

Bone health in nonmetastatic prostate cancer: what's the big deal?

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ABSTRACT

Since 2000, the medical community has become increasingly aware of bone health in men with prostate cancer on androgen deprivation therapy (ADT)—mainly because of new therapies that have been shown to reduce bone loss and associated fractures in this patient population. The threat of bone complications has become even more concerning in the prostate-specific antigen era, because ADT is initiated earlier (with biochemical recurrence after local treatment) and maintained longer before the appearance of metastatic disease. The present review examines the relevance of bone health in nonmetastatic prostate cancer, with a discussion of the new treatment modalities available.

KEY WORDS

Prostate cancer, androgen deprivation therapy, bisphosphonates, skeletal-related events

1. INTRODUCTION

The place of bone protection in nonmetastatic prostate cancer (PCa) is still ill-defined. Yet patients in increasing numbers are receiving hormone deprivation therapy for biochemical recurrence after definitive local treatment, which puts them at increased risk for bone loss [1].

The concept of increased susceptibility to metastasis in patients with declining bone mineral density (BMD) has been put forth by some authorities and may justify early intervention to preserve bone in this patient population [2]. Furthermore, regardless of metastatic status, bone fractures from decreased BMD may be associated with decreased survival in PCa patients [3]. The clinical relevance of initiating bone protection early in the natural history of the disease is of sufficient importance to justify several randomized studies now underway whose results should be available soon.

Here, we sketch the rationale for bone preservation in patients with nonmetastatic PCa, with a special emphasis on the physiopathologic basis of bone loss, potential prevention strategies, and guidelines. We also discuss upcoming studies aimed at answering the question of whether bone preservation is beneficial in the nonmetastatic setting.

2. DISCUSSION

2.1 Lower BMD Correlates with Increased Risk of Fracture

It is now widely accepted that androgen deprivation therapy (ADT) accelerates the decline of BMD in men [4]. The danger of BMD loss is real and often translates into an increased risk of bone fracture in patients experiencing such loss. In a study that sampled 50,613 patients from the Surveillance, Epidemiology and End Results database, a higher percentage of patients receiving ADT than not receiving ADT had osteoporosis. Additionally, at 5 years, the risk of bone fracture in patients receiving ADT was almost double that in patients not undergoing hormone ablation [4].

It has been established that previous bone fractures predict for future ones, and even fractures that may be considered minor, such as vertebral compression, are clinically relevant [5]. What is perhaps more compelling is that fractures correlate with decreased survival. In a case–control study analyzing a sample of 97,142 Medicare claims, Lau *et al.* showed that patients with vertebral compression fractures had a mortality rate twice that of matched controls [6]. Furthermore, the mortality rate was greater for men than for women [6]. Another study, by Oefelein and colleagues [7], demonstrated that skeletal fractures were common in men with PCa and lowered mean survival by 39 months. The relative risk of death for affected patients in that study increased by a factor of almost 7.

2.2 Effect of ADT on Bone Metabolism in Men

Decreased BMD and higher rates of bone fracture have been documented not only in patients receiving ADT but also in those undergoing surgical castration [4,8,9].

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Surprisingly, the fractures are often not related to metastasis; instead, they are related mostly to osteopenia or osteoporosis, analogous to the process that takes place in postmenopausal women. This observation becomes even more concerning with the realization that the rate of osteopenia and osteoporosis in men on ADT is probably greater than what has been measured in comparable cohorts of postmenopausal women [10]. Compounding this situation is the fact that, even before being placed on ADT or having bone metastases, patients with a diagnosis of PCa exhibit reduced BMD as compared with age-matched subjects. Hypogonadism, lower vitamin D, lower calcium intake, and heredity may account for that observation. Notably, BMD loss generally does not occur when anti-androgens are used as monotherapy [11].

In the setting of patients with PCa on or off ADT, these facts provide a reasonable rationale for prophylactic measures similar to those being applied in postmenopausal women.

2.2.1 Vitamin D and Calcium

It is generally recommended that patients receiving ADT be systematically started on oral vitamin D and calcium. Yet the efficacy of this regimen in preventing BMD loss during ADT is not established [12]. These agents were insufficient to slow bone decay in the placebo arms of trials assessing pamidronate and zoledronic acid in the setting of cancer treatment–induced bone loss (CTIBL) [13,14]. Further, the absorption of oral calcium and vitamin D may be reduced in PCa patients. That being said, initiation of vitamin D and calcium remains a required, albeit suboptimal, first step in PCa patients receiving ADT.

2.2.2 Oral Bisphosphonates in Nonmetastatic PCa

Currently, the only oral bisphosphonate approved by the U.S. Food and Drug Administration for the treatment of non-cancer-associated osteoporosis in men is alendronate. When used in hypogonadal men, this oral agent fails to prevent non-vertebral fractures [15]. Its use in men with PCa on ADT may therefore be insufficient—not to mention the fact that alendronate has not been specifically approved for patients with CTIBL [15]. Furthermore, the toxicity of alendronate may be significant: a retrospective study of alendronate-treated women showed a 60% increase in outpatient visits or hospital admissions for acid-related upper gastrointestinal disorders in treated patients [16]. Other molecules, such as etidronate, have been specifically tested in men receiving ADT without showing significant efficacy for BMD preservation in that patient population [17].

Table I provides an overview of the oral bisphosphonates available for men on ADT.

2.2.3 Intravenous Bisphosphonates in Nonmetastatic PCa

Pamidronate and zoledronic acid are potent nitrogen-containing intravenous bisphosphonates that have

TABLE I Treatments for skeletal morbidity and loss of bone mineral density (BMD) in men on androgen deprivation therapy (ADT)

Agent (brcand)	*Type*	*Approved indications*	*Utility for*	
			BMD loss during ADT	*Bone metastases*
Calcium and vitamin D	Supplement (oral)	Osteoporosis (variable efficacy)	NA	NA
Estrogen-based therapy	Hormonal (oral)	Postmenopausal osteoporosis	BMD preserved (low tolerability)	NA
Calcitonin (Miacalcin[b])	Bone metabolism hormone	Postmenopausal osteoporosis	Bone resorption reduced, but not normalized	NA
Etidronate (Didronel[c])	Bisphosphonate (oral)	Paget disease only (used off-label for osteoporosis)	Limited efficacy in reducing bone loss	No significant efficacy
Alendronate (Fosamax[d])	Bisphosphonate (oral)	Prevention and treatment of osteoporosis in men and women	NA	NA
Pamidronate (Aredia[b])	Bisphosphonate (intravenous)	Treatment of bone lesions in patients with multiple myeloma or breast cancer	Significant reduction of bone loss compared with placebo	Limited efficacy in reducing skeletal morbidity
Zoledronic acid (Zometa[b])	Bisphosphonate (intravenous)	Treatment of bone metastases from any solid tumour[e] or primary bone lesions from multiple myeloma	Significant increase in BMD compared with placebo, and increased BMD over baseline levels	Significantly reduced skeletal morbidity and risk of skeletal complications; significant reductions in bone pain, even after 24 months of therapy[f]

[a] Adapted from Saad, 2002 [18].
[b] Novartis Pharmaceuticals, St. Louis, MO, U.S.A.
[c] Pfizer Canada, Kirkland, QC.
[d] Merck and Co., Whitehouse Station, NJ, U.S.A.
[e] Prostate cancer must have progressed during treatment with one hormonal therapy regime.
[f] Compared with placebo control.
NA = not assessed in a randomized controlled clinical trial.

demonstrated significant advantages relative to oral agents [12,19,20]. To prevent CTIBL in men on ADT, they may be administered every 3 months (as compared with the daily or weekly regimen for oral bisphosphonates).

In a randomized placebo-controlled study published by Smith *et al.,* intravenous pamidronate 60 mg administered on a 3-monthly schedule reduced BMD loss (as measured in the spine and hip) over 48 weeks of treatment in men receiving leuprolide [21]. In another randomized double-blind placebo-controlled study with a crossover design, Diamond *et al.* demonstrated that metabolic markers for bone degradation were decreased in serum for at least 6 months after a single infusion of pamidronate 90 mg in men on ADT (as compared with a placebo control group) [22]. However, despite preventing CTIBL in men receiving ADT for PCa, intravenous pamidronate did not significantly increase BMD measurements above baseline values [23].

To assess protection against CTIBL, zoledronic acid (4 mg by infusion every 3 months) was tested in a 12-month randomized double-blind placebo-controlled trial in men with nonmetastatic PCa receiving ADT (n = 106). In contrast to other bisphosphonates, zoledronic acid not only prevented CTIBL, it also increased BMD compared with baseline at all measured sites [13]. The BMD improvements were particularly marked in the lumbar spine ($p < 0.001$). During that study, zoledronic acid showed a favourable toxicity profile, with no detectable adverse effects on renal function at any time. Probably because of the short follow-up, no measurable improvement in fracture rate could be detected in the treatment arm.

Current trials are aiming to answer the question of whether bisphosphonate therapy in nonmetastatic PCa patients may delay the appearance of metastases. If that hypothesis is correct, the significant amount of time between biochemical failure and appearance of metastases in the natural history of PCa will require the timing of bisphosphonate therapy to be defined with respect to optimization of cost-effectiveness.

Zoledronic acid is the first bisphosphonate to show a protective effect against skeletal-related events in patients with metastatic castration-resistant PCa. Zoledronic acid was shown to have a potency approximately 850 times that of pamidronate [24]. Pamidronate was tested in a randomized placebo-controlled study in 643 patients with metastatic PCa having progressed under ADT, and skeletal complications were observed to be reduced by 22% [25]. Zoledronic acid (4 mg monthly) reduced by 48% the mean annual incidence of skeletal-related complications (0.77 events/year vs. 1.47 events/year for placebo, p = 0.005) and prolonged the median time to first skeletal-related event by more than 5 months (488 days vs. 321 days for placebo, p = 0.009). The ongoing risk of skeletal complications was also reduced by 36% in both the 15- and 24-month data sets [14,25], which may imply that the benefits of therapy were sustained during the 24-month span of the study. Throughout the study, zoledronic acid 4 mg, as compared with placebo, consistently reduced bone pain, with significant differences at the 3-, 9-, 21-, and 24-month time points (each $p \leq 0.05$) [25]. Such outcomes compare favourably with studies in metastatic breast cancer patients receiving intravenous bisphosphonates [13].

Besides measurable outcomes related to therapy, bisphosphonates also provide an emotional rampart for patients that otherwise have few therapeutic options, thus giving them and their treating physicians a sense of empowerment that may translate into an improved quality of life [26–28].

One concern that has received increased attention in the bisphosphonate literature is osteonecrosis of the jaw (ONJ), which has been reported as a complication mainly of intravenous therapy [29]. This disorder presents in the maxillofacial region as exposed bone that does not show signs of improvement after 8 weeks of therapy. Despite its relative gravity, ONJ is probably a very rare adverse event (1/10,000 to <1/100,000 patient–treatment years) when bisphosphonates are used at therapeutic or prophylactic doses for osteoporosis. In more recent studies using bone-preserving agents with different mechanisms of action, ONJ has been observed at least as frequently as it has been with bisphosphonate therapy [30]. That finding implies that the disorder is probably related to osteoclast inhibition and does not represent a class effect of bisphosphonates *per se.* The specific cause of ONJ is not yet well defined. Risk factors such as pre-existing dental pathology, maxillofacial surgery, and the use of dental prostheses have been identified. Prevention aims at avoiding those risk factors and having regular dental checkups during therapy [31–33].

2.3 The Role and Relevance of Receptor Activator of Nuclear Factor κB and Its Ligand in Bone Metabolism

Bone mass is not static; it is the result of a dynamic equilibrium between osteoblasts (the cells that create bone matrix) and osteoclasts (the cells that degrade the matrix). Osteoblasts secrete receptor activator of nuclear factor κB ligand (RANKL), which binds its receptor (RANK) on osteoclasts, thus triggering maturation, activation, and prolonged survival of the latter cells. By its effect on osteoclasts, RANKL therefore promotes bone resorption [34]. To regulate the activity of RANKL, the endogenous decoy receptor osteoprotegerin binds RANKL and prevents its interaction with RANK, thus cutting short activation of the osteoclasts.

2.3.1 Denosumab

Denosumab is a fully human monoclonal antibody that specifically targets RANKL. Administered by subcutaneous injection twice annually, it prevents bone loss [35]. Denosumab has been shown to have activity in postmenopausal osteoporotic women. In this patient population, denosumab lowered the

incidence of bone fractures [36,37]. It also protected against BMD loss in osteopenic postmenopausal women taking adjuvant aromatase inhibitors for breast cancer [38].

In a phase III randomized placebo-controlled clinical trial assessing subcutaneous denosumab (60 mg every 6 months) in 1468 men with non-metastatic PCa receiving ADT, the drug significantly improved BMD in the lumbar spine (primary endpoint) by 6.7% ($p < 0.001$), total hip by 4.8% ($p < 0.001$), femoral neck by 3.9% ($p < 0.001$), and distal radius by 5.5% ($p < 0.001$) at 24 months. By the end of the trial, the risk of new vertebral fractures was significantly reduced by 62% ($p = 0.006$). Patients recruited into this study had a more favourable BMD than is usually observed in an average PCa population on ADT. It is therefore reasonable to assume that in the latter scenario, risk reduction may be more substantial. It is noteworthy that denosumab, used prophylactically in a twice-yearly regimen, had a favourable toxicity profile [39].

2.4 Guidelines on Surveillance of Bone Density in Men on ADT

An authoritative international panel of experts has put forward basic guidelines for screening and investigating patients receiving ADT [40]. As a first step, risk stratification according to readily obtainable clinical data such as age, smoking history, and body weight should be applied (see Table II). After this categorization, patients will be assigned to one of two risk groups: low or high risk. Then, dual-energy X-ray absorptiometry or a quantitative computed tomography scan is obtained to help assess BMD. Using these basic clinical data, follow-up proceeds according to the flow chart depicted in Figure 1.

TABLE II Risk stratification for bone loss[a]

Risk level	*Characteristics*
Low	No high-risk characteristics
High	Presence of at least 1 of • Androgen deprivation therapy for more than 6 months • Previous fracture or fractures • Family history of osteoporosis • Low body weight • Smoking • Excessive alcohol consumption • Corticosteroid use • Medical comorbidities • Low vitamin D levels

[a] Adapted from Saad *et al.,* 2008 [41].

An unanswered question involves the timing of therapy with respect to initiation and duration. Most authorities agree that starting early is probably the optimal strategy.

2.5 General Recommendations on Preventive Measures for BMD Loss in Men Taking ADT

As first-line prophylaxis, basic recommendations include smoking cessation and reduction of alcohol intake. Increasing physical activity, particularly through a regular training program and resistance exercise, should be encouraged [40,43–45].

Supplementation with vitamin D (400 IU daily at a minimum) and calcium (500 mg daily at a minimum) represents an interesting first-line prophylactic measure in patients on ADT. Unfortunately, these agents are not potent enough to preserve BMD during ADT [12]. However, their use remains a required minimum in this patient population.

Finally, available options for preventing bone loss and fractures in patients receiving ADT now include denosumab as well as bisphosphonates, which should be considered at least in patients categorized as high risk or having low BMD [39].

3. SUMMARY

Bone health should be of concern for every physician caring for patients with nonmetastatic PCa on ADT. The consequences of bone-related events on quality of life and overall survival are of sufficient magnitude to justify early prophylaxis against bone loss. Results of ongoing trials using bisphosphonates or denosumab in the nonmetastatic setting are eagerly anticipated and will help shed light on the efficacy of these agents in preventing or delaying the appearance of bone metastases.

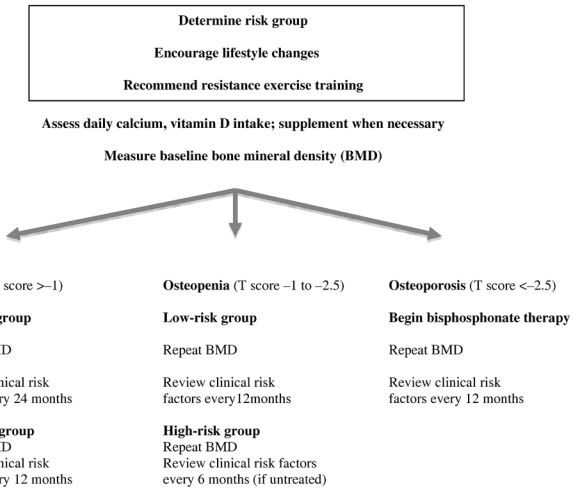


FIGURE 1 Flow chart for bone follow-up in patients on androgen deprivation therapy (adapted from Higano 2004 [42]).

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5. CONFLICT OF INTEREST DISCLOSURES

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