Bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy

Management guidelines on behalf of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society, and the Urological Society of Australia and New Zealand

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ABSTRACT

- Androgen deprivation therapy (ADT) in men with prostate cancer increases the risk of osteoporotic fractures, type 2 diabetes and, possibly, cardiovascular events.
- There is considerable uncertainty about the risk–benefit ratio of ADT in non-palliative treatment; the benefits of ADT in treating non-metastatic prostate cancer need to be carefully weighed against the risks of ADT-induced adverse events.
- Baseline assessment of bone health at the initiation of ADT should include measurement of bone mineral density (BMD) by dual energy x-ray absorptiometry and, in men with osteopaenia, a thoracolumbar spine x-ray.
- General measures to prevent bone loss, including regular physical activity, as well as ensuring calcium and vitamin D sufficiency, should be instituted routinely.
- All men with a previous minimal trauma fracture should receive pharmacological therapy unless contraindicated; for those who have not sustained a minimal trauma fracture, treatment is advised if the BMD T score is ≤ -2.0, or if the 10-year risk of a major osteoporotic fracture exceeds 20%.
- Men with prostate cancer who are receiving ADT should be closely monitored for weight gain and diabetes; intensive lifestyle intervention is recommended to prevent ADT-induced weight gain and insulin resistance.
- Management of the metabolic sequelae of ADT includes optimal reduction of cardiovascular risk factors, with particular attention to weight, blood pressure, lipid profile, smoking cessation, and glycaemic control.

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These management guidelines review the current evidence relating to bone and metabolic health in patients with non-metastatic prostate cancer who are receiving androgen deprivation therapy (ADT). They are primarily relevant for the large proportion of men with early, non-metastatic prostate cancer who often have excellent prognoses. These guidelines do not address the uncertainties about the risk–benefit ratio of non-palliative use of ADT, and do not offer guidance as to when to (or when not to) use ADT in treating early prostate cancer. The process used to develop this document is outlined in Box 1.

Prostate cancer is the most common solid organ cancer in Australian men, and 20 000 new cases are diagnosed in Australia each year.[1,2] The prevalence of prostate cancer is increasing because the population is ageing and prostate-specific antigen (PSA) testing is occurring more frequently. This has led to a profound shift towards detecting more clinically localised, low-risk prostate cancer.[3] Thus, the contemporary 5-year relative survival rate for men with all stages of prostate cancer combined is 98.1%.[4] With such a high rate of cancer-specific survival, treatment-related toxicity becomes a major consideration. More than 30% of men with prostate cancer die of cardiovascular disease, making this the most common cause of mortality in this patient population.[5,6]

ADT is the standard first-line therapy for metastatic prostate cancer, and usually involves depot preparations of gonadotrophin-releasing hormone (GnRH) agonists.[5] ADT also improves survival in men with non-metastatic, but locally advanced or high-risk localised prostate cancer.[5,7] However, ADT is increasingly being used in early-stage (localised) prostate cancer, for lower-volume extracapsular disease or as salvage therapy for biochemical PSA recurrence (defined as rising PSA levels in the absence of other signs of disease) — these are all situations in which a survival benefit has not been demonstrated.[5,8] The rate of use of ADT in North American men with non-metastatic prostate cancer increased from 3.7% in 1991 to 31% in

1 Consensus process and methods

Aim: To develop evidence-based recommendations for the assessment and management of bone and metabolic health in men with prostate cancer who are receiving androgen deprivation therapy (ADT).

Source: The writing group was commissioned by the Endocrine Society of Australia (ESA), the Australian and New Zealand Bone and Mineral Society (ANZBMS) and the Urological Society of Australia and New Zealand (USANZ).

Methods: Peer-reviewed journals indexed on the PubMed database and dated from 1966 to 30 November 2009 were reviewed. Multiple separate searches were performed, combining "prostate cancer" with the MeSH terms osteoporosis, fracture, bone density, bone loss, insulin resistance, metabolic syndrome, diabetes, cardiovascular, cardiovascular morbidity, cardiovascular mortality, and with the following terms for ADT: ADT, androgen-deprivation, androgen suppression, GnRH agonist, LHRH analog, and hormone therapy.

Levels of evidence: Our findings are graded according to National Health and Medical Research Council (NHMRC) levels of evidence (levels I, II, III [including III-1, III-2, III-3] and IV; available at http://www.nhmrc.gov.au/PUBLICATIONS/synopses/cp30syn.htm). If an NHMRC level of evidence for a clinically relevant aspect was lacking, consensus expert opinion of the writing group (designated consensus) was applied.

Final recommendations: The draft position statement was reviewed by the councils of the ESA, ANZBMS, and USANZ. Suggested changes were incorporated and the final document was approved by the councils of all three societies. ◆

2 Managing men with prostate cancer who are receiving androgen deprivation therapy (ADT) — general recommendations

- Management should consist of an individualised, multidisciplinary approach, involving, as appropriate, experts in urology, radiation and medical oncology, endocrinology, dietetics, exercise physiotherapy, and psychology. (Consensus).
- All patients should be counselled about the association of ADT and adverse bone and metabolic health before commencement of ADT. (Consensus).
- Adverse effects should be considered in the process of making decisions about commencing ADT for prostate cancer, especially in patients with a high baseline risk of fractures or cardiovascular events, and with low-risk prostate cancer, for which a survival benefit of ADT has not been established. (Consensus).

"Consensus" indicates the consensus expert opinion of the writing group in the absence of an available National Health and Medical Research Council level of evidence. ◆

1999, with 600 000 men in the United States receiving this therapy.[9] There are similar trends in Australia — an analysis of Health Insurance Commission data estimated that, in the 2003–04 financial year 16 000 men received GnRH agonists.[10] We repeated this analysis for 2008–09 and found that this number had increased to 23 500.[11] Thus, ADT, which intentionally reduces serum testosterone levels to the castrate range (< 5% of the normal level) and serum oestradiol levels to < 20% of the normal level,[12] has become the most common contemporary cause of severe male hypogonadism. Use of ADT for treating clinically localised prostate cancer is not subsidised by the Pharmaceutical Benefits Scheme (PBS) in Australia.

The expanded use of ADT in non-palliative treatment mandates a proper risk–benefit assessment in a multidisciplinary fashion (Box 2). Adverse effects of ADT are a consequence of induced hypogonadism and include fatigue, sexual dysfunction, hot flushes, and anaemia.[13] In this article, we will focus on the skeletal and metabolic complications of ADT, which are of particular concern because of their impact on morbidity and mortality in a patient population with a high background prevalence of these conditions.[14,15] In Austin Health's Endocrine Men's Health Clinic, all men with prostate cancer in whom ADT is commenced are routinely reviewed. A survey (unpublished) of the first 100 men referred with non-metastatic prostate cancer (mean age, 69 years; range 48–92 years), showed that 85% were overweight or obese, 51% had hypertension, 50% were current smokers, 25% had had previous cardiovascular events, 21% had known diabetes, and 25% had osteoporosis (defined as a T score at the hip or spine of < –2.5).

General recommendations for the management of men with prostate cancer who are receiving ADT are summarised in Box 2.

Bone health in men with prostate cancer who are receiving androgen deprivation therapy

Almost 30% of hip fractures worldwide occur in men.[16] Mortality after fracture is higher in men, with age-standardised mortality ratios of 2.2–3.2 compared with 1.7–2.2 in women.[17,18] ADT results in severe sex-steroid deficiency, and reduced bone-mineral density (BMD) and osteoporosis have been extensively documented in men receiving this therapy.[10,13,19,20]

The prevalence of both prostate cancer and osteoporosis increases with advancing age. Two uncontrolled studies in patients with newly diagnosed prostate cancer showed a high baseline prevalence of osteopaenia or osteoporosis in 60%[21] and 80%.[22] Thus, even in the absence of ADT, bone health is a concern in older men with prostate cancer.

Impact of androgen deprivation therapy on bone mineral density

BMD declines within months of the initiation of ADT,[23] reflecting the rapid decrease in sex steroid levels, which reach a nadir within 2 to 4 weeks. Rates of annual bone loss reported in prospective studies range from 2%–8% at the lumbar spine and 1.8%–6.5% at the femoral neck,[8,13,19,20,24,25] compared with 0.5%–1.0% in the general population of ageing men, and 2.0% in women during early menopause.[20]

Prospective studies showed that BMD loss was maximal within the first year of ADT.[23,26] Men in the highest tertile for bone turnover markers at 6 months experienced the greatest BMD loss at 12 months.[23] Cross-sectional studies suggest that BMD continues to decline with long-term ADT.[19,20] In the largest study of men on continuous ADT (390 men), the prevalence of osteoporosis was 35% in hormone-naïve patients, 43% after 2 years of ADT, and 81% after 10 or more years.[27] This suggests that osteoporosis is a very common consequence of long-term androgen deprivation.

Impact of androgen deprivation therapy on bone fractures

A number of epidemiological studies have associated ADT with an increased risk of fractures.[28-32] In a retrospective cohort study of more than 50 000 patients who survived at least 5 years after their diagnosis of prostate cancer, the number needed to harm for the occurrence of any fracture was 28 for the use of any GnRH agonist and 16 for orchidectomy.[30] A systematic review of population-based studies with a total of over 100 000 men calculated a summary relative risk for skeletal fracture associated with ADT of 1.23 (95% CI, 1.10–1.38) and for vertebral fracture associated with ADT of 1.39 (95% CI, 1.20–1.60).[33]

Evidence from intervention studies

Lifestyle, calcium and vitamin D

Resistance exercise reduces fatigue and improves muscle strength and balance in men with prostate cancer that is being managed with ADT,[34,35] and this may in turn decrease the risk of falls. Calcium supplementation in men with prostate cancer has been debated,[19] as epidemiological studies have suggested a possible association between high calcium intake and an increased risk of prostate cancer.[36] However, daily calcium intake of less than 1500 mg per day has not been associated with increased risk.[19]

A retrospective analysis of 87 men receiving ADT showed an independent association of vitamin D deficiency with spinal fractures ($P = 0.003$).[37] In contrast to demonstrated antifracture efficacy in men older than 50 years,[18] it is unknown whether calcium and vitamin D supplementation independently improve BMD or reduce fracture risk in men with prostate cancer who are receiving ADT.

Bisphosphonate therapy

Bisphosphonates, including pamidronate,[38,39] zoledronic acid,[40-43] alendronate[44,45] and risedronate[46,47] prevent ADT-induced loss of BMD in randomised controlled trials. While patients receiving ADT and who were given placebo lost 2%–8% of BMD per year, patients randomly allocated to bisphosphonate therapy had either stable

BMD, or increases of up to 8% at the lumbar spine and of 2% at the hip.[38-47] There have been no trials of adequate size or duration to determine the effect of bisphosphonate therapy on fracture incidence. Further, no trials have compared the efficacy of the different bisphosphonates to guide the choice of drug.

Other pharmacotherapy

Treatments for ADT-induced osteoporosis that are not currently available to Australian men include denosumab and raloxifene. To-date, the only randomised controlled trial that has shown anti-fracture efficacy used denosumab, a fully human monoclonal antibody against the receptor activator of nuclear factor kappa-B ligand. In this study of men with non-metastatic prostate cancer and mild osteopaenia at baseline, the number needed to treat with denosumab for 3 years to prevent a new vertebral fracture was 42 ($P = 0.006$).[48] In an open-label study of 48 men receiving ADT, 12 months of therapy with raloxifene, a selective oestrogen receptor modulator (SERM), increased BMD at the hip by 1.1% compared with a 2.6% loss in untreated control patients ($P < 0.001$).[49] Preliminary data from a large multicentre trial suggest that toremifene, another SERM, similarly led to small (1.3%–1.8%) but significant increases in BMD.[50]

Despite compelling evidence of reduced BMD and increased fracture risk in men receiving ADT, awareness of this issue is poor among health professionals, and osteoporosis remains undertreated.[21,51,52] A Canadian study found that bone health was discussed with only one in seven patients who were commencing ADT. Further, lifestyle measures or calcium and vitamin D supplementation were recommended in fewer than 20%, despite 60% having osteopaenia or osteoporosis at baseline.[21] In US veterans receiving ADT, BMD was measured in only 13%, and 19% received calcium and vitamin D.[52] Men receiving ADT for prostate cancer need a well coordinated, multidisciplinary approach to manage their skeletal health.

Recommendations — assessment and management of bone health

Key points of evidence and key recommendations for the management of bone health in men receiving ADT are summarised in Box 3.

Assessment

All men should have a baseline assessment of fracture risk. Risk factors for osteoporosis should be ascertained,[18] and absolute baseline fracture risk may be estimated using mathematical tools such as the World Health Organization fracture risk assessment tool (FRAX; http://www.shef.ac.uk/FRAX) or the Garvan Institute's fracture risk calculator (http://www.fractureriskcalculator.com). However, neither of these algorithms is validated for men with prostate cancer who are receiving ADT.

BMD should be measured by dual energy x-ray absorptiometry in all patients at the time of commencement of ADT. In men with osteopaenia, thoracolumbar spine x-rays should be performed to exclude clinically silent vertebral fractures. BMD should be monitored yearly during the initial 2 years of ADT; thereafter, the monitoring frequency should be individualised.

Management

Lifestyle measures, calcium[53] intake and vitamin D supplementation (http://www.nhmrc.gov.au/publications/synopses/n35syn.htm) should be instituted routinely (Box 3).

3 Androgen deprivation therapy (ADT) and bone health

Key evidence points

- ADT is associated with reduced bone mineral density (BMD), osteoporosis and increased bone turnover (Evidence level III-2).
- ADT is associated with an increased risk of fracture (Evidence level III-2).
- Bisphosphonates, including pamidronate, zoledronic acid, alendronate and risedronate, prevent bone loss associated with ADT (Evidence level II).
- Denosumab increases BMD and reduces the incidence of new vertebral fractures in men receiving ADT for prostate cancer (Evidence level II).

Key recommendations

- Assessment at the commencement of ADT should include a history of minimal trauma fractures and risk factors for osteoporosis, BMD measurement by dual energy x-ray absorptiometry, and, in men with osteopaenia, postero-anterior as well as lateral thoracolumbar spine x-rays. (Consensus).
- General preventive and lifestyle measures include regular physical exercise, smoking cessation, and alcohol consumption of < 2 standard drinks per day. (Consensus).
- Ensure a total daily calcium intake of 1200–1500 mg through diet, supplements, or both, unless there is a history of renal calculi. (Evidence level I, in non-ADT subjects).
- Commence vitamin D supplementation as necessary to achieve a target serum vitamin D level > 75 nmol/L. (Evidence level I, in non-ADT subjects).
- In men with minimal trauma fracture, commence treatment with an antiresorptive agent such as a bisphosphonate. (Evidence level II).
- In men with a baseline BMD T score of < –2.0, initiate treatment with a bisphosphonate. (Consensus).
- In men who do not fit the above criteria, antiresorptive therapy should be individualised and based on a 10-year absolute risk of major osteoporotic fracture of > 20%. (Consensus).
- BMD measurement should be performed yearly during the first 2 years of ADT, with subsequent individualised frequency of testing. (Consensus).

Evidence levels are from the National Health and Medical Research Council (NHMRC; http://www.nhmrc.gov.au/PUBLICATIONS/synopses/cp30syn.htm). "Consensus" indicates the consensus expert opinion of the writing group in the absence of an available NHMRC level of evidence. ◆

Bisphosphonate therapy: All men with prostate cancer who are receiving ADT and who have a history of minimal trauma fracture should be commenced on antiresorptive therapy with a bisphosphonate, unless contraindicated.

There is currently insufficient evidence specific to men with prostate cancer who are receiving ADT to make evidence-based recommendations as to if and when bisphosphonate therapy for primary prevention should be commenced. Current National Osteoporosis Foundation guidelines for the general male population recommend pharmacologic therapy for primary prevention in men over 50 years of age with a T score less than –2.5, or for whom the 10-year major osteoporotic fracture probability exceeds 20% (http://www.nof.org/professionals/clinical-guidelines).

We recommend that bisphosphonate therapy should be instituted as primary prevention if the BMD T score is ⩽ –2.0. However, this recommendation is outside of current Australian PBS guidelines and funding for treatment. A cut-off BMD T score of ⩽ –2.0

has also been recommended for women with non-metastatic breast cancer when initiating aromatase inhibitor therapy, as these women experience similar rates of bone loss and increases in fracture risk as men beginning ADT.[54] While bisphosphonates are recommended (and subsidised by the Australian PBS) for primary fracture prevention at a T score cut-off of <–1.5 in glucocorticoid-induced osteoporosis,[55] current evidence is insufficient to recommend such a cut-off for men receiving ADT. Nevertheless, denosumab reduced vertebral fracture risk in men who were receiving ADT and who had a median T score of –1.5 at randomisation, with 42 men needed to treat to prevent one fracture.[48]

Management of bone health should be reviewed 1–2-yearly in men on continuous ADT. Management should also be re-evaluated after cessation of ADT, as the gonadal axis may recover in some men, with more rapid recovery reported in younger men (< 65 years) or those who had a shorter duration of ADT (< 24–30 months).[20]

Metabolic health in men with prostate cancer who are receiving androgen deprivation therapy

In men, even mildly reduced testosterone levels are associated with increased insulin resistance, type 2 diabetes and features of the metabolic syndrome.[56] Men receiving ADT have testosterone levels in the castrate range,[10] and are expected to be at even higher risk of developing such complications.

Impact of androgen deprivation therapy on body composition

Androgens are important determinants of body composition in males; testosterone therapy increases lean body mass and decreases fat mass in hypogonadal men.[57] Men undergoing ADT have increased fat mass compared with eugonadal controls with prostate cancer who are not receiving ADT.[58] In longitudinal studies, GnRH-agonist therapy increased fat mass by 10% and decreased lean body mass by 3%, with 80% of these changes occurring within the first 3 months of therapy.[59-61] Thus, ADT effectively causes "sarcopenic obesity".[62] While increased abdominal fat mass promotes insulin resistance, reduced lean body mass aggravates insulin resistance by reducing glucose uptake in muscle.[63] In addition, reduced muscle mass may increase falls risk.

Impact of androgen deprivation therapy on insulin resistance and glucose metabolism

Studies have shown that ADT-induced accumulation of abdominal fat mass correlates with a 26%–65% increase in insulin levels and corresponding decreases in insulin sensitivity.[60,64,65] In these short-term prospective studies (< 6-months), fasting glucose levels do not change, indicating that compensatory hyperinsulinaemia temporarily prevents the development of type 2 diabetes. However, multiple population-based studies show a significant association between longer-term ADT (> 12 months) and incident diabetes.[9,13] In the largest study, of more than 73 000 men, the risk of new diabetes was significantly increased, with an adjusted hazard ratio of 1.44.[66] ADT also required intensification of antihyperglycaemic treatment in men with pre-existing diabetes.[67]

Impact of androgen deprivation therapy on lipid profile

In prospective studies of ADT of 3 to 12 months duration, triglyceride levels increased by 25%, total cholesterol by 7%–10% and high-density lipoprotein cholesterol by 8%–20%, whereas changes in low-density lipoprotein cholesterol were variable.[9,13]

Impact of androgen deprivation therapy on cardiovascular risk

Given that insulin resistance is an independent cardiovascular risk factor,[68] there is concern that ADT increases the risk of cardiovascular events, which are already the most common cause of death among men with prostate cancer.[5,6] Population-based studies have shown significant but modest associations between ADT and cardiovascular disease. In a systematic review based on more than 80 000 patients, ADT was associated with a 17% increase in cardiovascular mortality.[33] It has been estimated that 10 ischaemic heart disease events a year occur for every 1000 men receiving ADT.[69] A study of 23 000 men showed an absolute hazard ratio of 1.20 for serious cardiovascular morbidity, even after 1 year of ADT,[70] and a pooled analysis of three randomised trials reported a shorter time to fatal myocardial infarction in men treated with ADT for 6 months compared with men who were not treated with ADT.[71] Thus, with the caveats that these observational studies may have had confounders and included a relatively small number of events, even short-term ADT (for 6–12 months) may have a deleterious effect on cardiovascular health. However, no published intervention study has assessed insulin resistance, glycaemia, or cardiovascular risk in this patient population.

Assessment and management of metabolic health

Despite the absence of high-level evidence of outcome benefits specific to men with prostate cancer who are receiving ADT, we recommend close monitoring and intervention, especially during the first year of ADT, given that the available data suggest that metabolic complications occur within 3 to 6 months (Box 4). Although not specifically listed in current guidelines from Diabetes Australia, ADT should be considered a risk factor for developing diabetes. Macrovascular targets for men with prediabetes should be the same as for those with established diabetes.[72,73] In men with pre-existing diabetes, antiglycaemic therapy may need to be intensified to maintain individualised glycated haemoglobin targets. There is currently no evidence that routine cardiac-stress testing or carotid artery ultrasound imaging affect outcomes, especially in asymptomatic patients.

Unresolved issues

Clearly, current information is inadequate to assess the risk–benefit ratio of ADT in a large proportion of men with prostate cancer. Controlled trials are required to better define the effect of ADT on survival in men with localised prostate cancer or biochemical PSA recurrence to determine the optimal duration of ADT, and the value of intermittent ADT. Randomised intervention trials using pharmacological therapy, powered for fracture outcomes, are needed to provide more definitive criteria for when to institute such treatment for primary prevention of fractures in men receiving ADT, and to guide the optimal duration of therapy. The role of using intermittent ADT to minimise adverse effects while maintaining anti-tumour efficacy will need to be further defined. The impact of ADT on glucose metabolism and cardiovascular events, and the value of preventive strategies, will need to be defined more precisely in prospective studies. Such information will help to avoid overuse of ADT, especially for men who have a high baseline risk of fractures

4 Androgen deprivation therapy (ADT) and metabolic health

Key evidence points

- Short term ADT (3–6 months) is associated with increased fat mass, decreased muscle mass, and increased insulin resistance (Evidence level IV).
- Long term ADT (> 12 months) is associated with an increased incidence of incident type 2 diabetes (Evidence level III-2).
- ADT for more than 6–12 months increases cardiovascular morbidity and mortality (Evidence level III-2).
- Men with pre-existing diabetes may require intensification of diabetes treatment according to individualised glycated haemoglobin targets (Evidence level IV).
- There are currently no intervention studies that show a reduction of ADT-induced metabolic complications.
- There is currently no evidence to recommend routine cardiac-stress testing or carotid artery ultrasound imaging in asymptomatic men.

Key recommendations

- Before commencing ADT, metabolic risk assessment should include: body mass index, waist circumference, blood pressure, fasting blood glucose level, oral glucose tolerance test (if the fasting glucose level is between 5.5 mmol/L and 6.9 mmol/L), and a fasting lipid profile. (Consensus).
- During the first year of ADT, metabolic assessment should be repeated at 6 months and 12 months, with subsequent individualised frequency of testing. (Consensus).
- Intensive lifestyle intervention, guided by the baseline metabolic risk, should be instituted to prevent weight gain and worsening of insulin resistance. (Evidence level I, in non-ADT subjects).
- Management includes reducing cardiovascular risk factors, and particularly, encouraging smoking cessation. Blood pressure should be < 130/80 mmHg, and lipid targets should be set according to National Heart Foundation of Australia guidelines (http://www.heartfoundation.org.au/Professional_Information/Clinical_Practice/Lipid_Management/Pages/default.aspx). (Evidence level I, in non-ADT subjects).

Evidence levels are from the National Health and Medical Research Council (NHMRC; http://www.nhmrc.gov.au/PUBLICATIONS/synopses/cp30syn.htm). "Consensus" indicates the consensus expert opinion of the writing group in the absence of an available NHMRC level of evidence. ◆

and cardiovascular events but low-risk prostate cancer. We recommend that those treating these patients pay particular attention to any new evidence in this field.

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Competing interests

Mathis Grossmann is principal researcher of an investigator-initiated trial on the role of bisphosphonates in preventing micro-architectural decay in men with non-metastatic prostate cancer who are receiving androgen deprivation therapy, which is partially supported by Novartis Pharmaceuticals, and has received honoraria for educational lectures from AstraZeneca. Christopher Gilfillan is a member of an AstraZeneca prostate cancer advisory board and has received honoraria for educational lectures from sanofi-aventis and Merck.

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