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Bone mineral density, pathological fractures and bisphosphonate therapy in prostate cancer patients on androgen deprivation therapy

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Objectives. The aim of the study is to evaluate the changes of bone mineral density (BMD), incidence of pathological fractures and to asses the effect of bisphosphonate therapy in prostate cancer patients (PCa) on androgen deprivation therapy (ADT) with the use of LHRH.

Methods. In this prospective study bone mass density (BMD) was assessed by dual x-ray absorptiometry (DXA) in 97 PCa patients and 89 patients of compared group. DXA was examined at baseline and patients in the study group were subjected to ADT. PCa patients with osteoporosis were treated by calcium, vitamin D, and bisphosphonate and the subsequent DXA was made after 10 months. All other PCa patients (non-osteoporotic) had DXA examined every 12-14 months.

Results. Patients of the study group had significantly lower baseline L1-L4 and total hip BMD ($p=0.028$, $p=0.022$). BMD was significantly lower in L1-L4 and total hip ($p=0.004$, $p<0.001$, resp.) after 10-14 months and in L1-L4, femoral neck, and total hip ($p=0.001$, $p=0.037$, $p< 0.001$, resp.) after 20-26 months of ADT. After the treatment for osteoporosis with bisphosphonate a significant increase of BMD ($p=0.04$) was found in a total of 23 patients. Overall, the incidence of fractures after 20-26 months of ADT was 8.5 %.

Conclusions. Osteopenia is very common in hormone naive PCa patients. There was a significant loss of BMD after 12 months of ADT which was progressive while the patients were on ADT. Bisphosphonate therapy was effective after 20 months of treatment. The incidence of pathological fractures was 7-fold higher in the study group.

Key words: prostate cancer, bone mineral density, androgen deprivation therapy, fractures, bisphosphonate

Introduction

Prostate cancer (PCa) is the most common visceral malignancy in men and the probability of developing such cancer is increasing with age (Liska et al. 2007; Jemal et al. 2009). Androgen deprivation therapy (ADT) for advanced PCa is considered as standard for more than 60 years. It has been demonstrated that ADT significantly reduces tumor growth and improves the survival beyond 3 years after competition (Bolla et al. 1997). However, a majority of data showed several adverse effects of ADT, the most considerable of them being the loss of bone mineral density (BMD) resulting in increased fracture risk (Shahinian et al. 2005). Skeletal fractures negatively correlate with overall survival in men with PCa (Oefelein et al. 2002), while the maintaining of skeletal health is crucial for the quality of life and survival (Saad et al. 2004). Among the typical features of PCa is the ability to metastasize into bones in more than 80 % of cases (Bubendorf et al. 2000) and the treatment of resulting pathological fractures is complicated and expensive (McKiernan et al. 2004). It has been reported

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that hormone naive patients with advanced PCa have low initial BMD and relatively high prevalence of osteopenia and osteoporosis (Ziaran et al. 2009).

The diagnosis of osteoporosis is based on WHO definitions which were originally developed for women (Kanis et al. 1994). When based on male cutoffs, 1-2 million (3-6 %) of men have osteoporosis and 8-13 million (28-47 %) have osteopenia, but when based on female cutoffs, less than one million (1-4 %) have osteoporosis and 4-9 million (15-33 %) have osteopenia (Looker et al. 1997). While these data may seem disturbing, it is believed that the osteoporosis in US is substantially underdiagnosed and undertreated (Kiebzak et al. 2002). For these reasons, there is an increasing concern about ADT-related bone loss and skeletal complications in males with PCa treated by ADT.

Current guidelines recommend the assessment of bone mineral density (BMD) previous to the start of ADT and yearly thereafter (Diamond et al. 2004) with dual-energy x-ray absorptiometry (DXA) which is considered the standard method to measure BMD (WHO 1994). International Society for Clinical Densitometry (ISCD) recommended that central skeleton sites (lumbar spine, total hip and femoral neck) are the most appropriate locations to asses BMD (Kanis et al. 2005).

In accordance with these guidelines, we performed prospective study to determine the loss of BMD, the incidence of pathological fractures and the effect of antiresorptive therapy in patients on long term ADT for PCa. When using systematic search on www.pubmed.com with keywords "prostate cancer, bone loss, bisphosphonate, fracture" there are not much such designed studies, if any.

Subjects and Methods

Patients. A total of 97 patients (mean age 73.4 ± 6.3 years [SD]; range 63-79 years; mean prostate specific antigen [PSA] 15.4 ± 7.5 ng/ml [SD]) with locally advanced PCa were included in the study group. All of them had verified PCa by a prostate biopsy. The areas of bone mineral density (gm/cm^2) were measured in femoral neck, total hip and lumbar spine and were examined via dual x-ray absorptiometry (DXA, QDR 4500, Hologic Inc, Bedford, MA) prior to the start of androgen deprivation therapy (ADT). All examinations were performed by the same device and the results were evaluated by the same experienced osteologist. Patients with osteoporosis diagnosed at baseline DXA examination or thereafter, had another DXA examination after 10 months. Patients with normal BMD or osteopenia at baseline had another examination after 12 or 14 months.

Osteoporotic patients were advised to increase daily dietary calcium intake (up to 1500 mg), prescribed calcium supplements (Calcium effervescens, Slovakofarma, 500 mg twice a week), vitamin D (Vigantol oil Merck, 500 µg/ml, 10 drops a week) and bisphosphonate (risendronate, Risendros Zentiva, 35 mg per week).

Patients were given LHRH agonists, every 3 or 6 months. Patients with skeletal metastases diagnosed on bone scan were excluded from the study. In all of them biochemical parameters (serum creatinine, urea, ALT, AST, GMT, ALP, ionogram, serum glucose) were estimated to exclude metabolic disorders and chronic renal failure. All of them were also mobile, and had no history of pathologic fractures.

For the comparison of BMD data also the group of 89 patients (mean age 71.9 ± 6.7 years [SD], range 64-78 years, mean PSA 2.4 ± 1.8 ng/ml [SD]) has been followed which were selected according to the following criteria: no history of oncological disease, no history of chronic metabolic disease, no history of pathological fractures, all were mobile. Patients of this compared group were subjected to the same biochemical tests as the study group.

Statistical evaluation was performed with the use of Statistical Package for Social Sciences SPSS version 17 (IBM SPSS Statistics NY, USA). Quantitative variables are presented as mean and standard deviation. Non-parametric Mann-Whitney U test was used to compare independent quantitative variables between two groups. Chi-square test was used to compare qualitative variables between two or more groups. Two-tailed test was used for all comparisons. The value of $p<0.05$ was considered as statistically significant.

Results

BMD examinations

1. Baseline (first) BMD examination. A total of 57 patients (58.7 %) of the study group had initial BMD at L1-L4 and/or at femoral neck below the normal reference level (osteopenia or osteoporosis), while 39 patients (40.2 %) had osteopenia either at L1-L4 (18 patients) or at femoral neck (21 patients) only, but 18 patients (18.5 %) had osteoporosis either at L1-L4 (11 patients) or at femoral neck (7 patients) (Table 1).

Among the compared group, 37 patients (41.6 %) had initial BMD at L1-L4 and/or at femoral neck or total

hip below the normal reference level (osteopenia or osteoporosis), while 30 patients (33.7 %) had osteopenia at L1-L4 (14 patients) or femoral neck and/or at total hip (16 patients), 7 patients (7.9 %) had osteoporosis at L1-L4 (4 patients) or at femoral neck and/or total hip (3 patients) (Table. 1).

For all BMD values at the first examination see Table 1.

2. Second BMD examination (after 10-14 months of ADT). A. L1-L4. In the study group osteoporosis was found in 17 patients (6 new cases) and osteopenia in 21 patients (11 new cases). Four patients had fractures at L1-L4. In the compared group osteoporosis was found in 4 patients (2 new cases) and osteopenia in 13 patients (4 new cases). The loss of L1-L4 BMD after 10-14 months of ADT in the study group was statistically significant ($p<0.01$).

B. Femoral neck. In the study group osteoporosis was found in 7 patients (5 new cases) and osteopenia in 28 patients (6 new cases). Femoral fractures were not found. In the compared group osteoporosis was found in 3 patients (2 new cases) and osteopenia in 18 patients (5 new cases).

The loss of femoral neck BMD in both groups was not significant ($p= 0.534$) (Table 1).

C. Total hip. In the study group the loss of total hip BMD in study group was statistically significant ($p<0.001$) (Table 1) and 4 cases of lumbar fractures (4.1 %) were found, while in the compared group no fractures were found.

For all BMD values at the second examination see Table 1.

3. Third BMD examination (after 20-26 months of ADT). A. L1-L4. In the study group osteoporosis was found in 18 patients (10 new cases) and osteopenia in 37 patients (21 new cases). In the compared group osteoporosis was found in 7 patients (6 new cases) and osteopenia in 18 patients (8 new cases). The loss of BMD at L1-L4 after 20-26 months of ADT in the study group was statistically significant ($p<0.001$) (Table 1).

B. Femoral neck. In the study group osteoporosis was found in 12 patients (6 new cases) and osteopenia in 36 patients. In the compared group osteoporosis was found in 7 patients (5 new cases), and osteopenia in 17 patients (7 new cases). The loss of femoral BMD in the study group was statistically significant ($p=0.037$) (Table 1).

C. Total hip. In study group the loss of total hip BMD was statistically significant ($p<0.001$) (Table 1). After 20-26 months of ADT a total of 5 patients (6.1 %) had fractures of L1-L4 and 2 patients (2.4 %) had fractures of femoral neck. Overall, the incidence of fractures after 20-26 months of ADT was 8.5 %. In the compared group one patient (1.1 %) had L1-L4 fracture and no femoral fractures were found.

For all BMD values at the third examination see Table 1.

Assesment of bisphosphonate therapy

As stated above, patients with diagnosed osteoporosis were advised to increase daily calcium and vitamin D3 intake and were treated with bisphosphonates.

Study group. After 10 months of bisphosphonate treatment (resindronate, 35 mg per week) a total of 18 patients had osteoporosis (among them 11 patients at L1-L4, and 7 patients at femoral or total hip) in the study group. After the treatment, BMD decreased in three patients (among them in two at L1-L4 as well as in one at femoral neck), while in 6 patients it increased (but remained osteoporotic) and in 9 patients increased and has been classified as osteopenia. After the 2nd DXA examination (10-14 months of ADT treatment) 23

Table 1

Data on bone mineral density (BMD) in various locations

Variable	Location	Study group	Compared group	P
Baseline BMD	L1-L4	1.0217 ± 0.1592	1.0622 ± 0.1298	< 0.05
	Femoral neck	0.8067 ± 0.1036	0.8273 ± 0.8750	NS
	Total hip	0.9161 ± 0.1723	0.9428 ± 0.1625	< 0.05
BMD after 10-14 months	L1-L4	0.9786 ± 0.1470	1.0382 ± 0.1501	< 0.01
	Femoral neck	0.7625 ± 0.1119	0.8053 ± 0.0771	NS
	Total hip	0.8717 ± 0.1690	0.9274 ± 0.1674	< 0.001
BMD after 20-26 months	L1-L4	0.8860 ± 0.0902	0.9845 ± 0.1060	0.001
	Femoral neck	0.6684 ± 0.0895	0.7506 ± 0.0836	0.037
	Total hip	0.7757 ± 0.1498	0,8978 ± 0.1510	<0.001

Table 2

Bone mineral density (BMD) in both groups after 10 months of biophosphonate therapy

Variable	Baseline BMD	BMD after 10 months of bisphosphonate therapy	P
Study group	0.7386 ± 0.0987	0.7506 ± 0.0907	0.286
Compared group	0.7482 ± 0.1027	0.7846 ± 0.0909	0.065

Table 3

Bone mineral density (BMD) in both groups after 10 months of biophosphonate therapy

Variable	Baseline BMD (after 2nd examination)	BMD after 20 months of bisphosphonate therapy	P
Study group	0.7416 ± 0.0995	0.7612 ± 0.1107	0.04
Compared group	0.7490 ± 0.1104	0.7906 ± 0.1034	NS

patients were found with osteoporosis (among them 16 patients at L1-L4, 7 patients at femoral and/or total hip). The increase of BMD in this group was not statistically significant (Table 2).

After 20 months of bisphosphonate treatment BMD decreased in three patients (one at L1-L4, two at femoral neck), it patient remained unchanged (at L1-L4) in on patient, while in 7 patients it increased (but still remained osteoporotic) and in remaining 12 patients in increased to osteopenia. The increase of BMD in this group was statistically significant (Table 3).

2. Compared group. After the initial examination a total of 7 patients with osteoporosis were found (four at L1-L4 and three at femoral neck). After 10 months of biphosphonate treatment, BMD increased in all patients, but two remained osteoporotic (at L1-L4), while five remaining patients were classified as osteopenic, but the increase of BMD was not statistically significant (Table 2).

After the second examination (at 10-14 months) we found three patients with osteoporosis (two at L1-L4 and one at femoral neck). After a total of 20 months of bisphosphonate treatment (at the third DXA examination), BMD increased in all patients to osteopenia. However, due to the low number of patients we did not perform statistical analysis (Table 3).

Discussion

Osteopenia is very common in patients with advanced PCa prior to start of ADT, in this group the loss of BMD is usually rapid due to long-term ADT. Previously, we found significantly lower BMD in patients with PCa prior to ADT (Ziaran et al. 2009). Despite the lack of data concerning osteoporosis and osteopenia in patients prior to the start of ADT one study shows different results - 35.4 % had osteopenia with an increase to more than 80 % after 10 years of ADT. Osteoporosis was not common in these patients (Morote et al. 2007). No other particular data about the BMD of men who will undergo ADT were found using Medline/PubMed medical databases. A large cross-sectional analysis showed that the vast majority of older men receiving ADT for PCa have either osteopenia or osteoporosis (Bruder et al. 2006).

Our data showed that the loss of total hip and L1-L4 BMD after 10-14 months of ADT was significantly higher than that found in the compared group. These results are similar to those found by Melton et al. (2003). The loss of femoral neck BMD was not significant. The reason of this "disproportion" remains unknown. Information regarding this result is scarce in scientific literature. Bruder et al. (2006) reported proportional loss of both L1-L4 and femoral neck BMD while in contrast, Abrahamsen et al. (2007) found more rapid loss in femoral BMD.

We found four lumbar fractures (4.1 %), but no femoral fractures after 10-14 months in the study group which shows that the risk of bone fractures was relatively high even after short term ADT. Similar results were also reported by Malcolm et al. (2007). In contrast, we found no fractures in the control group.

Some studies reported most significant BMD loss within the first year of ADT (Israeli et al. 2008). In our study, the loss of BMD was similar, if not more pro-

nounced after 2 years of ADT. Our results also suggest that the loss of BMD depends on the duration of ADT. Long - term ADT leads to a significant loss of L1-L4, femoral and total hip BMD, and inevitably leads into higher risk of skeletal- related events. The incidence of fractures in the study group was 6.1 % and 2.4 % of L1 – L4 and femoral neck, respectively. Overall, the incidence of fractures after 20-24 months of ADT was 8.5 %, while the incidence of fractures in the control group after was 1.1 %. Thus, the difference was 7-fold. Other studies present similar results (Lopez et al. 2005). These results show that the patients with ADT, especially long-term, are in the great risk of skeletal related events. Patients with advanced PCa are difficult to treat (because of age, poor general condition, major surgery risk etc.) and that is why the clinicians should be aware of the skeletal status of these patients (McKiernan et al. 2004).

Bone fractures often imply severe consequences for the quality of life. A proximal femur or vertebral fracture in elderly men is an event that often leads to permanent disability. The possibility of recovery from such events is minimal, with a five-year mortality which is significantly higher in men than in women (Center et al. 1999).

Moreover, ADT has other adverse effects on body composition including the decrease in lean body mass and muscle size (Smith et al. 2002). These body composition changes may result in frailty and increase the risk of falls in older men (Fried et al. 2001). All these factors should be taken into consideration prior to the start of ADT.

BMD is inversely related to fracture risk in men and women (Cummings et al. 1993). Thus, males treated with ADT should have BMD measured before the initiation of ADT and then periodically (Kanis et al. 2005). This would help in the early detection of osteoporosis (Agarwal et al. 2005) and allows early treatment to prevent serious consequences.

The effect of bisphosphonate therapy on bone is well documented (Smith et al. 2001). However, we failed to prove its efficacy after the second DXA examination. This may be due to lower number of patients treated with bisphosphonate therapy (18 patients). On the other hand, the increase of L1-L4 BMD after the 3rd DXA examination (after two years of treatment) was statistically significant ($p<0.04$) in the study group which is in agreement with the findings by Ishizaka et al. (2007). Fortunately, we did not observe any jaw osteonecrotic events such as reported by Raffaelli et al. (2010).

In conclusion, this study provides the complex information about the baseline BMD in PCa patients as well as about the effect of ADT on the loss of BMD and on the incidence of fractures on one side as well as about that of bisphosphonate therapy on the other.

Osteopenia is very common in men with PCa who will receive ADT. These results showed significantly lower initial BMD in patients with advanced PCa as compared to patients of the same age without PCa. Moreover, the use of ADT in PCa patients resulted in further significant loss of BMD and thus in 7-fold higher risk of skeletal fractures after 24 months. It is highly recommended to examine BMD prior to the start of ADT and then periodically in PCa patients. Periodic measurement of BMD while on ADT would help in the early detection of osteoporosis. The physician should always bear in mind adverse effects of the ADT and to detect them early. The bisphosphonate therapy was found effective, well tolerated, and safe in the treatment of ADT related osteoporosis.

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