

Changes in Bone Mineral Density in Patients with Prostate Cancer Treated with Androgen Deprivation Therapy

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ABSTRACT

Osteoporosis is a complication of permanent androgen deprivation in men with prostate carcinoma, following either bilateral orchiectomy or treatment with GnRH agonists. The present approach to the problem of osteoporosis includes prevention, adequate follow-up and appropriate treatment as an imperative of contemporary urological and endocrinological management of these patients. Bone densitometry was performed in 18 patients who were on GnRH agonists treatment during 1–3 years. The patients under therapy were followed clinically, PSA (prostate-specific antigen) values were determined and bone scintigraphy was performed. The bone mineral density values in 13 patients indicated osteopenia, whereas in one patient the finding was compatible with osteoporosis. Four patients had normal bone mineral density findings. Bone densitometry should be performed before initiation of treatment with GnRH agonists in order to quantify the therapy-related bone loss. Prevention of development of osteoporosis and its complications depends on the assessment of pharmacological treatment in this group of patients, including e.g. bisphosphonates and possible intermittent androgen deprivation.

Key words: prostate cancer, bone mineral density, BMD, androgen deprivation therapy

Introduction

Osteoporosis represents a special concern for men with prostate carcinoma¹. It is well known that osteoporosis is not a disease that affects only women.

Androgen deprivation therapy by either bilateral orchiectomy, gonadotropin-releasing hormone (Gn-RH) agonist treatment or combined androgen blockade decreases bone mineral density and increases fracture risk in men with prostate cancer^{2–4}.

Bone mineral density is inversely correlated with fracture risk in men and women^{5–7}.

Men experience approximately 33% of all hip fractures and mortality after hip fractures is even higher in men than in women⁸.

Early primary androgen-deprivation therapy improves survival for men with locally advanced, nonmetastatic prostate cancer⁹. Adjuvant androgen-deprivation therapy improves survival for men with lymph-node positive prostate cancer treated with radical prostatectomy and pelvic lymphadenectomy¹⁰ as well as in men with locally advanced prostate cancer treated with radiation therapy¹¹.

A Working Group of the World Health Organization (WHO) has defined normal finding, osteopenia, and osteoporosis in women based on bone mineral density (BMD) compared with the value in young adults.

The long-term side effects of androgen deprivation therapy have become increasingly important, however, they are seldom considered by either patients or physicians, since the male population receiving endocrine therapy for prostate cancer has recently grown to include apparently healthy subjects with a rather low risk of disease progression and relatively long life expectancies^{12,13}.

Patients and Methods

Between 1999 and 2002 bone densitometry was performed in 18 patients with prostate carcinoma who were on permanent androgen deprivation with GnRH-agonists (duration of therapy range from at least 12 up to 36 months).

Treatment modalities included LH-RH hormone analogues (buserelin acetate, goserelin), and total androgen blockade with an LH-RH analogue and nonsteroidal anti-androgen.

The patients were followed clinically, including determination of PSA (prostate-specific antigen) values and bone scintigraphy. Patients had locally advanced, lymph node positive, or recurrent prostate carcinoma, with no radiographic evidence of bone metastases.

Since the understanding of the issue of osteoporosis and its complications is a relatively new aspect of follow-up, especially in this group of patients, densitometry was not performed before treatment initiation, but after therapy duration of 1–3 years.

The patients did not have concomitant bone metabolic disease, primary hyperparathyroidism or chronic hypercortisolism, as recorded by medical history. They had no prior hormonal treatment, and no prior or concomitant treatment with bisphosphonates or other drugs known to affect bone metabolism.

World Health Organization classification of osteoporosis was applied: (T-scores ≥ -1 were considered normal, scores of < -1 and up to -2.5 were considered osteopenic, and scores ≤ -2.5 were considered osteoporotic).

However, whether the same limits should be used in men is still controversial, because men have larger bones and a higher peak bone mass. Bone mineral density was determined by dual-energy X-ray absorption (DEXA) in three centers. DEXA measurements of lumbar vertebrae L2-L4, total hip, femoral neck and trochanteric region were evaluable for all patients.

BMD was expressed in standard deviation units relative to young adults (T score).

Subsequently, 99m-Tc methylene diphosphate whole body bone scanning was performed.

Results

The values of bone mineral density ranged within limits that define osteopenia in 13 patients. The treatment duration in this group of patients was 24–36 months. The patient age was 53–78 years.

Osteoporosis was diagnosed by measurement of bone mineral density in one patient. The patient had been on permanent androgen deprivation for 18 months and aged 74.

The bone mineral density values were normal in 4 patients, with therapy duration between 12 and 36 months. The patients' age was 57–74 years.

One patient, aged 74, who was diagnosed with osteoporosis based on measurement of bone mineral density had been on treatment for 18 months. Another patient, also aged 74, had been on therapy for 3 years, yet had a normal BMD finding (Table 1).

All men had stable and normal PSA levels (< 4.0 ng/mL).

TABLE 1
PATIENTS BONE MINERAL DENSITY (T SCORE) AFTER ANDROGEN DEPRIVATION THERAPY

No.	Duration of therapy (months)	Age (years)	Total hip (T score)	L2-L4 (T score)	Diagnosis
1.	12	57	-0.44	-0.4	normal
2.	18	61	0.4	-0.3	normal
3.	36	74	1.0	0.0	normal
4.	12	72	0.28	0.49	normal
5.	24	56	-1.1	-1.7	osteopenia
6.	12	69	-1.1	0.51	osteopenia
7.	36	53	-1.77	-2.01	osteopenia
8.	16	60	-1.4	-1.7	osteopenia
9.	14	69	-1.1	0.1	osteopenia
10.	24	78	-1.1	-1.7	osteopenia
11.	24	70	-1.39	-1.76	osteopenia
12.	12	65	-1.2	-1.5	osteopenia
13.	15	67	-1.1	-1.6	osteopenia
14.	20	71	-1.4	-2.0	osteopenia
15.	18	68	-1.0	-1.7	osteopenia
16.	14	64	-1.1	-2.0	osteopenia
17.	18	69	-1.1	-1.3	osteopenia
18.	18	74	-2.33	-3.7	osteoporosis

Discussion

Androgen-deprivation therapy is prescribed with increasing frequency for men with prostate carcinoma. There is growing concern about the effects of such therapy on the skeleton¹⁴. There are also some other factors that can contribute to fracture risk as diet, smoking, lifestyle, and treatment-related loss of lean body mass¹⁵. The specific subgroup of male patients featuring possible osteoporosis represents another example of bone loss related to sex differences¹⁶.

The results of BMD measurement in a small group of patients suggest that there is loss of bone mass in most of patients and that measurement of bone mineral density should be performed before initiation of GnRH-agonists treatment, since this therapy accelerates bone loss and increases fracture risk. Androgen deprivation therapy may increase fracture risk by decreasing both BMD and lean body mass^{15,17}. There is no recommended time limit for LH-RH hormone analogue therapy, and so it is expected that many patients will ultimately be treated for a long time¹⁸.

Results of a study by Smith et al. suggested that routine BMD screening is warranted in hormone-naive men and the additional risks of treatment related bone loss may influence individual decisions about the timing and duration of androgen-deprivation therapy¹.

The effect of intermittent androgen deprivation on bone mineral density was reported by Higano et al. In this series 9 months of combined androgen deprivation

therapy was followed by an off period, in which androgen deprivation therapy was withheld until PSA increased to a predetermined threshold. An increased BMD in the period of rest suggests that this treatment modality may be advantageous over continuous administration for limiting bone loss¹⁹.

Several studies published up to date have suggested that treatment with bisphosphonates may prevent bone loss in the hip and lumbar spine during androgen deprivation

therapy^{20,21}. Additional studies are necessary to evaluate the effects of oral bisphosphonates on BMD and fracture risk in men receiving androgen deprivation therapy for prostate carcinoma¹⁵.

Recent studies indicate that for men with prostate carcinoma who are at high risk for osteoporosis and fractures, clinical management should be dictated by the results of radiographic and DXA skeletal assessment¹⁴.

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PROMJENE MINERALNE GUSTOĆE KOSTIJU U BOLESNIKA S KARCINOMOM PROSTATE NAKON ANDROGENE DEPRIVACIJE

SAŽETAK

Osteoporozna je komplikacija trajne androgene deprivacije u muškaraca s karcinomom prostate. Ona nastaje kao posljedica bilo bilateralne orhidektomije ili primjenom agonista GnRH. U današnjem pristupu problemu osteoporoze, prevencija i odgovarajuće praćenje bolesnika, te terapija, nameću se kao imperativ suvremenog urološkog i endokrinološkog liječenja. U 18 bolesnika koji su bili na terapiji GnRH agonistima u trajanju od 1–3 godine, učinjena je denzitometrija kostiju. Bolesnici su za vrijeme trajanja terapije praćeni klinički, određivane su vrijednosti PSA, te je učinjena scintigrafija skeleta. U 13 bolesnika vrijednosti mineralne gustoće kostiju upućivale su na osteopeniju, a kod jednog bolesnika nalaz je govorio u prilog osteoporozi. U četiri bolesnika nalaz mineralne gustoće kostiju bio je potpuno uredan. Prije uključivanja pacijenata u terapiju GnRH agonistima nužno je učiniti denzitometriju kostiju da bi se mogao kvantificirati gubitak induciran terapijom. U cilju prevencije razvoja osteoporoze kao i njenih komplikacija, u ovoj grupi bolesnika nužno je stoga procijeniti i potrebu za medikamentoznim pristupom bolesti npr. bisfosfonatima, uz eventualnu intermitentnu androgenu deprivaciju.