Managing Bone Loss in Men With Locally Advanced Prostate Cancer Receiving Androgen Deprivation Therapy

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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.

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

Androgen deprivation therapy with orchiectomy or LHRH agonists has been shown to substantially improve survival time in patients with PC who have locally advanced disease.[1] Despite its increasing use ADT is not an innocuous treatment. Appropriate monitoring and management of ADT induced AEs, such as metabolic changes, sexual dysfunction, cognitive and mood changes, hot flashes, anemia and skeletal complications, are critical to achieving optimal outcomes in these patients.[1]

Bone density loss and related fractures were recently established as significant AEs associated with ADT. The results of several prospective studies show that BMD is decreased by 0.6% to 4.6% yearly in patients with nonmetastatic PC receiving ADT, a rate that exceeds the gradual age related bone loss of 0.5% to 1.0% yearly observed in healthy men and equal to or greater than that in perimenopausal women, a population in which the risk of osteoporosis is clearly established.[2–12] Additionally, patients with PC who experience ADT related fractures have lower overall survival than patients without fractures (121 vs 160 months, $p = 0.04$).[13]

Despite recent study results showing stable or increased BMD with SERMs such as raloxifene and toremifene, and bisphosphonates such as alendronate, pamidronate and zoledronic acid most patients receiving ADT do not receive adequate counseling or therapy aimed at preventing or treating ADT induced bone loss.[8–11,14–18] We reviewed the prevalence, pathogenesis, diagnosis, prevention and treatment of bone loss in patients with nonmetastatic PC receiving ADT.

MATERIALS AND METHODS

An extensive and comprehensive MEDLINE® literature search was performed using PubMed and the search terms prostate neoplasms, diphosphonates, bone density, osteoporosis, metabolic bone diseases, androgen antagonists, hormonal antineoplastic agents, orchiectomy, leuprolide and goserelin, and the key words pamidronate, zoledronic acid and bisphosphonate. English articles were retrieved and evaluated.

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DIAGNOSIS OF ADT INDUCED BONE LOSS

BMD testing is considered the gold standard for diagnosing and assessing the severity of osteoporosis and fracture risk in women, while its use in men is less defined.[19] BMD can be determined by several noninvasive methods, of which DEXA and quantitative computerized tomography are the most common. DEXA is usually the method of choice because it can easily measure BMD at multiple skeletal sites with minimal radiation exposure.[20] Quantitative computerized tomography is more sensitive but less precise than DEXA scans, exposes patients to more radiation and is subject to quality control errors.[20,21] However, this method is particularly useful for assessing BMD in elderly men with conditions, eg degenerative spinal diseases, that may artificially increase LS BMD measurements using DEXA.[19]

Individual BMD measurements were compared with those of a control population of young healthy patients with peak BMD, resulting in a T score expressing the difference in the number of SDs from the mean of the control population.[22] A Z score, which expresses the difference in the number of SDs between the BMD in an individual and the mean value in a group of adults of the same age and gender, may also be reported.[22] Appendix 1 shows WHO diagnostic criteria for bone loss using T scores in white women.[23] Although these criteria are applied to men, the validity of applying these criteria to men has been questioned because men tend to have larger bones and a higher peak bone mass than women.[20]

Before attributing bone loss in patients with PC only to ADT, secondary causes of bone loss should be considered and/or treated. They include but are not limited to hypothyroidism, VitD deficiency, renal disease, liver disease, osteomalacia and Paget's disease.[20]

PREVALENCE OF ADT INDUCED BONE LOSS AND FRACTURES IN PATIENTS WITH NONMETASTATIC PC

The results of several prospective studies show that all forms of ADT cause annual BMD losses of up to 4.6% (table 1).[2–11] Compared with patients not receiving ADT or healthy controls men with nonmetastatic PC receiving ADT have a 5 to 10-fold higher 1-year bone loss rate.[4] The most significant loss of BMD usually occurs within year 1 of therapy and annual BMD losses are similar in men receiving an LHRH agonist with or without an antiandrogen (LHRH agonist alone vs LHRH agonist plus antiandrogen −2.1% to −4.6% vs −0.6% to −4.5%).[2,4–7,9]

Whether this BMD loss translates into an increased rate of fragility fractures in patients with nonmetastatic PC has not been prospectively evaluated in clinical trials. However, the results of several large, retrospective studies clearly demonstrate an increased fracture risk in this patient population.[24–26] For example, using claims data from 1998 to 2003 Smith et al reported increases in the fracture risk associated with LHRH agonist therapy for any fracture (RR 1.21, 95% CI 1.09–1.34, p <0.001), TH fracture (RR 1.76, 95% CI, 1.33–2.33, p <0.001) and vertebral fracture (RR 1.18, 95% CI, 0.94–1.48, p = 0.155).[26] In another observational study of more than 25,000 patients with nonmetastatic PC the RR of any fracture was 1.37 (95% CI, 1.2–1.57) in patients receiving 9 or greater doses of an LHRH agonist during year 1 following the diagnosis of PC.[25]

RISK FACTORS FOR BONE LOSS AND FRACTURES IN MEN RECEIVING ADT

Preexisting Conditions and Lifestyle Factors

While numerous risk factors have been identified for postmenopausal osteoporosis, including age, personal or family history of fracture, Asian or Hispanic heritage, smoking and cortisone use, only a few groups have evaluated the contribution of preexisting conditions or lifestyle factors to ADT induced bone loss in patients with PC (Appendix 2).[2,27–32] Based on these study results no lifestyle factor emerged as a reliable predictor for bone loss in patients with PC with the possible exception of BMI. In 2 of these studies low baseline BMI predicted increased BMD loss and 1 showed a positive association with BMI and BMD, suggesting that larger body mass may lessen the risk of bone loss in this patient population.[27–29]

Preexisting Bone Loss and Duration of ADT

The results of several studies showed preexisting osteopenia (T score less than −1 and more than −2.5) in 20% to 56% of

TABLE 1. *BMD change in patients with nonmetastatic PC receiving ADT*

References	No. Evaluable Pts	ADT Type	Mean % BMD Change/Yr		
			LS	TH	FN
Berruti et al[2]	35	LHRH agonist + antiandrogen × 6 wks	−2.3	−0.6*	NR
Daniell et al[3]	26	Orchiectomy or LHRH with/without antiandrogen	NR	NR	About −4
Greenspan et al[4]	30	LHRH agonist, antiandrogen, complete androgen blockade	−4	−2.5	NR
Higano et al[5]	17	Intermittent complete androgen blockade	−4.5†	−2.5†	NR
Israeli et al[11]	110	LHRH agonist with/without antiandrogen	−2.0	−2.1	NR
Maillefert et al[6]	7	LHRH agonist	−4.6	NR	−3.9
Mittan et al[7]	15	LHRH agonist	−2.8	−3.3	−2.3
Ryan et al[10]	51	LHRH agonist	−2.1	−2.4	−2.4
Smith et al[9]	22	LHRH agonist + antiandrogen × 4 wks	−3.3	−1.8	NS‡
Smith et al[8]	37	LHRH agonist with/without antiandrogen	−2.2	−2.8	−2.1

* Left hip measurements reported.
† DEXA performed between 9 and 12 months after start of therapy.
‡ No significant change from baseline.