Original Article

Bone Mineral Density in Patients with Metastatic Prostate Cancer with or without Androgen Deprivation Therapy

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ABSTRACT

Prostate cancer commonly metastatize to skeletal sites. Androgen deprivation therapy (ADT), the primary treatment of metastatic prostate cancer, may result in osteoporosis. Bone mineral density evaluation during androgen deprivation therapy can detect patients at risk of osteoporotic fractures. **Objectives:** 1-To determine BMD (T-score) in patients with metastatic prostate cancer with or without androgen deprivation therapy. 2-To compare BMD in metastatic prostate cancer patients with age matched controls. **Study Design:** case-control study. **Setting**: Urology Department, Allied Hospital Faisalabad. **Materials and Methods:** BMD of patients with metastatic prostate cancer (30 with ADT, 30 without ADT sampled with non-probability convenience method) were compared with age matched control group of 60 subjects. Inclusion criteria. Group-I: 60-80 years aged consecutive patients of carcinoma prostate who have been taking anti androgen therapy at least six months. Group-II: 60-80 years consecutive patients with metastatic prostate cancer who have not started any antidrogen deprivation therapy. Group-III: 60-80 years aged healthy men from general population (preferably from patient's family) without prostate cancer. Exclusion criteria: From all groups, men taking for any reason, chemotherapy , radiation thyroxin, warfarin, corticosteroids, methrotrexate, anticonvulsants, post organ transplant therapy, chronic heparin, antipsychotic medications, long term lithium therapy and calciuretic diuretics were not included in the study**. Results:** Out of 120 subjects, 31% had normal BMD, 27% osteopenia, 42% osteoporosis. In metastatic prostate cancer patients taking ADT (n=30), 7% subjects had normal BMD, 37% osteopenia and 56% osteoporosis. In metastatic prostate cancer patients without ADT (n=30), 13% subjects had normal BMD, 63% osteopenia, 24% osteoporosis. In healthy controls (n=60), 52% subjects had normal BMD, 33% osteopenia, 15% osteoporosis. **Conclusions:** BMD is affected by prostate cancer and its treatment. Bisphosphonates use should be rationalized according to the patients need. **Key Words:** Metastatic Prostate cancer, ADT, BMD.

INTRODUCTION

Prostate cancer is the most common malignancy in males older than 50 years of age .Most of the deaths from prostate cancer are due to advanced disease[1].It almost exclusively metastasizes to bones[2]. High incidence of bone metastasis in prostate cancer causes pain, fractures and spinal cord compression. Androgen manipulation for treatment of prostate cancer was first described by Huggins and Hodges [3] and it is still a treatment of choice with patients with advanced prostate cancer[4].These agents results in osteoporosis and increased bone fragility.[5] Consequently, men with prostate cancer are at risk of adverse bone effects both from disease and treatment[6]. Both estrogen and testosterone are important in maintaining bone formation. These hormones decrease in aging men.[7] As a result, BMD decreases significantly with increasing age.[8] Peak bone mass occurs in third decade of life and after that there is 0.5 to 1% loss of BMD yearly. Serial bone densitometry evaluation during androgen deprivation therapy is recommended to detect patients at risk of osteoporotic fractures.[9] Bisphosphonates are medications used to treat diseases which result in weakened bones like osteoporosis, osteopenia or bone cancer and they are also used intravenously in treatment of multiple myeloma and breast cancer.[10,11] The present study was conducted to measure BMD

changes in normal population as well as patients with metastatic prostate cancer with or without ADT and to rationalize use of bisphosphonates in metastatic prostate cancer patients.

BONE DENSITY AND OSTEOPOROSIS

Bone Density is a term used in quantifying the mineralization of bone. It can be measured through different techniques and results are reported as T-score and Z-score. T-score is the number of standard deviations below the average for a young adult at peak bone density. The Z-score is the number of standard deviations below an average person of same age, race and gender. Osteoporosis is the most common metabolic bone disease and contributes to fractures particularly in the elderly. In osteoporosis there is a reduction in the amount of bone per unit volume [12] . As the prevalence of prostate cancer and osteoporosis both increase with age, many patients at diagnosis of prostate cancer may already have osteoporosis. Indeed, patients with prostate cancer about to undergo ADT (without bone metastases) have been found to have lower BMD than age-matched controls. The additional impact of ADT on bone metabolism has the potential to influence morbidity and mortality in prostate cancer [13] .The World Health Organization has defined osteoporosis as a bone mineral density of more than 2.5 standard deviations (T score <2.5) below the mean value for young adults. According to WHO standards. Normal bone: T-score better than -1. Osteopenia: T-score between -1 and -2.5 Osteoporosis: T-score less than -2.5.

MATERIALS AND METHODS

Study was conducted at Urology Department, Allied Hospital Faisalabad. It was a case-control study. With non-probability convenience sampling technique were included, sixty patients of metastatic prostate cancer, out of which 30 were on androgen deprivation therapy, while 30 without androgen deprivation therapy. These 60 patients with prostate cancer were matched with age matched control group of 60 healthy men without prostate cancer.

INCLUSION CRITERIA

Group-I: 30 consecutive patients with prostate cancer and with age range of 60-80 years who have been taking anti androgen therapy for at least six months. Group-II: 30 consecutive patients with prostate cancer and with age range of 60-80 years who have not started any antidrogen deprivation therapy. Group-III: 60 healthy men from general population (preferably from patient's family) with age range of 60-80 years but without prostate cancer.

EXCLUSION CRITERIA

From all groups, men who were taking for any reason, chemootherapy, radiation, thyroxin, warfarin, corticosteroids, methrotrexate, anticonvulsants, post organ transplant therapy, chronic heparin, antipsychotic medications, long term lithium therapy and calciuretic diuretics were not included in the study.

DATA COLLECTION PROCEDURE

Sixty consecutive patients with histopathologically and radiologically proven metastatic prostate cancer were taken, both from out-patient and in-patient departments of Allied Hospital Faisalabad buhealthy men was taken from general population. Informed consent was taken . Bone mineral density (BMD) was measured with a bone mineral density meter and T-score were recorded. All informations were recorded on a specially designed Performa.

DATA ANALYSIS

All the data was entered in SPSS and analyzed through its statistical package. The quantitative variables like age, duration of illness, duration of androgen deprivation therapy, bone mineral density (T-score) were presented as Mean and S.D. The qualitative variables like normal bone density, osteopenia, osteoporosis, were presented as frequency and percentages. For comparison of quantitative variables, T-test has been applied. For comparison of qualitative variables, Chi-square test has been applied. P value $\leq$ 0.05 is considered as significant.

RESULTS

In this study, 120 subjects were studied. Sixty subjects had metastatic prostate cancer, out of which 30 were those who were already on ADT for at least six months while 30 had metastatic prostate cancer but treatment with ADT was not started till they presented to us. 50% subjects were taken from normal population as control group. Ages of all subjects ranged from 60-80 years. Cross tabulation of different

variables showed a strong negative correlation of BMD(T-score) with age (P-value < .05) and duration of illness (P-value < .05), however decrease in BMD by increasing the duration of ADT showed significance at 10% level (table-1). Table-2, 3 and 4 are showing Means and S.E of BMD (T-score) with confidence intervals of subjects of different groups (Table-2) ,age subgroups in all subjects (Table-3) and age sub-groups of individual groups (Table-4).Analysis of variance for BMD score of subjects showed a highly significant (P-value < .001) difference in mean BMD score of different groups and also highly significant difference in age subgroups (P-value <.001)(Table-5). Analysis of qualitative variables to see the frequency and distribution of BMD scores showed that out of 120 , only 37% subjects have normal BMD(BMD score better than -1) out of which 84% subjects belong to group-III (healthy controls), 11% belongs to group-II (disease only) and only 5% belong to group-I (disease +treatment)(Table-6).Total 50% subjects have osteopenia (BMD score -1 to 2.5), out of which 40 % subjects belong to group-III (healthy controls), 38 % belongs to group-II (disease only) and 22 % belong to group-I (disease + treatment) (Table-6). Total 33 % subjects have osteoporosis (BMD score - < 2.5), out of which 27 % subjects belong to group-III (healthy controls), 21 % belongs to group-II (disease only) and 52% belong to group-I (disease +treatment) (Table-6). Fig. 9-1, 2 and 3 are showing frequency of normal BMD, osteopenia and osteoporosis in individual groups .In group-I (metastatic prostate cancer patients taking ADT) 7% subjects have normal BMD, 37% subjects have osteopenia and 56% have osteoporosis (Fig-1). In Group-II (metastatic prostate cancer patients without ADT), 13% subjects have normal BMD, 64% subjects have osteopenia and 23% have osteoporosis (Fig-2).In healthy controls, 52% subjects have normal BMD, 33% subjects have osteopenia and 15% have osteoporosis(Fig-3). Fig.4 is showing frequency of normal BMD, osteopenia and osteoporosis in all subjects.

DISCUSSION

Prostate cancer is one of the most common cancers affecting men worldwide [14]. Its incidence is rising annually by 2-3% [15]. Bone metastasis occurs in >80% of patients with advanced–stage disease[16,17] resulting in significant skeletal morbidity.[18] The primary modality of treatment for patients with metastatic prostate cancer is hormonal therapy [5] which is done by either orchidectomy or LH-releasing hormone agonists.[19] Effects of ADT include not only suppression of tumor growth, but also adverse effects on various bodily functions.[20] Advancing prostate cancer negatively impacts normal bone physiology not only by direct tumor involvement but also by osteoporotic effect of ADT.[21] Although increasing age and ADT are known risk factors for osteoporosis, advanced CAP itself is an independent predictor.[21] BMD may decrease by 4% to 13% yearly in men receiving such therapy.[22] The present study was conducted to see BMD changes in metastatic prostate cancer patients with and without treatment with ADT as well as osteoporosis in these patients in comparison with healthy population of same age group. 60 patients were enrolled in the study and their BMD (T-scores) was measured and was compared with BMD of 60 age-matched healthy controls. This study is comparable to the work done by Hussain SA, Weston R, Stephenson RN, George E, Parr NJ in year 2003. They found that 42% of men diagnosed with prostate cancer had osteoporosis and 37% had osteopenia before initiating ADT compared with a 27% incidence of osteoporosis in the age matched control group.[23]This study is comparable to the work done by Smith MR, McGovern FJ, Fallon MA, Schoenfeld D, Kantoff PW, Finkelstein JS in year 2001. They described that men with prostate cancer may experience significant bone loss due to disease even before ADT initiation. They evaluated 41 patients with prostate cancer and no history of ADT with baseline BMD studies and found that 14 (34%) had osteopenia or osteoporosis.[22] This study is comparable to the work done by Andrew Wilcox and Molly L Carnes in year 2006.They evaluated one hundred and seventy-four subjects, with a mean age of.[24]This study is comparable to the work done by 76 years and median duration of 21 months of ADT, and

found that more than 50% of men who have undergone bone densitometry after starting ADT had osteoporosis Susan L. Greenspan, Penelope Coates, Susan M. Sereika, Joel B. Nelson, Donald L. Trump and Neil M. Resnick in year 2005.They found that Men with chronic ADT had a 2.0 ± 0.6% reduction in T-Score (BMD). They also declared that Men with prostate cancer who are initiating ADT have a 5- to 10-fold increased loss of bone density at multiple skeletal sites compared with either healthy controls or men with prostate cancer who are not on ADT.[25] This study is comparable to the work done by Tsutomu Nishiyama, Fumio Ishizaki, Tsutomu Anraku, Hisanobu Shimura, and Kota Takahashi who found a significant decrease (P-value < 0.023) in BMD after ADT.[19] Bisphosphonates are medications used to treat malignancy induced hypercalcemia.[16] Other indications are in diseases which result in weakened bones including osteoporosis, osteopenia, or bone cancer. Until recently, bisphosphonates have not been demonstrated significant clinical benefit in prostate cancer patients with bone metastases[15] proven by the fact that contrary to osteloytic bone metastases resulting from breast cancer and multiple myeloma, bone metastases in patients with prostate cancer are primarily osteoblastic, which result in the deposition of calcium in bones. Thus, the role of bisphosphonates in management of prostate cancer becomes controversial.[5] However, in some patients with prostate carcinoma and a diffuse metastatic invasion of the skeleton, there is indirect biochemical and histologic evidence of osteomalacia which can be aggravated by bisphosphonate administration because of the transient high prevalence of osteoblastic activity over bone resorption, which also occasionally causes the appearance of symptomatic hypocalcemia.[26] Analysis of the cost-effectiveness of using pamidronate (a bisphosphonate) in patients with breast cancer have shown that its use is associated with high incremental cost per adverse event avoided 27,28[0]. Zoledronic acid is a more expensive agent than pamidronate, and the incremental cost of preventing each skeletal-related event in patients with prostate cancer is likely to be high and not cost-effective. Thus, zoledronic acid cannot be recommended as a standard therapy for men with prostate cancer and metastases to bone.[5] However bisphosphonates have a documented role in treatment of ADT associated bone loss.[7]

CONCLUSION

Men with prostate cancer have bone loss at presentation. Initiation of androgen deprivation therapy further decreases BMD. Early diagnosis of bone loss is essential in men with advanced prostate cancer who are initiating ADT. Patients treated with ADT should have baseline and periodic bone densitometry scans to assess BMD for fracture risk. As no oral or intravenous medication has been approved to prevent bone loss from androgen deprivation therapy. Therefore, until it is proved that drug therapy with bisphosphonates decreases the risk of fracture, treatment can not be recommended in all patients on Androgen deprivation therapy. Use of bisphosphonates, which are very costly drugs should be rationalized in a developing country like Pakistan and should not be prescribed blindly.

Table-1
Correlations of BMD with different variables

Variables & No. of subjects	BMD	P-values
Age n=120	- .579**	.000 <.01
Duration of illness n=60	- .385**	.002 < .01
Histopathology n=60	- .108^{NS}	.412
Duration of ADT n=30	-.312^{NS}	.094*

BMD bone mineral density, NS Not significant,
*significant at 10% level
**Highly significant

Table-2

Means of BMD (T-Score) for subjects of three groups along with confidence interval

Group	Mean	Std. Error	95% Confidence interval	
			Lower bound	Upper Bound
1 (n=30)	-2.643	.181	-3.002	-2.284
2 (n=30)	-1.932	.272	-2.470	-1.393
3 (n=60)	-1.530	.133	-1.793	-1.266

n=120

Table-3

Mean BMD (T-Score) for subjects of age sub-groups of all subjects along with confidence interval

Group	Mean	Std.Error	95% Confidence interval	
			Lower bound	Upper Bound
60-65	-1.231	.156	-1.539	-.922
66-70	-1.754	.134	-2.021	-1.488
71-75	-2.750	.343	-3.430	-2.069
76-80	-2.405	.247	-2.894	-1.915

n=120

Table-4

Mean BMD (T-Score) of subjects in age sub-groups of each group along with Confidence Interval

Group	Age Group	Mean	Std. Error	95% Confidence Interval	
				Lower Bound	Upper bound
1(n=30)	60-65	-2.486	.336	-3.152	-1.820
	66-70	-2.243	.238	-2.714	-1.772
	71-75	-2.920	.398	-3.708	-2.132
	76-80	-2.925	.444	-3.806	-2.044
2(n=30)	60-65	-1.170	.281	-1.727	-.613
	66-70	-1.856	.222	-2.297	-1.416
	71-75	-3.000	.889	-4.762	-1.238
	76-80	-1.700	. 513	-2.717	-2.044
3(n=60)	60-65	-.03	.162	-.358	-.285
	66-70	-1.164	.238	-1.635	-.693
	71-75	-2.329	.336	-2.995	-1.663
	76-80	-2.589	.296	-3.176	-2.002

Age groups (years) : 60-65 , 66-70 , 71-75 ,76-80)

BMD bone mineral density,

* Significant,

** Highly significant,

NS non significant

Table-5

Analysis of variance for BMD (T-Score) in different groups

Source of variance	Sum of squares	Degree of freedom	Mean Square	F-value	P value
Among all groups	19.403	2	9.702	12.277**	.000
Among Age groups	21.010	3	7.003	8.863**	.000
Interaction b/w groups and age groups	16.482	6	2.747	3.476 **	.004
Error	85.344	108	.790		
Total	479.660	119			

Age groups (years): 60-65, 66-70, 71-75 , 76-80)

BMD bone mineral density

* significant

** highly hignificant

NS non significant

Table-6

Frequency and Distribution of the normal BMD, osteopenia and osteoporosis in different groups

	Group-I	Group-II	Group-III	Total
Normal BMD	02 (5%)	4(11%)	31(84%	37(31%)
Osteopenia	11 (22%)	19(38%)	20(40%)	50(41%)
Osteoporosis	17 (52%)	7(21%)	9(27%)	33(28%)
	30	30	60	120(100%)

Chi- square = 34.546 P <. 001

Figure-1
Frequency of normal BMD, osteopenia and osteoporosis in group-I

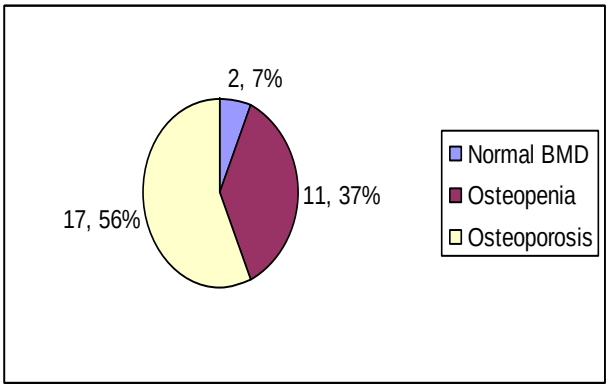
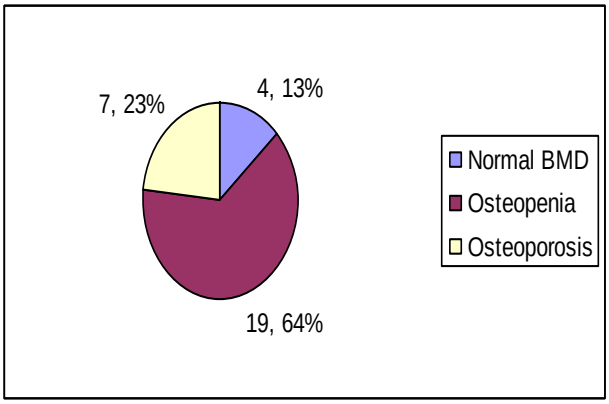


Figure-2
Frequency of normal BMD, osteopenia and osteoporosis in group-II



Fiure-3
Frequency of normal BMD, osteopenia and osteoporosis in group-III

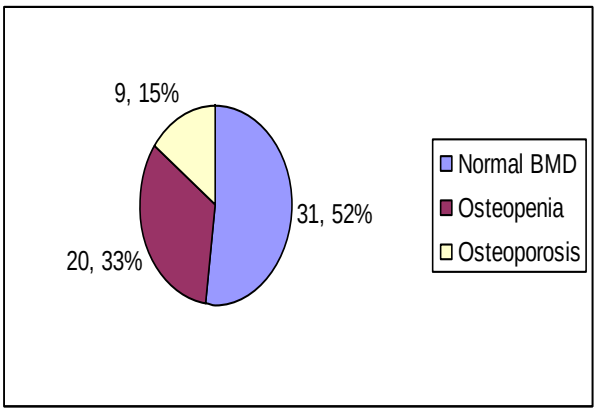
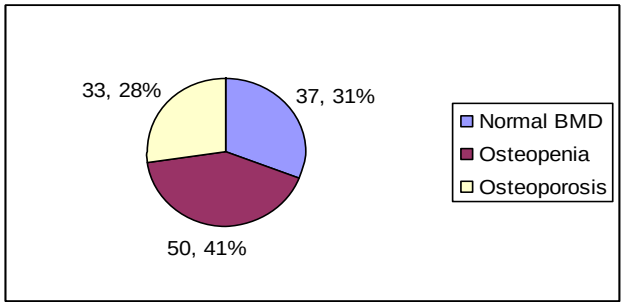


Figure-4
Frequency of normal BMD, osteopenia and osteoporosis in all subjects



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