BJU Int. Author manuscript; available in PMC 2017 January 12.

Published in final edited form as:
BJU Int. 2009 March ; 103(6): 753–757. doi:10.1111/j.1464-410X.2008.08156.x.

Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer

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Abstract

OBJECTIVE—To determine whether clinicians discuss bone-specific side-effects with patients on androgen-deprivation therapy (ADT) for prostate cancer, or prescribe lifestyle and pharmacological interventions for low bone mineral density (BMD), as decreased BMD is a common side-effect of ADT, leading to increased risk of fracture.

PATIENTS AND METHODS—Sixty-six men (mean age 70.6 years) with non-metastatic prostate cancer and starting continuous ADT were enrolled in a prospective longitudinal study. BMD was determined by dual X-ray absorptiometry (DXA) at baseline. Patients were interviewed to obtain their medical histories, and charts were reviewed to determine whether clinicians documented potential bone side-effects in clinic notes, and made lifestyle and/or medication recommendations. Both were done at the start of ADT, and 3 and 6 months later. Patients were classified based on DXA T-score as having normal BMD, as osteopenic, or osteoporotic.

RESULTS—At baseline, 53% of patients had osteopenia and 5% had osteoporosis. Within 6 months of starting ADT, general side-effects and bone-specific side-effects of ADT were documented as being discussed with 26% and 15%, respectively. Clinicians recommended lifestyle interventions to 11% of patients. Pharmacological interventions (calcium, vitamin D, and/or bisphosphonates) were recommended to 18% of all patients within 6 months of starting ADT, and to 26% and 67% of osteopenic and osteoporotic patients, respectively.

CONCLUSIONS—A minority of patients is being informed of bone-specific side-effects of ADT. Lifestyle and drug interventions to prevent declines in BMD were recommended uncommonly. Practices around bone health for men starting ADT are suboptimal.

Keywords

androgen-deprivation therapy; bone mineral density; osteoporosis; prostatic neoplasms; quality of care; side-effects

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CONFLICT OF INTEREST
None declared.

INTRODUCTION

Androgen-deprivation therapy (ADT) is used commonly in the treatment of prostate cancer, and is being used increasingly to treat men with asymptomatic, non-metastatic disease [1,2]. Among the common side-effects of ADT is a decline in bone health, as measured by decreases in bone mineral density (BMD) [3,4]. Loss of BMD is associated with an increased risk of fracture, which is of particular concern among older men [5,6].

Several studies have shown that most of the decline in BMD takes place in the first year of ADT, during which some authors have reported decreases in BMD of almost 10% [3,7–9]. These declines can lead to osteoporosis, along with associated morbidity and mortality.

In managing bone health among patients on ADT, clinicians have been advised to screen patients for osteoporosis before starting ADT using dual X-ray absorptiometry (DXA) [10,11]. Furthermore, both lifestyle (smoking cessation, moderating alcohol intake, and regular exercise) and pharmacological (calcium, vitamin D, and bisphosphonates) interventions have been recommended to help prevent bone loss [10,11]. Despite this, our group has previously shown that few surveyed clinicians would order a baseline DXA test or prescribe bisphosphonates to hypothetical patients undergoing ADT [12]. Three retrospective studies have evaluated the actual management of bone health in similar patient populations, and found major gaps in care [13–15].

Little work has been done to determine whether clinicians discuss side-effects related to bone health with patients, and subsequently prescribe lifestyle and pharmacological interventions for a low BMD. These are important quality-of-care issues for men with prostate cancer, as up to half of these men will be treated with some form of ADT after diagnosis [1] and up to a fifth will have a fracture [5]. The objective of the current study was to prospectively assess these management practices using both clinician-reported documentation of patient encounters and patient interviews in a cohort of men starting ADT for non-metastatic prostate cancer.

PATIENTS AND METHODS

The study was part of a larger prospective matched-cohort study of health outcomes in men undergoing ADT. In the larger investigation, men aged ≥50 years with non-metastatic prostate cancer starting continuous ADT were enrolled in a 12-month prospective longitudinal study. Three groups of men were enrolled: men starting continuous ADT, men with prostate cancer but who were not on ADT, and healthy controls who did not have prostate cancer. Men were seen at baseline (at the start of ADT) and at 3, 6 and 12 months later.

We restricted the present sample to those men starting ADT. Clinical interviews and chart reviews were conducted to elicit sociodemographic and medical information at baseline. Calcium and vitamin D intake were noted, as was the use of other prescription and non-prescription medications.

At the 3- and 6-month visits, specific questions were asked of patients about any changes to medications and medical history. The charts of the patients' prostate cancer specialists (either radiation oncologist or urologist) were also reviewed at these times to determine whether clinicians: (i) made a note of the BMD test result; (ii) discussed the bone-specific side-effects of ADT; (iii) made lifestyle recommendations (smoking cessation, moderating alcohol intake, taking regular exercise); and (iv) made recommendations for bone-specific medications, including calcium, vitamin D, bisphosphonates, calcitonin, parathyroid hormone, or a selective oestrogen receptor modulator. The charts of the patients' family physicians were not reviewed. Patients were considered to be taking calcium and vitamin D if the daily intake from supplements was ≥ 1000 mg and ≥400 IU, respectively.

The BMD was determined at baseline by DXA of the lumbar spine and left hip. Following the WHO classification, patients were classified based on DXA as having normal BMD (T-score >−1), osteopenia (−2.5 to <−1), or osteoporosis (<−2.5) based on the lowest T-score at the lumbar spine (L1–L4), total hip, or femoral neck. A copy of the test result (including T-score and a summary statement of the BMD result) was sent within 2 weeks of the DXA to both the patient's prostate cancer specialist who prescribed the ADT, and the family physician. The test result was accompanied by a covering letter noting that the test was done as part of a study, and did not include any formal recommendations for how to address the results.

Double data entry was used to ensure accuracy. All charts were reviewed by the primary author (A.H.P.). A random sample of 10 patient charts was re-abstracted by a second reviewer (S.M.H.A.) to ensure accuracy; there was complete agreement between reviewers. Given the study objectives, our analyses were primarily descriptive. Baseline characteristics were described using means for continuous variables and proportions for categorical variables. We calculated the proportion of men who were taking any bone-specific medications at baseline (before DXA and starting ADT) and 3 and 6 months later. We also calculated the proportion of men for whom their prostate cancer specialist had made any mention of potential bone side-effects of ADT, lifestyle recommendations, or bone-specific drug recommendations. For the latter outcome, we considered a bone-specific drug to have been recommended if any of calcium, vitamin D or a bisphosphonate was recommended, regardless of dose, to a patient not already taking these medications at baseline. Outcomes were examined by baseline BMD status.

RESULTS

Of the 76 patients starting ADT, 10 were excluded for various reasons (missing baseline data in two; withdrawal from the study in three; and refusal to undergo a DXA test in five). Chart reviews and patient interviews were conducted for 66 patients (mean age 70.6 years, range 55–84). Twenty-eight patients (42%) had normal BMD, 35 (53%) had osteopenia and three (5%) had osteoporosis before starting ADT. Among all patients, 68% were current or former smokers, and 76% reported consuming at least one alcoholic beverage daily. Eight patients (11%) were taking natural or herbal products, excluding calcium and vitamin D. Additional baseline data (including stratification by BMD) are shown in Table 1.

All patients were seen in clinic at 3 and 6 months after the diagnosis of prostate cancer. The results of BMD tests were documented as having been discussed with 21% of patients within 3 months of diagnosis (Table 2); this increased to 32% by 6 months. At both 3 and 6 months, patients with worse BMD appeared more likely to have had their BMD test result documented (Table 2). For example, at 6 months, among patients with a normal BMD, osteopenia and osteoporosis, the BMD test result was documented in 21%, 37% and two of three, respectively. General side-effects of ADT were discussed with 26% of all patients (32% of normal BMD, 20% of osteopenic, and one of three osteoporotic). Bone-specific side-effects of ADT were noted to have been discussed with 15% of patients within 6 months, although there did not appear to be a relationship with baseline BMD; among patients with normal BMD, osteopenia and osteoporosis at baseline, bone-specific side-effects were noted for 14%, 17% and none, respectively, by 6 months.

Lifestyle changes (any of smoking cessation, moderating alcohol intake, or regular exercise) were documented as being recommended to 11% of all patients by 6 months. Again, there was no obvious relationship between recommending lifestyle changes and BMD, with 7%, 14%, and none of patients with normal BMD, osteopenia or osteoporosis, respectively, receiving such recommendations.

Pharmacological interventions (calcium, vitamin D, or a bisphosphonate) were documented as being recommended to 18% of all patients within 6 months of starting ADT, and to 4%, 26% and two of three patients with normal BMD, osteopenia and osteoporosis, respectively. No physician recommended parathyroid hormone, calcitonin or a selective oestrogen receptor modulator.

As shown in Table 2, 15% and 30% of all patients reported taking calcium and vitamin D, respectively, at the start of ADT. Within 6 months of initiating ADT, these increased to 23% and 38%, respectively. Within 6 months of the start of ADT, 26% of osteopenic patients (but none of the osteoporotic patients) were taking calcium. In the same period, 43% of patients with a normal BMD were taking vitamin D, compared to 31% of patients with osteopenia and two of three with osteoporosis. Only one patient was taking a bisphosphonate within 6 months of starting ADT.

DISCUSSION

In this prospective study we examined the management of bone health-related side-effects in men with non-metastatic prostate cancer before and after starting ADT. There were four main findings. First, osteopenia was common but osteoporosis was relatively rare in these older men starting ADT. Second, bone-specific potential side-effects of ADT were documented uncommonly as having been discussed with patients within 6 months of starting ADT. The low rate of documentation did not seem to be influenced by BMD at baseline. Third, recommendations about lifestyle and pharmacological interventions to improve bone health were also rarely documented, except in the case of men with osteoporosis at baseline. Fourth, a minority of men was taking calcium, vitamin D and/or bisphosphonates at baseline, and the use increased only slightly within 6 months of starting ADT.

A small majority of patients in our study (53%) had osteopenia before starting ADT. In the absence of any intervention to improve bone health, these patients are at significant risk of developing osteoporosis while on ADT. The occurrence of osteopenia and osteoporosis among the present patients was similar to those of men aged ≥50 years in the National Health and Nutrition Examination Survey III [16], and similar to or slightly higher than in several studies of men with prostate cancer who were initiating or not taking ADT [3,17]. Several other studies have documented similar rates of osteopenia, but considerably higher rates of osteoporosis among hormone-naive men [9,18]. Differences in selection, overall health and socio-economic status of patients among studies might partly explain the differences in observed proportions of men with osteoporosis across studies.

Clinicians in the present study rarely documented the bone-specific side-effects of ADT. There are at least three potential reasons. First, clinicians might not recognize the significance of bone side-effects among men undergoing ADT. Although these side-effects are well documented [4,7], our group and others have shown that BMD itself is measured uncommonly in patients on ADT [12–15], and consequently remains unmonitored over the course of ADT. To overcome this, we used DXA in all patients and provided a copy of test results to the attending clinician. However, it was noted that clinicians did not make explicit reference to discussing these side-effects with patients. This illustrates the need to create evidence-based guidelines of bone health practices among men with ADT, and ensure their endorsement and dissemination by speciality societies, as well as broad implementation among clinicians. Second, it is possible that clinicians discussed but did not document bone-specific side-effects. There was greater documentation of general side-effects of ADT than bone-specific side-effects, and it is possible that declines in bone health were included in these discussions; a limitation of our study was in not using a structured interview to ask patients specifically about their recall of such discussions during the consultation. Despite this, discussion of general side-effects of ADT was documented for only a third of patients. Finally, clinicians might have been too busy or felt it was not their responsibility to deal with issues of bone health [19]. It is important to include a discussion of who would be responsible (i.e. prostate cancer specialist, primary-care practitioner, osteoporosis expert, or other) for dealing with bone health issues in any disseminated guidelines.

Lifestyle interventions were also recommended rarely to patients. Studies have shown that stopping smoking and alcohol use, as well as increased exercise, can decrease or prevent bone loss in general populations [20,21], although none of these strategies has been tested specifically in men on ADT.

The current study corroborates the findings of others in documenting that only a minority of men on ADT is taking calcium, vitamin D and bisphosphonates. Recent studies have shown that <20% of men on ADT with declining bone health are taking calcium and/or vitamin D [13–15,22]. Wilcox *et al.* [14] also observed that there were no changes in the number of men taking calcium and vitamin D over the course of ADT treatment.

Although calcium and vitamin D are important for attenuating declines in BMD [23,24], they are not sufficient for most men on ADT. In randomized trials of pamidronate [7], zoledronic acid [8,25] and alendronate [26] to prevent ADT-induced bone loss, patients in

the control arms, all of whom were receiving supplemental calcium and vitamin D, had bone loss over 6–12 months of follow-up. Bisphosphonates have been shown to improve BMD in men on ADT in the above trials, but none of the studies showed a reduction in fractures. This might partly explain the reluctance of clinicians to recommend bisphosphonates.

Three previous retrospective studies examined the management of bone health in a similar patient population, and found suboptimal monitoring of BMD and low use of pharmacological interventions to prevent bone loss [13–15]. By contrast to these studies, all the present patients were screened for osteoporosis with DXA, and were asked specifically about use of non-prescription medication. We also assessed lifestyle interventions in addition to pharmacological interventions. However, our study had several limitations, including a modest sample size and recruitment of patients from a single tertiary cancer-care centre. These factors, along with the fact that clinicians were aware that patients were enrolled in a non-interventional study that included an assessment of BMD, probably suggest that the quality of bone health care is even worse in the broader community of prostate cancer clinicians. Even though our patients were from one centre, our results are consistent with those of previous publications, and suggest that suboptimal bone health care for men on ADT is quite common. Also, documentation (particularly clinic notes) was used as a proxy for what clinicians actually did. Direct observation would be a preferred but more expensive and intrusive approach, and might introduce its own biases. Instead, we chose to conduct interviews with patients that included questions about actual medication use, which corroborated our findings from chart audits. Documentation of advice to patients in clinical notes is a crucial component of good-quality healthcare and sound medicolegal practice. Finally, we did not specifically examine the doses of calcium and vitamin D. In particular, 400 IU of vitamin D daily is probably suboptimal [24]. Using a higher threshold for adequate dosing of vitamin D would have led to even fewer men in our study being classified as being on adequate therapy.

In summary, a minority of patients is being informed of bone-specific side-effects of ADT, and lifestyle and pharmacological interventions to attenuate or prevent declines in BMD were recommended uncommonly. There is a need to address these deficits through increased awareness, creation and implementation of high-quality clinical practice guidelines, and increased referral of patients to endocrinologists and osteoporosis clinics. The possibility of developing a multidisciplinary clinic involving experts in bone health working alongside prostate cancer clinicians in the management of men on ADT should also be explored.

Acknowledgments

Financial disclosure: Supported in part by grants from the National Cancer Institute of Canada and by a Research Scientist Award from the National Cancer Institute of Canada (Dr Alibhai).

Abbreviations

ADT	androgen-deprivation therapy
BMD	bone mineral density
DXA	dual X-ray absorptiometry

References

1. Meng MV, Grossfeld GD, Sadetsky N, Mehta SS, Lubeck DP, Carroll PR. Contemporary patterns of androgen deprivation therapy use for newly diagnosed prostate cancer. Urology. 2002; 60(Suppl 1): 7–11.
2. Shahinian VB, Kuo YF, Freeman JL, Orihuela E, Goodwin JS. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. Cancer. 2005; 103:1615–24. [PubMed: 15742331]
3. Greenspan SL, Coates P, Sereika SM, Nelson JB, Trump DL, Resnick NM. Bone loss after initiation of androgen deprivation therapy in patients with prostate cancer. J Clin Endo Metab. 2005; 90:6410–7.
4. Alibhai SM, Gogov S, Allibhai Z. Long-term side effects of androgen deprivation therapy in men with non-metastatic prostate cancer: a systematic literature review. Crit Rev Oncol Hematol. 2006; 60:201–15. [PubMed: 16860998]
5. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med. 2005; 352:154–64. [PubMed: 15647578]
6. Smith MR, Boyce SP, Moyneur E, Duh MS, Raut MK, Brandman J. Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol. 2006; 175:136–9. [PubMed: 16406890]
7. Smith MR, McGovern FJ, Zietman AL, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med. 2001; 345:948–55. [PubMed: 11575286]
8. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. J Urol. 2003; 169:2008–12. [PubMed: 12771706]
9. Morote J, Morin JP, Orsola A, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology. 2007; 69:500–4. [PubMed: 17382153]
10. Diamond TH, Higano CS, Smith MR, Guise TA, Singer FR. Osteoporosis in men with prostate carcinoma receiving androgen-deprivation therapy: recommendations for diagnosis and therapies. Cancer. 2004; 100:892–9. [PubMed: 14983482]
11. Duncan GG, Corbett T, Lukka H, Warde P, Pickles T. GU radiation oncologists consensus on bone loss from androgen deprivation. Can J Urol. 2006; 13:2962–6. [PubMed: 16515750]
12. Alibhai SM, Rahman S, Warde PR, Jewett MA, Jaffer T, Cheung AM. Prevention and management of osteoporosis in men receiving androgen deprivation therapy: a survey of urologists and radiation oncologists. Urology. 2006; 68:126–31. [PubMed: 16844454]
13. Tanvetyanon T. Physician practices of bone density testing and drug prescribing to prevent or treat osteoporosis during androgen deprivation therapy. Cancer. 2005; 103:237–41. [PubMed: 15597384]
14. Wilcox A, Carnes ML, Moon TD, et al. Androgen deprivation in veterans with prostate cancer: implications for skeletal health. Ann Pharmacother. 2006; 40:2107–14. [PubMed: 17132807]
15. Yee EF, White RE, Murata GH, Handanos C, Hoffman RM. Osteoporosis management in prostate cancer patients treated with androgen deprivation therapy. J Gen Intern Med. 2007; 22:1305–10. [PubMed: 17634780]
16. Kanis JA, Johnell O, Oden A, De Laet C, Mellstrom D. Diagnosis of osteoporosis and fracture threshold in men. Calcif Tissue Int. 2001; 69:218–21. [PubMed: 11730254]
17. Miyaji Y, Saika T, Yamamoto Y, et al. Effects of gonadotropin-releasing hormone agonists on bone metabolism markers and bone mineral density in patients with prostate cancer. Urology. 2004; 64:128–31. [PubMed: 15245949]
18. Planas J, Morote J, Orsola A, et al. The relationship between daily calcium intake and bone mineral density in men with prostate cancer. BJU Int. 2007; 99:812–5. [PubMed: 17378843]
19. Saigal CS. Moving beyond guidelines to improve the quality of care for men with prostate cancer. J Clin Oncol. 2007; 25:5348–9. [PubMed: 18048813]
20. Vincent KR, Braith RW. Resistance exercise and bone turnover in elderly men and women. Med Sci Sports Exerc. 2002; 34:17–23. [PubMed: 11782642]

21. Ward KD, Klesges RC. A meta-analysis of the effects of cigarette smoking on bone mineral density. Calcif Tissue Int. 2001; 68:259–70. [PubMed: 11683532]

22. Malcolm JB, Derweesh IH, Kincade MC, et al. Osteoporosis and fractures after androgen deprivation initiation for prostate cancer. Can J Urol. 2007; 14:3551–9. [PubMed: 17594745]

23. Tang BM, Eslick GD, Nowson C, Smith C, Bensoussan A. Use of calcium or calcium in combination with vitamin D supplementation to prevent fractures and bone loss in people aged 50 years and older: a meta-analysis. Lancet. 2007; 370:657–66. [PubMed: 17720017]

24. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B. Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA. 2005; 293:2257–64. [PubMed: 15886381]

25. Ryan CW, Huo D, Demers LM, Beer TM, Lacerna LV. Zoledronic acid initiated during the first year of androgen deprivation therapy increases bone mineral density in patients with prostate cancer. J Urol. 2006; 176:972–8. [PubMed: 16890673]

26. Greenspan SL, Nelson JB, Trump DL, Resnick NM. Effect of once-weekly oral alendronate on bone loss in men receiving androgen deprivation therapy for prostate cancer: a randomized trial. Ann Intern Med. 2007; 146:416–24. [PubMed: 17371886]

TABLE 1

Baseline patient characteristics

Variable	All	Normal BMD	Osteopenia	Osteoporosis
n (%)	66 (100)	28 (42.4)	35 (53.0)	3 (4.6)
Mean (range) age, years	70.6 (55–84)	70.4 (59–79)	70.3 (55–84)	74.7 (66–81)
Smoking status, *n* (%)				
Current smoker	5 (8)	1 (4)	3 (9)	1
Former smoker	40 (61)	20 (71)	18 (51)	2
Never smoked	21 (32)	7 (25)	14 (40)	0
Mean years smoked	17.9	20.4	13.8	41.7
Alcohol use, *n* (%)				
None	16 (24)	6 (21)	8 (23)	2
Casual *	37 (56)	17 (61)	19 (54)	1
Excessive	13 (20)	5 (18)	8 (23)	0

* defined as consuming two or fewer beers, glasses of wine, and/or spirits per day.

TABLE 2

The clinicians' discussion of BMD and treatment recommendations, and the patient-reported intake of medication within 6 months of diagnosis

Variable	All	Normal BMD	Osteopenia	Osteoporosis
n (%):				
BMD test result mentioned				
3 months	14 (21)	5 (18)	7 (20)	2
6 months	21 (32)	6 (21)	13 (37)	2
Bone-specific side-effects discussed				
3 months	8 (12)	3 (11)	5 (14)	0
6 months	10 (15)	4 (14)	6 (17)	0
Lifestyle change recommended				
3 months	7 (11)	2 (7)	5 (14)	0
6 months	7 (11)	2 (7)	5 (14)	0
Drugs prescribed *				
3 months	7 (11)	1 (4)	4 (11)	2
6 months	12 (18)	1 (4)	9 (26)	2
Calcium				
baseline	10 (15)	5 (18)	5 (14)	0
6 months	15 (23)	6 (21)	9 (26)	0
Vitamin D				
baseline	20 (30)	11 (39)	7 (25)	2
6 months	25 (38)	12 (43)	11 (31)	2
Bisphosphonates				
baseline	0	0	0	0
6 months	1 (2)	0	1 (3)	0

Values are cumulative over time.

* Includes only those patients who were not taking calcium and vitamin D at baseline. Drugs prescribed/recommended included calcium, vitamin D, or a bisphosphonate.