ORIGINAL ARTICLE

Bone mineral density change: Comparison between prostate cancer patients with or without metastases and healthy men (a North African ethnic group)☆


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Abstract

Aim: To evaluate total body bone mineral density and regional bone mineral density in patients with prostate cancer with and without metastases, and to correlate them with bone scintigraphy findings.

Patients and methods: 135 patients with prostatic carcinoma and 50 healthy subjects were investigated with bone scintigraphy and dual-energy X-ray absorptiometry. The bone scintigraphic findings were classified as normal (score 0: n = 55), abnormal but not typical for metastases (score 1: n = 45), and typical pattern of metastases (score 2: n = 35).

Results: The patients with bone metastases prostate cancer had significantly higher total bone mineral density and regional bone mineral density of trunk and pelvis than healthy controls and prostate cancer patients without bone metastases. There was a significant positive correlation between bone scan score and total bone mineral density and regional bone mineral density of trunk and pelvis (r = 0.328; P < 0.05; r = 0.60; P < 0.001; r = 0.480; P < 0.001, respectively).

Conclusion: Bone metastasis is a major cause of morbidity in prostatic cancer; bone loss during hormonal treatment is currently effective. Our results show that patients of prostate cancer with bone metastases have increased bone mineral density (BMD) in the pelvis and trunk, possibly because of a predominance of osteoblastic over osteolytic metastases demonstrated by 99mTc MDP bone scan.

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KEYWORDS
Prostate cancer; Scintigraphy; Bone mineral density; Bone metastasis


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Introduction

A number of large-scaled studies carried out in western countries have proven a positive relationship between serum PSA level and prevalence of positive bone scan findings, in newly diagnosed prostate cancer patients. The prognosis and survival of these men depend greatly on whether or not skeletal metastatic disease can be identified at the time of the diagnosis. About 80–85% of patients who die of prostate cancer have skeletal involvement. Bone metastasis of prostatic carcinoma is mostly osteoblastic and is a frequent case. Bone metastasis is a major cause of morbidity in prostatic cancer with associated problems including pain and pathological fractures. Thus, detecting and monitoring of the bone lesions are crucial for the treatment of prostatic carcinoma. Bone scintigraphy using Technetium 99m (Tc-99m) labeled diphosphonates is the most widely used technique for the detection and surveillance of metastatic spread to the skeleton. The uptake of diphosphonates depends on both local blood flow and osteoblastic activity. Although the actual uptake mechanism is still not clear, diphosphonates are probably incorporated into the hydroxyapatite crystal on the bone surface. The use of Tc-99m labeled diphosphonates depends on osteoblastic response, which accompanies bone destruction by a metastasis. This phenomenon also occurs in predominantly lytic lesions, which are usually associated with an attempt at bone repair and will, therefore, appear as areas of increased tracer accumulation on bone scan. Early diagnosis of bone loss and treatment to improve bone health are important to protect the patient from fractures. Dual-energy X-ray absorptiometry (DXA) is the most widely used method of measuring BMD because of its advantages of high precision, short scan times, and stable calibration in clinical use. The fundamental principle behind DXA is the measurement of the transmission through the body of X-rays of 2 different photon energy levels. Because of the dependence of the attenuation coefficient on the atomic number and photon energy, the measurement of the transmission factors at 2 energy levels enables the areal densities (i.e., the mass per unit projected area) of 2 different types of tissue to be inferred. In DXA scans, these are taken to be bone mineral (hydroxyapatite) and soft tissue, respectively. This exam can be used to monitor spine, hip, wrist, heel, finger, or total body BMD. An expert panel from the international society for clinical densitometry has determined that the spine is the preferred site of densitometry for the serial measurement to monitor changes in BMD. In this study, we aimed to evaluate the relationship between the value of bone mineral density and bone scintigraphy in patients with prostate cancer.

Materials and methods

Patients

135 consecutive patients (with a mean age of 67.6 ± 7.4 years), newly diagnosed, histologically confirmed adenocarcinoma of the prostate and 50 healthy subjects (with a mean age of 66.9 ± 6.8 years) were studied. None had had diseases such as renal failure, hepatic disease, metabolic or inflammatory bone diseases, and recent traumatic fractures. For all patients and healthy subjects, bone scintigraphy and bone mineral density were performed.
The ethics committee of our university military hospital and Medical Faculty approved the study protocol. Informed consent was obtained from the patients and controls.

**Bone scintigraphy**

Bone scans were performed after injection of 555 MBq (15 mCi) technetium-99m-labeled methylene diphosphonate (MDP). For each patient, images were obtained under the same conditions after repositioning of the patient in a standard position using a double-head gamma camera system (Siemens E-Cam dual-head, variable-angle system, Berlin, Germany) equipped with high-resolution collimators for low energy. The photon peak was centered at 140 keV with a 20% window. The bone scintigraphic findings were evaluated by the consensus of 2 experienced observers at the time of diagnosis. The bone scintigraphic results in patients with prostate cancer were classified as score 0: patients have prostate cancer with entirely normal bone scintigraphy (n = 55), score 1: patients have prostate cancer with non-typical lesions in bone scintigraphy (n = 45), and score 2: patients have prostate cancer with typical metastatic lesion in known bones (1 or more; lumbar and thoracic, spines, pelvic bones, etc.) (n = 35).

**Bone mineral density (BMD)**

Bone mineral density (in grams per square centimeter) was measured in the total body, head, trunk, pelvis, arms, and legs by dual-energy-ray absorptiometry (XR-46 bone densitometer with dynamic filtration; Norland Corp., Fort Atkinson, WI). The Norland XR-465 was calibrated daily, 30 min after the apparatus was turned on. Quality was controlled using a calibration standard and quality control phantom.

**Statistics**

Data were analyzed using the statistical package SPSS for Windows (Ver. 9.05; SPSS Inc., Chicago, IL). Results were expressed as mean ± SD. Statistical significance was set at the 0.05 levels. Comparison between groups was assessed by one-way ANOVA and Tukey HSD-test. Correlation analysis was performed to assess the relation between bone scan score and BMD values.

**Results**

Demographic characteristics and BMI values of patients and controls are summarized in Table 1. There was no difference of age and BMI between cancer patients and control group (P > 0.05).

Table 2 lists the results of the total and regional bone mineral density in head, trunk, pelvis, arms, and legs in prostatic cancer patients and healthy controls. Total BMD in cancer patients was not significantly different from those of healthy control (P > 0.05). Also, there was no difference in BMD values of head, arms, and legs between the two groups, but the bone mass of both trunk and pelvis was found to be higher in cancer patients than in the control group (P < 0.05).

Table 3 shows the BMD values of patients with bone metastases in accordance with the extent of disease score. In the metastases group (bone scan score 2), 25 of the patients (71%) had metastases in spine, 25 patients (71%) in the pelvis, and 20 patients (57%) in both spine and pelvis. The values of the patients who have bone scan score of 1 were not significantly different from those without bone metastases. Total bone mineral density and regional bone mineral density of the trunk and pelvis in patients with bone scan score 2 were significantly higher than healthy controls (P < 0.05, P < 0.001, and P < 0.001, respectively), bone scan score 0 (P < 0.05, P < 0.001, and P < 0.001, respectively) and bone scan score 1 (P < 0.01, P < 0.001, and P < 0.05, respectively) (Table 3). But the regional bone mineral density of head, arms, and legs did not differ between the groups. Although there were no correlations between bone scan score and regional BMD of head, arms, and legs (r = 0.09, P = 0.504, r = 0.20, P = 0.057, r = 0.003, P = 0.985, respectively), there was a significant positive correlation between bone scan score and total and regional BMD of trunk and pelvis (r = 0.32, P < 0.05, r = 0.60, P < 0.01, r = 0.48, P < 0.01, respectively).

**Discussion**

Due to the increasing awareness of the disease entity, the advent of the prostate specific antigen (PSA) testing for screening or early diagnosis and the improvement in life expectancy of the male population, the epidemiology of PCa in the North-African ethnie have changed.\(^1\,^4\) In our city, the incidence of new cases of PCa is rapidly increasing, from 358 new cases registered in 1997 to 1068 cases in 2007, nearly tripling in 10 years. According to our national cancer register, a crude incidence rate is rising and the disease is being found earlier as well. However, the mortality from PCa is relatively static, with the number of deaths at 121 in 1997 and 289 in 2007, respectively. This implies that an increasing number of our citizens are living with prostate cancer.

Considering that the skeleton is the most painful and debilitating site of metastasis from PCa, skeletal screening is crucial in management planning and assessing the prognosis in the early disease state. Skeletal scintigraphy is the gold standard investigation in diagnosing bone metastases; it is more sensitive than skeletal radiography and serum alkaline phosphatase levels, it is good in its accessibility, non-invasiveness, low radiation dose, and above all, its ability to evaluate the entire skeletal system.\(^4\)

Total body bone densitometry enables the measurement of total body bone mineral density and regional bone mineral density. The total body bone densitometry has been judged to be the best bone mass measurement technique for discriminating between normal and abnormal subjects.\(^4\,^3\) Total hip is suggested when the spine analysis is technically invalid. The goals of BMD are to identify patients at risk, to monitor the rate of bone loss, and to guide the implementation of treatments to preserve bone health. Bone health recommendations from an interdisciplinary panel support BMD assessment of patients before the initiation of androgen deprivation therapy (ADT) and recommended...
Table 1  Demographic characteristics and BMI values of patients and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 135)</th>
<th>Controls (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Score 0 (n = 55)</td>
<td>Score 1 (n = 45)</td>
<td>Score 2 (n = 35)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>67.1 ± 7.1</td>
<td>67.5 ± 7.3</td>
<td>67.9 ± 7.5</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.1 ± 3.1</td>
<td>25.5 ± 3.4</td>
<td>25.4 ± 3.8</td>
</tr>
</tbody>
</table>

Table 2  Mean values ± SD of the total and regional bone mineral density (g/cm²) in head, trunk, pelvis, and legs in patients with prostate cancer and controls.

<table>
<thead>
<tr>
<th></th>
<th>Patients (n = 135)</th>
<th>Controls (n = 50)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>1.548 ± 0.163</td>
<td>1.504 ± 0.182</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Trunk</td>
<td>1.095 ± 0.171</td>
<td>0.958 ± 0.144</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1.150 ± 0.198</td>
<td>L2.1 ± 0.128</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Arms</td>
<td>0.828 ± 0.125</td>
<td>0.819 ± 0.114</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Legs</td>
<td>1.042 ± 0.110</td>
<td>1.004 ± 0.108</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Total</td>
<td>1.060 ± 0.155</td>
<td>1.023 ± 0.143</td>
<td>&gt;0.05</td>
</tr>
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</table>

BMI = body mass index.

regular follow-up to monitor bone loss during hormonal treatment. Recently, bone densitometry has been developed extensively as a tool for evaluating bone mass. However, there have been few densitometric studies of bone mass in patients with metastatic prostate cancer. These studies report differences in axial and peripheral bone mass. Given the discrepancies in the findings of regional bone densitometry in patients with osseous metastases of prostate cancer, we decided to evaluate total body bone mineral density and regional bone mineral density in patients with prostate cancer with and without metastases, and to compare them with bone scintigraphy.

Cancer cells spread to the bone via the blood and enter an environment unlike that of the visceral organs. The bone matrix is hard and relatively acellular with low metabolic activity. Yet, within this matrix area, there is a plethora of growth factors for the osteoclasts and osteoblasts, the key players in bone reformation. Once the cancer cells are attached and begin to grow, they can affect the bone with the exception of the prostate and cause an osteolytic response characterized by breakdown of the matrix; in contrast, prostate cancer bone metastases are generally osteosclerotic, characterized by excessive bone formation because of prostate cancer having caused an imbalance

Table 3  Mean values ± SD of the total and regional bone mineral density (g/cm²) in head, trunk, pelvis, arms and legs in patients with prostate cancer, regarding bone scan score.

<table>
<thead>
<tr>
<th>Bone scan score</th>
<th>0 (n = 55)</th>
<th>1 (n = 45)</th>
<th>2 (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>1.583 ± 0.200</td>
<td>1.497 ± 0.115</td>
<td>1.556 ± 0.139</td>
</tr>
<tr>
<td>Trunks</td>
<td>1.005 ± 0.124</td>
<td>1.058 ± 0.156</td>
<td>1.271 ± 0.119</td>
</tr>
<tr>
<td>Pelvis</td>
<td>1.065 ± 0.135</td>
<td>1.135 ± 0.239</td>
<td>1.305 ± 0.117</td>
</tr>
<tr>
<td>Arms</td>
<td>0.802 ± 0.088</td>
<td>0.798 ± 0.152</td>
<td>0.903 ± 0.109</td>
</tr>
<tr>
<td>Leg</td>
<td>1.054 ± 0.125</td>
<td>1.011 ± 0.109</td>
<td>1.061 ± 0.073</td>
</tr>
<tr>
<td>Total</td>
<td>1.033 ± 0.152</td>
<td>1.007 ± 0.150</td>
<td>1.172 ± 0.104</td>
</tr>
</tbody>
</table>

| a P < 0.001 is significantly greater than that of bone scan score 0. |
| b P < 0.001 is significantly greater than that of bone scan score 1. |
| c P < 0.001 is significantly greater than that of bone scan score 0. |
| d P < 0.05 is significantly greater than that of bone scan score 1. |
| e P < 0.05 is significantly greater than that of bone scan score 0. |
| f P < 0.05 is significantly greater than that of bone scan score 1. |
favouring an osteosclerotic response. Our findings show that the patients with bone metastases prostate cancer had significantly higher total bone mineral density and regional bone mineral density of the trunk and pelvis than healthy controls and prostate cancer patients without bone metastases, whereas the regional bone mineral density of head, arms, and legs did not differ between the groups. Galasko reported that 70% of the patients with prostate cancer have bone metastases; on the other hand, Tofe et al. reported that these metastases are located mainly in the spine (60%), pelvis (57%), and less frequently in the skull (14%) and in the arms and legs (38%). Our results coincide with these findings: no differences were found in the regional bone mineral density of the head, arms, and legs between patients with prostate cancer and healthy controls, but there were differences between the BMD of pelvis and trunks of patients and controls.

There are discrepancies in the findings of regional bone density in patients with osseous metastases of prostate cancer. Rico et al. found that patients with prostate cancer and bone metastases had decreased bone mass. They interpreted the result as being due to the predominantly osteolytic rather than the osteoblastic nature of the metastases. However, androgen deprivation therapy, caused by either bilateral orchidectomy or treatment with a gonadotrophin-releasing hormonal agonist, decreases bone mineral density. As bone loss may be increased by hormonal manipulation, if BMD is measured after such a treatment, it will probably be at lower levels compared with the pretreatment values. Tanaka et al. found no differences in the regional bone mass of the arms in comparisons of patients with prostate cancer and bone metastases with healthy subjects, but they found a higher regional bone mineral mass in the spinal column of the patients with prostate cancer than in the healthy subjects. They concluded that metastases demonstrated by Tc-99m MDP bone scan were predominantly osteoblastic metastases. Our results coincide with those of Chang et al. and Rico et al. They evaluated BMD of lumbar spines in 30 prostate cancer patients with lumbar spine metastases and compared them with cancer patients without lumbar metastases. They found that BMD in lumbar spine increases in patients with lumbar spine metastases. In our study group, the patients with metastases had higher level of total and regional BMD of trunk and pelvis than the prostate cancer patients without metastases. As metastases of prostate cancer are located generally in the pelvis and trunk, they may probably increase BMD in these regions. Also, we found that there was a significant positive correlation between bone scan score and regional BMD of trunk and pelvis ($r = 0.60$, $P < 0.01$, $r = 0.48$, $P < 0.01$, respectively).

In fact the baseline BMD and the rate of bone loss vary in different men. BMD should therefore be measured before hormonal treatment (ADT) is started and be repeated periodically during the treatment. Lower axial or peripheral BMD levels correspond with increased risk of pathologic fractures, which, in turn, correlate with decreased survival. Therefore, BMD monitoring can identify cases in which treatment intervention to prevent fractures is warranted. Effective treatments of bone loss during ADT are currently available, and can be useful to preserve bone health in this setting.

**Conclusion**

Total body bone densitometry has been judged to be the best bone mass measurement technique for discriminating between normal and abnormal subjects. A significant positive correlation was found in our ethnie, between bone scan score and total bone mineral density and regional bone mineral density of trunk and pelvis. Our results show that patients of prostate cancers with metastases demonstrated by Tc-99m MDP bone scan have increased BMD in the pelvis and trunk, possibly because of a predominance of osteoblastic over osteolytic metastases demonstrated by Tc-99m MDP bone scan.

**Conflict of interest**

The authors have no conflicts of interest to declare.

**References**
