

Hormones and Healthy Bones
Joint Project of
National Osteoporosis Foundation and Association of Reproductive Health Professionals

Literature Review (January 2009)
Prostate Cancer Treatment

1. 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.
Abstract: OBJECTIVES: To determine the current practice of clinicians in the diagnosis and management of osteoporosis among men taking androgen deprivation therapy (ADT), because ADT leads to decreased bone mineral density (BMD) and fractures. METHODS: We sent out a survey to Canadian urologists and radiation oncologists. The survey included questions about BMD testing, treatment practices, referral patterns, and risk of osteoporosis. RESULTS: The surveys were returned by 170 of 294 respondents (response rate 58%). Few respondents would obtain a baseline BMD in patients starting ADT. Forty percent would order a repeat BMD test after starting ADT if the baseline BMD were normal or unknown, but more than two thirds would if the baseline BMD showed osteoporosis. In men with a normal BMD starting ADT, respondents recommended weight-bearing exercises (58%), calcium (50%), vitamin D (47%), and bisphosphonate (6%) supplements. In men with osteoporosis at baseline, the use of nonprescription therapies increased slightly and bisphosphonate use increased to 44%. If osteoporosis were diagnosed, 11% would treat the patient themselves. The estimated risk of developing osteoporosis within 1 year of starting ADT with a normal baseline BMD ranged from 0% to 90% (median 20%). CONCLUSIONS: To our knowledge, this is the first survey of its kind. The key findings included that few physicians would order a baseline BMD test, would prescribe bisphosphonates for prevention but almost one half would consider bisphosphonates to treat established osteoporosis, and wide variations exist in the practice patterns and risk perception surrounding ADT-related osteoporosis. Evidence-based guidelines are needed to help physicians deal effectively with osteoporosis prevention and management among men taking ADT.
2. Bae DC, Stein BS. The diagnosis and treatment of osteoporosis in men on androgen deprivation therapy for advanced carcinoma of the prostate. *J Urol*. 2004;172:2137-44.
Abstract: PURPOSE: Androgen deprivation therapy (ADT) for advanced prostate cancer increases the risk of osteoporosis. Thus, the practicing urologist should be aware of the appropriate assessment and management. In this article we review the tests designed to diagnose osteoporosis as well as treatment options. We also review methods to monitor the response to therapy and make recommendations for management. MATERIALS AND METHODS: We performed a MEDLINE (1966 to 2004) search for the terms male, osteoporosis, bone mineral density, prostate cancer, androgen deprivation therapy, bisphosphonates, estrogen and the combinations thereof. We then constructed a management algorithm based on the best evidence available. RESULTS: Dual energy x-ray absorptiometry of the hip is the gold standard test for osteoporosis. Biochemical markers of bone turnover are not suitable for diagnosis but they have been shown to be useful for monitoring the response to treatment. Smoking cessation, weight bearing exercise, and vitamin D and calcium have been shown to help improve bone mineral density (BMD). Bisphosphonates have been demonstrated to increase BMD and decrease fracture risk in men with osteoporosis. Estrogens have also recently been shown to decrease bone turnover

and increase BMD in men on ADT. CONCLUSIONS: Hip dual energy x-ray absorptiometry should be performed in all men who are anticipated to be on long-term ADT. In addition, all men on ADT should receive vitamin D and calcium supplementation, and perform regular weight bearing exercise. The value of smoking cessation cannot be overstated. In men who have osteopenia or osteoporosis bisphosphonate therapy should be initiated. Estrogen therapy has shown promise but specific recommendations cannot be made at this time.

3. Body JJ, Bergmann P, Boonen S, et al. Management of cancer treatment-induced bone loss in early breast and prostate cancer -- a consensus paper of the Belgian Bone Club. *Osteoporos Int*. 2007;18:1439-50.

Abstract: Cancer treatment-induced bone loss (CTIBL) is one of the most important side effects of adjuvant antineoplastic treatment in hormone-dependent neoplasms. Chemotherapy, GnRH analogs and tamoxifen can induce marked bone loss in premenopausal women with early breast cancer. Aromatase inhibitors (AIs) are replacing tamoxifen as the preferred treatment for postmenopausal women. As a class effect, steroidal (exemestane) and non-steroidal (anastrozole and letrozole) AIs increase bone turnover and cause bone loss (4%-5% over 2 years). When compared to tamoxifen, the risk of getting a clinical fracture under AI treatment is increased by 35%-50%. In patients with prostate cancer, androgen deprivation therapy (ADT) increases bone turnover, reduces bone mass (4%-5% per year) and increases the fracture rate depending on the duration of therapy. Zoledronic acid can prevent accelerated bone loss induced by goserelin in premenopausal women, by letrozole in postmenopausal women and by ADT in men. More limited data indicate that weekly alendronate or risedronate could also be effective for preventing CTIBL. Initiation of therapy early, prior to the occurrence of severe osteoporosis, rather than after, may be more effective. Bisphosphonate treatment should be considered in osteoporotic but also in osteopenic patients if other risk factor(s) for fractures are present.

4. Bruder JM, Ma JZ, Basler JW, Welch MD. Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. *Urology*. 2006;67:152-5.

Abstract: OBJECTIVES: To determine the prevalence of osteopenia and osteoporosis by central (spine and hip) and peripheral (radius) bone mineral density (BMD) in men with prostate cancer undergoing androgen-deprivation therapy (ADT). Low BMD and fractures are prevalent in this group of men. Most published studies on ADT-related bone loss have documented the loss of BMD in the spine and hip as measured by dual x-ray absorptiometry. In one study, the loss of BMD was most pronounced at the radius. METHODS: In a chart review of patients receiving ADT, the spine and hip BMD results were recorded in 89 patients. Of these 89 patients, the BMD of the radius was also recorded in 53. RESULTS: In the 89 patients with BMD measurements of the spine and hip, 24 (26.9%) had osteoporosis of the hip or spine as defined by a T score of -2.5 or less, and 45 patients (50.6%) had osteopenia (T score -1.0 to -2.5). In the subset of 53 patients who also had the BMD of the radius measured, the results of the BMD of the radius changed the category of diagnosis in 18 patients (34%). The prevalence of osteoporosis increased from 25% to 53% when the results of the radius were included. CONCLUSIONS: Men with prostate cancer treated with ADT have a high prevalence of osteopenia and osteoporosis as determined by peripheral and central BMD measurements. The use of the peripheral BMD measurement appears to identify more patients with osteoporosis and suggests its use in the evaluation of osteoporosis in men receiving ADT.

5. Conde FA, Sarna L, Oka RK, Vredevoe DL, Rettig MB, Aronson WJ. Age, body mass index, and serum prostate-specific antigen correlate with bone loss in men with prostate cancer not receiving androgen deprivation therapy. *Urology*. 2004;64:335-40.
Abstract: OBJECTIVES: Preexisting osteopenia and osteoporosis in men with prostate cancer are of concern due to accelerated bone loss during androgen deprivation therapy (ADT). We sought to identify risk factors for osteoporosis in men with prostate cancer who have not received ADT to help determine which patients may need bone mineral density (BMD) testing prior to ADT. METHODS: Lumbar spine and hip BMD testing were performed using dual-energy x-ray absorptiometry in 34 men with nonmetastatic prostate cancer who were not receiving ADT. The demographic, health status, lifestyle, and disease variables (Gleason score, clinical stage, and prostate-specific antigen level) were obtained and analyzed using univariate and multivariate methods for their role in spine and hip BMD levels. RESULTS: Of the 34 men, 73.5% had osteopenia (55.9%) or osteoporosis (17.6%) of the spine and/or hip. On univariate analysis, aging, lower body mass index, and elevated prostate-specific antigen level correlated significantly with bone loss in the spine and hip. Regression models showed age independently predicted bone loss in the spine ($R^2 = 0.14$). Prostate-specific antigen was an independent predictor of low BMD in the trochanter ($R^2 = 0.18$), and body mass index independently predicted low BMD in the femoral neck ($R^2 = 0.19$). Compared with men younger than 70 years old, men 70 years old or older had less BMD in the spine ($P = 0.017$), femoral neck ($P = 0.047$), and trochanter ($P = 0.030$). CONCLUSIONS: A high prevalence of osteopenia or osteoporosis was found in men with prostate cancer not receiving ADT. Consideration should be given to performing BMD studies in men older than 70 years and with slender stature before initiating ADT.
6. Dickman PW, Adolfsson J, Astrom K, Steineck G. Hip fractures in men with prostate cancer treated with orchiectomy. *J Urol*. 2004;172:2208-12.
Abstract: PURPOSE: Androgen deprivation therapy increases the risk of osteoporosis related fractures. This issue is of increasing importance in men with prostate cancer as increasingly more undergo androgen deprivation therapy and therapy is administered sooner following diagnosis. Data directly addressing the long-term fracture risk in men diagnosed with prostate cancer are limited. MATERIALS AND METHODS: Using population based registries in Sweden we studied the incidence of hip fractures in 17,731 men diagnosed with prostate cancer from 1964 to 1996 who were treated with bilateral orchiectomy within 6 months of diagnosis. The fracture incidence was compared to the incidence in 43,230 men diagnosed with prostate cancer but not treated with orchiectomy and in 362,354 of similar age who were randomly selected from the general population. RESULTS: Men treated with orchiectomy were at increased risk for hip fracture. The estimated relative risk comparing men who underwent orchiectomy to population controls was 2.11 (95% CI 1.94 to 2.29) for femoral neck fractures and 2.16 (95% CI 1.97 to 2.36) for intertrochanter fractures. An increased risk of hip fracture was observed as early as 6 months after orchiectomy and the relative risk remained fairly constant up to 15 years following orchiectomy. CONCLUSIONS: Hip fracture risk increases almost immediately following orchiectomy and the excess risk persists for at least 15 years. This side effect should be considered when assessing the merits of androgen deprivation therapy, particularly in symptom-free men diagnosed with localized prostate cancer. Measures to prevent osteoporosis should be considered in men undergoing androgen deprivation therapy.

7. Eastham JA. Bone health in men receiving androgen deprivation therapy for prostate cancer. *J Urol.* 2007;177:17-24.

Abstract: PURPOSE: Patients with recurrent or metastatic prostate cancer generally receive androgen deprivation therapy, which can result in significant loss of bone mineral density. We explored androgen deprivation therapy related bone loss in prostate cancer, current treatments and emerging therapies. MATERIALS AND METHODS: Literature published on the pathogenesis and management of androgen deprivation therapy related bone loss was compiled and interpreted. Recent drug therapy findings were reviewed, including treatment guidelines. RESULTS: Men with prostate cancer often present with bone loss and the initiation of androgen deprivation therapy can trigger further rapid decreases. This results in an increased fracture risk, and greater morbidity and mortality. Early detection of osteoporosis through androgen deprivation therapy screening and prompt initiation of therapy are critical to prevent continued decreases. Lifestyle changes such as diet, supplementation and exercise can slow the rate of bone loss. Pharmacological therapy with oral and intravenous bisphosphonates has been demonstrated to prevent or decrease the bone loss associated with androgen deprivation therapy. However, important differences exist among various bisphosphonates with respect to efficacy, compliance and toxicity. Only zoledronic acid has been shown to increase bone mineral density above baseline and provide long-term benefit by decreasing the incidence of fracture and other skeletal related events in men with bone metastases. CONCLUSIONS: Androgen deprivation therapy associated bone loss adversely affects bone health, patient quality of life and survival in men with prostate cancer. Increased awareness of this issue, identification of risk factors, lifestyle modification and initiation of bisphosphonate therapy can improve outcomes. Education of patients and physicians regarding the importance of screening, prevention and treatment is essential.

8. Galvao DA, Spry NA, Taaffe DR, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. *BJU Int.* 2008;102:44-7.

Abstract: OBJECTIVE: To assess the effects of androgen deprivation therapy (ADT) on whole-body and regional muscle, fat and bone mass in men with prostate cancer without metastatic bone disease. PATIENTS AND METHODS: Seventy-two men aged 44-88 years underwent spine, hip and whole-body dual-energy X-ray absorptiometry scans at baseline and after 36 weeks of ADT. The change in whole-body and regional lean mass (LM), fat mass (FM), and bone mineral content and density (BMD) were determined. In addition, the prostate specific antigen (PSA), serum testosterone and haemoglobin levels were measured, and the level of physical activity and fatigue assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-30. RESULTS: The upper limb, lower limb, trunk and whole-body LM decreased by a mean (sem) of 5.6 (0.6)%, 3.7 (0.5)%, 1.4 (0.5)% and 2.4 (0.4)% ($P < 0.01$), respectively, while FM increased by 20.7 (3.3)%, 18.7 (2.7)%, 12.0 (2.5)% and 13.8 (2.3)% ($P < 0.001$). Hip, spine, whole-body and upper limb BMD decreased by 1.9 [corrected] (0.3)% [corrected], 3.3 [corrected] (0.4)%, 1.6 [corrected] (0.3)% and 1.3 (0.3)% ($P < 0.001$), but not lower limb BMD. Serum testosterone, PSA and haemoglobin levels decreased by 93.3 (0.4)%, 98.2 (0.5)%, and 8.8 (0.9)% ($P < 0.001$), respectively. In addition, physical activity levels decreased and levels of fatigue increased. CONCLUSION: After 36 weeks of ADT there was a significant decrease in whole-body and regional LM and bone mass, while whole-body and regional FM increased in older men with prostate cancer. Strategies to counteract changes in soft tissue and bone mass during ADT should be formulated to minimize the risk of sarcopenia, osteoporosis and obesity.

9. Gomella LG. Contemporary use of hormonal therapy in prostate cancer: managing complications and addressing quality-of-life issues. *BJU Int.* 2007;99 Suppl 1:25-9; discussion 30.

Abstract: While both short- and long-term androgen deprivation therapy (ADT) are effective for treating prostate cancer, with the clinical benefits patients can often have significant side-effects. It is important that these complications are recognized and managed appropriately so that adverse effects on the patient's quality of life (QoL) are minimized. The incidence of deaths from prostate cancer has decreased over the last decade, probably as a result of various factors including improved screening and diagnosis, improved treatments, and better risk assessment to help guide therapy. A meta-analysis of prostate cancer trials comparing the use of early vs late hormonal therapy found that 10-year overall survival increased by up to 20% between 1990 and 2000, and this was attributed to the earlier use of hormone therapy (HT) in these patients. Data from the USA Cancer of the Prostate Strategic Urological Research Endeavor database also suggest a significant decrease in risk in the last two decades in the USA, with more patients being identified with low-risk disease at diagnosis. In addition, there has been an increase in recent years in the use of HT at all stages of prostate cancer. The extensive use of ADT has raised concerns about potential adverse effects. ADT might be associated with a range of adverse effects that vary in their degree of morbidity and effect on the patient's QoL. They include hot flashes, osteoporosis, loss of libido or impotence, and psychological effects, e.g. depression, memory difficulties or emotional lability. Effective strategies are available for managing the major side-effects of HT, but to many patients these unwanted effects are often less important than the benefits of treatment. An investigation of health-related QoL found that men with prostate cancer receiving ADT had a poorer QoL than those not receiving ADT, but the difference was less pronounced after controlling for comorbidities. Many new therapies are currently under investigation which aim to maximize the clinical effects of ADT while reducing the adverse effects.

10. Greenspan SL. Approach to the prostate cancer patient with bone disease. *J Clin Endocrinol Metab.* 2008;93:2-7.

Abstract: Prostate cancer is the most common visceral malignancy in men. Androgen deprivation therapy (ADT) is commonly used in patients with nonmetastatic prostate cancer and is associated with significant bone loss and fractures. The greatest bone loss occurs during initiation of ADT. Men should have assessment of skeletal integrity with bone mineral density examination by dual x-ray absorptiometry of the hip and spine. Men with fragility fractures or osteoporosis by bone density should be considered for bisphosphonate therapy. Men with low bone mass may need antiresorptive therapy, depending on other risk factors. Men with a normal bone mineral density should be followed up closely with bone densitometry while on ADT. All men should receive preventive measures with calcium (1200 mg daily in divided doses), vitamin D (800-1000 IU/d), and weight-bearing exercise. Men should be evaluated for additional secondary causes of bone loss including vitamin D insufficiency. Guidelines are needed for androgen-induced bone loss screening and treatment.

11. 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 Endocrinol Metab.* 2005;90:6410-7.

Abstract: CONTEXT: Although androgen deprivation therapy (ADT) for prostate cancer is associated with bone loss, little is known about when this bone loss occurs. OBJECTIVE: We postulated that men on ADT would experience the greatest bone loss acutely after

initiation of ADT. DESIGN AND SETTING: We conducted a 12-month prospective study at an academic medical center. PATIENTS OR OTHER PARTICIPANTS: We studied 152 men with prostate cancer (30 with acute ADT, < 6 months; 50 with chronic ADT, > or = 6 months; and 72 with no ADT) and 43 healthy age-matched controls. MAIN OUTCOME MEASURES: We assessed bone mineral density (BMD) of the hip, wrist, total body, and spine; body composition; and markers of bone turnover. RESULTS: After 12 months, men receiving acute ADT had a significant reduction in BMD of 2.5 +/- 0.6% at the total hip, 2.4 +/- 1.0% at the trochanter, 2.6 +/- 0.5% at the total radius, 3.3 +/- 0.5% at the total body, and 4.0 +/- 1.5% at the posteroanterior spine (all $P < 0.05$). Men with chronic ADT had a 2.0 +/- 0.6% reduction in BMD at the total radius ($P < 0.05$). Healthy controls and men with prostate cancer not receiving ADT had no significant reduction in BMD. Both use and duration of ADT were associated with change in bone mass at the hip ($P < 0.05$). Men receiving acute ADT had a 10.4 +/- 1.7% increase in total body fat and a 3.5 +/- 0.5% reduction in total body lean mass at 12 months, whereas body composition did not change in men with prostate cancer on chronic ADT or in healthy controls ($P < 0.05$). Markers of bone formation and resorption were elevated in men receiving acute ADT after 6 and 12 months compared with the other men with prostate cancer and controls ($P < 0.05$). Men in the highest tertile of bone turnover markers at 6 months had the greatest loss of bone density at 12 months. CONCLUSIONS: Men with prostate cancer who are initiating ADT have a 5- to 10-fold increased loss of bone density at multiple skeletal sites compared with either healthy controls or men with prostate cancer who are not on ADT, placing them at increased risk of fracture. Bone loss is maximal in the first year after initiation of ADT, suggesting initiation of early preventive therapy.

12. Isbarn H, Boccon-Gibod L, Carroll PR, et al. Androgen Deprivation Therapy for the Treatment of Prostate Cancer: Consider Both Benefits and Risks. *Eur Urol*. 2008.
Abstract: CONTEXT: Androgen deprivation therapy (ADT) is increasingly used for the treatment of prostate cancer (PCa), even in clinical settings in which there is no evidence-based proof of prolonged overall survival (OS). ADT, however, may be associated with numerous side effects, including an increased therapy-related cardiovascular mortality. OBJECTIVE: To discuss different clinical settings in which ADT is currently used and to critically weigh the benefits of ADT against its possible side effects. EVIDENCE ACQUISITION: A MEDLINE search was conducted to identify original articles and review articles addressing the efficacy and side effects of ADT for the treatment of PCa. Keywords consisted of prostate cancer, hormonal therapy, adverse effects, radical prostatectomy, and radiotherapy. The articles with the highest level of evidence for the various examined end points were identified with the consensus of all authors and were reviewed. EVIDENCE SYNTHESIS: Even short-term use of ADT may lead to numerous side effects, such as osteoporosis, obesity, sarcopenia, lipid alterations, insulin resistance, and increased risk for diabetes and cardiovascular morbidity. Despite these side effects, ADT is commonly used in various clinical settings in which a clear effect on improved OS has not been shown. CONCLUSIONS: ADT is associated with an increased risk of multiple side effects that may reduce quality of life and/or OS. Consequently, these issues should be discussed in detail with patients and their families before initiation of ADT. ADT should be used with knowledge of its potential long-term side effects and with possible lifestyle interventions, especially in settings with the highest risk-benefit ratio, to alleviate comorbidities.
13. Israeli RS, Ryan CW, Jung LL. Managing bone loss in men with locally advanced prostate cancer receiving androgen deprivation therapy. *J Urol*. 2008;179:414-23.

Abstract: **PURPOSE:** We reviewed the pathogenesis, diagnosis, prevalence, prevention and treatment of bone loss in patients with nonmetastatic prostate cancer receiving androgen deprivation therapy. **MATERIALS AND METHODS:** Using PubMed we performed a comprehensive literature search to identify articles on bone mineral density loss in patients with nonmetastatic prostate cancer receiving androgen deprivation therapy. Pertinent articles were reviewed and evaluated. **RESULTS:** Bone mineral density loss and related fractures were recently established as significant adverse events associated with androgen deprivation therapy. Patients with nonmetastatic prostate cancer receiving androgen deprivation therapy experience annual bone mineral density losses of 0.6% to 4.6% with the most significant loss within year 1 of therapy. In addition to calcium and vitamin D supplements, current treatment options for androgen deprivation therapy induced bone loss include synthetic estrogens, selective estrogen receptor modulators and bisphosphonates. Recent safety concerns have been identified, including renal dysfunction with intravenous bisphosphonates and osteonecrosis of the jaw with oral and intravenous bisphosphonates. However, minimal renal dysfunction and no cases of osteonecrosis of the jaw have been reported in this setting. **CONCLUSIONS:** Because the most significant bone mineral density loss occurs within year 1 of androgen deprivation therapy and most fractures in healthy men occur in those without osteoporosis, early intervention is warranted to prevent skeletal morbidity in patients with nonmetastatic prostate cancer receiving androgen deprivation therapy. Although the majority of and the most compelling evidence supports the use of bisphosphonates for preventing and treating androgen deprivation therapy induced bone loss, further study is needed to define the optimal regimen, timing of initiation and duration of therapy as well as long-term efficacy and safety.

14. Krupski TL, Foley KA, Baser O, Long S, Macarios D, Litwin MS. Health care cost associated with prostate cancer, androgen deprivation therapy and bone complications. *J Urol.* 2007;178:1423-8.

Abstract: **PURPOSE:** We ascertained the health care costs of androgen deprivation therapy and related skeletal events. **MATERIALS AND METHODS:** Using data from the MarketScan Medicare Supplemental and Coordination of Benefits Database, we identified cases with International Classification of Disease, 9th Revision codes indicating a diagnosis of prostate cancer who initiated androgen deprivation therapy between 1999 and 2002. The control group consisted of patients with prostate cancer with no androgen deprivation therapy use, matched by age, geographic region, insurance plan and index year. All had followup data for at least 36 months. The occurrence and cost of osteoporosis and any bone fracture were assessed using a propensity score matched sample. **RESULTS:** Of the 8,577 eligible men with prostate cancer, 3,055 initiated androgen deprivation therapy and 5,522 did not. At the time of androgen deprivation therapy initiation those on androgen deprivation therapy had more severe comorbidity (3.1 vs 2.6, $p < 0.001$) and proportionally more bone metastases (2.8% vs less than 0.6%, $p < 0.001$) but no difference in fracture rate. After 3 years of followup the androgen deprivation therapy group experienced significantly more fractures (18.7% vs 14.6%, $p < 0.001$). The mean unadjusted total cost of health care during the 36-month period was \$48,350 per person for cases and \$26,097 for controls. **CONCLUSIONS:** Among men with prostate cancer, those on androgen deprivation therapy cost the health care system almost twice as much as those not on androgen deprivation therapy. After controlling for differences in health status, the majority of the excess cost is attributable to androgen deprivation therapy and then to a lesser extent, the fractures. These results suggest that the bone complications of osteoporosis and fractures in men on androgen deprivation therapy have important economic consequences.

15. Kumar RJ, Barqawi A, Crawford ED. Preventing and treating the complications of hormone therapy. *Curr Urol Rep.* 2005;6:217-23.
Abstract: Hormonal manipulation in the form of androgen-deprivation therapy for prostate cancer was introduced by Huggins and Hodges in 1941 and resulted in a Nobel Prize in 1966. Hormonal therapy initially had been used in metastatic prostate cancer, but the indications have been expanded including failed local therapy, locally advanced prostate cancer, and neoadjuvant or adjuvant therapy in high-risk localized prostate cancer. In view of the magnitude of the problem of prostate cancer and relatively frequent use of hormonal manipulation, it is important for clinicians to be aware of common side effects, prevention, and treatment to improve quality of life and reduce morbidity and mortality in patients with prostate cancer. This review focuses on the common side effects of hormonal treatment such as osteoporosis, anemia, hot flashes, erectile dysfunction, muscle wasting, gynecomastia, decline in cognitive function, depression, increase in body fat and metabolic changes, and their prevention and treatment.
16. Lopez AM, Pena MA, Hernandez R, Val F, Martin B, Riancho JA. Fracture risk in patients with prostate cancer on androgen deprivation therapy. *Osteoporos Int.* 2005;16:707-11.
Abstract: Although a decrease in bone mass is a well-known side effect of hormone therapy for prostate carcinoma, its clinical significance is unclear, as there is only scanty information about the incidence of fractures. Therefore, the aim of this study was to determine the risk of non-metastatic fractures in patients with prostate cancer undergoing androgen deprivation therapy. We performed a retrospective cohort study that comprised 288 patients with cancer who were subjected to androgen deprivation therapy (ADT). All were given LHRH agonists, and most of them also received peripheral androgen receptor blockers. The results were compared with a control group of 300 men that were not receiving ADT. The incidence rates of peripheral and vertebral fractures in the group of men on ADT were 1.9 and 0.8 per 100 patient-years, respectively. Incidence rates in the control group were 0.5 and 0.2, respectively. In the whole study group, 35 patients had at least one fracture during follow-up (25 on ADT, ten controls). Thus, the number of patients with at least one fracture was significantly higher in the group on ADT ($P = 0.001$ by the log-rank test). The unadjusted risk ratio was 4.2 (CI 2.0-8.9). A similar value (risk ratio 3.6; CI 1.6-7.7, $P = 0.001$) was found after it was adjusted for other factors, such as age or prior fractures. Therefore, ADT is associated with a fourfold increase in the incidence rate of both peripheral and vertebral fractures. Although the absolute incidence remains relatively small, preventive measures should be considered for high-risk patients.
17. 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.
Abstract: INTRODUCTION: Androgen deprivation therapy (ADT) is widely utilized for treatment of localized and advanced prostate cancer (CaP). ADT is associated with increased rates of osteoporosis; however, its impact on fracture risk is not completely understood. We investigated incidence and predisposing factors for osteoporosis and fractures in a large, contemporary, single institution series of patients treated with ADT for CaP. METHODS: We retrospectively reviewed medical records of all patients who received ADT for CaP between 1/1989 and 7/2005. Primary endpoints of investigation were osteoporosis and non-pathologic fractures. Independent variables included age, race, body mass index (BMI), pretreatment serum PSA, Gleason sum, clinical stage, ADT type (medical versus surgical) and schedule (continuous versus intermittent), and receipt of calcium, vitamin D or bisphosphonate supplementation. Data were analyzed by Chi-square test, Student's t-test, Linear Regression, and Logistic Regression ($p < 0.05$ significant).

RESULTS: A total of 395 patients were analyzed (mean age 71.7 years, 59% African American, 41% Caucasian/other). At mean follow-up of 66.1 months, 92 (23%) patients developed osteoporosis and 27 (7%) patients developed non-pathologic fractures. On univariate analysis, age, race, BMI, and ADT duration were significantly associated with osteoporosis development, while BMI, ADT duration, and presence of osteoporosis were significantly associated with fracture incidence. Regression analysis revealed that age > 70 at ADT initiation, continuous ADT, and increased treatment duration predicted osteoporosis development, while only osteoporosis was independently predictive of fracture development. **CONCLUSIONS:** Patients receiving continuous ADT for CaP are at increased risk for developing osteoporosis which may lead to fractures, with an incidence of 7% in our study population.

18. Mohile SG, Mustian K, Bylow K, Hall W, Dale W. Management of complications of androgen deprivation therapy in the older man. *Crit Rev Oncol Hematol*. 2008;[Epub ahead of print].
Abstract: Prostate cancer is the most common malignancy in older men. With the aging of the population, the number of older men with prostate cancer will grow rapidly. Androgen deprivation therapy (ADT) is the mainstay of treatment for men with systemic disease and is increasingly utilized as primary therapy or in combination with other therapies for localized disease. Side effects of therapy are multifold and include hot flashes, osteoporosis, and adverse psychological and metabolic effects. Recent research has illustrated that ADT can negatively impact the functional, cognitive, and physical performance of older men. Patients with prostate cancer, despite recurrence of the disease, have a long life expectancy and may be subjected to the side effects of ADT for many years. This review highlights the complications of ADT and approaches to management. We also provide recommendations for assessment and management of ADT complications among the most vulnerable and frail older male patients.
19. 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.
Abstract: **OBJECTIVES:** To know the prevalence of osteoporosis in patients with prostate cancer according to the duration of androgen deprivation therapy (ADT). **METHODS:** Dual energy x-ray absorptiometry was used to assess the bone mineral density (BMD) at the lumbar spine, femoral neck, Ward's triangle, trochanter, and total hip in 390 patients free of bone metastases. Osteoporosis was diagnosed if a T-score of less than 2.5 was detected at any measurement site. A subset of 124 patients were hormone naive at BMD testing, and 112 had undergone ADT for 2 years, 61 for 4 years, 37 for 6 years, 35 for 8 years, and 21 for 10 years or longer. **RESULTS:** The osteoporosis rate was 35.4% in hormone-naïve patients, 42.9% after 2 years of ADT, 49.2% after 4 years, 59.5% after 6 years, 65.7% after 8 years, and 80.6% after 10 or more years. Conversely, the rate of normal BMD decreased from 19.4% in hormone-naïve patients to 17.8% after 2 years of ADT, 16.4% after 4 years, 10.8% after 6 years, 5.7% after 8 years, and 0% after 10 or more years of ADT. **CONCLUSIONS:** The prevalence of osteoporosis seemed high in hormone-naïve patients with prostate cancer, and it increased to more than 80% after 10 years of ADT. Because of the increased risk of bone fractures in those patients, clinicians should be aware of the impact of ADT on BMD to prevent bone mass loss.
20. Panju AH, Breunis H, Cheung AM, et al. Management of decreased bone mineral density in men starting androgen-deprivation therapy for prostate cancer. *BJU Int*. 2008; [Epub ahead of print].

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.

21. Ryan CW, Huo D, Stallings JW, Davis RL, Beer TM, McWhorter LT. Lifestyle factors and duration of androgen deprivation affect bone mineral density of patients with prostate cancer during first year of therapy. *Urology*. 2007;70:122-6.

Abstract: **OBJECTIVES:** Androgen deprivation therapy (ADT) is associated with loss of bone mineral density (BMD) and increased fracture risk. We sought to examine the impact of ADT and lifestyle variables on BMD in 120 patients with prostate cancer without bone metastases entering a randomized clinical trial. **METHODS:** A total of 120 patients with prostate cancer and without bone metastases who had been treated with ADT for less than 12 months were enrolled in a clinical trial of zoledronic acid versus placebo. BMD measurements of the femoral neck, total hip, and lumbar spine were obtained before starting the study treatment by dual energy x-ray absorptiometry. The subjects answered a questionnaire regarding possible osteoporosis risk factors, including dairy product use, caffeinated beverage use, smoking history, alcohol intake, calcium/vitamin D supplementation, thyroid medication, and exercise. **RESULTS:** The median duration of ADT was 3 months (range 0 to 12). Osteopenia or osteoporosis (T score of less than -1) was detected in two thirds of the subjects at one or more measured sites. The mean baseline BMD Z scores were femoral neck -0.091 +/- 0.959, total hip 0.122 +/- 1.005, and lumbar spine 0.657 +/- 1.789. On multiple linear regression analysis, the duration of ADT was negatively associated with the Z score at all three sites and the body mass index, calcium/vitamin D supplementation, and alcohol use were positively associated with the Z score. **CONCLUSIONS:** BMD loss is a function of the duration of ADT during the first year of therapy. The body mass index, calcium/vitamin D supplementation, and alcohol use were associated with greater BMD, even after controlling for ADT exposure.

22. Saad F, Adachi JD, Brown JP, et al. Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol*. 2008;26:5465-76.

Abstract: **PURPOSE:** Bone loss resulting from the treatment of breast and prostate cancer is an emerging problem. Bisphosphonates have a potential role in the prevention of this

cancer treatment-induced bone loss (CTIBL). **METHODS:** Studies evaluating the incidence and prevalence of CTIBL in early breast and prostate cancer patients and trials evaluating the preventative role of bisphosphonates were identified by a search of the PubMed and Cochrane Library databases through the end of March 2008. Reference lists from retrieved articles were cross referenced, and further information was obtained from relevant scientific meetings. **RESULTS:** Several therapies commonly used in the treatment of women and men with breast and prostate cancers, in particular the aromatase inhibitors (AIs) for breast cancer and androgen deprivation therapy (ADT) for prostate cancer, are associated with significant bone loss and with an increase in fracture risk. The use of bisphosphonates seems to attenuate the bone loss, although the long-term impact remains unclear because of insufficient follow-up. **CONCLUSION:** Adjuvant endocrine therapy with an AI or androgen deprivation can be considered a risk factor for the development of osteopenia, osteoporosis, and bone fracture, which can be mitigated by appropriate bisphosphonate therapy. Clear identification of risk factors for osteoporosis in individual patients should aid treatment decisions about whether to use bisphosphonates when starting or switching to an AI or ADT. Patients need to be educated about this risk and other measures to avoid this complication, including lifestyle modifications that may benefit their general and bone health.

23. Saad F, Perrotte P, Benard F, McCormack M, Karakiewicz PI. Bone health in men with prostate cancer: diagnostic and therapeutic considerations. *Can J Urol*. 2005;12 Suppl 2:9-15.

Abstract: With current treatments, men usually survive many years after being diagnosed with prostate cancer. However, the systemic effects of prostate cancer and therapies such as androgen deprivation therapy (ADT) can undermine skeletal integrity, resulting in skeletal complications that may erode quality of life (QOL). Prostate cancer patients are at risk for fractures from cancer treatment-induced bone loss. In addition, they are also at risk for pathologic fractures, severe bone pain, and other sequelae from bone metastases, which almost invariably occur during the progression of prostate cancer. This review investigates the incidence and pathophysiology of bone loss and skeletal morbidity in prostate cancer patients and reviews available treatment options for maintaining skeletal health throughout the continuum of care for these patients. Several supportive interventions are available to prevent generalized and localized bone loss, including calcium and vitamin D supplements and bisphosphonates. Oral calcium and vitamin D supplementation alone, however, appears to be insufficient to prevent bone loss during ADT. New generation bisphosphonates such as zoledronic acid can prevent bone loss for patients on ADT and can reduce skeletal morbidity for those with bone metastases.

24. Tuck SP, Francis RM. Testosterone, bone and osteoporosis. *Front Horm Res*. 2009;37:123-32.

Abstract: Osteoporosis and osteoporotic fractures are generally considered to mainly affect older postmenopausal women, but up to 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men. Osteoporotic fractures in men are associated with substantial morbidity, greater excess mortality than in women and account for almost 25% of the cost of osteoporotic fractures in the UK. One of the major secondary causes of osteoporosis in men is hypogonadism, which is found in up to 20% of men with symptomatic vertebral fractures and 50% of elderly men with hip fractures. This chapter outlines the pathogenesis of osteoporosis in men, placing particular emphasis on the importance of sex steroids in the maintenance of bone health. The effects of hypogonadism on the skeleton are described, as well as the consequences of androgen deprivation therapy in men with prostate cancer.

Finally, we review the effects of testosterone replacement in hypogonadism and explore other options for the treatment of osteoporosis secondary to loss of sex steroids in men.

25. Wang W, Yuasa T, Tsuchiya N, et al. Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. *Endocr Relat Cancer*. 2008;15:943-52.
Abstract: Androgen-deprivation therapy (ADT) of patients with prostate cancer (PCa) is known to reduce bone mineral density (BMD). However, the most studies examined Caucasian or black patients and the effects of ADT on the bone metabolism of East Asians are unclear. Therefore, we performed a cross-sectional study to elucidate the influence of ADT on bone metabolism in Japanese patients. In total, 101 native Japanese patients with PCa were enrolled. They consisted of 58 ADT-treated and 43 hormone-naïve patients. The BMD in the lumbar spine, total hip, and femoral neck was measured by dual energy X-ray absorptiometry and expressed in s.d. units relative to young adult men (T-score) or age-matched men (Z-score). Serum levels of bone metabolism markers were also measured. The BMDs at the three sites revealed that 2.3% (1/43) and 8.6% (5/58) of the hormone-naïve and ADT-treated PCa patients had osteoporosis respectively, but this difference failed to achieve statistical significance ($P=0.294$). The two groups also did not differ significantly in their Z-scores of the three sites, and univariate and multivariate analyses indicated that ADT was not a significant risk factor for decreased BMD. In addition, a significant correlation between the duration of ADT and BMD was not observed for all three sites measured. However, the ADT-treated patients had significantly higher serum levels of N-terminal telopeptide of type I collagen (NTx) than the hormone-naïve patients ($P=0.017$). To our knowledge, this is the first study to demonstrate the low prevalence of osteoporosis in both ADT-treated and hormone-naïve Japanese PCa patients. Moreover, ADT did not significantly increase the prevalence of osteoporosis in this Japanese population.
26. Weingard KK. Nursing implications of androgen deprivation therapy-associated bone loss. *Urol Nurs*. 2006;26:261-9; quiz 270.
Abstract: Men with locally advanced and nonmetastatic prostate cancer are generally treated with androgen deprivation therapy (ADT) to suppress tumor growth. This treatment, however, is associated with decreased bone density and increased fracture risk, which can lead to increased morbidity and mortality. Nurses play a key role in patient education by promoting lifestyle changes such as diet and exercise that can improve bone strength and decrease risk of ADT-associated bone loss. Pharmacologic interventions using bisphosphonates can significantly reduce bone loss and fracture risk in patients with prostate cancer receiving ADT.
27. 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.
Abstract: BACKGROUND: Common risk factors for osteoporosis in older men include smoking, heavy use of alcohol, propensity to falls, and use of bone-toxic medications such as prednisone. There is also increasing appreciation of the skeletal risk faced by men receiving androgen deprivation therapy (ADT) for prostate cancer. Measures to prevent bone loss in such patients are available. OBJECTIVE: To test the following hypotheses in a population of veterans receiving ADT for prostate cancer: (1) fracture risk factors in addition to androgen deprivation would be found in most patients, (2) bone mass measurements would be assessed in a minority of patients, and (3) a minority of the subjects would receive bisphosphonate therapy or have contraindications for such treatment. METHODS: We conducted a retrospective chart review of male veterans

receiving ADT from 1993 through 2001, at the Veterans Affairs Medical Center, Madison, WI. RESULTS: One hundred and seventy-four subjects met study criteria, with a mean age of 76 years and median duration of 21 months of ADT. Eighty-one percent had risk factors in addition to ADT. Only 13% underwent bone density measurement by dual energy X-ray absorptiometry (DXA) and, of those measured, more than half had osteoporosis. Only 19% of the men received both calcium and vitamin D supplements. Antiresorptive therapy was provided to 11% of men, although more than two-thirds had no contraindications to therapy. A total of 24 men sustained a fracture after starting ADT. For men who did undergo bone density measurement, 77% received antiresorptive therapy. Of those who exhibited osteoporosis by DXA scan, 85% received antiresorptive therapy. CONCLUSIONS: Male veterans receiving ADT for prostate cancer received inadequate evaluation and treatment for osteoporosis. Based on our data, a simple and practical strategy to prompt further evaluation and improved care may be to undertake bone density measurements in men prior to or soon after commencing ADT.

28. 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.

Abstract: BACKGROUND: The use of androgen deprivation therapy (ADT) for prostate cancer has increased substantially in recent years, exposing more men to potential treatment complications, including osteoporosis and fractures. OBJECTIVE: To determine whether men treated with ADT for prostate cancer received osteoporosis screening, prevention, or treatment. DESIGN: Cross-sectional observational study using a retrospective review of electronic medical records. SUBJECTS: One hundred seventy-four patients with prostate cancer on ADT or status-post orchiectomy enrolled in primary care at the New Mexico Veterans Affairs Health Care System as of July 2005. MEASUREMENTS: Patient demographics, tumor characteristics (Gleason score, stage, last PSA value, documented bone metastases), history of hip or vertebral fracture, osteoporosis risk factors (number of ADT shots, diabetes, smoking, heavy alcohol use or prescriptions for corticosteroids, thyroid hormone or dilantin). We defined recommended management as performing DXA scans or prescribing bisphosphonates, calcitonin, calcium or vitamin D. RESULTS: Just 60 of 174 (34%) patients received recommended osteoporosis management based on DXA scans (13%) or treatment with oral or IV bisphosphonates (21%), calcitonin (1%), calcium (16%) or vitamin D (10%). On multivariate analysis, bone metastases, higher last PSA, and younger age at diagnosis were associated with recommended management, whereas Hispanic race/ethnicity was inversely associated. CONCLUSIONS: Most men treated with ADT for prostate cancer did not receive osteoporosis screening, prevention or treatment. Evidence for advanced cancer though not risk factors for osteoporosis or fracture-was associated with receiving osteoporosis management. Further research is needed to identify optimal strategies for screening, prevention, and treatment in this population.