Need for Measurement of Bone Mineral Density in Patients of Prostate Cancer Before and After Orchidectomy: Role of Quantitative Computer Tomography

MM Agarwal*, AK Mandal**, N Khandelwal**, SK Singh**

Abstract

Background: Androgen deprivation therapy is the first-line systemic treatment of prostate cancer, orchidectomy remaining the most common mode in view of cost-effectiveness and better compliance. Accelerated bone loss is common after orchidectomy, which exacerbates osteoporosis already common in this patient-population. We studied the need of periodic measurement of bone mineral density after orchidectomy.

Material and Methods: Fifty five patients of adenocarcinoma prostate opting for orchidectomy were prospectively studied. Follow up ranged from 6 to 18 months. Lumbar spinal (L1-L3) trabecular bone mineral density (BMD) was measured with quantitative computed tomography (QCT) at baseline and every 6 months after orchidectomy, and compared with preoperative values.

Results: Mean (±SD) age of the patients was 69.9±7.9 years and BMD 115.7 ± 35.7 mg/cm² with T-score -1.89 ± 1.26 and Z-score 0.30 ± 1.30. Thirty three percent patients were osteoporotic at baseline, as defined by a T-score <-2.5. Fall of BMD six months after orchidectomy was statistically significant (12.1%, p=0.0001) increasing the proportion of osteoporotics to 49%. Twenty four patients completing 12 months follow up, were separately analyzed and showed similar fall in BMD in first 6 months of follow up (13%) and further 8% loss in next six months. Ten patients were followed up for 18 months, and these did not show significant loss of BMD beyond 12 months (p=0.9).

Conclusions: Osteoporosis is common in hormone-naive population affected by prostate cancer and orchidectomy leads to accelerated exacerbation of this bone loss. Periodic measurement of BMD using QCT after ADT would help in early detection of osteoporosis. ©

INTRODUCTION

Prostate cancer is the fourth most common malignancy in men worldwide amounting to 30% of new cancer cases and is the cause of death of 3% of all men older than 50 years. The incidence and mortality varies among regions, being lowest in Asian developing countries and one of the highest in the United States.¹

Androgen deprivation therapy (ADT) is the first-line systemic therapy in treatment of adenocarcinoma of prostate. It offers an efficacious and durable form of treatment with 60-70% clinical response rate² and reported longevity of up to 10-15 years (mean 24-30 months).³ It is indicated in patients with metastatic (lymph-nodal or distant) disease at presentation or who develop it after curative radical treatment.⁴ Moreover, in patients with locally advanced prostate cancer, hormone therapy combined with local radiation has consistently demonstrated improvement in treatment outcome over radiation alone.⁵

Hormone therapy or endocrine manipulation is aimed at either decreasing the production of endogenous androgens (by orchidectomy, luteinizing hormone releasing hormone (LHRH) agonists, estrogens) or at blocking the androgen receptors (steroidal or pure antiandrogens). Orchidectomy is likely to continue as a common and popular modality, especially in developing countries, due to low-cost and one-time treatment leading to better compliance.

ADT produces so called andropause by either of the mechanisms, and is associated with various side-effects namely decreased libido and potency, fatigue, loss

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of muscle strength (sarcopenia), anemia, hot-flashes, gynecomastia, depression, decrease in cognitive function and accelerated bone loss, all collectively referred to as ‘castration syndrome’. Reported prevalence of osteopenia in prostate cancer patients is 31-38% and that of osteoporosis is 25-63% which is higher than age-matched general population (6%). Osteoporosis incurs a great amount of largely unrecognized morbidity in the form of bone-pains and fragility-fractures (especially spine, hip and wrist), by virtue of both being more common than general population as well as by accelerated bone loss after ADT.

This high incidence of low bone mass and its implications have led investigators to indicate a need for bone mineral density determination at the onset of androgen ablation and at periodic intervals thereafter to begin appropriate therapy. We studied the need of periodic measurement of bone mineral density before and after orchidectomy.

**Material And Methods**

We prospectively studied 55 men with histologically proven adenocarcinoma prostate, who opted for orchidectomy. The study-protocol was approved by the institutional ethics-committee. Informed consent was taken from all the patients before enrolment in the study. All patients underwent Tc⁹⁹m-MDP bone scintigraphy to rule out metastasis at lumbar vertebral level L1-L3 followed by measurement of trabecular bone mineral density (BMD) at L1-L3 vertebral level using quantitative computed tomography (QCT). BMD was measured every 6 months during follow up after excluding bony metastasis in lumbar spine.

Vertebral mineral density was measured with a commercial CT scanner (GE medical systems, Light Speed plus, Milwaukee, WI) at 160 mA and 120 KV using QCT-5000TM bone densitometry system software. The subjects were scanned supine with hips flexed to straighten the lumbar lordosis for improving the contact with a tripartite reference phantom, which was positioned under subject’s back covering T10 through L4. Bone mineral density was determined in the midplane of three lumbar vertebrae (L1-L3) in a single 10 mm thick slice obtained at each level. These vertebrae were chosen because they provide a large area for measurement of pure trabecular bone and because they are usually spared in the degenerative changes common at L4-L5 level. The QCT-5000TM software analyzes each axial image in the sequence in which it is taken and computes the BMD in mg/cm² (of calcium hydroxyapatite equivalent) based on the simultaneous calibration provided by the phantom. It also aggregates the result of analyzing all of the slices and computes the mean BMD, the T-score and the Z-score. This avoids all manual calculations increasing accuracy and precision. T and Z scores are defined as number of standard deviation from mean BMD values of healthy young adults and age-matched adults. A composite male reference data-base (provided by the General Electric Co., Milwaukee, WI), compiled from various studies from different ethnicities, was used for comparison.

WHO working-group guidelines were used to define osteoporosis based on BMD compared to the reference value in young adults (as standard deviation, SD; T-score). Upto one SD below reference value is considered as normal BMD, between 1-2.5 SD osteopenia and ≥ 2.5 SD below reference value, osteoporosis. Association of fragility fractures with BMD in osteoporotic range is considered severe osteoporosis. These definitions were originally defined for Caucasian women and are also used for men due to lack of separate validated definitions (studies are going on to find out separate definitions for men). All patients underwent bilateral total orchidectomy under local or regional anesthesia, using the standard technique. The patients were seen on follow up at 6 weeks and then every 3 monthly for routine checkup and evaluation of response to treatment. Post-orchidectomy, the patients were encouraged to maintain a healthy diet and activity schedule. Patients who developed symptoms of osteoporosis were given appropriate treatment in consultation with the department of endocrinology.

**Statistical Analysis**

All data was fed into Microsoft-excel worksheet and analyzed using SPSS 10.0(2) computer software for Windows. Normalcy of data was tested and confirmed using normal quantile plots for all variables. All the variables are presented as mean ± SD. Effect of orchidectomy on BMD was analyzed applying ‘paired t-test’. The effect of PSA, presence of bony metastasis and age on BMD was evaluated using ‘independent sample t-test’. In addition, bivariate analyses were done to assess the interactions between continuous variables. Complex interplay among more than two variables was studied using multivariate linear regression analysis. Correlation-coefficients were tested for significance using t-test. Correlation coefficients were compared using multiple regression analyses. p values ≤ 0.05 were considered statistically significant.

**Results**

Baseline patient-characteristics are described in Table 1. Before orchidectomy 24% patients (13/55) had normal BMD, whereas, 43% (24/55) were osteopenic and 32.7% (18/55) osteoporotic. Six months after orchidectomy, repeat QCT was done and a drop in BMD was observed in 51 out of 55 patients. This fall was statistically significant (mean 13.5%, range 4.9-44.6%) with mean BMD at 6 months, 101.7±34.9 mg/cm² (p=0.0001). The drop in BMD was observed at all vertebral levels (p=0.0001) (Table 2). The proportion of osteoporotics...
increased to 49% (p=0.0001). There was a statistically significant inverse relation between baseline BMD and percentage loss in first six months after orchidectomy (p=0.018). This trend lost its statistical significance in next 6 month follow up (p=0.3), which may suggest a profound effect of orchidectomy.

Of all patients, 24 completed 12 months of follow up and 10, 18 months. A statistically significant fall in BMD was observed from 6-month to 12-month follow up (110.9 mg/cm² at 6 month to 102.0 at 12 month; p=0.01). This was maximum at L1 level (p=0.0001) and minimum at L3 (p=0.81). BMD did not change significantly from 12 to 18 month follow up (p=0.9) (Fig. 1).

Twenty four percent of all patients had bone scan suggestive of metastasis. Serum prostate-specific antigen (PSA) was significantly higher in these patients as compared to those without metastases (mean PSA 97.2 ng/ml and 38.5 ng/ml, respectively; p=0.0001). There was no significant difference in BMD between the two groups with mean BMD of patients with no bony metastasis and those with metastasis 115.3 mg/cc and 117.1 mg/cc, respectively (p=0.88). Patients with serum PSA more than 50 ng/ml had lower BMD than those with less value (108.8 mg/cm² and 121.3 mg/cm², respectively) which was statistically significant when controlling for presence of bony metastasis (p=0.03). Difference between Z-scores was even more significant (p=0.01).

Four patients (7.27%) developed fractures (two-hip, two lumbar spine) during the 18 month follow up. All these patients had T-score less than -2.5 (osteoporotic).

**DISCUSSION**

Osteoporosis is common in the age-group of men affected by prostate cancer and it has been suggested that prostate cancer patients may be at a higher risk for osteoporosis than general population. Our results (osteoporotics 32.7% and osteopenics 43%) were in concordance with those of Wei et al who reported that before starting androgen deprivation therapy (ADT), 38% of prostate cancer patients had osteopenia and 25% were frankly osteoporotic. This may be explained by certain genetic factors and high prevalence of low levels of calcium and vitamin D, acquired hypogonadism and low serum estradiol in this group of patients. Notably, these factors also contribute to osteoporosis. Recently, another mechanism of low BMD in these patients has been described. Metastatic prostate cancer cells to bone lead to disruption of physiologic bone remodeling by release of paracrine (transforming growth factor and parathyroid hormone-related protein) and endocrine substances (parathormone), as evidenced by various biochemical and histomorphometric studies. We could not demonstrate any difference in lumbar spinal BMD between patients with or without bony metastasis. This may be explained by the fact that most of our patients with bony metastases had it only at one or two sites (small bulk). Interestingly, a significant trend of lower BMD in those with PSA >50 ng/ml was observed (which is generally indicative of advanced disease), which points to an endocrine mechanism of accelerated bone loss. Other factors e.g. age, dietary calcium, physical activity, body-mass index, smoking and alcohol, which have been found by many (including ourselves) influential on BMD, may also have affected the BMD.

Men, in general reach higher peak bone mass than

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<th>Table 1 : Patient-characteristics at presentation (n=55)</th>
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<td><strong>Factor</strong></td>
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<td>Age (years)</td>
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<tr>
<td>Baseline PSA (ng/ml)</td>
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<td>Baseline mean BMD (mg/cc)</td>
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<td>Baseline Z-score (no. of SD)</td>
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<th>Table 2 : Change in BMD at vertebral L1-L3 level in first 6 months following orchidectomy (n=55)</th>
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<tr>
<td><strong>Vertebral level</strong></td>
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<td>L1</td>
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*level of significance at p ≤ 0.05.
women. Nevertheless, both tend to lose bone mass after mid-20s at a rate of 0.5-1.0% per year. Women after menopause develop accelerated loss (1-2% per year). Men after orchidectomy are more deprived of circulating sex-steroids (deprived of both androgens and estrogens) than postmenopausal women, in whom ovary still produces a substantial amount of testosterone. Therefore, degree of accelerated bone-loss may be more in men after ‘andropause’. In the present study, we observed marked bone loss as early as by six months after orchidectomy (loss of 13.5%, p=0.0001), which continued till 12 months (further loss of 5.5%, p=0.01). We did not find significant difference beyond 12 month follow up. This is in contrast to observation of Daniell et al who reported continued loss of BMD beyond 36 months. Definite comment is not possible due to small number of patients in our study. Several studies have reported 5.7-6.6% loss of spinal BMD as measured by QCT in 6months after starting LHRH agonists which is nearly double when compared to studies using dual energy X-ray absorptiometry (DXA). This indicates more sensitive nature of QCT, as it directly measures trabecular BMD (the bone-compartment showing differential early loss of bone) unlike DXA which measure integral bone-density. Moreover, the QCT, unlike DXA, is not affected by osteophytosis, sclerotic cortical metastasis and aortic calcification, which are often seen in older people. These merits of QCT have partially overcome its disadvantages i.e. cost, availability and radiation exposure. The normative data developed for T-score and BMD for DEXA and QCT are comparable.

Although exact incidence of fragility-fractures in these patients is unknown, many studies are now available indicating an increased incidence, ranging from 5-14%. In our study, the observed incidence was 7.27% (4/55) at 18 months of follow up. Although, all these patients had BMD in osteoporotic range, possibility of metastasis can not be ruled out in absence of biopsy of fracture site.

Utility of performing any screening test depends on the prevalence and morbidity of disease, incidence of new cases in the at-risk population, sensitivity of screening modality and availability of treatment if detected early. Therefore, in the light of above discussion, a high prevalence of osteoporosis in prostate cancer patients, accelerated bone loss and increased fracture-rate after orchidectomy, availability of sensitive QCT and increasing use of bisphosphonates (alendronate, pamidronate, zoledronic acid and neridronate) in prevention and treatment of osteoporosis in this group of patients, routine preoperative screening with QCT is desirable. Recently, recommendations for bone-loss-management strategies have been published indicating the need of bone densitometry before commencing ADT and follow up studies depending on presence or absence of osteoporosis and other risk factors, e.g. smoking, alcohol, lack of physical activity, lean and thin stature and low dietary calcium intake.

Studies have shown that markers of bone turn-over correlate with BMD, as well as predict fracture-risk independent of BMD, making these important in diagnosis as well as monitoring response of therapy. Therefore, results of our study may have been further validated by incorporating measurement of markers.

**CONCLUSION**

Present study highlights the high prevalence of osteoporosis in hormone-naive prostate cancer patients and impact of androgen deprivation therapy on skeletal health as evidenced by a marked decrease in bone density. The results of this study will increase the awareness of clinicians and researchers regarding the magnitude of problem as well as means of early diagnosis of osteoporosis among prostate cancer patients both before and after orchidectomy. An early assessment of bone density will help in their long-term management to ensure maintenance of skeletal integrity during androgen ablation for prostate cancer. We recommend spinal QCT for measurement of BMD at baseline and every six months after initiation of ADT in patients not having bony metastases in lumbar vertebrae, especially when PSA is more than 50 ng/ml.

**REFERENCES**

11. Faulkner KG, Orwell E. Implications in the use of T-scores.


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**Announcement**

**Election for the Governing Body of API and Faculty Council of ICP**

Election process by Postal Ballots is on for the following posts of API and ICP for the year 2008-2009.

**API**
- President Elect 1
- Vice President 1
- Governing Body Members 4
- Eight Zonal Members
  - (Central, East, West, North, South, Mid South, North West, Mid East)

**ICP**
- Dean Elect 1
- Vice Deans 3
- Faculty Council Members 5
- Eight Zonal Members
  - (Central, East, West, North, South, Mid South, North West, Mid East)

Ballot Papers for these elections shall be sent to all the Life Members and Fellows and same need to be sent back to API Office by **31st August 2007**.

In case a member does not receive the ballot paper, he/she can send a written request under his/her signature to API Office at the address given below for issue of duplicate ballot paper so that duplicate ballot paper could be send to them. Duplicate Ballot Paper will be issued from **1st August** onwards.

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