*Original Article*

**Received on** 08.08.2016, **Accepted on** 17.08.2016

New Indian Journal of Surgery
Volume 7 Number 3, September - December 2016
DOI: https://dx.doi.org/10.21088/nijs.0976.4747.7316.1

# Prospective Evaluation of Bone Mineral Density after Orchiectomy in Northern Indian Patients of Advanced Carcinoma Prostate

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**Abstract**

The prostate is an androgen-dependent organ. Prostate cancer, the second leading cause of death for men, is androgen dependent so androgen suppression remains the mainstay of treatment for advanced and metastatic disease. Cancer treatment induced bone loss is one of the complications associated with androgen deprivation therapy (ADT) in prostate cancer patients. It is of particular concern because it can lead to osteoporosis and bone fractures, which not only negatively impact patient quality of life but also overall survival. However, these studies were performed in western countries; moreover study of Japanese men with prostate cancer found that they had a low prevalence of osteoporosis that was not increased by ADT.

Evaluation of bone mineral density changes along with biochemical markers was done on patients of carcinoma prostate undergoing androgen deprivation therapy in form of castration. Sixteen patients of carcinoma prostate who have under gone androgen deprivation therapy were enrolled in the study.They were followed within the period of 1 year to study BMD changes by dual-energy X-ray absorptiometry (DEXA) scan. BMD was measured at 0, 1, 3 & 6 months during follow-up after excluding bony metastasis in thelumbar spineand femoral neck. We found statistically significant loss of BMD after orchiectomy with BMD decreasing up to 2% at 1 month, up to 5% at 6 month at lumbar spine and a decrease of 2.2% at 1 months & 6.7% at 6 month at femoral neck ($p< 0.001$), resulting in an increased incidence of osteoporosis from 24% pre operatively to 48% 6 months after orchiectomy.

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## Introduction

Prostate cancer is the fourth most common male malignant neoplasm worldwide. Its incidence varies widely between countries and ethnic populations and disease rates differ by more than 100-fold between populations. In men, prostate cancer is the most common malignancy in western countries and the second leading cause of solid cancer mortality in elderly men(1).

Androgen exposure of the prostate plays an important but incompletely defined role in prostate carcinogenesis.Oestrogen is also important in prostate cancer development and may have varying effects, depending on local tissue activity of oestrogen receptor-α and oestrogen receptor- β [1].

Androgen deprivation therapy (ADT) is used in cases of advanced lesions of prostate. There are four therapeutic approaches for androgen deprivation therapy in current clinical use: ablation of androgen sources, inhibition of androgen synthesis, antiandrogens, and inhibition of LHRH or LH release [2].

Bilateral orchiectomy quickly reduces circulating testosterone levels. Traditionally, castration was considered to be achieved if testosterone levels were lowered to a threshold of 50 ng/dl (1.73 nmol/l), a definition determined more by measurement methods derived from the use of old assay methods than by evidence. Serum testosterone levels in three-quarter patients after surgical castration drop to less than 20

ng/dl (0.69 nmol/l) [3].

In India most patients presents in advance stages or after spread of metastasis and are usually given androgen deprivation therapy mainly as castration.

Cancer treatment induced bone loss is one of the complications associated with androgen deprivation therapy (ADT) of patients with prostate cancer. It is of particular concern because it can lead to osteoporosis and bone fractures, which not only negatively impact patient quality of life but also overall survival [4]. However, these studies were performed in western countries; moreover study of Japanese men with prostate cancer found that they had a low prevalence of osteoporosis that was not increased by ADT. Japanese study found that, although the ADT treated patients did have significantly lower BMD values, t-scores, and z-scores than the hormone naive patients.There was no concomitant significant increase in the prevalence of osteoporosis in the ADT treated patients who had been treated with ADT for an average of 30.7 months [5]. Studies show significant association between low serum testosterone levels and high Gleason score, advanced pathologic stage, and poor outcome [6,7].

The relationship between hormonal levels BMD and prostate cancer carcinogenesis may be further complicated by racial differences that western and Asian (Japanese) men with prostate cancer differ markedly in the prevalence of osteoporosis [8].

These observations lead to hypothesise those Indian men with prostate cancer may differ in terms of the influence of ADT on BMD due to racial or environmental differences. Further research comparing the BMDs and occurrence and characteristics of prostate cancer in these different populations is needed.

## Methods

### *Patients*

We prospectively studied men with histologically provenadvanced prostate adenocarcinoma advised ADT and who opted to undergo orchiectomy. Informed consent was obtained from all patients before enrolment in the study. Total study duration was 12 months. Height, weight, body mass index (BMI), smoking status, and alcohol use were noted.Detailed history was noted especially for urinary symptoms. A thorough systemic examination was also performed.

All patients underwent initial lumbar spine X–ray to rule out metastasis at the lumbar vertebral level followed by measurement of BMD at lumbar segments 1–3 (L1–L3) using DEXA (Dual energy x ray absorptiometry)scan.

BMD was measured at 0, 1, 3 & 6 months during follow-up after excluding bony metastasis in the lumbar spine. BMD was measured using a DEXA scanner (Hologic Discovery Ci Bone Densitometer – 2007).

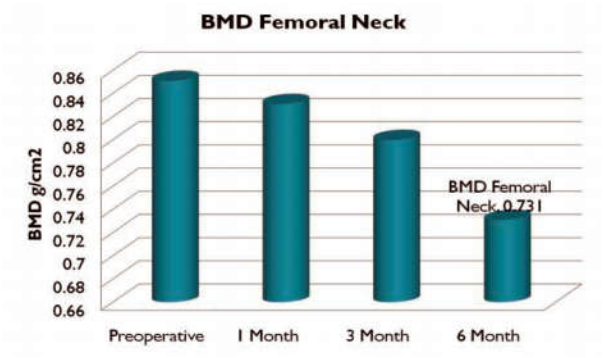


**Fig. 1:**

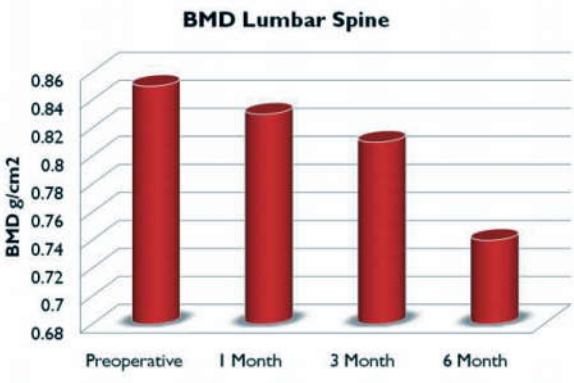


**Fig. 2:**

The L1–L3 lumbar vertebrae were chosen, because they provide a large area for measurement of pure trabecular bone and usually are spared in the degenerative changes common at L4–L5 level. It also computes the T-score and the Z-score, which are defined as the SD from the standard young adult mean BMD and the age-matched mean BMD, respectively. Therefore, all manual calculations are avoided, increasing the accuracy and precision of the procedure. A composite male reference data base (provided by manufacturer), which was compiled from various studies among different ethnicities, was used for comparison.

Physical activity was assessed by asking relevant questions regarding daily activities over a 1-week period of the patient's usual schedule. Physical activity was classified into 5 grades based on the type of activity performedand numbered from 1-5 as follows:

1. lying down,
2. sedentary (e.g., sitting in an office, walking _ 30 minutes only once per week),
3. regular purposeful walking (for 45–60 minutes at least 3 times per week) or the equivalent,
4. moderately heavy work (e.g., carrying weight up to 5 kg, climbing up to 50 stairs per day, jogging, etc.),
5. heavy weight lifting or the equivalent.

With increasing grade of physical activity, there was an increasing level of weight-bearing activity. This assessment also was performed by one investigator to minimize interviewer bias.

All patients underwent bilateral, Sub capsularorchiectomy under local or regional anaesthesia using the standard technique. The patients were discharged on the same day after orchiectomy.

The patients were seen on followup at 4-6 weeks, 3 months, 6 months, and 12 months after orchiectomy for routine check-ups and evaluation of response to treatment. After orchiectomy, the patients were encouraged to maintain a healthy diet and activity schedule.

Patients were also evaluated for PSA levels, testosterone levels, parathyroid hormone levels; alkaline and acid phosphatise levels, along with routine haematological investigations.

Patients who developed symptoms of osteoporosis were given appropriate treatment.

*Statistical Analysis*

All data were entered onto a Microsoft-Excel worksheet and were analyzed using SPSS 17.0 [2] computer software for Windows (SPSS Inc., Chicago, IL).

Normalcy of data was tested and confirmed using normal quantile plots for all variables. The results for all variables are presented as the mean ± SD. The effect of orchiectomy on BMD was analyzed by using Student *t* tests for paired data. The effects of physical activity, height, weight, BMI, smoking, and alcohol were analyzed individually by applying an independent-sample Student t test with the variables divided into two groups and a one-way analysis of variance (ANOVA) when there were more than two variables. Correlation coefficients were tested for significance using pearson's correlation coefficients. P values <0.05 were considered statistically significant.

## Results

Maximum incidence of carcinoma prostate is in 60 -80 years. BMD shows significant changes after orchiectomy ; decreasing up to 2% at 1 months up to 13% at 6 month at lumbar spine. BMD shows significant changes after orchiectomy; decreasing up to 2.2% at 1 months up to 6.7% at 6 month at femoral neck. Alkaline phosphatise however didn't show any statistically significant change. The base line BMD shows a positive correlation with physical activity with Pearson's correlation coffecient of 0.73 and negative correlation with smoking. No significant correlation was detected with alcohol use and BMI.

## Discussion

Carcinoma prostate is mainly a disease of elderly male. It is rarely diagnosed in men younger than 50 years, accounting for less than 0.1% of all patients. Peak incidence occurs between the ages of 70 and 74 years, with 85% diagnosed after the age of 65 years [8].

We have also found that majority of patients belong to age group 60-80 with mean age of 72 years.

Both androgens and estrogens are essential modulators of bone biology in men [9]. Orchiectomy, by removing the major source of androgens (and thereby causing marked reductions in the circulating levels of both androgens and estrogens), causes accelerated bone loss. In this situation, a man is even more deprived of circulating sex steroids than postmenopausal women, in whom the ovaries still produce a substantial amount of testosterone [10].

In contrast to the extensive studies in women, it is not clear how BMD defines osteoporosis in men or how well it predicts fractures. Aging men tend to loose cancellous bone at a rate of 12% per decade and cortical bone at a rate of 0.5–1% per year [11].

Men with no metastatic prostate cancer receiving continuous or intermittent ADT can have significant bone mineral density (BMD) loss as early as the first 6–12 months after starting ADT [12,13].

We found statistically significant loss of BMD after orchiectomy ( 2% at 1 month and 6% at 6 months; $P < 0.001$) resulting in an increased incidence of osteoporosis from 24% pre operatively to 48% 6 months after orchiectomy.

The prevalence of osteoporosis is higher than that in the general population (up to 6%), and some investigators have reported that it is due to certain

environmental and genetic predisposing factors that are common to both prostate carcinoma and osteoporosis [14].

In some patients, measurements at the L1 vertebrae may be obscured by lower ribs. However, we did not encounter any such problem in our study. It is well recognized that osteoarthritis involving the spine or aortic calcifications may overestimate BMD as measured by DEXA. This may mask age-related bone loss, especially in men who have a higher incidence of osteoarthritis in the spine and aortic calcifications [11].

Not surprisingly, the use of the spine as a site for determining osteoporosis in men has been in question, although measuring the spine density by computerized tomography or lateral spine by DEXA may overcome this obstacle. However in our study, we have taken X –ray of lumbar spine preoperatively to rule out any bony metastasis, osteoarthritis &other calcifications in the surrounding structures.

Furthermore, to our knowledge, not many studies are available on the effect of orchiectomy on loss of BMD.Daniell et al. reported a 4.1% loss of BMD at the hip (DXA) 1 year after patients underwent orchiectomy. At 2 years, 10% BMD loss (range, 2.5–17%) was observed [15]. Clarke et al. reported a 20% loss of bony material in iliac crest biopsies from 9 men within 7 months after orchiectomy (16).]Mayank et al. reported a 13 % decrease in BMD during first 6 months and 18% at 12 months afterorchiectomy [17].

Many investigators have found that weight-bearing exercises are beneficial in the maintenance of bone massin addition to retarding bone loss and reducing the fracture rate [18,19]. We found a statistically significant relation between physical activity and baseline BMD with Pearson's correlation coefficient of 0.73. However, a significant correlation with bone loss was not found. Despite these conflicting results, in the light of the current data, patients should be advised to do regular weight bearing exercises in the form of regular walking for 1 hour per day at least 3 times per week. Other activities, such as cycling, gardening, climbing stairs, jogging also are encouraged [19].

Besides androgen deprivation another possibility for lower total hip BMD at baseline in men with prostate cancer is the release of cytokines from prostate cancer tumour cells. It is known that prostate cancer tumour cells produce cytokines such as IL-6, which is known to modulate cancer cell growth and increase bone resorption. In clinically localized prostate cancer, the preoperative plasma IL-6 predicted biochemical progression after surgery [20]. If the subjects with lower total hip BMD were actively losing BMD before therapy, the loss seen after GnRHanalogue would likely be exaggerated. Perhaps men with the diagnosis of prostate cancer begin to lose bone in the hip before GnRHtherapy [11].

Heavy alcohol abuse and smoking are strong risk factors for bone loss and fracture in both men and women [21, 22] but no statistically significant relation was found with alcohol in our study.

Lean stature and thin build have been identified as significant risk factors for osteoporosis in both men and women, whereas obesity has a protective role [23].

The protective role of obesity can be explained by higher serum estrogen levels in obese men secondary to peripheral aromatization of androgens in adipose tissue. Estrogens play an important role in bone metabolism in both men and women [24] . Conversely, some investigators have found no relation or an inverse relation between loss of BMD and obesity [17, 25]. This contradicts the known protective effect of obesity on osteoporosis risk and has been explained by the larger post castration decreases in serum estrogen levels derived from the peripheral conversion of testosterone in fatty tissue. We didn't find any statistically significant association with weight and BMI of the patient.

Morote J et al and Brown MW found increase in bone specific alkaline phosphatise in patients undergoing androgen deprivation therapy [26,27]. However we did not find any statistically significant result in alkaline phosphatise level in our study.

It is estimated that the optimal dietary calcium for middle aged men (age < 65years) and women (premenopausal) is 1000 mg per day or, for older individuals, 1200–1500 mg per day[28,29].

Retrospective and longitudinal studies have provided conflicting evidence about the association of calcium intake, adult bone mass, and the risk of osteoporosis in later life.In 1984, the Consensus Development Conference on Osteoporosis first suggested that increased intake of calcium may prevent osteoporosis. Since then, many studies have suggested a slower rate of bone loss and fewer fractures with adequate dietary levels of calcium and vitamin D [30,31,32].

One limitation of the current study was that it did not incorporate the measurement of markers of bone turn-over. Studies have shown that these markers correlate with BMDand predict fracture risk independent of BMD, making them important in both diagnosing and monitoring responses to therapy [33, 34]. Nevertheless, the current study highlighted the

impact of hormone ablation therapy and certain modifying factors on skeletal health, as evidenced by a marked decrease in bone mass. The results of this study may increase the awareness of clinicians and medical researchers regarding the severity of osteoporosis among patients with prostate carcinoma. Because these patients are easy to identify, an early assessment of bone mass and bone turn-over may help in their long-term management to ensure maintenance of skeletal integrity during androgen ablation therapy for prostate carcinoma.

In a study authors evaluated the BMD of Lumbar spine and both proximal thighs by means of dual energy X ray densitometry at the end of treatment period and at end of no treatment period. He found that during the first treatment period 44 of 56 patients experienced the reduction in BMD in both lumbar spine and thighs. Total testosterone level in all patients dropped to castration level. During the first period of no treatment there was an increase in BMD ( p <0.05) in 30 of 44 patients. The median time to recovery to total testosterone level to the level >50 ng/dl was 91 days and > 1oo ng/dl was 110 days. The changes in BMD positively correlated with the changes in total testosterone level ( correlation 0.18 [95% CI,0.04-0.27], p= 0.009). Decline in total testosterone level in serum was followed by decline in BMD value and vice versa [35].

In a study by Greenspan, et al bone mineral density (BMD) of the hip, wrist, total body, and spine body composition; and markers of bone turnoverwas assessed and after 12 months of follow up he found that men receiving acute ADT had a significant reduction in BMD of 2.5 +/- 0.6% at the total hip, 2.4 +/- 1.0% at the trochanter, 2.6 +/- 0.5% at the total radius, 3.3 +/- 0.5% at the total body, and 4.0 +/- 1.5% at the posteroanterior spine (all P < 0.05). Men with chronic ADT had a 2.0 +/- 0.6% reduction in BMD at the total radius (P < 0.05). Healthy controls and men with prostate cancer not receiving ADT had no significant reduction in BMD. Both use and duration of ADT were associated with change in bone mass at the hip (P < 0.05) [36].

The relationship between androgen activity reduction and osteoporosis was first demonstrated in a study in which bone density in 12 men who underwent orchiectomy was compared with that of normal controls [37]. In another, larger study, [38] there was a 14% incidence of fractures in a group with orchiectomy compared with controls, who had an incidence of 1%. Another study has shown that androgen castration can cause 5% to 10% loss in BMD [39]. There is some evidence that hormone-naïve patients with prostate cancer have BMD lower than expected for their age [40] suggesting a further risk in these men with the administration of hormonal treatment for prostate cancer, probably doubling the risk of osteoporotic fractures.

Furthermore, our observation of a higher rate of loss of BMD after orchiectomy versus LHRH agonists (compared with other studies) needs further evaluation in comparative studies.

## Conclusion

In conclusion, osteoporosis is common in elderly individuals who also are affected by ADT in prostate carcinoma patients. At time of presentation, we found that 46% of our patients were osteopenic and 24% were osteoporotic. Orchiectomy leads to accelerated bone loss, which was indicated by a 13% loss of BMD and a doubling at the 6 month follow up visit. BMD shows significant changes at femoral neck decreasing up to 2.2% at 1 month to 6.7% at 6 month after orchiectomy and in lumber spine also it shows significant changes decreasing up to 2% at one month and up to 13% at 6 months. Maximum incidence of Carcinoma Prostate was between 60 -80 years of age. No Significant changes were detected with alcohol use. BMD using QCT would help in the early identification and treatment of osteoporosis in these patients .Maintenance of body weight, weight-bearing physical activity, avoidance of smoking and alcohol, and possibly adequate dietary calcium are some measure to maintain bone mass.

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