
<td>6 m fast walk (s); Group 2, 3.5 ± 0.3, P = 0.013</td>
<td>Group 2: 70 age-matched healthy controls</td>
<td>Leg extension (kg): Group 1, 49.1 ± 4.1 vs Group 2, 46.0 ± 3.8, P = 0.567</td>
<td>6 m backward walk (s); Group 2, 2.8 ± 1.5 vs Group 3, 1.6 ± 1.0, P = 0.044</td>
</tr>
</tbody>
</table>

Strength and endurance outcomes:
- Muscular strength
- Muscle endurance
- Physical activity

Subjective physical performance measures:
- Fatigue Severity Score
- Fatigue based on quality of life questionnaire

Fatigue Severity Score worse after 12 weeks, P < 0.001

Reported falls in the last 1 year 14.9% in Group 1 vs 2.8% in Group 2, P = 0.02

SPPB score 10.0 ± 2.2 vs 10.3 ± 2.1, P = 0.41

Frailty score based on Fried’s criteria, P = 0.20

56% abnormal SPPB at baseline and 20% had worse scores after 12 weeks

22% reported falls in last 3 months

5% physical disability

24% impairment ADLs

22% reported falls in last 3 months

5% physical disability

56% abnormal SPPB at baseline

20% had worse scores after 12 weeks
Physical performance  Subjectively, men undergoing ADT consistently reported an increase in fatigue, decline in the quality of life, and decline in physical activity and physical function compared with control groups (see Table 2). Decreases in objective measures of physical performance (defined as functional tasks), however, have been more difficult to demonstrate among this cohort.

Cross-sectional case–control studies have yielded conflicting results. Men who had received ADT for 6–24 months had no change in their lower limb physical function measured by the short physical performance battery (SPPB), frailty scores, 6-min walk time (6MWT), or timed up and go (TUG) results compared with control groups (Joly et al. 2006, Clay et al. 2007, Bylow et al. 2011). Galvao et al. (2009a) recruited men who had been on ADT for a relatively shorter duration (<2 months) and it was the only cross-sectional study to demonstrate a decrease in all physical performance parameters measured (6 m walk time, 400 m walk time, 6 m backwards walk time, and chair rise time) in men undergoing ADT compared with controls. This was despite variable deficits in muscle strength.

Two longitudinal case–control studies have been carried out to assess physical performance. Levy et al. (2008) showed no significant change at 2 years compared with baseline in 4 m walk time, chair rise time, and SPPB. Only one study recruited men newly commencing ADT compared with prostate cancer controls and healthy controls (Alibhai et al. 2010a). No changes were observed in 6MWT or TUG over 12 months in the ADT group despite subjective reports of decline in physical function in a quality of life questionnaire. Moreover, in controlled studies, ADT has not been demonstrated to increase the risk of falls once age, comorbidities, and clinical characteristics are taken into account (Bylow et al. 2011).

Physical function outcomes are clearly very heterogeneous despite plausible hypotheses that deficits in function follow loss of muscle mass and strength. It is possible that more marked declines in strength and performance are seen soon after commencement of ADT, and those treated for longer durations may have compensated for any initial impairment, which may explain the differences in findings between the various studies. Furthermore, previous tests employed, such as SPPB or TUG, are probably inadequate or insensitive assessments of muscle function and physical performance and further research is required in this area.

In summary, adverse effects on body composition are clearly observed in men undergoing ADT with a decrease

<table>
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<tr>
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<th>Design</th>
<th>No. of subjects</th>
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<th>Subjective physical performance measures</th>
<th>Objective physical performance measures</th>
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<tr>
<td>Alibhai et al. (2010a)</td>
<td>Longitudinal case–control study</td>
<td>259</td>
<td>12 months</td>
<td>Group 1: 87 men commencing LHRH agonists for non-metastatic disease Group 2: 86 men not on ADT Group 3: 86 age-matched healthy controls</td>
<td>Grip strength:</td>
<td>Group 1, P = 0.04; remained stable in Group 2, P &lt; 0.001 and ↑ in Group 3, P &lt; 0.001</td>
<td>SF-36 physical function score:</td>
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</tbody>
</table>

6MWT stable in Group 1, P < 0.05, improved in Group 2 and 3, P < 0.05 and ↓ in Group 2 and 3, P < 0.01. TUG scores stable across all groups, P > 0.10.

Data expressed as mean ± S.D. QoL, quality of life; SF-36, Short-Form 36-item Health Survey; gppb, short physical performance battery; 6MWT, 6 min walk test; TUG, timed up and go test.
in LBM of approximately 2–4% and a concomitant increase in fat mass of approximately 10–20% in the first 12 months leading to ‘sarcopenic obesity’. The mechanisms underlying these effects are probably multifactorial (Fig. 1). Experimental evidence indicates that testosterone deficiency may promote stem cell differentiation into adipocytes and may also have motivational effects leading to decreased physical activity (Ng Tang Fui et al. 2014). Androgen-deficient mice have decreased voluntary activity, which may account for increased adiposity and reduced muscle mass (Rana et al. 2011). Furthermore, adipose tissue releases pro-inflammatory cytokines, which themselves may lead to sarcopenia (Waters & Baumgartner 2011).

The increase in fat and loss of muscle mass are associated with a decrease in predominantly upper body strength, including maximum chest press and hand grip strength. Men undergoing ADT also report a subjective decrease in the quality of life and increased fatigue compared with controls. Objective measures of physical performance are, however, much more variable, with many studies demonstrating no significant changes in the measures of endurance, dexterity, walking speed, measures of frailty, and lower limb performance. The discordant results for physical performance in the various studies may be related to the heterogeneous inclusion criteria with men entering studies on variable durations of ADT for various indications, unmatched baseline characteristics, variability in test conditions, and procedures, as well as lack of test sensitivity for detecting subtle changes in physical performance. Given the relatively small loss of muscle mass relative to fat mass, changes in physical performance may not be readily detectable despite subjective feelings of fatigue in patients.

Intervention studies

Interventions to mitigate the adverse effects of ADT on muscle and fat have been poorly studied. Exercise is the most effective intervention based on current evidence and should be recommended to all men commencing ADT; however, limitations include cost, adherence, sustainability, implementation, and safety in the setting of medical comorbidities. As such, multiple novel anabolic strategies including selective androgen receptor modulators (SARMs) and myostatin antagonists are also under investigation.

Exercise and ADT Although physical performance outcomes have been variable in men undergoing ADT, several exercise studies have been carried out with an aim of improving musculoskeletal health. It has recently been shown in an RCT that exercise can prevent adverse body composition changes associated with ADT (Table 3). Compared with usual care, a supervised combination of resistance and aerobic exercise at commencement of ADT can maintain lean mass and prevent gains in fat mass over 3 months (Cormie et al. 2014). In doing so, muscle strength (chest and leg press 1-RM) improved in the exercise group compared with usual care; however, no changes were observed in functional tasks such as balance, stair climb time, and 6 m walk time. All other RCTs evaluating exercise in men undergoing ADT have focused on rehabilitation rather than prevention and have recruited men receiving longer durations of ADT (mean duration over 12 months; Table 3). RCTs and uncontrolled exercise trials have recently been summarized in a systematic review (Gardner et al. 2014).

The largest RCT randomized 155 men receiving ADT (mean duration 13 months) to an intervention group (n=82) of supervised resistance exercise three times per week for 12 weeks or to a wait-list control group (n=73) (Segal et al. 2003). The exercise group improved their muscular endurance (chest and leg press repetitions) and improved fatigue and quality of life compared with controls. Body composition was not measured; however, there was no change in weight or waist circumference. Three other RCTs have shown improvements in muscle strength with supervised combination aerobic and resistance exercise programs; however, other measures such as body composition, cardiorespiratory fitness, functional performance, and balance assessments have been more variable (Segal et al. 2009, Galvao et al. 2010, Bourke et al. 2011). Benefits of exercise with regard to fatigue and quality of life have been supported in these RCTs. In contrast, predominantly unsupervised, light exercise has been shown to have no effect on fitness, fatigue, quality of life, or BMI (Culos-Reed et al. 2007, 2010).

Furthermore, education alone with cognitive behavioral skills is insufficient at improving quality of life and physical activity levels (Carmack Taylor et al. 2006). Results from these studies indicate that supervised, group-based, combination resistance and aerobic exercise training is more beneficial at improving outcomes for men undergoing ADT.

General guidelines in a systematic review and from the American College of Sports Medicine roundtable recommend aerobic and resistance exercise training in a group-based setting if available for patients with prostate cancer (encompassing but not solely inclusive of patients on ADT;
<table>
<thead>
<tr>
<th>References</th>
<th>Groups</th>
<th>No. of subjects</th>
<th>Duration of follow-up</th>
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<tr>
<td>Cormie et al. (2014)</td>
<td>Group 1: Resistance and aerobic exercise – supervised, twice weekly</td>
<td>63</td>
<td>3 months</td>
<td>Non-metastatic PC commencing ADT</td>
<td>Between-group differences – Group 1 vs Group 2:</td>
</tr>
<tr>
<td></td>
<td>Group 2: Usual care</td>
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<td></td>
<td>↑ Lean mass, ( P = 0.019 )</td>
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<td>↓ Fat mass, ( P = 0.001 )</td>
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<td>BMD: NS</td>
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<td>↑ Muscle strength (chest press 1-RM, ( P = 0.004 ); leg press 1-RM, ( P &lt; 0.001 ))</td>
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<td>↑ Cardiorespiratory fitness (( \text{VO}_2 ) peak), ( P = 0.004 )</td>
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<td>Balance (6 m backwards walk): NS</td>
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<td>6 m walk time: NS</td>
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<td>Stair climb time: NS</td>
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<tr>
<td>Segal et al. (2003)</td>
<td>Group 1: Resistance exercise – supervised, three times weekly</td>
<td>155</td>
<td>12 weeks</td>
<td>PC (all stages) receiving ADT (mean duration 13 months)</td>
<td>Between-group differences – Group 1 vs Group 2:</td>
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<td></td>
<td>Group 2: Wait-list control group</td>
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<td>Weight: NS</td>
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<td>Waist circumference: NS</td>
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<td>↑ Muscle endurance (↑ chest press repetitions, ( P = 0.009 ); ↑ leg press repetitions, ( P &lt; 0.001 ))</td>
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<tr>
<td>Segal et al. (2009)</td>
<td>Group 1: Resistance exercise – supervised, three times weekly</td>
<td>121</td>
<td>24 weeks</td>
<td>PC (all stages) commencing radiotherapy (61% on ADT)</td>
<td>Between-group differences:</td>
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<tr>
<td></td>
<td>Group 2: Aerobic exercise – supervised, three times weekly</td>
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<td>Weight: NS</td>
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<td></td>
<td>Group 3: Usual care</td>
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<td>Fat mass: NS</td>
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<td>↑ Muscle strength (chest press 8-RM: Group 1 vs Group 3, ( P &lt; 0.001 ); Group 2 vs Group 3, ( P = 0.006 ), leg press 8-RM: Group 1 vs Group 3, ( P &lt; 0.001 ), Group 2 vs Group 3: NS)</td>
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<td>Cardiorespiratory fitness: NS</td>
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<td>Between-group differences – Group 1 vs Group 2:</td>
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<td>↑ lean mass, ( P = 0.047 )</td>
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<td></td>
<td>↑ Muscle strength (chest press, leg press, seated row, and leg extension 1RM), all ( P &lt; 0.01 )</td>
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<td>Cardiorespiratory fitness: NS</td>
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<td>Improved 6-m walk time, ( P = 0.024 )</td>
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<td>Improved 6-m backward walk time, ( P = 0.039 )</td>
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<td>Between-group differences – Group 1 vs Group 2:</td>
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<tr>
<td>Galvao et al. (2010)</td>
<td>Group 1: Resistance and aerobic exercise – supervised, twice weekly</td>
<td>57</td>
<td>12 weeks</td>
<td>Non-metastatic PC on ADT (mean duration 14 months)</td>
<td>Weight: NS</td>
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<tr>
<td></td>
<td>Group 2: Usual care</td>
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<td>Waist-to-hip ratio: NS</td>
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<td>↑ Muscle strength (maximum voluntary torque), ( P = 0.033 )</td>
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<td>Cardiorespiratory fitness</td>
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<td>↑ Physical performance (30-s sit to stand), ( P &lt; 0.001 )</td>
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<tr>
<td>Bourke et al. (2011)</td>
<td>Group 1: Resistance and aerobic exercise – supervised</td>
<td>50</td>
<td>12 weeks</td>
<td>PC (all stages) on ADT (mean duration 30 months)</td>
<td>Between-group differences – Group 1 vs Group 2:</td>
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<tr>
<td></td>
<td>Group 2: Standard care</td>
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<td>Weight: NS</td>
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<td>Waist-to-hip ratio: NS</td>
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<td>↑ Muscle strength (maximum voluntary torque), ( P = 0.033 )</td>
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<td>Cardiorespiratory fitness</td>
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<td>↑ Physical performance (30-s sit to stand), ( P &lt; 0.001 )</td>
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</table>
Further studies are underway involving larger numbers of patients undergoing ADT with longer periods of exercise (6–12 months) to examine the effects of exercise on bone density, and quality of life as well as blood pressure, lipids, and glycemic control (Newton et al. 2009). The exact duration and type of exercise are not clear, and future larger RCTs are required to address the optimal duration and mode of exercise training, to determine best strategies for implementation and retention, as well as to examine other potential benefits on physical performance as well as cardiovascular outcomes.

Selective androgen receptor modulators Nonsteroidal SARMs are an emerging class of anabolic agents, which are designed as full agonists in muscle and bone, and partial agonists with minimal androgenic activity in prostate, skin, and hair. There are no data on the use of SARMs in men with prostate cancer; however, in animal models, the partial antagonist activity of individual SARMs has been used for androgen suppression in the prostate and to treat benign prostatic hyperplasia (Gao et al. 2004). Furthermore, novel SARMs have been shown in experimental cell models of prostate cancer to have anti-tumor activity (Tesei et al. 2013). However, more preclinical evidence and, possibly, the development of even more tissue-selective SARMs will be necessary before these agents can be tested in men with prostate cancer. One group may be men with hypogonadism following ‘cure’ of prostate cancer, where evidence for potential safety of even conventional testosterone therapy is emerging, although this is restricted to small case series and remains controversial.

The unique tissue selectivity of SARMs has led to the development of several drugs undergoing clinical trial evaluation for various causes of sarcopenia and cachexia for use in both men and women. The most advanced SARM in development is enobosarm (GTx-024), which has demonstrated, in healthy elderly men and women, a dose-dependent increase in total LBM, a decrease in fat mass, and improvement in stair climb power (SCP) (used as a measure of physical function) when compared with placebo (Dalton et al. 2011, Dobs et al. 2013). In patients with non-small cell lung cancer, two double-blind, placebo-controlled RCTs demonstrated a significant benefit of enobosarm on LBM; however, benefits on SCP were inconsistent between studies (Crawford et al. 2013). Despite inconsistencies in physical function results, preliminary post-hoc analyses have shown that those who gained more than 1 kg of LBM had greater improvements in SCP and in overall survival, which is promising. Final survival analyses...
are, however, yet to be completed and it is unclear whether SCP is a good measure of physical function.

Other SARMs in early development have shown similar results. MK-0773 in an RCT for elderly women with sarcopenia has shown improvements in LBM, but no change compared with placebo in muscle strength and physical performance measures (Papanicolaou et al. 2013). Similarly, a phase 1 study of LGD-4033 in healthy young men demonstrated a reasonable safety profile with dose-dependent increases in LBM (Basaria et al. 2013). Although early in their developmental phase, there is no doubt that the potential benefits of SARMs will be evaluated in larger RCTs to assess their efficacy not only in aging-associated sarcopenia and cancer-related cachexia, but also in chronic illness-associated wasting and in minimizing the side effects of ADT. One potential drawback of SARMs is that they are non-aromatizable and therefore do not restore E2. Given the evidence (see ‘Future agents’ section) that E2 is important for preventing loss of bone mass, SARMs may not improve bone architecture directly, although they may do so by their anabolic effect on muscle, which may indirectly improve bone properties by effects on mechanical load or myokine crosstalk with bone. Moreover, there is emerging evidence that E2 deficiency may be a crucial element in the pathogenesis of other adverse effects of male hypogonadism, such as fat accumulation and sexual dysfunction (Finkelstein et al. 2013).

Myokines as therapies for sarcopenic obesity Skeletal muscle is a secretory endocrine organ with myokines producing endocrine, paracrine, and autocrine effects, the pathways of which may be targeted as a novel strategy to improve muscle strength and function (Pedersen & Febbraio 2012). With the increasing aging population and a substantial number also suffering from frailty and sarcopenia, interest has gathered in developing anabolic therapies to counteract difficulty commencing ADT to prevent increase in fat mass and development of insulin resistance. It is plausible that this could be of benefit for men newly undergoing ADT (Bhasin et al. 2011). Interleukin 6 (IL6), initially thought to be an inflammatory cytokine, is another myokine that is secreted in active muscle in response to exercise and has a role in metabolism (Pedersen 2011). It is thought that there is a significant crosstalk between IL6 secreted from muscle, with β-cells of the pancreas, hepatocytes and adipocytes. Infusion of IL6 in healthy volunteers increased endogenous glucose production and lipolysis within the muscle. Transgenic mice with elevated levels of human IL6 had improved nutrient homeostasis, improved insulin sensitivity, enhanced central leptin activity, and protection from diet-induced obesity (Sadagurski et al. 2010). It is plausible that this could be of benefit for men newly commencing ADT to prevent increase in fat mass and development of insulin resistance.

Other myokines undergoing investigation include leukemia inhibitory factor, which stimulates satellite cell proliferation within muscle, and irisin, which that drives the ‘browning’ of white adipose tissue into mitochondriarich brown fat to increase energy expenditure (Pedersen & Febbraio 2012). Future research will allow a greater understanding of the role of myokines and their ability to communicate with and regulate other organs such as...
pancreas, fat, bone, and liver, as well as enable development of therapeutic strategies to manipulate these pathways to potentially alleviate some of the adverse effects of ADT.

**Bone effects of ADT**

Androgens and estrogens are vital in regulating bone remodeling and play a role in achieving peak bone mass as well as maintaining bone integrity. Osteoporosis and osteopenia in men have been an under-recognized issue and this is of particular significance given the high mortality rate, up to 37.5%, associated with minimal trauma fractures in men (Ebeling 2008). Low bone density is highly prevalent among men even before commencement of ADT. An audit of 236 men (mean age 70 years) newly commencing ADT showed that 11% had osteoporosis and 40% osteopenia; 61% of the men with osteoporosis were unaware of the diagnosis (Cheung et al. 2013). The sex steroid deficiency associated with ADT further compounds the low bone density and attention to bone health in these men is essential.

**Observational studies**

**Bone mineral density changes** Multiple observational studies of men undergoing ADT demonstrate a decline in bone mineral density (BMD) at multiple skeletal sites when compared with men with prostate cancer not undergoing ADT or age-matched healthy controls (see Table 1; Basaria et al. 2002, Berruti et al. 2002, Preston et al. 2002, Greenspan et al. 2005, Galvao et al. 2008). Annual loss of bone mass in prospective studies ranges from 2 to 8% at the lumbar spine and 1.8 to 6.5% at the femoral neck, which is eight- to tenfold higher than the 0.5–1.0% loss in the general population of aging men (Grossmann et al. 2011). Although bone decay is slowly progressive with long-term ADT, the greatest losses in BMD occur in the first year after initiation with BMD changes observed within months, reflecting the rapid decrease in sex steroid levels (Hamilton et al. 2010). Associated with this are increases in bone turnover markers, which occur within 3–6 weeks (Falahati-Nini et al. 2000). BMD at the distal radius is the site of greatest decline in men undergoing ADT, which has also been reported to be the site which is the strongest predictor of fracture risk in the general male population (Melton et al. 1998, Preston et al. 2002, Greenspan et al. 2005). Early markers that predict loss of bone mass during ADT to identify high-risk men are lacking; however, high-bone-turnover markers have been shown to predict subsequent bone density loss in one study and may be a useful tool for monitoring individuals undergoing ADT (Greenspan et al. 2005).

**Micro-architectural changes** BMD, as measured by DEXA that assesses areal BMD in two dimensions, explains only approximately 60% of fracture risk (Greenspan et al. 2012). As such, new strategies to risk-stratify men requiring treatment for osteoporosis at commencement of ADT are needed.

High-resolution peripheral quantitative computed tomography (HR-pQCT) to assess cortical and trabecular microarchitecture is a non-invasive technique that measures three-dimensional volumetric BMD and may provide further insight into the structural basis of bone fragility in men undergoing ADT. In a study of 26 men newly commencing ADT, total volumetric density decreased by 5.2% at the distal radius and 4.2% at the distal tibia (both P<0.001) after 12 months follow-up (Hamilton et al. 2010). Moreover, a decrease in cortical bone was observed (~11.3% for radius and ~6.0% for tibia (all P<0.001)), which was markedly underestimated by DEXA (~2.6 to ~3.9%). This challenges the previous concept that sex steroid deficiency predominantly affects trabecular bone.

High-resolution magnetic resonance imaging (HR-MRI) is another promising technique that has been shown to increase detection of vertebral fractures and osteoporosis compared with DEXA in men undergoing ADT (Greenspan et al. 2012). In a cohort of men receiving ADT for over 6 months, vertebral fractures were diagnosed in 37%; however, only 7% were classified with osteoporosis by DEXA. The addition of HR-MRI to DEXA at the spine, hip, and femoral neck added substantially to the prediction of moderate–severe vertebral fractures on multivariate analyses (P<0.05). The longer duration of ADT showed the greatest decline in bone microarchitecture at the distal radius, which is concordant with results from several other studies, indicating that this is the most sensitive site to sex steroid deficiency (Preston et al. 2002, Greenspan et al. 2005, Hamilton et al. 2010).

As BMD measured by DEXA underestimates loss of bone mass, these novel techniques of HR-pQCT and HR-MRI provide new insights into the three-dimensional microarchitecture and structural changes involved in bone decay in men undergoing ADT. Future larger studies are required to determine if these techniques can be used to more accurately risk stratify patients for early treatment and predict future fractures.

**Fracture risk** In an analysis of 50 613 men with prostate cancer in the SEER-Medicare linked database in
the USA, 19.4% of those undergoing ADT had a fracture compared with 12.6% of men not undergoing ADT \((P<0.001; \text{Shahinian et al. 2005})\). A further analysis of 80,844 patients from the same database demonstrated a 34% increased risk of fracture with ADT and those that experienced a fracture had double the mortality rate \((HR 2.05; \text{Beebe-Dimmer et al. 2012})\). Fracture rates increased with cumulative ADT dose but decreased with an increasing number of months since last use. Consistent with these findings, a Canadian study of 19,079 men demonstrated a 65% increased risk of fragility fracture with ADT compared with those with no prior ADT \((\text{Alibhai et al. 2010b})\). Age, prior osteoporosis, chronic kidney disease, and dementia were independent predictors of fracture. These large registry studies have demonstrated that ADT increases fracture risk by over 30%, with an estimated number of harms of one fracture for every 30 patients treated \((\text{Grossmann & Zajac 2011, Grossmann et al. 2013})\). Furthermore, given that ADT-associated fractures have higher all-cause mortality than the general population, this highlights the need to optimize bone health in all men commencing ADT and to develop novel predictors to risk-stratify patients for fracture prevention \((\text{Van Hemelrijck et al. 2013})\).

### Interventions to prevent loss of bone mass in men undergoing ADT

**Vitamin D, calcium, and exercise** Evidence for exercise, vitamin D, and calcium supplementation specifically in men undergoing ADT to improve BMD or prevent fracture is lacking; however, men belonging to this group are at risk of losing bone mass and fractures. Recent RCTs examining the effect of resistance and aerobic exercise in men undergoing ADT have shown no effect of a short-term exercise program \((3\text{ months})\) or a longer-term \((12\text{ months})\) exercise program on BMD \((\text{Cormie et al. 2014, Winters-Stone et al. 2014})\). Further RCTs are underway \((\text{Galvao et al. 2009b, Newton et al. 2009})\). In the general population, resistance training and/or weight-bearing exercise has been shown to increase BMD in healthy older men \((\text{Ebeling 2008})\) and there is also clear evidence for improvement in BMD of the spine and hip with exercise in postmenopausal osteoporosis \((\text{Bonaiuti et al. 2002})\).

High dietary calcium supplementation has been associated with an increased risk of prostate cancer \((\text{Smith 2007})\); however, there is no evidence that calcium is causally related, and supplementation at \(<1500\text{ mg daily}\) has shown no influence on prostate cancer progression \((\text{Greenspan 2008})\). A meta-analysis of 63,897 participants in randomized trials demonstrated that calcium intake of 1200 mg or calcium with vitamin D \((800\text{ IU or more daily})\) was associated with a 12% risk reduction for fractures in both men and women over 50 years of age \((\text{Tang et al. 2007})\). The large majority of studies of bisphosphonates to prevent loss of bone mass have included supplementation for all participants \((\text{Table 4})\). Despite some controversy, for men undergoing ADT who are at high risk of bone decay, general lifestyle measures of regular aerobic, weight-bearing and resistance exercise, minimization of alcohol and smoking, maintenance of calcium intake of 1200 mg daily, and vitamin D supplementation are recommended by experts \((\text{Ebeling 2008, Greenspan 2008, Grossmann et al. 2011})\).

**Bisphosphonates** Multiple randomized, placebo-controlled trials using zoledronic acid, risedronate, alendronate, and neridronate have demonstrated efficacy of bisphosphonates in preventing loss of bone mass associated with ADT \((\text{Table 4})\). Studies have demonstrated that bisphosphonates increase BMD in men undergoing ADT compared with groups receiving placebo regardless of baseline BMD and also suppress bone turnover markers. Both oral and i.v. bisphosphonates are well tolerated in these studies.

A meta-analysis of randomized trials demonstrated that bisphosphonates had a substantial effect in preventing fractures \((\text{risk ratio (RR), 0.80; } P=0.005)\) and osteoporosis \((\text{RR, 0.39; } P<0.00001)\) \((\text{Serpa Neto et al. 2012})\). Zoledronic acid, the most potent of the bisphosphonates, had the lowest number needed to treat \((\text{NNT})\) to prevent a fracture of 14.9 \((\text{pamidronate 38.4, alendronate 41.6, and clodronate 52.6})\) as well as the lowest NNT to prevent development of osteoporosis of 2.68. Most studies have used zoledronic acid 4 mg 3 monthly; however, for osteoporosis treatment, a dose of 5 mg annually is the recommended dose, and a single dose of 4 mg has proven to be efficacious in increasing BMD at the lumbar spine, total hip, and femoral neck compared with placebo after 12 months follow-up \((\text{Table 4; Michaelson et al. 2007})\). Optimal dosing frequency is unclear; however, no difference in efficacy was observed in a study comparing dose frequencies \((\text{monthly to 6-monthly})\) with all doses improving BMD over 30 months \((\text{Rodrigues et al. 2010})\). This indicates that less frequent dosing may well be sufficient. Furthermore, zoledronic acid may have a prolonged action for up to 36 months, with a single dose of 4 mg resulting in a sustained decrease in bone turnover markers and continual significant increases in BMD up until 36 months in a group of cancer survivors \((\text{Brown et al. 2007})\). It is not known whether similar effects would...
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<th>References</th>
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<th>Calcium and vitamin D supplementation</th>
<th>No. of subjects</th>
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<th>Group characteristics</th>
<th>Outcomes</th>
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</thead>
</table>
| Smith et al. (2001) | Group 1: Pamidronate 60 mg i.v. 3 monthly; Group 2: Placebo | Yes                                     | 47             | 48 weeks              | Non-metastatic PC     | At 48 weeks, between-group differences – Group 1 vs Group 2:  
LS BMD 3.8% (95% CI 1.8–5.7%)  
TH BMD 2.0% (95% CI 0.7–3.4%)  
Bone turnover markers  
Group 1: bsALP and osteocalcin ↓ initially then returned to baseline by 48 weeks. NTx ↓ initially then ↑ after 12 weeks  
Group 2: bsALP, osteocalcin, and NTx ↑ over 48 weeks |
| Diamond et al. (2001) | Group 1: Pamidronate 90 mg i.v. single dose; Group 2: Placebo | No                                      | 21             | 6 months              | Metastatic PC on ADT for >6 months | Group 1: ↑ LS QCT, +7.8 ± 1.5%, P = 0.0005  
Group 2: ↓ LS QCT, −5.7 ± 1.6%, P = 0.0001  
↓ FN BMD −2.3 ± 0.7%, P = 0.0007  
At 12 months, between-group differences – Group 1 vs Group 2:  
LS BMD 7.8% (95% CI 5.6–10.0%, P < 0.001)  
TH BMD 3.9% (95% CI 2.5–5.3%, P < 0.001)  
FN BMD 3.3% (95% CI 1.4–5.2%, P > 0.001) |
| Smith et al. (2003) | Group 1: Zoledronic acid 4 mg i.v. 3 monthly; Group 2: Placebo | Yes                                     | 106            | 12 months             | Non-metastatic PC newly commencing ADT | Group 1, LS BMD and TH BMD: no significant change  
Group 2, LS BMD −4.9 ± 2.5%, P = 0.002  
TH BMD −1.9 ± 1.5%, P = 0.04  
DPD and bsALP not significantly different in Group 1 but ↑ in Group 2 (P < 0.05) |
| Morabito et al. (2004) | Group 1: Neridronate 25 mg i.m. monthly; Group 2: Placebo | Yes                                     | 48             | 12 months             | Non-metastatic PC with osteoporosis | Group 1, ↑ LS BMD 3.7% (95% CI 2.8–4.6%), P < 0.001  
Group 2, ↓ LS BMD 1.4% (95% CI −2.7 to −0.03%), P = 0.045  
↑ FN BMD 1.6% (95% CI 0.4–2.8%), P = 0.008  
Between-group differences:  
LS BMD 5.1% (CI 3.5–6.7%, P < 0.001)  
FN BMD 2.3% (CI 1.0–3.7%, P < 0.001)  
Decreased bone turnover markers in Group 1  
Between-group differences:  
LS BMD 6.7%, P < 0.0001  
TH BMD 3.7%, P < 0.0001  
Decrease in NTX and bsALP in Group 1 |
| Greenspan et al. (2007) | Group 1: Alendronate 70 mg weekly; Group 2: Placebo | Yes                                     | 112            | 12 months             | Non-metastatic PC on ADT for <6 months | Group 1, ↑ LS BMD 3.7% (95% CI 2.8–4.6%), P < 0.001  
Group 2, ↓ LS BMD 1.4% (95% CI −2.7 to −0.03%), P = 0.045  
↑ FN BMD 1.6% (95% CI 0.4–2.8%), P = 0.008  
Between-group differences:  
LS BMD 5.1% (CI 3.5–6.7%, P < 0.001)  
FN BMD 2.3% (CI 1.0–3.7%, P < 0.001)  
Decreased bone turnover markers in Group 1  
Between-group differences:  
LS BMD 6.7%, P < 0.0001  
TH BMD 3.7%, P < 0.0001  
Decrease in NTX and bsALP in Group 1 |
| Ryan et al. (2007) | Group 1: Zoledronic acid 4 mg i.v. 3 monthly; Group 2: Placebo | Calcium only                             | 42             | 12 months             | Non-metastatic and metastatic PC on ADT for <12 months | Between-group differences:  
LS BMD 4.2%  
FN BMD 7.1% |
| Israeli et al. (2007) | Group 1: Zoledronic acid 4 mg i.v. 3 monthly; Group 2: Placebo | Yes                                     | 215            | 12 months             | Non-metastatic PC on ADT for <12 months | Between-group differences:  
LS BMD 6.7%, P < 0.0001  
TH BMD 3.7%, P < 0.0001  
Decrease in NTX and bsALP in Group 1 |
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<tr>
<td>Michaelson et al.</td>
<td>Group 1: Zoledronic acid 4 mg i.v. single dose Group 2: Placebo</td>
<td>Yes</td>
<td>40</td>
<td>12 months</td>
<td>Non-metastatic PC with T-score &gt; −2.5 (mean duration 12 months)</td>
<td>Between-group differences – Group 1 vs Group 2: LS BMD↑ 7.1% (95% CI 4.2–10.0%, P&lt;0.001) TH BMD↑ 2.6% (95% CI 0.9–4.3%, P=0.004) Bone turnover markers: serum NTx and bsALP ↓ in Group 1, P=0.01</td>
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<td>Group 2: Alendronate 70 mg weekly for 24 months Group 2: Placebo</td>
<td>Yes</td>
<td>112</td>
<td>24 months</td>
<td>Non-metastatic PC</td>
<td>At 24 months between-group differences – Group 1 vs Group 2: LS BMD 3.79% ± 1.22, P=0.002 FN BMD 2.59±1.17%, P=0.028 Group 1 vs Group 3: LS BMD 4.66±1.07%, P&lt;0.001 FN BMD 3.75±1.04%, P&lt;0.001 Group 2 vs Group 3: LS BMD 0.87±1.01%, P=0.392 FN BMD 1.16±1.00%, P=0.247 Delayed alendronate had less gains in BMD at all sites P&lt;0.05 Men who had ADT for &lt;36 months had greater gains in BMD with alendronate than those who had ADT for &gt;36 months</td>
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<tr>
<td>Greenspan et al.</td>
<td>Group 1: Alendronate 70 mg weekly for 24 months Group 2: Placebo</td>
<td>Yes</td>
<td>40</td>
<td>12 months</td>
<td>Newly commencing ADT</td>
<td>At 12 months, between-group differences Group 1 vs Group 2: LS BMD 8.25% (95% CI 2.96–13.54%, P=0.0004) TH BMD 5.7% (95% CI 4.6–6.9%, P=0.0008) FN BMD 6.9% (95% CI 4.6–9.2%, P=0.0393) Group 1, ↓ urine NTx (9.5±10.8%, P&lt;0.0001) Group 2, ↓ urine NTx (70.3±15.7%, P&lt;0.0001) At 24 months, between-group differences Group 1 vs Group 2: Stratum 1: LS BMD 8.25% (95% CI 2.6–13.5%, P=0.0029) TH BMD 1.87% (95% CI 0.22–3.51%, P=0.005) Stratum 2: LS BMD 3.83% (1.58–6.07), P=0.0013 TH BMD, P=NS At 12 months, between-group differences (Group 1 vs Group 2): LS BMD 4.8%, P&lt;0.01 TH BMD 2.9%, P&lt;0.01 FN BMD 3.5%, P&lt;0.01 At 24 months, between-group differences (Group 1 vs Group 2): LS BMD 5.3%, P&lt;0.05 TH BMD 3.2%, P&lt;0.05 FN BMD 3.4%, P&lt;0.05 In Group 3 (n=11), decrease in BMD at all sites but less than that of Group 2</td>
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<tr>
<td>Satoh et al.</td>
<td>Group 1: Zoledronic acid 4 mg i.v. single dose Group 2: Placebo</td>
<td>No</td>
<td>93</td>
<td>23 months</td>
<td>Veterans with non-metastatic PC</td>
<td>Between-group differences: LS BMD 11.7% (95% CI 9.6–13.4%, P=0.0004) TH BMD 5.7% (95% CI 4.6–6.9%, P=0.0008) FN BMD 6.9% (95% CI 4.6–9.2%, P=0.0393)</td>
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<td>Group 2: Placebo</td>
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<td>At 12 months, between-group differences (Group 1 vs Group 2): LS BMD 8.25% (95% CI 2.96–13.54%, P=0.0029) TH BMD 1.87% (95% CI 0.22–3.51%, P=0.005) Stratum 2: LS BMD 3.83% (1.58–6.07), P=0.0013 TH BMD, P=NS</td>
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<tr>
<td>Bhoopalam et al.</td>
<td>Group 1: Zoledronic acid 4 mg i.v. 3 monthly Group 2: Placebo</td>
<td>Yes</td>
<td>187</td>
<td>24 months</td>
<td>Non-metastatic PC newly commencing ADT (&lt;30 days)</td>
<td>At 12 months, between-group differences (Group 1 vs Group 2): LS BMD 4.8%, P&lt;0.01 TH BMD 2.9%, P&lt;0.01 FN BMD 3.5%, P&lt;0.01 At 24 months, between-group differences (Group 1 vs Group 2): LS BMD 5.3%, P&lt;0.05 TH BMD 3.2%, P&lt;0.05 FN BMD 3.4%, P&lt;0.05 In Group 3 (n=11), decrease in BMD at all sites but less than that of Group 2</td>
</tr>
<tr>
<td>Casey et al.</td>
<td>Group 1: Zoledronic acid 4 mg i.v. 3 monthly Group 2: Placebo</td>
<td>Yes</td>
<td>93</td>
<td>23 months</td>
<td>Veterans with non-metastatic PC</td>
<td>Between-group differences: LS BMD 11.7% (95% CI 9.6–13.4%, P=0.0004) TH BMD 5.7% (95% CI 4.6–6.9%, P=0.0008) FN BMD 6.9% (95% CI 4.6–9.2%, P=0.0393)</td>
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<td>Group 2: Placebo</td>
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<td></td>
<td>At 12 months, between-group differences (Group 1 vs Group 2): LS BMD 8.25% (95% CI 2.96–13.54%, P=0.0029) TH BMD 1.87% (95% CI 0.22–3.51%, P=0.005) Stratum 2: LS BMD 3.83% (1.58–6.07), P=0.0013 TH BMD, P=NS At 12 months, between-group differences (Group 1 vs Group 2): LS BMD 4.8%, P&lt;0.01 TH BMD 2.9%, P&lt;0.01 FN BMD 3.5%, P&lt;0.01 At 24 months, between-group differences (Group 1 vs Group 2): LS BMD 5.3%, P&lt;0.05 TH BMD 3.2%, P&lt;0.05 FN BMD 3.4%, P&lt;0.05 In Group 3 (n=11), decrease in BMD at all sites but less than that of Group 2</td>
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<tr>
<td>Kapoor et al. (2011)</td>
<td>Group 1: Zoledronic acid 4 mg i.v. 3 monthly Group 2: Placebo</td>
<td>Yes</td>
<td>41</td>
<td>12 months</td>
<td>Non-metastatic PC with osteoporosis or osteopenia</td>
<td>At 12 months, between-group differences – Group 1 vs Group 2: LS BMD 7.11%, P = 0.003 TH BMD 1.56%, P = 0.278 FN BMD 5.53%, P = 0.009 NTx, osteocalcin, and bALP all lower in Group 1 At 12 months between-group differences – Group 1 vs Group 2:</td>
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<td>Izumi et al. (2009, 2011)</td>
<td>Group 1: Risedronate 2.5 mg oral daily – had a lower baseline BMD, not randomized Group 2: Placebo</td>
<td>No</td>
<td>60</td>
<td>24 months</td>
<td>Non-metastatic PC (median duration 15.5 months)</td>
<td>At 12 months between-group differences – Group 1 vs Group 2: LS BMD/young adult mean ratio 4.7%, P &lt; 0.0001 At 24 months between-group differences: LS BMD/young adult mean ratio 10.13%, P &lt; 0.0001 Bone turnover markers: urine DPD and serum bALP ↓ significantly after 12 and 24 months in Group 1 At 12 months between-group differences – Group 1 vs Group 2: LS BMD + 3.6%, P &lt; 0.0001 TH BMD not significant</td>
</tr>
<tr>
<td>Klotz et al. (2013)</td>
<td>Group 1: Alendronate 70 mg weekly Group 2: Placebo</td>
<td>Yes</td>
<td>191</td>
<td>12 months</td>
<td>Non-metastatic PC commencing ADT</td>
<td>No difference in incident vertebral fractures between groups: Zoledronic acid prevented BMD loss in Groups 2 and 4 compared with 1 and 3 (P &lt; 0.01)</td>
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<tr>
<td>Choo et al. (2013)</td>
<td>Group 1: Risedronate 35 mg weekly Group 2: Placebo</td>
<td>Yes</td>
<td>104</td>
<td>24 months</td>
<td>Non-metastatic PC with osteoporosis</td>
<td>No difference in incident vertebral fractures between groups: Zoledronic acid prevented BMD loss in Groups 2 and 4 compared with 1 and 3 (P &lt; 0.01)</td>
</tr>
<tr>
<td>Denham et al. (2013)</td>
<td>Group 1: 6 months ADT Group 2: 6 months ADT and zoledronic acid Group 3: 18 months ADT Group 4: 18 months ADT and zoledronic acid</td>
<td>Yes</td>
<td>1071</td>
<td>36 months</td>
<td>Non-metastatic PC commencing ADT</td>
<td>No difference in incident vertebral fractures between groups: Zoledronic acid prevented BMD loss in Groups 2 and 4 compared with 1 and 3 (P &lt; 0.01)</td>
</tr>
</tbody>
</table>

PC, prostate cancer; LS, lumbar spine; TH, total hip; FN, femoral neck; BMD, bone mineral density; bALP, bone-specific alkaline phosphatase; DPD, deoxypyridinoline; NTx, N-terminal telopeptide.
be observed in patients on continuous ADT. Ultimate choice of anti-resorptive agent should be individualized, taking into consideration the potential adverse effects of the different bisphosphonates, such as osteonecrosis of the jaw or gastrointestinal effects.

Anti-resorptive agents have clear anti-fracture effects; however, despite zoledronic acid being the most potent bisphosphonate, ADT-associated fracture risk reduction is only 23% (Serpa Neto et al. 2012). This may be because anti-resorptive treatment is especially less effective at preventing the ADT-associated loss of cortical (vs trabecular) bone. This is consistent with evidence that, in postmenopausal women, zoledronic acid was less effective in increasing cortical volumetric BMD compared with trabecular bone and, as such, further strategies are required to augment the fracture risk reduction in men undergoing ADT (Yang et al. 2013).

Denosumab Denosumab, a fully human MAB against receptor activator of nuclear factor kβ ligand, is the only drug to show efficacy at preventing new vertebral fractures in men with non-metastatic prostate cancer undergoing ADT (Smith et al. 2009a). In the HALT Prostate Cancer RCT of denosumab (60 mg) vs placebo, lumbar spine BMD increased by 5.6% in the denosumab group when compared with a loss of 1.0% in the placebo group (P<0.001) with differences observed as early as 1 month and sustained through 36 months. The denosumab group also had a decreased incidence of new vertebral fractures at 36 months (1.5 vs 3.9% with placebo, P=0.006).

Further subgroup analyses showed that denosumab significantly and consistently increased BMD at all skeletal sites (lumbar spine, total hip, and distal radius) and in every subgroup analyzed, including those of older age, longer duration of ADT, lower baseline T scores, bone turnover markers, and prevalent vertebral fractures (Smith et al. 2009b). Bone turnover markers also were significantly suppressed in the denosumab group compared with the placebo group (Smith et al. 2011).

These studies have led to Food and Drug Administration Approval in the USA for the use of denosumab to increase bone mass in men at high risk of fracture undergoing ADT for non-metastatic prostate cancer.

Future agents New anabolic bone agents are in development, as the only currently available anabolic agent teriparatide (recombinant PTH) is contraindicated in those with bone metastases and should be used with caution in cancer. Future anabolic agents targeting the Wnt signaling pathway through inhibition of the Wnt antagonists sclerostin and Dickkopf-related protein 1 (DKK1) are promising. Romosozumab (anti-sclerostin antibody) has recently been shown in a phase 2 study to have anabolic effects greater than teriparatide and alendronate in postmenopausal women (McClung et al. 2014). Serum sclerostin levels have been shown to be elevated in prostate cancer, particularly in men receiving ADT compared with controls (Garcia-Fontana et al. 2014). Anti-DKK1 antibodies stimulate bone formation in animal models and clinical trials are underway in humans for treatment of osteoporosis (Ke et al. 2012). Specific long-term studies will need to occur to ensure that these agents have no interaction with prostate cancer progression or adverse effect on bone metastases.

Sex steroid deficiency as a result of ADT leads to castrate levels of both testosterone and E2. Recent evidence has indicated that E2, derived from aromatization of testosterone, is largely responsible for regulating bone resorption and some of the key consequences of male hypogonadism. Results from most observational studies indicate that circulating E2 is more closely associated with reduced BMD and increased fracture risk in men than testosterone (Falalati-Nini et al. 2000, Mellstrom et al. 2008). However, the effects of E2 on male bone structure, and especially cortical bone, the main determinant of bone structural strength, are largely unknown. A phase 2 study of a novel selective estrogen receptor α agonist demonstrated not only anti-tumor efficacy, but also a reduction in bone turnover markers, albeit with a concerning increase in venous thromboembolic events (Yu et al. 2014). Further research is needed to elucidate whether manipulation of E2 in men undergoing ADT in the setting of low testosterone will have beneficial effects on bone or other side effects related to hypogonadism as well as a favorable safety profile.

With future treatments targeting multiple mechanisms, combination treatments may have complementary effects on improving bone health and fracture risk reduction in men undergoing ADT.

Conclusion Many novel treatments are in the pipeline to mitigate the adverse effects of ADT on muscle and bone. Given the endocrine toxicities of ADT, this treatment should be reserved for those in whom a survival benefit has been proven. Evaluation of bone health and muscle function should occur at commencement of and during ADT with optimization of musculoskeletal health. Future well-designed, prospective controlled studies are required to
elucidate effects of ADT on physical performance, which are currently lacking, and larger RCTs are required to test the efficacy of medical therapies and exercise interventions to target proven deficits and to ensure safety in men with prostate cancer.

Declaration of interest
The authors are researchers in an investigator-initiated trial on the role of bisphosphonates in preventing micro-architectural bone decay in men with non-metastatic prostate cancer, who are receiving androgen deprivation therapy, which is partially supported by Novartis Pharmaceuticals.

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