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**Original Research Article**

# Incidence of low bone mineral density in patients with advanced prostate cancer before hormonal manipulation

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## ABSTRACT

**Background:** Prostate cancer is the second most commonly diagnosed cancer in men with an estimated 1.3 million cases diagnosed in 2018 according to the most recent International Agency for Research on Cancer (IARC) report. A large proportion of men still present with advanced disease and in this situation androgen deprivation therapy (ADT) is the mainstay of treatment. Prostate cancer is largely androgen-dependent and responds to endocrine therapy. ADT is an effective treatment modality which decreases the rate of disease progression, alleviates symptoms, and prolongs patients' survival. ADT can be achieved through surgery (i.e., bilateral orchidectomy) or medical therapy (gonadotropin releasing hormone agonists, antagonists and antiandrogens).

**Methods:** With the approval from institutional ethic committee, a case control study was planned at the urology outpatient department (OPD) at SMS Hospital from April 2019 to March 2020. Based on inclusion and exclusion criteria, 44 patients with newly diagnosed advanced prostate cancer and requiring hormone manipulation were enrolled in study. Age matched control (age±2 years) was selected from patients attending urology clinics with conditions other than prostate cancer. Ratio of cases and control was kept 1:1. Written consent was taken from all participants.

**Results:** Total 88 patients were enrolled in study, 44 in each group. The age of patients ranged from 57 to 86 years among the case group and 55–85 among the control group. Mean age of cases was 65.24±6.8 and control was 64.98±7.6 years (p=0.25). Body mass index which is calculated with standard formula (weight in kg/height in meter square) was significantly high among controls (24.20±2.46) in comparison to cases (23.42±2.84). Statistically significant difference was observed among case and control groups for PSA (p=0.0001) and serum calcium (p=0.005) however difference for alkaline phosphatase (ALP), parathyroid hormone (PTH) and vitamin D was found insignificant (p>0.05).

**Conclusions:** Low bone mineral density in patients with advanced prostate cancer before hormonal manipulation is nearly 50%. PSA and serum calcium level were significant different among case and control however this difference was not found for ALP, PTH and vitamin D. Consideration should be given to performing BMD studies in these men before initiating treatment, to avoid or minimize potential bone-related complications in these patients.

**Keywords:** Bone mineral density, Prostate cancer, Parathyroid hormone

## INTRODUCTION

Prostate cancer is the second most commonly diagnosed cancer in men with an estimated 1.3 million cases diagnosed in 2018 according to the most recent International Agency for Research on Cancer (IARC) report.[1] A large proportion of men still present with advanced disease and in this situation androgen deprivation therapy (ADT) is the mainstay of treatment.[2,3]

Prostate cancer is largely androgen-dependent and responds to endocrine therapy. ADT is an effective treatment modality which decreases the rate of disease progression, alleviates symptoms, and prolongs patients' survival. ADT can be achieved through surgery (i.e., bilateral orchidectomy) or medical therapy (gonadotropin releasing hormone agonists, antagonists and antiandrogens).[4]

Men diagnosed with prostate cancer are now living longer. This improved survival is mainly attributed to advances in treatment, impact of early screening and earlier detection on mortality. As patients are now living with prostate cancer for longer, the long-term impact of prostate cancer and its treatment on bone health in men is increasingly recognized.[5]

Recently there has been increasing concern about the effect of castration on bone metabolism as testosterone is essential for maintaining bone mass in men.[6,7] However, there is also evidence that prostate cancer itself is a significant risk factor for osteoporosis, and hence fracture, by causing disturbances in bone turnover and mineralization even before ADT.[8,9] Thus, predicting and preventing the progression of osteoporosis in patients with prostate cancer is of critical importance. Before initiating ADT, it is necessary to identify the causes of bone loss and related risk factors for osteoporosis. There is a major need to determine ways to treat patients with prostate cancer undergoing ADT without increasing the risk of osteoporosis.

Unfortunately, many patients with prostate cancer do not receive necessary and guideline-recommended interventions to protect bone health, such as calcium and vitamin D supplementation, fracture risk assessments, or antiresorptive therapy with denosumab or bisphosphonates. Consequently, patients who progress to metastatic, castration-resistant prostate cancer face a dramatically increased risk of symptomatic skeletal events secondary to both osteoporosis and bone metastases.[10,11]

The prevalence of low BMD in men with prostate carcinoma prior to androgen-deprivation therapy has not been evaluated adequately.

Thus, this study was planned to determine the incidence of osteoporosis in men with locally advanced (T3–T4) and/or metastatic prostate cancer requiring hormone manipulation therapy.

### *Objective*

Objective of the study was to determine incidence of low bone mineral density in patients with advanced prostate cancer before hormonal manipulation.

## METHODS

With the approval from institutional ethic committee, a case control study was planned at the urology outpatient department (OPD) at SMS Hospital from April 2019 to March 2020. Based on inclusion and exclusion criteria, 44 patients with newly diagnosed advanced prostate cancer and requiring hormone manipulation were enrolled in study. Age matched control (age±2 years) was selected from patients attending urology clinics with conditions other than prostate cancer. Ratio of cases and control was kept 1:1. Written consent was taken from all participants. A predesigned, pretested questionnaire was used to record all necessary information of enrolled participants. Patients were subjected to detail history, thorough clinical examination and required investigations to find out clinical stage of prostate cancer, bone mineral density, serum PSA, calcium, alkaline phosphatase and creatinine. Patients with locally advanced, lymph node positive, metastatic or recurrent prostate carcinoma and with no prior androgen-deprivation therapy and the patients who were willing to participate in study and given written consent were included in the study whereas men with other bone disorders or secondary causes of osteoporosis, including those with hyperthyroidism, Cushing disease, chronic liver disease, or serum creatinine 2.0 mg/dl and men, if they had received glucocorticoids, bisphosphonates, calcitonin, or suppressive doses of thyroxine within 1 year of enrollment were excluded from the study.

### *Clinical stage of prostate cancer*

The clinical stage (T) of the tumour was determined by a DRE. Biopsies were taken from all patients to confirm the diagnosis of cancer and the Gleason sum score was used to assess the histological grade of the tumour.

### *Bone mineral density testing*

BMD of the patients was assessed using accu DEXA device from Lone Oak Medical Technologies. It is a self-contained, table-top unit, employing Dual Energy X-ray Absorptiometry (DEXA) technology. BMD was checked at the point of diagnosis before commencement of androgen deprivation therapy. BMD of the posterior-anterior (PA) lumbar spine (lumbar spinal segments 1–4 [L1–L4]), the lateral lumbar spine (L2–L4) and the total hip were determined. Bones with obvious deformities or focal sclerosis were not analyzed. Vertebrae with visible overlap from ribs or the pelvis were eliminated from the analysis of lateral spine scans. BMD of the patient and that of the established norm were measured in units called standard deviations (SDs). The more the standard deviations below 0 indicated as negative numbers, the

lower the BMD of the patient and the higher the risk of fracture occurrence. A T –score less than −1 is considered normal or healthy. A T score between −1 and −2.5 indicates that patient has low bone mass (osteopenia). A T score of −2.5 or lower indicates that patient has osteoporosis. The greater the negative number, the more severe the osteoporosis.

***Other assays***

Serum parathyroid hormone (PTH) was measured with a two-site immunoradiometric assay kit (Allegro; Nichols Institute) with a working range between 1 pg/ml and 1000 pg/ml, a normal range of 10–60 pg/ml, a detection limit of 1–2 pg/ml, and intra-assay and inter-assay coefficients of variation of 1.8–3.4% and 5.6–6.1%, respectively.

Serum testosterone was measured by radioimmunoassay using a commercial kit (Diagnostic Products, Los Angeles, CA) with an intra-assay coefficient of variation of approximately 5% for values within the normal range and 18% for values in the castrate range and with an inter-assay coefficient of variation of 7–12%.

Thyroid-stimulating hormone was measured using a two-site sandwich immunoassay (Chiron Diagnostics, East Walpole, MA) with a normal range from 0.35 m IU/ml to 5.50 m IU/ ml, a detection limit of 0.004 m IU/ml, and an intra-assay coefficient of variation of 3.5–15.8%.

Serum 1,25 dihydroxyvitamin D was measured using a radioreceptor assay (Nichols Institute) with a sensitivity of 5 pg/mL and intra-assay and inter-assay coefficients of variation of 11% and 16%, respectively.

***Ethical clearance***

Enrollment of patients was started after taking ethical clearance from institutional ethic committee. Written consent was taken from all the participants.

***Statistical analysis***

Statistical analysis was performed with statistical package for the social sciences (SPSS) 20.0 (trial version). Data was presented in form of tables and graphs.

Student t- test and Fischer's exact test were used as test of significance and p value of <0.05 was considered statistically significant.

## RESULTS

Total 88 patients were enrolled in study, 44 in each group. The age of patients ranged from 57 to 86 years among the case group and 55–85 among the control group. Mean age of cases was 65.24±6.8 and control was 64.98±7.6 years (p=0.25). Body mass index which is calculated with standard formula (weight in kg/height in meter square) was significantly high among controls (24.20±2.46) in comparison to cases (23.42±2.84).

Statistically significant difference was observed among case and control groups for PSA (p=0.0001) and serum calcium (p=0.005) however difference for ALP, PTH and vitamin D was found insignificant (p>0.05) (Table 1).

**Table 1: Clinical and biochemical characteristics of men with prostate cancer and control.**

| Variables | Case (n=44) | Control (n=44) | P value* |
|---|---|---|---|
| **Age (years)** | 65.24±6.8 | 64.98±7.6 | 0.86 |
| **BMI** | 23.42±2.84 | 24.20±2.46 | 0.03 |
| **PSA (ng/ml)** | 19.22±11.78 | 5.65±2.98 | 0.0001 |
| **Calcium (mg/dl)** | 8.9±0.4 | 9.1±0.6 | 0.005 |
| **ALP (IU/l)** | 89.57±45.6 | 83.56±42.6 | 0.32 |
| **PTH (pg/ml)** | 44.36±22.34 | 45.28±21.56 | 0.76 |
| **Mean BMD T score** | 1.94±1.7 | 0.78±1.5 | 0.001 |
| **Vitamin D (ng/ml)** | 21.4±4.6 | 22.2±5.8 | 0.47 |

*Calculated by student t test and p value <0.05 was consider as statistically significant

The BMD categories based on the T score were analyzed for the case and control group. In the case group, before starting ADT, 23 (52.27%) patients had normal BMD, 13 (29.55%) patients had osteopenia while 08 (18.18%) patients had osteoporosis. In the control group, 34 (77.28%) patients had normal BMD, 09 (20.45%) patients had osteopenia while 01 (2.27%) patients had osteoporosis. Using Fischer's exact test for categorical tables, there was a statistical significance between the BMD categories of the two groups (p=0.04). Mean BMD T score was significantly higher (p=0.001) among cases of prostate cancer (1.94±1.7) then control (0.78±1.5) (Table 2).

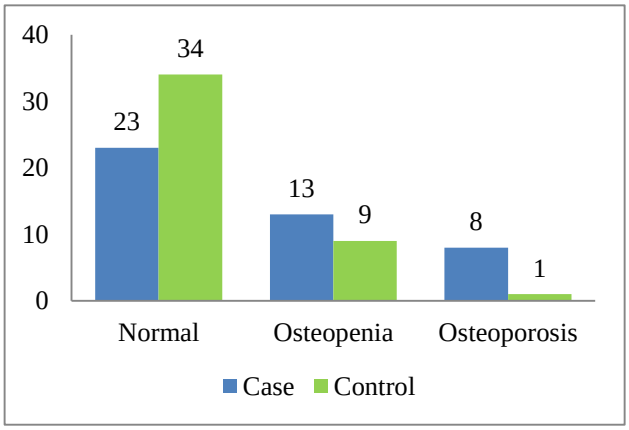


**Figure 1: Distribution of cases and controls according to BMD categories.**

**Table 2: BMD among cases and controls.**

| Variables | Case (n=44) % | Control (n=44) % | P value |
|---|---|---|---|
| **BMD group** | | | |
| Normal ≥1) | 23 (52.27) | 34 (77.28) | 0.04* |
| Osteopenia (−1 to −2.5) | 13 (29.55) | 09 (20.45) | |
| Osteoporosis (≤2.5) | 08 (18.18) | 01 (2.27) | |

*Calculated by Fischer's exact test and p value <0.05 was consider as statistically significant.

## DISCUSSION

Protecting and improving bone health is critical when managing all stages of prostate cancer. As the prevalence of prostate cancer and osteoporosis increases with age, many patients may already have osteoporosis when diagnosed with prostate cancer.[12] Prostate cancer patients are now living longer, and many patients receive several lines of therapy, which can have a cumulative impact on bone health over a period of years.[13] Unfortunately, many patients with prostate cancer do not receive necessary and guideline-recommended interventions to protect bone health, such as calcium and vitamin D supplementation or fracture risk assessments. Early recognition and optimization of bone health is therefore important in these patients' group.

In this study, 44 patients with advanced prostate cancer were compared with 44 controls for BMD before starting hormonal manipulation. Mean age of advanced prostate cancer patients was 65.24±6.8 and control was 64.98±7.6 years. In the case group, before starting ADT, 52.27% patients had normal BMD, 29.55% patients had osteopenia while 18.18% patients had osteoporosis. Mean BMD T score was significantly higher (p=0.001) among cases of prostate cancer (1.94±1.7) then control (0.78±1.5). Study done by Hussainet et al found osteoporosis among 42% of men with newly diagnosed advanced prostate cancer before commencing hormone manipulation therapy while 37% were osteopenic and 21% had normal BMD.[14] The mean BMD in men with prostate cancer was 6.6% lower than the control group (p=0.006). Ojewuyi et al study prostate cancer among Nigerian men and observed normal BMD in 55.8%, osteopenia in 29.9% and osteoporosis in 14.3% cases before ADT.[15] They found mean BMD of the case group (pre- ADT) was much lower than that of the control group, −0.78±1.7 and 0.26±1.5, respectively. Sun-Ouck Kim et al observed higher incidence of osteopenia (16.67%) and osteoporosis (52.38%) of the spine (mean T-score -2.66±3.20) among cases.[12]

In present study, body mass index was significantly high among controls (24.20±2.46) in comparison to cases (23.42±2.84). Statistically significant difference was observed among case and control groups for PSA (p=0.0001) and serum calcium (p=0.005) however insignificant difference was observed for ALP, PTH and vitamin D (p>0.05). Significant higher level of PSA was established by various studies among men with prostate cancer.[12,16,17]

Similarly to present study, PSA was found significantly higher (p=0.004) among case (17.12±14.93) than control groups (9.65±9.61) by Sun-Ouck Kim.

Body mass index was found at higher site (27±63) among cases studied by Smith while Kim observed BMI 23.80±2.94 and 22.98±2.60 among cases and controls respectively with no significant difference (p=0.08). Similarly, no statistical difference was established between the control and prostate cancer group for height, weight or BMI by Hussainet. Serum calcium, creatinine, PTH and vitamin D was found within normal range in study done by Smith.

BMD is an important determinant of fracture risk prospective studies show that the risk of fracture increases progressively with decreasing BMD.[18-20] Osteoporosis results in significant number of fractures each year in the India, causing severe pain and disability to individual sufferers.

### *Limitations*

Limited number of patients and the incidence of osteoporotic fractures has been reported to be greater than pathological fractures in men with prostate cancer receiving LHRH analogue therapy. Because of that, clinical implications of bone loss have been well recognized and managing skeletal health in such patients is an emerging challenge.

## CONCLUSION

Low bone mineral density in patients with advanced prostate cancer before hormonal manipulation is nearly 50%. PSA and serum calcium level were significant different among case and control however this difference was not found for ALP, PTH and vitamin D. Consideration should be given to performing BMD studies in these men before initiating treatment, to avoid or minimize potential bone-related complications in these patients.

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