Nursing Implications of Androgen Deprivation Therapy-Associated Bone Loss

Kerri K. Weingard

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.

Men with prostate cancer who have a rising prostate-specific antigen (PSA) level after definitive therapy with or without evidence of metastatic disease are commonly treated with androgen deprivation therapy (ADT). This is accomplished by chemical castration, generally using a gonadotropin-releasing hormone (GnRH) agonist and/or surgical removal of the testes (bilateral orchietomy), resulting in a chronic deficiency of testosterone (Ghloz, Conde, & Rutledge, 2002; Miyamoto, Messing, & Chang, 2004). The application of ADT has broadened to include not only men with metastatic disease, but also those with locally advanced disease and nonmetastatic disease following biochemical relapse. The combination of pathologic involvement and treatment-related impact on bone health in men with prostate cancer makes osteoporosis a major concern in this population.

It is well established that the use of ADT is associated with bone loss and fractures (Daniell, 1997; Maillefert et al., 1999) resulting in increased morbidity and mortality for many patients (Oefelein, Ricchiuti, Conrad, & Resnick, 2002). This is in addition to the normal age-associated loss of bone mineral density (BMD) that characterizes osteoporosis (Parsons, 2005). Moreover, many men with prostate cancer have significant bone loss prior to initiating ADT, further increasing their risk. Men with locally advanced or recurrent disease and no evidence of bone metastases have decreased trabecular BMD of the lumbar spine that was lower than expected for this age group (Smith, McGovern, Fallon et al., 2001). In light of the adverse effects on bone health, the potential for other serious health-related risks, and the increased demands these impose on nurses, nurses must focus attention on the importance of bone health and preventing and treating ADT-associated bone loss.

Urology nurses have a unique opportunity to foster bone health and prevent bone loss for their patients on ADT (Leslie, 2000; Maxwell & Viale, 2005). As in other therapeutic areas, nurses generally are perceived to have more time available for patient counseling than physicians. Patients, therefore, are likely to be more open with nurses to discuss any problems they may have, such as adverse effects of ADT and its treatment or psychological/emotional issues (Wright, 1998).

Nurses can also aid in early identification of high-risk patients (by conducting a thorough medical history), explain results of BMD testing to patients and families, and help promote preventive measures to reduce the risk of bone loss. Additionally, nurses can teach patients how to implement lifestyle changes such as proper diet, vitamin supplementation, and exercise that can maintain bone health. For those patients with prostate cancer who are receiving bisphosphonate therapy for ADT-associated bone loss, the importance of compliance and its impact on outcome also should be emphasized.

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ADT-Associated Bone Loss

Androgen deprivation therapy, in the form of treatment with GnRH agonists or bilateral orchiectomy, results in decreased levels of testosterone and estrogen, hormones that modulate bone metabolism. In men with prostate cancer, this hypogonadism increases bone resorption, causing greater bone turnover (see Figure 1). The result is rapid loss of BMD within 6 to 12 months of initiating ADT (Greenspan, Coates, & Sereika, 2005). The rate of ADT-associated bone loss can be significant (Daniell et al., 2000) and substantially greater than that seen in normal age-matched controls not treated with ADT (Preston et al., 2002). One study reported BMD loss averaged 4% during years 1 and 2 after chemical castration and 2% per year after year 4, much greater than the loss of 0.5% per year in healthy men of similar age (Daniell et al., 2000).

The decrease in BMD may be influenced by obesity, age, and exercise habits (Daniell et al., 2000) and strongly correlates with an exponential increase in fracture risk (see Figure 2) (Daniell, 1997; Melton, Alothman et al., 2003). In one study of 429 men who had undergone orchiectomy for prostate cancer, an estimated 40% experienced new fractures within 15 years compared with 19% for a normal population (Melton, Alothman et al., 2003). Similar results were noted when such men were compared with prostate cancer patients who did not undergo orchiectomy (Daniell, 1997). This finding is clinically significant because skeletal fractures in these patients decrease median survival by 39 months and increase risk of death nearly 7-fold (Oefelein et al., 2002). Thus the use of ADT in patients with prostate cancer increases the rate of bone loss and fractures, leading to greater morbidity and mortality as well as higher health care costs (Melton, Gabriel et al., 2003; Orsini, Rousculp, Long, & Wang, 2005).

Assessment of ADT-Associated Bone Loss In the Clinical Setting

Risk factors. A variety of factors can increase the risk of ADT-associated bone loss and subsequent bone fracture (see Table 1) (National Osteoporosis Foundation, 2003; NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy, 2001; Orwoll & Klein, 1995). Poor lifestyle habits such as smoking, excessive alcohol use, low calcium intake, and inadequate weight-bearing exercise can play a major role. Additional risk factors include prolonged exposure to steroids, treatment with selected anticancer agents, and use of other medications (such as anticonvulsants and aluminum-containing antacids) as well as medical conditions associated with low testosterone levels. Chronic diseases of the lungs, kidneys, and gastrointestinal (GI) tract that alter hormone levels may also predispose patients to increased
Bone loss. The probability of fractures is greater in patients with advanced age, Caucasian ethnicity, and a family history of fragility fractures.

**Screening for bone health.** The gold standard for measuring BMD in patients at risk of bone loss and fracture relies on a technique known as central dual-energy X-ray absorptiometry (DXA) (National Osteoporosis Foundation, 2003). DXA can rapidly measure BMD at multiple skeletal sites, including the spine, proximal femur, and total body. This technique, which employs a low radiation dose, can be performed in the office setting. Peripheral BMD can be assessed using peripheral DXA and single-energy x-ray absorptiometry (SXA). Other approaches for measuring BMD include quantitative ultrasound and quantitative computed tomography (Boehm & Link, 2004).

Results of BMD measurements are reported as a T-score or Z-score. The T-score reflects the number of standard deviations (SD) by which a patient’s bone mass differs from the mean BMD of a healthy young individual (Higano, 2003). The T-score is a good indicator of the risk of fracture, with larger negative changes indicating progressive bone loss and a concomitant increase in fracture risk (Marshall, Johnell, & Wedel, 1996; National Osteoporosis Foundation, 2003). A T-score of -1, representing a loss of 10% to 20% bone mass compared with healthy young adults, indicates bone density within normal limits (see Table 2). Patients with a T-score 1 SD below the mean (for example, -1 to -2.5) are considered to have osteopenia, or low bone mass, while a score of < -2.5 indicates osteoporosis. The presence of a fracture and a T-score < -2.5 defines severe osteoporosis. A related parameter, the Z-score, compares BMD to expected age and sex-matched controls and thus accounts for normal age-related bone loss (National Osteoporosis Foundation, 2003).

In light of the impact of low testosterone levels on bone loss and data clearly demonstrating ADT effects on bone health, men who receive ADT should ideally be screened for bone loss at evaluation and at yearly intervals (Diamond, Higano, Smith, Guise, & Singer, 2004; Ross & Small, 2002). Unfortunately, Medicare will only reimburse for BMD evaluation every 2 years.

Biochemical markers of bone formation and resorption may also have clinical utility in determining the risk of rapid bone loss and fracture (Miller et al., 1999). Normal bone is in a state of equilibrium in which the rate of bone formation equals the rate of bone resorption, a process modulated by estrogens and androgens. Measurement of circulating levels of markers of bone turnover can indicate bone loss and may guide therapy. Surrogates for bone formation include bone alkaline phosphatase and osteocalcin, while bone resorption can be assessed through measurement of deoxypyridinoline, N-telopeptide of type I collagen (NTX), and pyridinoline. Using commercially available assays, these markers can be detected in the serum (for bone formation) or urine (bone resorption). At present, however, the measurement of bone markers has limited utility in the clinical evaluation of individual patients (NIH Consensus Development Panel, 2001) and is not used commonly in the urology setting.

### Managing ADT-Associated Bone Loss

A multidisciplinary approach is recommended for optimal management of ADT-associated bone loss. As discussed in the following sections, proper nutrition, exercise, and other lifestyle changes can all lead to increased BMD and improved bone strength (see Table 3). For patients with prostate cancer who have existing osteoporosis prior to initiating ADT or while receiving ADT, treatment with bisphosphonates can significantly increase BMD (Smith et al., 2003) and may decrease the incidence of fracture (Saad et al., 2002).
Nutritional intervention. Changes in diet and lifestyle can promote bone health and thus decrease the risk of bone loss and fractures. Dietary modification is a simple and effective means of raising levels of minerals and vitamins, such as calcium and vitamin D, to reduce bone loss, and to improve bone density and quality (Nieves, 2002; Srivastava & Deal, 2002). Calcium is essential for bone formation and maintenance of healthy bones. Daily calcium intake of approximately 1,200 mg can be achieved by consuming dairy products, green leafy vegetables, and nuts, or intake of bioavailable calcium supplements (taken in several small doses during the day). Sources of vitamin D include exposure to sunlight (10 to 15 minutes for 2 to 3 times/week), dietary supplementation (400 to 800 IU daily), and certain foods such as fortified milk, liver, and fatty fish and oils. Patients receiving bisphosphonates for treatment of ADT-associated bone loss (described later) are advised to take daily supplementation that includes calcium and vitamin D to maintain proper bone nutrition. Recent data suggest that elderly patients may require higher doses of vitamin D (700 to 800 IU/day) to reduce risk of fracture (Bischoff-Ferrari et al., 2005).

Drug therapy for ADT-associated bone loss. Bisphosphonates have been used effectively to treat bone loss caused by cancer therapy and ADT (see Table 4). By binding to the surface of bone undergoing remodeling, bisphosphonates inhibit bone degradation and resorption through several mechanisms. They also decrease the number of mature bone-degrading osteoclasts and their recruitment to bone. Osteoclasts can ingest bisphosphonates, which inhibits the activity of the osteoclasts and further blocks bone degradation (Fleisch, 2000).

Bisphosphonates can have multiple clinical benefits in patients with, or at risk for, bone loss. These compounds include oral formulations such as etidronate (Didronel®), ibandronate (Boniva®) and alendronate (Fosamax®), and intravenous (IV) bisphosphonates like pamidronate (Aredia®) and zoledronic acid (Zometa®). It should be noted that bisphosphonates

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<th>Table 3. Approaches to the Management of Androgen Deprivation Therapy-Associated Bone Loss</th>
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<td><strong>Exercise</strong></td>
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<td>- Limit alcohol intake</td>
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<th>Table 4. Bisphosphonates for Treating ADT-Associated Bone Loss</th>
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<td><strong>Mechanism of Action</strong></td>
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<td>- Inhibit osteoclasts, blocking bone degradation and resorption that occur with ADT</td>
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<td><strong>Bone Effects</strong></td>
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<tr>
<td>- Preservation of bone loss seen with ADT</td>
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<td>- Increase bone mineral density *</td>
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<td>- Reduction in fracture risk</td>
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<td>- Decrease in bone pain from metastases</td>
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<td>- Reduction in or prevention of skeletal-related events †*</td>
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<tr>
<td><strong>Important Side Effects</strong></td>
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<tr>
<td>- Oral: GI toxicity (esophagitis, dysphagia, esophageal or gastric ulcers)</td>
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<td>- IV: flu-like symptoms</td>
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<td>- Acute renal toxicity †</td>
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<td>- Osteonecrosis of the jaw (rare)</td>
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* With zoledronic acid only.
† Skeletal-related events include pathologic fracture, radiation or surgery to bone, spinal cord compression, and hypercalcemia of malignancy.
‡ With rapid IV administration of high-dose bisphosphonates.
are not chemotherapy and can be used in conjunction with other cancer therapies. Effects of certain bisphosphonates include halting bone loss caused by ADT or other cancer therapies, reducing occurrence of fractures, decreasing bone pain from metastases, and reducing or preventing skeletal-related events (SREs) such as pathologic fracture, radiation or surgery to bone, spinal cord compression, and hypercalcemia of malignancy (Brown, Neville-Webbe, & Coleman, 2004; Saad et al., 2004).

Several researchers have examined the efficacy of oral and IV bisphosphonates in men with advanced prostate cancer. Diamond, Campbell, Bryant, and Lynch (1998) used oral etidronate to treat cancer treatment-associated bone loss in men who had received combined androgen blockade for prostate cancer. Etiordonate decreased the rate of ADT-associated bone loss but did not significantly increase BMD. Similarly, IV pamidronate prevented bone loss in prostate cancer patients but did not have a substantial improvement on BMD (Smith, McGovern, Zietman et al., 2001). Saad and colleagues (2002) evaluated zoledronic acid for preventing bone metastases in men with hormone-refractory prostate cancer. This agent significantly decreased the rate (33.2% vs. 44.2%; \( p=0.021 \)) and delayed the onset (median 420 days vs. 321 days; \( p=0.011 \)) of SREs compared with placebo (see Figure 3). The overall proportion of patients experiencing fractures was reduced from 22.1% with placebo to 13.1% with zoledronic acid (\( p=0.015 \)). Patients treated in the zoledronic acid arm showed a 25% reduction in the proportion of patients with SREs. The number of patients having an SRE decreased from 44% in the placebo arm to 33% in the zoledronic arm. Zoledronic acid also prevented bone loss and increased BMD in men who received ADT for nonmetastatic prostate cancer (Smith et al., 2003). These results demonstrate that bisphosphonates can prevent ADT-associated bone loss in men with prostate cancer, but only zoledronic acid was effective in increasing BMD and in reducing SREs and fractures in patients with metastatic disease.

**Bisphosphonate toxicity:** Two forms of bisphosphonates exist, oral and IV, and each is associated with a specific spectrum of activity and side effect profile. Oral bisphosphonates, such as alendronate, risedronate, and ibandronate, are poorly absorbed in the GI tract (<5% of oral dose), and uptake can be further reduced by food and coffee (Baker, 2002). Consequently, high doses (several large capsules or tablets) must be administered, which can cause significant GI toxicity such as esophagitis, dysphagia, and esophageal or gastric ulcers. These adverse effects can also occur if oral bisphosphonates are not taken according to instructions. To improve absorption and minimize GI side effects, these drugs should be taken with a full glass of water on an empty stomach, and patients must remain upright for at least 30 to 60 minutes, depending on dosing schedule (Conte & Guarneri, 2004).

Bisphosphonates administered intravenously, such as pamidronate and zoledronate, are generally well tolerated. Flu-like symptoms (muscle and joint pain, low-grade fever, nausea) occur in approximately 20% of patients treated with IV formulations, primarily after only the first dose (Conte & Guarneri, 2004). Symptoms begin several hours to days after initiation of

**Figure 3.** Zoledronic Acid Reduces Skeletal-Related Events and Fractures in Men With Hormone-Refractory Prostate Cancer and Bone Metastases

![Graph showing skeletal-related events and fracture incidence](image-url)

**Source:** Saad et al., 2002.
therapy but generally resolve following treatment with acetaminophen or a short course of low-dose steroids.

Since bisphosphonate therapy is associated with hypocalcemia, serum levels of calcium, phosphate, and magnesium should be monitored regularly. Severe, transient bone, joint, and/or muscle pain have been reported in a limited number of patients treated with bisphosphonates (Conte & Guarneri, 2004).

Rare cases of osteonecrosis of the jaw (ONJ) have been reported in patients treated with nitrogen-containing bisphosphonates such as zoledronic acid and pamidronate. Among 1,203 Web-based survey respondents with myeloma or breast cancer who were treated with bisphosphonates for 3 years, ONJ was reported in 10% of patients who received zoledronic acid and in 4% of patients treated with pamidronate (Durie, Katz, & Crowley, 2005). In contrast, a retrospective review of 943 patients with metastatic breast cancer who received these bisphosphonates found a much lower incidence of 0.6% (Van Poznak et al., 2004).

Recently published guidelines concluded that an accurate determination of the incidence of ONJ in patients on bisphosphonates was not possible due to inconsistencies in the literature (Ruggiero et al., 2006). Risk factors include prior or concomitant chemotherapy, radiotherapy or steroid therapy, trauma, infection, and a history of or current dental problems (Marx, 2003; Ruggiero et al., 2006).

The incidence of ONJ appears to increase with time on bisphosphonate therapy, particularly for zoledronic acid (Durie et al., 2005). Affected patients often have underlying dental problems, such as a recent dental extraction or infection. An oral examination is recommended prior to initiating bisphosphonate therapy to identify any pre-disposing conditions, and patients should notify their dental professionals of their bisphosphonate therapy and delay dental procedures while on therapy. Urology nurses should discuss the risk of this adverse event with their patients prior to initiating therapy and reinforce the importance of proper oral hygiene for patients on bisphosphonates.

Rapid IV administration of high doses of bisphosphonates can be associated with acute renal toxicity. This adverse effect has been reported in patients treated with either non-nitrogen-containing bisphosphonates (for example, clodronate, etidronate) (Bounameaux, Schifferli, Montani, Jung, & Chatelain, 1983; O’Sullivan, Akbari, & Cadnapaphornchai, 1994) or nitrogen-based bisphosphonates (zoledronic acid, pamidronate, alendronate) (Janssen von Doorn, Neyns, Van der Neipen, & Verbeelen, 2001; Markowitz et al., 2003; Zazgornik, Grafinger, Biesenbach, Hubmann, & Fridik, 1997). A comparative study of IV bisphosphonates in patients with breast cancer reported similar incidences of grade 3 or 4 serum creatinine increases after 2 years of IV zoledronic acid, pamidronate, or ibandronate (Conte & Guarneri, 2004). Any increases in serum creatinine levels were generally not clinically significant and, overall, no significant differences have been noted between various bisphosphonates in this regard.

In light of the potential effects of bisphosphonates on renal function, however, serum creatinine should be monitored at baseline and before each infusion (Conte & Guarneri, 2004; Hillner et al., 2003). In patients with significant elevations in serum creatinine, dosing should be withheld until levels return to within 10% of baseline. Care should be taken to ensure that the appropriate drug dose and schedule are used.

Limited data are available on the safety of bisphosphonates in patients with pre-existing renal insufficiency. Multiple cycles of bisphosphonates and pre-existing renal insufficiency are risk factors for further renal deterioration and progression to renal failure and the need for dialysis. Patients with hypercalcemia of malignancy with deteriorating renal function should be carefully evaluated as to the potential risks and benefits of continuing bisphosphonate therapy. Factors that could exacerbate renal impairment, such as use of other nephrotoxic drugs and dehydration, must be identified and managed.

For patients with hypercalcemia and mild to moderate renal impairment (serum creatinine <400 mol/L or <4.5 mg/dL), dose adjustment of zoledronic acid is not indicated prior to initiating therapy (Novartis Pharmaceuticals, 2006).

Compliance. Consistent long-term compliance is essential to maintain the activity of oral bisphosphonates. Failure to fully adhere to the prescribed regimen can result in decreased efficacy and/or discontinuation due to the complexity of orally administered bisphosphonates or GI toxicity. A study of nearly 1,000 patients taking bisphosphonates for osteoporosis revealed that 20% of patients ended therapy within the first year because of adverse effects or not fully understanding the results of their bone density tests (Tosteson et al., 2003). Among breast cancer patients with bone metastases who received oral clodronate therapy, retention of part of the compliance was only 74% (Paterson et al., 1993). Other researchers suggest that approximately 35% of patients discontinued clodronate treatment due to noncompliance or early withdrawal related to drug toxicity (Kristensen et al., 1999; Robertson, Reed, & Ralston, 1995). Inconsistent adherence to oral bisphosphonates (<80% of prescribed dose) or early termination...
Table 5. Role of Nurses in the Prevention and Treatment of Androgen Deprivation Therapy-Associated Bone Loss in Patients With Prostate Cancer

1. Educate patients who are beginning ADT on the potential for bone loss and fracture risk.
2. Review risk factors and recommendations for bone density screening.
3. Ensure that patients understand results of their bone density test.
4. Reinforce the importance of maintaining healthy bones.
5. Recommend specific changes in diet that can improve bone health.
6. Instruct patients on how to use supplementation to achieve necessary levels of calcium and vitamin D that can prevent or delay ADT-associated bone loss.
7. Work with physician and patient to develop appropriate exercise program to strengthen muscles and bones, which should include weight-bearing and resistance exercises.
8. Counsel patients on other beneficial lifestyle changes, such as limiting smoking and alcohol intake.
9. Review potential side effects of bisphosphonates to facilitate reporting of toxicities and early interventions.
10. Reinforce importance of compliance with bisphosphonate therapy.

Conclusion

Patients with prostate cancer who receive ADT face significant health risks associated with this type of therapy. ADT usage can result in decreased BMD and increased probability of bone fractures. As disease progresses, SREs can occur, resulting in increased morbidity and mortality, greater health care costs, and decreased quality of life. It is therefore essential for patients initiating ADT to be evaluated for bone loss at diagnosis and at regular intervals during therapy, using validated methods such as DXA. Patients with significant bone loss or at increased risk can be managed using a number of approaches, including changes in diet, weight-bearing and resistance exercise, vitamin supplementation, and bisphosphonate therapy.

In prostate cancer patients who experience significant bone loss, pharmacologic intervention should be initiated. Bisphosphonates are effective at preventing ADT-associated bone loss and reducing fracture risk. While several can prevent bone loss, only zoledronic acid increases BMD and decreases skeletal events in the metastatic setting for patients with hormone-refractory prostate cancer. Intravenous bisphosphonates may be superior to their oral analogues due to improved bioavailability, lower GI toxicity, and increased efficacy. Further study could support a role for bisphosphonates in treating early-stage disease to preserve BMD and perhaps to prevent the occurrence of metastases.

There are several ways in which nurses can improve the care and outcome of patients with ADT-associated bone loss (see Table 5). Patients at risk for bone loss should be referred for appropriate diagnostic evaluation and treatment. Those who are already receiving ADT should be counseled as to the possible side effects of therapy to minimize their impact and ensure compliance. Education regarding the importance of regular exercise and other positive lifestyle changes, including decreasing alcohol and caffeine intake and ensuring vitamin supplementation and proper diet, can help prevent bone loss and reduce the risk of fracture. Nurses play a crucial role in identifying and addressing patients’ emotional and psychological needs related to bone loss such as fear, decreased mobility and independence, and effects on overall quality of life. The education nurses provide improves bone health, quality of life, and long-term outcomes for their patients with prostate cancer who are receiving ADT.

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