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Original article:

Carcinoma Prostate and Bone Health – An Indian prospective

[1]Dr. Arun Makkar* , [2]Dr Rajeev Sood, [3]Dr Sandeep Kumar

[1]Assistant Professor, VMMC and Safdarjung Hospital, New Delhi

[2]Professor, ABIMS Dr RML Hospital, New Delhi

[3]Associate Professor, VMMC and Safdarjung Hospital, New Delhi.

Corresponding author *

Abstract:

Introduction-Carcinoma prostate (CaP) patients with skeletal metastases, on ADT and co-existing osteoporosis have more bone events. In this study we evaluate the bone health kinetics in the management of CaP patients.

Material and methods - A prospective observational study was performed in 101 consecutive patients of CaP (on ADT or hormone naïve). The bone density was measured with DEXA Scan at lumbar spine, left/right femur neck at 1st visit, 3rd and 6th month. Patients with negative T-Score were started on zolendronic acid (Z) or denosumab (D).

Results- Forty seven patients were started on Z, out of them, 27 (57.5 %) were significantly improved and showed positive change in BMD with improvement in T-score ($p < 0.05$). Five patients with borderline renal function at 3rd month were shifted to D. Also, 15 patients did not improve at 3rd month and they were shifted to D. Out of these 20 patients on D, 16 patients showed improvement in BMD though p value was not significant.

Thirty nine patients were given D as initial treatment modality and showed significant improvement ($p < 0.05$). Out of the 15 patients who had high baseline BMD, 11 showed positive change (p value not significant) with calcium and vitamin D supplementation only at 3 and 6 month BMD measurements. Four patients were started on Z at 3rd month.

Conclusion - There is a need to sensitize urologists regarding bone health kinetics and early preventive or curative measures. Thus in turn prevent fractures and other skeletal related events in this group of population.

Keywords: Carcinoma prostate, bone health, osteoporosis, bone events.

Introduction:

Carcinoma Prostate (CaP) is the fifth most common cancer in the world, [1] most prevalent in Caucasians and least prevalent among Asians.[2, 3] In India, it is the second most common cancer found in males (5.28%) as registered in Delhi region in The National Cancer Registry Program (NCRP).[4] For advanced and metastatic prostate cancer, ADT (androgen deprivation therapy) is the prime mode of treatment. In contemporary times, awareness of the potential bone-health complications consequent to ADT use is increasing. Multiple studies have shown that increased duration of ADT leads to significant bone loss and increased fracture risk that negatively affects quality of life (QOL). Majority of men with CaP are older

than 65 and already at risk for osteoporosis or fragility fracture. [5] Skeletal events related to bone loss and bone metastases are common complications of prostate cancer and its treatment with ADT.[6] Malhotra *et al.* have reported that Indians have low bone mineral density (BMD) as compared to western Caucasians and osteoporotic fractures are common in them compared to west.[7]

Osteoporosis (due to ADT) and complications due to bone metastases including bone pain, vertebral collapse, pathological fractures and spinal cord compression are frequently overlooked in men with CaP. All such patients should have their BMD monitored and should be offered preventive measures, along with calcium and vitamin D supplementation. The European Association of Urology (EAU) recommends baseline estimation of BMD before initiating ADT and annually as well if T-Score s in between -1.0 and -2.5 in CaP patients Patients with low BMD should be offered bone targeted therapies like Bisphosphonates or Denosumab which have shown promise in reducing fracture risk. [8,9] Independently, CaP patients with skeletal metastases and co-existing osteoporosis have more bone related complications, further putting Indian population at high risk.[10] In this study we have evaluated bone health and its kinetics in the management of CaP patients.

Methods:

A prospective observational study was performed in uro-oncological division, from November 2016 to March 2018, in 101 patients of CaP (on ADT or naïve). All patients between age 45 to 85 yrs with biopsy proven CaP on Acute (<6 months) / Chronic (>6 months) ADT were observed for change in their BMD measurements using Dual Energy X-ray Absorptiometry (DEXA) Scan at 3 monthly intervals.

The bone density was measured at three sites including lumbar spine, left and right femur neck at first month followed by at 3rd and 6th month follow up.

The patients under study were distributed into 3 groups at 3 months as per their baseline BMD and metastatic assessment. The patients with high baseline BMD at presentation (T score $\geq$ 0) were observed with no additional medication. Of these cases, those who had stable BMD after 3 months on repeat DEXA scan were continued on “observation” protocol {Observation Group (Obs)}. However, those who showed deterioration were started on zoledronic acid and labeled as “Observation to zoledronic acid” (Obs to Z) group.

The patients with negative T score at presentation were started on Zoledronic acid. The patients who showed improvement in bone health on zoledronic acid at 3 monthly BMD assessments were continued with same treatment (Z group), whereas those patients who were deteriorated were shifted onto denosumab, labeled as “zoledronic acid to denosumab” (Z to D) group.

The patients with extensive skeletal metastasis at presentation or who had deranged kidney function tests (KFTs) were started on Denosumab (“D” group) as primary therapy.

Each of these groups was analyzed for BMD changes (improvement or deterioration) as per earlier discussed protocol. Changes in BMD were analyzed using ANOVA and independent T test using SPSS v20.

The patients with positive increase in their BMD were labeled as "improved" cases. Patients with positive change in T score or age matched score were also labeled as "improved" cases.

Patients showing negative change in BMD were labeled as "deteriorated" cases. Similarly, cases with negative changes in T score or age matched score were also labeled as "deteriorated" cases.

If a patient had positive change at one site and negative change at another site then the patient was labeled as "not improved". Such cases were shifted to other modality of treatment.

Results:

In the present study, a total of 101 patients with an age range of 45 to 85 years were enrolled, of which 11 patients had localized disease and had undergone radical prostatectomy as a primary treatment. Ninety patients had metastatic disease or were found to be non-operable and were given Androgen Deprivation Therapy (ADT). Out of 90 patients who were started on ADT, 16 patients were surgically castrated and 74 patients were on medical ADT. One patient succumbed to Castrate resistant prostate cancer (CRPC) disease and hence follow up data could not be recorded. The distribution of patients among all the treatment modality groups is shown in Table 1.

Different modalities of treatment and supplementation improved the BMD of 92.1% patients, while 7.9 % of patients continued deteriorating despite different therapies. Calcium and vitamin D supplementation were given in 15 patients with good baseline BMD. Although, BMD improved in certain patients with supplementation only, but p value for change in BMD was not significant. At the same time, change over normal BMD was not expected in this group. Also, administration of bicalutamide was comparable in all groups under study.

The change in BMD with "zoledronic acid" group (n=27) was compared at all the three sites and FRAX (Fracture Risk Assessment Tool) score was calculated. In lumbar region (L1- L4) the change in BMD from baseline to third month was found to be clinically significant (p=0.005). At the same time, changes from 3rd to 6th month were also significant (p=0.047). When BMD at 1st visit was compared with BMD at 3rd visit, the changes were highly significant (p=0.0001). Similarly, in left femoral neck significant improvement was noted in BMD at 3rd and 6th month follow up (p=0.022 & 0.049 respectively). The results at right femoral neck also matched the improvement in lumbar and femoral region.

The mean change in BMD at different regions with "denosumab" (n=39) treatment was calculated. In lumbar region there was significant change from baseline BMD value (p=.011). The change in BMD of femur region in first three months was insignificant but was significant from baseline to 6th month follow up visit (p=.013) though. In right femur neck region the improvement was significant from 0 to 3rd month, 3rd to 6th month and also from 1st to 6th month. (p= .008). However, in one patient the denosumab was stopped because the patient developed osteonecrosis of jaw (ONJ).

In another group ("Obs to Z"), a total of four patients showed deterioration of BMD on observation and were shifted to zoledronic acid (n= 4).

Of patients ("Z to D" group) in whom zoledronic acid was started at first visit but did not show improvement at 3 months, 20 patients were shifted to Denosumab therapy further and again analyzed for change in BMD at 6 months. This change was significant when compared from baseline to 6th month (p=.001)

The results with different treatment modalities are combined in the bar charts {bar diagram (Figure 1)}. The change in T score at 3 visits was also calculated as represented in bar diagram (Figure2). Similar observations were made in left femur neck region. The percentage improvement in BMD from baseline was compared in patients (n= 47) who were started on zoledronic acid with patients (n=39) in whom denosumab was started as primary therapy. The results were calculated using independent sample t test. The improvement was more in Denosumab group ($p < 0.05$).

Gradual improvement was noted in T-Score in patients included in this study as depicted in Table 2.

Overall, in lumbar region, BMD measurement was 1.0537 g/cm^2 at 1st visit which was increased to 1.1501 g/cm^2 at 3rd month ($p<.05$), with further increase to 1.1926 g/cm^2 ($p<.05$) at 6th month follow up. Similarly in left femur neck region, the baseline BMD was 0.7749 g/cm^2 which showed increment at 3rd month to 0.8292 g/cm^2($p<0.05$) which further increased to 0.902 g/cm^2 ($p<.05$) at 6th month follow up.

Table 1 Distribution of patients among all the treatment modalities

Group	Frequency	Percent	Frequency	Percent
	For First 3 months		**From 3rd to 6th month**	
D	39	38.6	39	38.6
Obs	15	14.9	11	10.9
Z	47	46.5	27	26.7
Obs to Z			4	4
Z to D			20	19.8
Total	101	100.0	101	100.0

There were 3 groups for first 3 months of study period, which were increased to 5 groups from 3rd to 6th month of study period after shifting to different treatment modality as per BMD measurements at 3rd month. D, Denosumab group, Obs, Observation group, Z, Zoledronic Acid group, Obs to Z, Observation to Zoledronic Acid group, Z to D, Zoledronic Acid to Denosumab group.

Table 2 Change in T – Score (Lumbar region) distribution at different visits

T score distribution at first visit (baseline)			
T score Range	Frequency	Percent	Valid Percent
Normal	28	27.7	27.7
Osteopenic (<-1 to >-2.4)	44	43.6	43.6
Osteoporotic (≤ -2.5)	29	28.7	28.7
T score distribution at 3rd month.			
Normal	33	32.7	33.0
Osteopenic (<-1 to >-2.4)	51	50.5	51.0
Osteoporotic (≤ -2.5)	16	15.8	16.0
T score distribution at 6th month			
Normal	39	38.6	39.4
Osteopenic (<-1 to >-2.4)	47	46.5	47.5
Osteoporotic (≤ -2.5)	13	12.9	13.1

With different treatment modalities, the percentage of patients with normal BMD was increased, while that of osteoporotic population was decreased. Paradoxical increase of osteopenic population at 3rd and 6th month reflects shift from osteoporotic to osteopenic range.

Table 3 WHO diagnostic categories based on bone mass density measurements

Classification	T-Score
Normal	-1.0 or higher
Osteopenia	Between -1.0 and -2.5
Osteoporosis	-2.5 or lower

WHO, World Health Organization

Figure 1- showing BMD in lumbar region showing stable or improvement in BMD in different subgroups.D, Denosumab group, Obs, Observation group, Z, Zoledronic Acid group, Obs to Z, Observation to Zoledronic Acid group, Z to D, Zoledronic Acid to Denosumab group

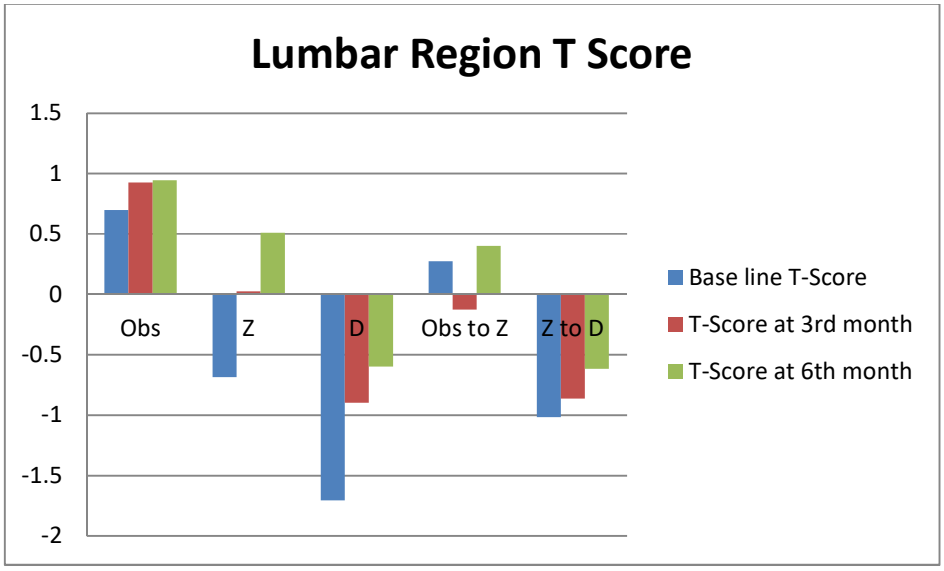
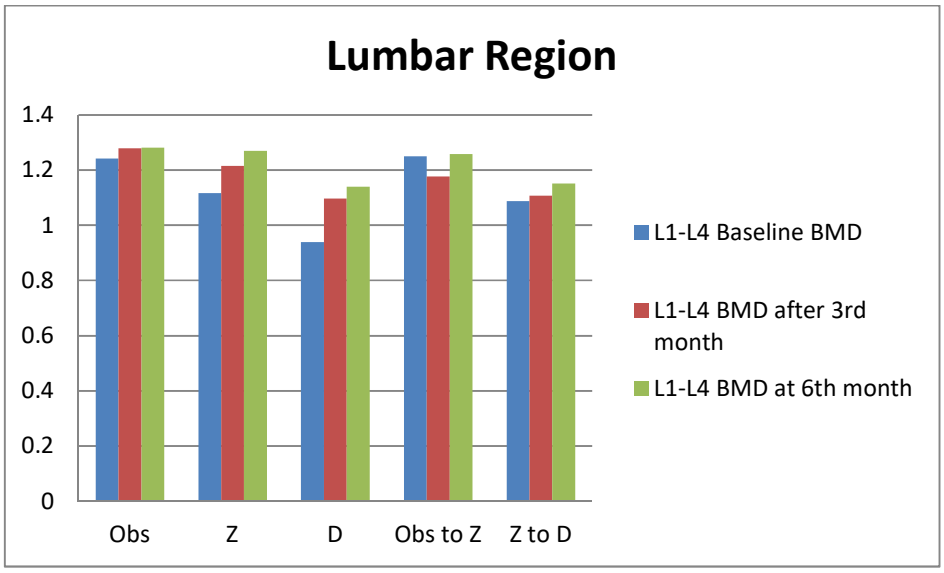


Figure 2- showing T-score in lumbar region showing gradual improvement in different subgroups**.** D, Denosumab group, Obs, Observation group, Z, Zoledronic Acid group, Obs to Z, Observation to Zoledronic Acid group, Z to D, Zoledronic Acid to Denosumab group



Discussion:

The majority of patients undergoing ADT do not receive guidance for prevention and treatment of osteoporosis. In addition, these patients have risk factors such as advanced age, bone metastasis and multiple co-morbid diseases.[15-18] In this study, total of 47 patients were started on zoledronic acid as a treatment for osteopenic and osteoporotic BMD assessment. Out of 47 patients, 27 (57.5 %) showed a significant improvement at 3rd month with positive change in BMD along with improvement in T score ($p < 0.05$). A number of studies have investigated the effect of intravenous and oral bisphosphonates in men with non-metastatic prostate cancer receiving ADT. Intravenous (IV) bisphosphonates like pamidronate 60 mg given every 12 weeks [12] or zoledronic acid 4 mg given every 3 months for 1 year [11, 13, 14] have prevented bone loss or increased BMD in men with CaP (newly initiated or on chronic ADT).In another study by Lang *et al*, zoledronic acid 4mg IV monthly for 6 months was given in men receiving ADT as primary therapy. They found an increase of BMD of 2.9% (p=.009) over baseline after 12 months and increase of 1.1 % (p=0.05) over baseline after 6 months [19]

The BMD kinetic study in Indian population clearly suggests that the patients who are on ADT need active treatment against the three major factors that includes metastatic disease, iatrogenic testosterone deficiency and their aging body as along with multiple co-morbidities of old age. In 6 month study period, none of our patient suffered pathologic fractures or new spinal cord compression. One patient underwent hyperbaric oxygen therapy and dental interventions for osteonecrosis of jaw. All the patients received vitamin D (60000 IU/week) and calcium (1200 mg/day in combination with vitamin D) supplementation. Periodically, their serum vitamin D levels were checked to avoid any toxicity. It is an established fact that calcium in combination with vitamin D significantly reduces the occurrence of fractures. Daily calcium doses of at least 1200 mg in combination with vitamin D reduces the fracture relative risk by 20% for people 50 years of age and older. [20]

Men on continuous ADT experience bone loss of up to 10% over 2 years and annual BMD decrements of –1.4%to –4.6% at the lumbar spine, –0.6% to –3.3% at thetotal hip, and –0.7% to –3.9% at the femoral neck. Patients who receive ADT are known to have increased relative risks for fracture 1.76 for hip and 1.18 for vertebrae as compared with those who did not receive ADT.[21]

When we divided our patients based on WHO classification for bone health (Table 3), we found a shift in paradigm towards normal T score range indicating effectiveness of treatment provided to them. (Table 2)

American Association of Urology (AUA) guidelines statements (which are not specific to any one index patient) offer preventive treatment for fractures and skeletal related events to CRPC patients. Clinicians can choose either denosumab or zoledronic acid while selecting a preventive treatment for skeletal related events for mCRPC (metastatic Castrate Resistant Prostate Cancer) patients with bony metastases. [23-25] National Comprehensive Cancer Network (NCCN) guidelines suggests that in hormone naïve carcinoma prostate patients (on ADT), treatment with osteoporotic treatment doses either denosumab (60 mg subcutaneously every 6 months) or zoledronic acid (5 mg IV annually) is recommended when the absolute

fracture risk warrants drug therapy. In men with CRPC, zoledronic acid (given intravenously every 3 to 4 weeks) or denosumab (120 mg subcutaneously every 4 weeks) is recommended. The optimum duration of therapy for either denosumab or zoledronic acid remains uncertain.[26]

The low rate of osteoporosis management observed in Carcinoma prostate patients on ADT, is consistent with one study we found addressing this issue. Tanvetyanon's study revealed that in men with CaP having bone metastases, only 14.7% patients received at least one intervention for osteoporosis prevention or treatment. Treatment included bisphosphonates, vitamin D, calcium, calcitonin or estrogen administration. The population was drawn from a large, suburban hospital and was mostly non-Hispanic White (64%) or African American (23%). The only predictor for receiving osteoporosis intervention was bone metastases. [27] At 3 monthly assessment of BMD measurement provided an opportunity of early recognition of osteoporosis or osteopenia and hence window for their timely management. This explains, to a large extent, the fact that none of the patient in this study, had any pathologic fracture during the study period.

Conclusion:

There is need to sensitize urologists regarding bone health kinetics and early preventive or curative measures while managing patients of carcinoma prostate. This in turn is likely to prevent fractures and other skeletal related events in this sub-group of population.

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