Bone Health in Men Receiving Androgen Deprivation Therapy for Prostate Cancer

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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.

Key Words: prostate, prostatic neoplasms, bone and bones, androgen antagonists, osteoporosis

Patients with clinically localized prostate cancer are usually treated with radical prostatectomy or radiation therapy. In cases of disease recurrence, most commonly manifesting as increasing prostate specific antigen, ADT is commonly used. This involves hypogonadism induction through orchiectomy, a GnRH agonist alone or combined androgen blockade (GnRH analogue plus antiandrogen).[1] While ADT suppresses tumor growth, controls symptoms and extends survival, it is associated with significant side effects, such as weight gain, loss of lean muscle mass, impaired concentration, decreased libido and hot flashes.[2] In addition, many patients treated with ADT experience rapid bone loss, which increases the risk of debilitating osteoporotic fractures.[3–5] BMD may decrease by 4% to 13% yearly in men receiving such therapy.[6] Moreover, men with prostate cancer may experience significant bone loss due to disease even before ADT initiation. Smith et al evaluated 41 patients with prostate cancer and no history of ADT with baseline BMD studies and found that 14 (34%) had osteopenia or osteoporosis.[7] This decrease in BMD was associated with hypogonadism, low vitamin D and insufficient dietary calcium. Similarly another study showed that 42% of men diagnosed with prostate cancer had osteoporosis and 37% had osteopenia before initiating ADT compared with a 27% incidence of osteoporosis in the age matched control group.[8] Because many men with prostate cancer are older, BMD losses are superimposed on the progressive decrease in bone density that accompanies normal aging.[8] The cumulative decrease in BMD is associated with an increased fracture risk,[5,9] which can result in increased morbidity and mortality.[10]

Earlier diagnosis of prostate cancer resulting from more widespread prostate specific antigen testing, earlier initiation and longer use of ADT, and increased survival in patients with prostate cancer have resulted in a greater number of men receiving ADT and for a longer duration. Moreover, this treatment is not limited to patients with metastatic disease. Therefore, the BMD loss associated with ADT is an increasingly prevalent and important problem in patients with prostate cancer. Urologists must consider the risks of such therapy as well as current approaches to the prevention and treatment of bone loss in patients receiving ADT.

PATHOPHYSIOLOGY OF ADT ASSOCIATED BONE LOSS

Normal bone is in a state of equilibrium with ongoing bone formation and resorption mediated by osteoblasts and os-

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teoclasts, respectively. Estrogens and androgens help maintain this balance between bone synthesis and degradation.[11] Estrogens regulate bone remodeling through direct effects on osteoblasts and osteoclasts. They prevent bone resorption by inhibiting osteoclasts and are required to maintain proper osteoblast functioning. Androgens such as testosterone also have direct effects on each cell type and it acts to decrease bone resorption via the aromatization of testosterone to estrogen. However, ADT disrupts this normal hormonal balance required for bone health. Severely hypogonadal men experience decreased BMD and severe bone architecture deterioration.[12] This is associated with increased bone resorption but not bone formation, as measured by biochemical markers of bone turnover.[13]

The rate of loss of BMD occurring with ADT is significantly greater than that in normal aging or female menopause. Normally men lose BMD at a rate of approximately 0.5% to 1.0% yearly starting in middle age.[2] Women lose bone mass at a similar rate until menopause, at which point this increases (approximately 3% yearly in the spine) for 5 years. Bone loss in women subsequently decreases to the earlier rate. In contrast, in men with prostate cancer treated with ADT bone loss was determined to be 4.6% and 3.9% at the lumbar spine and femoral neck, respectively, after 1 year with substantial changes evident as early as 6 months after ADT initiation.[14] Similar rapid decreases in BMD also occur following orchiectomy with 1 study showing a 15% decrease in trochanter BMD at 1 year.[15] Thus, bone loss associated with ADT is more rapid and severe than that in normal aging men or women with rates as much as 10-fold higher than normal.

ASSESSING RISK: MEASURING LOSS OF BMD

There are various technologies to assess BMD, including DXA, ultrasound, quantitative computerized tomography and radiographic absorptiometry. Although all methods are useful for predicting the fracture risk, the most commonly used measure is central DXA, which can assess BMD changes in the spine, hip, proximal femur and total body.[16] Central DXA is preferred to other measurements because it can be performed rapidly in the office and uses radiation doses lower than those of conventional x-ray.[16]

Results of BMD measurements are typically standardized and reported as a T-score. The T-score is the number of SDs by which patient measured bone mass deviates from the mean of the young normal population of the same sex at a given site.[17] T-scores are used to confirm a diagnosis of osteoporosis and assess disease severity as well as predict the fracture risk. According to WHO criteria patients with scores of –1 or greater are considered to be within the normal range. T-scores of –1 to –2.5 indicate osteopenia, –2.5 or less defines osteoporosis and –2.5 or less with at least 1 fracture indicates severe osteoporosis.[16] A T-score of –1 represents a 10% to 12% loss of bone mass compared with the mean in normal young adults, which increases the relative risk of fracture 1.5 to 2-fold.

Changes in BMD can also be inferred from measurement of bone metabolism biomarkers. Bone continually undergoes formation and resorption, and biochemical markers of the 2 processes can be detected in patient serum or urine. These surrogates may be useful for predicting the outcome or response to therapy.[18] Serum markers of bone formation include bone specific alkaline phosphatase and osteocalcin, while indicators of bone resorption that are detectable in urine include pyridinoline, deoxypyridinoline and N-telopeptide of type 1 collagen.[19] Changes in the levels of these markers occur in men with prostate cancer following ADT.[20]

Briefly, the detection of decreases in BMD can be used to identify patients with prostate cancer on ADT who are at increased risk for fracture. Early identification can facilitate prompt therapeutic interventions, such as prevention, lifestyle changes and/or medical therapy, as discussed.

IMPACT OF ADT ON BONE HEALTH

Numerous prospective studies have demonstrated that substantial bone loss occurs at multiple sites in men with prostate cancer treated with ADT (table 1). At 1 year BMD decreases from the baseline ranges of 1.8% to 3.9% at the hip and 5.3% to 10% at the radius. Other sites may experience even greater losses. For example, after 18 months of ADT the decrease in BMD was 7.1% in the lumbar spine and 6.6% in the femoral neck.[14] BMD has also been compared in men with prostate cancer treated with a GnRH agonist vs men in a normal age and sex matched control group. Although men in the control group had no decrease in BMD, men on ADT experienced BMD decreases at several skeletal sites, which attained statistical significance for the total hip and ultradistal radius at 1 year.[13]

This bone loss associated with ADT results in an exponential increase in the fracture risk. Decreases in BMD of 10% to 15% approximately double the risk of fracture.[21] Shahinian et al found that this was also true in men diagnosed with prostate cancer after they determined the incidence of fracture in more than 50,000 patients from 1992 through 1997.[9] Of patients who survived 5 or more years after diagnosis fractures occurred in 19.4% and 12.6% of those who did and did not receive ADT, respectively ($p < 0.001$). The fracture risk increased with the number of doses of GnRH agonist received. In another retrospective study fracture rates were evaluated in 288 patients with prostate cancer who received ADT compared with 300 patients in the control group who did not. The incidence of peripheral and vertebral fractures was 4-fold higher with ADT, representing a statistically significant difference.[22]

TABLE 1. *ADT associated BMD decreases*

References	No. Pts	Treatment	BMD Site (% decrease)	
Eriksson et al[15]	11	Orchiectomy	Hip (−9.6)	Radius (−4.5)
Maillefert et al[14]	12	GnRH agonist	Hip (−3.9)	Lt spine (−4.6)
Daniell et al[48]	26	Orchiectomy or GnRH agonist	Hip (−2.4)	
Berrut et al[3]	35	GnRH agonist	Hip (−0.6)	Lt spine (−2.3)
Higano et al[49]	36	Luteinizing hormone-releasing hormone agonist + antiandrogen	Hip (−2.7)	Lt spine (−4.7)
Mittan et al[13]	28	GnRH agonist	Hip (−3.3)	Radius (−5.3)