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Bone health management in prostate cancer patients receiving androgen deprivation therapy

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Abstract

Purpose: Patients receiving androgen deprivation therapy undergo a rapid decline in bone mineral density during the first 6 to 12 months of initiating therapy. The World Health Organization has developed and implemented the Fracture Risk Assessment Tool (FRAX) to predict the ten year risk of a major fracture & hip fracture. Additionally, the National Comprehensive Cancer Network and the National Osteoporosis Foundation have developed osteoporosis guidelines. This study aims to characterize the fracture risk (based on the FRAX tool) and the current management of bone health based on national guidelines compliance.

Methods: A retrospective chart review of patients receiving a LHRH agonist at our institution was conducted. Data collection commenced upon Institutional Review Board approval and included demographics, past medical history, medication regimen, history of androgen deprivation therapy, bone health and its management. The ten year fracture risk calculated with the collected information using the FRAX tool.

Results: A total of 174 subjects included with a mean age of 65.5 years, 71.8% had stage II prostate cancer, 97.7% received the LHRH agonist leuprolide for a mean of 13.8 ± 18.1 months. In addition to ADT, 57% of patients had ≥ 2 risk factors for developing osteoporosis. The risk of sustaining a major facture increased from 4% to 5.6% after the initiation of ADT ($P = <0.001$). The risk for sustaining a hip fracture rose from 1.3% to 2.2% ($P = <0.001$). National guideline compliance was found to be 9%, 5% and 3% respectively for obtaining Dual Energy X-ray Absorptiometry (DEXA) scans, calcium supplementation, and vitamin D supplementation.

Conclusion: In addition to predisposing risk factors for osteoporosis, ADT significantly increases the fracture risk in the prostate cancer population. There is room for improvement in the management of bone health as some intervention could have been made in over 90% of patients evaluated.

Keywords

Androgen-deprivation therapy, osteoporosis, prostate cancer

Background

Prostate cancer is the most common malignancy in males and the second leading cause of cancer-related mortality.[1] It is estimated that one in six men will develop prostate cancer in their lifetime.[2] However, the relative survival rates for prostate cancer are high: 100% at 5 years, 91% at 10 years, and 76% at 15 years.[2] Thus, minimizing the morbidity and mortality associated with the management of prostate cancer is at the forefront of caring for this population.

Management of prostate cancer is based on risk stratification and involves a variety of treatment strategies (Table 1). The proliferation of prostate cancer cells is dependent on the binding of dihydrotestosterone, a derivative of testosterone with a higher binding affinity, to the androgen receptor. Androgen-deprivation therapy (ADT) (given as a depot luteinizing hormone-releasing agonist with or without an antiandrogen) is the recommended treatment for men with locally advanced prostate cancer, biochemical relapse after resection or radiation, and metastatic prostate cancer.[3] ADT can be achieved surgically *via* bilateral

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Table 1. Prostate cancer risk stratification

Risk	Characteristics[a]	Treatment modalities
Low	T1–T2a	Active surveillance
	Gleason ≤ 6	Radical prostatectom
	PSA ≤ 10 ng/mL	External beam radiation
Intermediate	T2b–T2c	ADT 4–6 months
	Gleason 7	
	PSA 10–20 ng/mL	
High	T3–T4	Radical prostatectomy
	Gleason 8 to 10	External beam radiation
	PSA $>$ 20 ng/mL	ADT 2–3 years
		Continuous ADT

[a]Patient only needs to meet one of the criteria listed under 'Characteristics' to fall into risk category.

Table 2. Pharmacologic agents utilized to achieve ADT

Non-steroidal antiandrogens
Flutamide
Bicalutamide
Nilutamide
Steroidal antiandrogens
Megestrol
LHRH agonist
Leuprolide
Goserelin
Triptorelin
LHRH antagonist
Degarelix
Other
Ketoconazole

Table 3. National guideline recommendations[a]

Patient counseling
Smoking cessation
Limiting alcohol consumption
Weight-bearing exercise
BMD testing
Men 50 to 69 based on risk factors
All men $\geq$70 years old
Calcium and vitamin D supplementations
Men $\geq$ 50 years calcium $\geq$1200 mg per day
Men $\geq$ 50 years vitamin D 800–1000 IU per day
Bisphosphate therapy
FRAX risk $\geq$3% for hip fracture
FRAX risk $\geq$20% for major fracture
Osteopenia/osteoporosis on BMD

[a]Based on guidelines created by the NOF and the NCCN.

orchiectomy or pharmacologically (Table 2), most commonly utilizing luteinizing hormone-releasing hormone (LHRH) agonists. Adverse effects associated with ADT include: hot flashes, sexual dysfunction, hypogonadism, and osteoporosis.

Patients receiving ADT undergo a rapid decline in bone mineral density (BMD) during the first 6 to 12 months of initiating therapy. Osteoporosis is often under-diagnosed and under-prevented in men despite an estimated prevalence of 2 million and another 12 million men are at risk.[4,5] The major acquired causes of osteoporosis in men include: alcoholism, hypogonadism, and glucocorticoid therapy, of which the latter two are often found concomitantly in patients with prostate cancer. The use of ADT to manage prostate cancer indirectly and directly increases the fracture risk in this population. Indirectly, fracture risk is increased due to decreased muscle mass and increasing fall risk as a result of iatrogenic hypogonadism. The mechanism by which testosterone affects bone density is not completely understood. Androgens mediate osteoblast proliferation and differentiation, and increase bone matrix production and osteocalcin secretion presumably *via* the androgen receptor on osteoblasts.[6] Thus, ADT is believed to directly increase bone turnover and decrease BMD. Several prospective studies have established that BMD is significantly decreased in men receiving ADT in comparison to control groups. Interestingly, BMD loss in this population exceeded that seen in early menopause.[7] Fracture rates in men with prostate cancer who received ADT were described as a near-doubling of spinal fracture risk and a five-fold increase in hip fracture risk compared to matched controls.[8,9]

The World Health Organization (WHO) has developed and implemented the Fracture Risk Assessment Tool (FRAX) to predict the 10-year risk of a major fracture (defined as a fracture in the clinical spine, shoulder, or forearm) and hip fracture.[10] The FRAX tool accounts for the patient's age, gender, body mass index (BMI), history of previous fracture in the patient or their parents, smoking status, alcohol consumption, and the presence of rheumatoid arthritis or other secondary risk for osteoporosis and BMD. Additionally, the WHO, National Osteoporosis Foundation (NOF), and the National Comprehensive Cancer Network (NCCN) created guidelines (Table 3) to prevent and manage osteoporosis.[5,10,11] This study aims to characterize the fracture risk (based on the FRAX tool) and the current management of bone health based on compliance to national osteoporosis guidelines.

Methods

A retrospective chart review of patients receiving a LHRH agonist at our institution between 1 January 2007 and 1 January 2009 was identified *via* a pharmacy database. Patients were included if they were between 18 and 89 years, received at least one dose of a LHRH

Table 4. Demographics

		Average ± SD	Range
Age (years)		65.5 ± 9.7	47–88
		N	%
Race	African American	105	60.3
	Caucasian	67	38.5
	Hispanic	2	1.1
Smoking	Current	39	22.4
	Former	50	28.7
Alcohol	≥3 drinks/day	6	3.4
	<3 drinks/day	168	96.6
Stage	Stage II	125	71.8
	Stage III	29	16.7
	Stage IV	20	11.5
Agent	Leuprolide	170	97.7
	Triptorelin	4	2.3

agonist between the above-mentioned dates, and had a diagnosis of prostate cancer. Patients with metastatic bone lesions or incomplete records were excluded. Electronic medical and paper records for these patients were reviewed retrospectively from the time care was initiated until either metastatic lesions were identified in the bones or 1 August 2009 (whichever occurred first). Data collection commenced upon Institutional Review Board approval and included demographics, past medical history, medication regimen, history of ADT, and bone health and its management. Collected information on bone health included: fracture history, BMD screening data, assessment of secondary risk factors for osteoporosis, and bone health management. The 10-year fracture risk was calculated with the collected information using the FRAX tool. Study endpoints included characterizing the fracture risk in the prostate cancer population receiving ADT utilizing the FRAX tool and characterizing the current management of bone health based on osteoporosis guideline compliance. Duration of ADT was calculated based on the total exposure for patients receiving continuous hormone therapy and duration of the most recent cycle of ADT in patients being treated intermittently. Descriptive statistics were used for demographic data analysis and to characterize the current management of bone health. Paired *t*-test was used to compare 10-year fracture pre- and post-ADT (where $p < 0.05$ identifies a significant value).

Results

A total of 462 charts were reviewed, of which 174 subjects were included in the study with a mean age of 65.5 years. The remaining patients were excluded for the following reasons: presence of bone metastasis ($n = 213$), age >89 ($n = 43$), and incomplete records ($n = 32$). The majority (71.8%) of patients had stage II prostate cancer at the time of initial diagnosis and received a LHRH agonist for a mean of 13.8 ± 18.1 months. The group with stage II disease at diagnosis comprised patients receiving ADT intermittently for biochemical relapse (57.9%), neoadjuvantly to radiation or surgery (33.4%), and continuously for cancer progression (8.7%). Demographic data are summarized in Table 4. Fifty-four percent of patients received ADT for less than 6 months, while 20% and 26% of the patients received 7 to 12 months and >12 months of ADT, respectively.

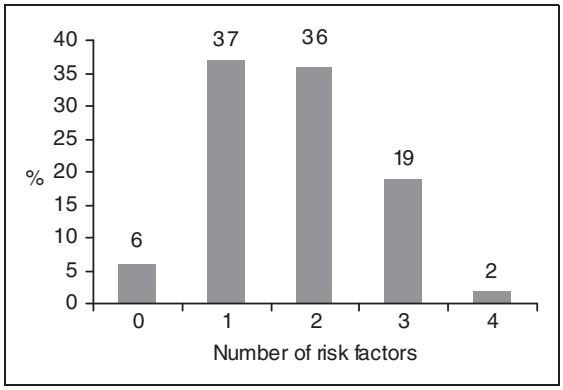

Figure 1. Risk factors for osteoporosis.

In addition to ADT, 57% of the patients had ≥2 additional risk factors for developing osteoporosis (Figure 1). The risks factors assessed were age over 70, Caucasian ancestry, BMI <25, smoking/alcohol intake, steroid exposure, and secondary risk factors for osteoporosis development (excluding ADT). Utilizing the FRAX tool, the 10-year estimated fracture risk was calculated. The risk for developing a major facture, defined as fracture of the clinical spine, shoulder, or forearm, increased from 4% prior to ADT to 5.6% after the initiation of ADT ($p \leq 0.001$). Similarly, the risk for sustaining a hip fracture rose from 1.3% to 2.2% ($p \leq 0.001$).

General counseling regarding adverse effects associated with ADT was documented in 15% and another 16% received specific counseling regarding the effects of ADT on bones. Bone health assessment was not documented in 69% of patients. Compliance to national osteoporosis guideline recommendations was found to be 9%, 5%, and 3% for obtaining dual energy X-ray absorptiometry (DEXA) scans, calcium supplementation, and vitamin D supplementation (Figure 2). Bisphosphonate therapy was indicated in 10% of the patients, of which 40% received one. Overall compliance (defined as obtaining a DEXA scan,

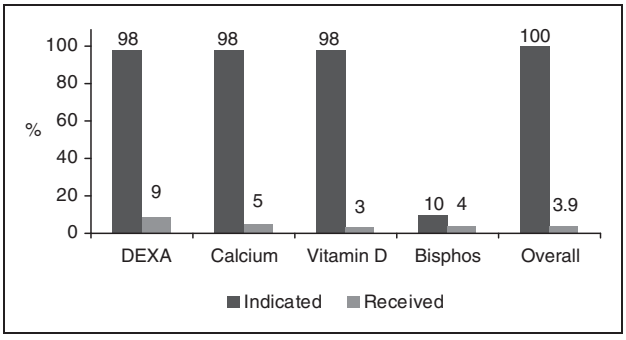

Figure 2. Compliance to national guideline measures.

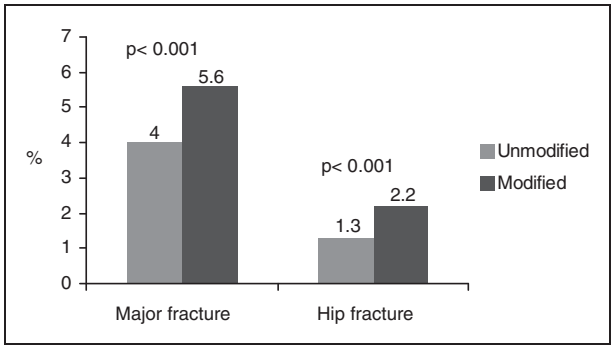

Figure 3. FRAX 10-year estimated fracture risk.

supplementing calcium, vitamin D, and administration of a bisphosphonate if indicated) was 3.9%.

Nine percent of patients ($n = 15$) were documented to have undergone a DEXA scan and results were available for nine patients. The average age of patients was 77.2 ± 4.6 years, 50% were Caucasian, and the average BMI was 27.2. Patients receiving a DEXA scan were on ADT for an average of 31.5 months. The FRAX score in this population accounting for ADT for sustaining a major fracture was 6.1% and 2.7% for hip fracture (Figure 3). Sixty-six percent of patients had a BMD in the osteopenic or osteoporotic range. Calcium and vitamin D supplementations were indicated in all these patients and supplemented in 22% of them. Bisphosphate therapy was indicated in six patients and initiated in 3.

Discussion

Fractures lead to back pain, decreased functional capacity, increased risk of future fractures, higher health care costs, and increased incidence of institutionalization and hospitalizations.[12,13] Additionally, fractures in men are associated with a decreased quality of life and increased mortality.[14] The overall healthcare costs associated with osteoporosis has been estimated to approach $17 billion annually.[13]

Metastatic prostate cancer bone lesions lead to bone disruption and pathological fractures, which are an important cause of morbidity. Initiation of adjunctive bisphosphonate in this subpopulation is a standard of care to prevent skeletal-related events.[15] Our study focused on osteoporotic risk rather than on pathological fractures as a consequence of the treatment of prostate cancer. In an effort to decrease confounders, patients with metastatic bone lesions were excluded. The demographics of the population evaluated in this study is similar to those of other studies evaluating osteoporosis in men receiving ADT.[16–19]

Many patients presenting with prostate cancer have pre-existing risk factors for sustaining a fracture prior to the initiation of ADT. In fact, over 70% of all prostate cancer cases occur in men >65 years of age with a median age of 68 years.[20] Pre-existing osteopenia/osteoporosis, subclinical vitamin D deficiency, and a plethora of comorbidities are also found in this population.[21] Unmodifiable risk factors identified in this study population included median age and Caucasian ancestry. Other identified risk factors include previous or current smoking status, BMI $< 25\,kg/m^2$, and secondary risk factors (i.e., osteogenesis imperfecta, diabetes mellitus type 1, drugs (excluding ADT)). Fifty-seven percent of patients had ≥ 2 assessable risk factors. However, the true number of risk factors is most likely higher, given the retrospective nature of this study and the lack of documentation regarding secondary risk factors.

BMD is considered the gold standard for diagnosing and assessing management of osteoporosis.[22] The duration of ADT directly correlates to the magnitude of decrease in BMD and subsequently to increased fracture risk. An analysis of over 50,000 men from the Surveillance, Epidemiology and End Results (SEER) program and medicare databases compared the risk of fracture in men with a diagnosis of prostate cancer who were treated with ADT versus those not receiving ADT.[23] No differences between study arms were detected in the year prior to ADT initiation. However, the proportion of patients with osteoporosis (6.92% vs. 3.69%, $p < 0.001$), fracture (19.37 vs. 12.63, $p < 0.001$), and fracture resulting in hospitalization (5.19% vs. 2.37%, $p < 0.001$) was higher in the ADT arm 1–5 years after treatment compared to patients who did not receive ADT. The risk of fracture was also found to directly correlate with the number of doses of LHRH agonist received. Due to the retrospective nature of our study, only a snapshot of androgen exposure was assessed. At first glance, over half the patients received ADT for ≤6 months. However, over 50% of the population was receiving intermittent hormone therapy (IHT) and only the last cycle (defined as therapy resuming after a break of greater 3 months)

was used to calculate duration. Therefore, the total exposure to ADT is likely to be greater than the calculated value. This method of calculating duration was selected as many patients were on IHT for numerous years and previously managed at other facilities; hence records were not available. Although increased duration of ADT directly correlates to increasing risk, studies also indicate that the greatest rate in decline in BMD is actually within the first 6–12 months of ADT.[24] Additionally, recent studies support extended duration of ADT and the direct correlation between duration and significance of adverse effects is well documented.[25–27] Thus, the overwhelming majority of patients with prostate cancer are at risk for bone-related complications upon the initiation of ADT.

Calcium and vitamin D supplementations are known to improve BMD and ultimately decrease fracture incidence.[28,29] Supplementations of both calcium and vitamin D are recommended for the majority of patients receiving ADT. Caution is needed when supplementing calcium in patients with metastatic bone lesions, as these patients are at risk for developing hypercalcemia. Bisphosphate therapy is recommended in prostate cancer patients receiving ADT with a $\geq$20% risk of a major fracture or $\geq$3% risk of hip fracture based on FRAX score.[5,10,11] Although long-term data on the incidence of fracture in men with prostate cancer treated with bisphosphonate therapy are unavailable, short-term results support its use.[30] Our study indicates that calcium and vitamin D supplementations were indicated in the overwhelming majority of patients; however, they were rarely provided. Similarly, out study shows that there is room for improvement in bisphosphate supplementation.

A retrospective study conducted by Tanvetyanon evaluated 184 patients receiving ADT for $\geq$1 year to identify independent predictors of receiving at least one physician initiated intervention to prevent or treat osteoporosis.[21] Interventions evaluated included: BMD evaluation *via* DEXA scan, initiation of bisphosphonates, calcium, vitamin D, calcitonin, or estrogen. Similar to the results of our study, most patients had multiple risk factors for osteoporosis and the majority of patients did not receive any intervention. Thirty-three physicians made 58 interventions in 27 patients. Overall, 14.7% of patients (95% CI, 9.5 −20.0%) received at least one intervention. In our study, 12.6% of the patients received at least one intervention. Of the six patients that received a DEXA scan in the above study, five had osteoporosis and one had osteopenia. The only predictor of receiving a intervention was the presence of bone metastasis. Fifty-one percent of interventions were made by primary care physicians, 27.3% by non-oncology related specialists, and 21.2% by oncologists. Inability to assess primary care interventions is a limitation to our study as it was conducted at a independent cancer center without complete access to records of non-oncology related physicians. Thus, interventions made outside our institution may not have been documented.

The FRAX tool, validated assessment software created by the WHO, predicts the 10-year estimated fracture risk based on known clinical risk factors with or without BMD test results.[31] To the investigators' knowledge, our study is the first study characterizing the fracture risk in the prostate cancer population utilizing the FRAX tool. As hypothesized, including ADT as a secondary risk factor significantly increased the 10-year risk of both a major fracture and a hip fracture. Even with the addition of ADT to the risk calculation, the average 10-year risk of sustaining a major fracture was well below the 20% threshold necessitating bisphosphonate supplementation per guidelines. However, the median 10-year risk for sustaining a hip fracture with the addition of ADT was 2.7%, trending toward the 3% risk necessitating bisphosphonate therapy. One of the major limitations of the FRAX tool is the need to primarily input dichotomous data. The tool is unable to account for extent of exposure to glucocorticoid, alcohol, smoking, or ADT. Additionally, minimal information regarding family history of fractures was identified in the medical records; thus, the tool assumed that this risk was not present. Therefore, the estimated 10-year fracture risk maybe underestimated in our population.

Compliance to national guidelines was assessed in five areas: obtaining a DEXA scan, supplementation of calcium, supplementation of vitamin D, bisphosphonate therapy, and overall compliance (defined as meeting all four previously mentioned interventions in indicated patients). Baseline assessment by clinicians was identified as either general (mention of discussion of adverse effects (ADRs) associated with ADT) or specific (documentation of discussion of specifically bone-related risks, documentation of calcium/vitamin D addition, bisphosphonate therapy, or obtaining DEXA scan). Low compliance to guideline measures may be subsequent to the lack of risk perception. Osteoporosis is frequently considered a disease of small-framed Caucasian or Asian elderly women. Sixty-nine percent of patients had no documentation of discussion of adverse effects associated with ADT. Additionally, due to the primary concern of preventing further spread of malignancy, the management of ADRs, specifically bone-health complications which remain silent until fracture incidence, may not be at the forefront of priorities. The management of prostate cancer is truly multidisciplinary as patients are seen by one of or a combination of medical oncology, radiation oncology, and surgical oncology services, increasing the difficulty of managing complications. Due to the

retrospective nature of this study, the low compliance rates may also be due to a lack of documentation. One method to improve compliance is educating the clinicians about the fracture risk in this population and available preventative measures.

Similar to our study, Wilcox et al.[32] conducted a retrospective analysis of veterans with prostate cancer receiving ADT to characterize risk factors and management of bone health in this population. A total of 174 patients were included with a mean age of 76, and the mean duration of ADT was 21 months. Thirteen percent of men underwent a DEXA scan, 19% received calcium and vitamin D supplementations, and 11% of the patients received bisphosphonate therapy. Investigators concluded this population has pre-existing risk factors for osteoporosis and received inadequate evaluation and treatment for osteoporosis.

Of the patients receiving a DEXA scan within our institution, 2/3 had osteopenia or osteoporosis. When reviewing the characteristics of these patients, it was easily noted these patients were at high risk based on age and BMI alone. However, DEXA scans were not ordered at baseline but, rather, only after patients received ADT for a prolonged period of time. DEXA scans were ordered for confirmation of clinical assessment rather then for prevention or treatment. No subsequent follow-up scans were conducted to evaluate management strategies.

Conclusion

Traditionally considered a comorbidity in the elderly female population, this study has characterized the substantial bone-health related complications in the prostate cancer population receiving ADT. However, the true risk is likely much greater as discussed above. There is great room for improvement in compliance to national guidelines as some intervention could have been made in over 90% of patients evaluated. Educating the multidisciplinary teams caring for prostate cancer patients regarding the risk of bone-related complications is one modality of optimizing care. As pharmacist-driven initiatives, collaborative practice agreement, and medication therapy management become routine responsibilities of the profession, optimization of the prevention and management of osteoporosis in prostate cancer patients receiving ADT can and should be actively incorporated in to daily practice.

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