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## Biochemical Bone Markers in Prostate Cancer Patients with Local and Advanced Bone Metastases

Received: May 05, 2000

**Abstract :** In the present study involving patients with bone metastases arising from prostate cancer, we measured urinary deoxypyridinoline (DPD) as a marker of collagen breakdown activity, serum total and bone-specific alkaline phosphatase activities and serum prostate specific antigen (PSA). This study included 20 patients with benign prostate hyperplasia (BPH) and 23 patients with carcinoma, 11 of had with bone metastases. DPD excretion in urine was significantly greater in prostate cancer patients with bone metastasis than in those with localised prostate cancer or BPH ( $p<0.001$ ), but the difference between the localised prostate cancer and BPH groups was

not significant ( $p>0.05$ ). The serum markers of bone formation [total alkaline phosphatase (T-ALP) and bone ALP (B-ALP)] displayed higher mean concentrations in the group with positive bone metastases than in the group with local disease ( $p<0.001$  for both). Serum T-ALP and B-ALP levels and urinary excretion of DPD were significantly correlated with the Soloway score ( $p=0.03$ ,  $p=0.01$  and  $p=0.01$  respectively). Urinary DPD and serum B-ALP and T-ALP may provide useful information for supplementing PSA and bone-scan results in evaluating bone-metastatic activity.

**Key Words:** Prostate cancer, Deoxypyridinoline, Bone markers

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### Introduction

Prostate cancer commonly causes osteoblastic metastases, which present problems in treating patients with advanced prostate cancer. PSA is widely accepted as the most important marker for detecting prostate cancer and for monitoring treatment (1). However, it has a low positive predictive value for bone metastases (2). Tumours infiltrating bone produce simultaneous bone destruction and reactive bone formation. Biochemical markers of bone metabolism have been studied as indicators of bone response, including urinary calcium (3), urinary hydroxyproline (4) and serum ALP (5), all of which are influenced by the rate of bone resorption. However, they are somewhat limited for routine clinical evaluation. New markers for bone metastasis are required in order to evaluate the activity and response of bone metastases of prostate cancer. When the bone matrix is resorbed, the cross-link residues, pyridinoline and DPD are released from the collagen molecules and eventually excreted in urine (6). Several reports suggest that the assay of these collagen cross-link residues may provide valuable markers of bone metastases in patients with prostate cancer (7) or breast cancer (8). In the

present study involving patients with bone metastases arising from prostate cancer, we measured urinary DPD as a marker of collagen breakdown activity, serum total and bone-specific alkaline phosphatase activities and serum PSA. The aim of the study was to investigate the relationship of these parameters and to determine the association between DPD and neoplastic bone involvement in patients with prostate cancer.

### Materials and Methods

This study included 20 patients with BPH and 23 patients with prostate carcinoma, 11 of whom had bone metastases. BPH was documented pathologically by prostate biopsy or transurethral resection. Patients with localised prostate cancer were found to have normal pelvic lymph nodes by computerised tomography, and normal results in bone scintigraphy. Localised cancer patients were treated with radiotherapy or radical prostatectomy, and metastatic cancer patients with hormone therapy. Diagnosis of bone involvement was performed with bone scintigraphy followed by radiological confirmation. Exclusion criteria were as

follows: any history of recent bone fracture, history of a second primary cancer or metabolic bone disease, current use of corticosteroids and any liver disease or other bone diseases leading to increases in ALP. All samples were drawn in the early morning after an overnight fast, and included spot urine specimens for measurement of creatinine and DPD, and blood specimens for measurements of PSA, T-ALP and B-ALP. The serum and urine specimens obtained were stored at  $-70^{\circ}\text{C}$  until the assay date. Urine DPD and serum PSA were measured by chemiluminescence (Immulite), and serum ALP and urine creatinine were measured with commercially available kits (Boehringer Mannheim, Germany). The expected values for DPD in man are 2.3-5.4 nM DPD/mM creatinine. In B-ALP, after the total activity of ALP was determined, bone-ALP was precipitated using the precipitant—a lectin from wheat germ—and the remaining ALP activity measured in the supernatant.

Bone scintigram metastatic burden was graded and patients were divided into 4 groups as described previously by Soloway et al. (9). The scans were graded as follows 1) less than 6 bony metastases each of which was less than 50% the size of a vertebral body (a lesion occupying the entire vertebral body was counted as 2 lesions); 2) 6 to 20 bone metastases; 3) more than 20 bone metastases but less than a “superscan” and 4) “superscan” (diffuse symmetrical uptake without visualisation of the kidneys) or its equivalent (greater than 75% of the ribs, vertebrae and pelvic bones). According this classification, of prostate carcinoma patients with bone metastasis, 4 were of grade 1, 3 of grade 2, and the remaining at grade 3.

Statistical Analysis: Differences between groups were tested using the non-parametric Mann-Whitney U-test. Correlations between Soloway score and parameters

were calculated using Spearman’s rank correlation test. A value of  $p < 0.05$  was regarded as significant.

**Results**

DPD excretion in urine was significantly greater in prostate cancer patients with bone metastasis than in those with to localised prostate cancer or BPH ( $p < 0.001$ ), but the difference between localised the prostate cancer and BPH groups was not significant ( $p > 0.05$ ). In the prostate cancer group with bone metastasis, although PSA values showed some overlap, statistically significantly different mean values were determined (Table 1). Serum markers of bone formation (T-ALP and B-ALP) displayed higher mean concentrations in the group with positive bone metastases than in the group with local disease ( $p < 0.001$  for both). We compared serum levels of T-ALP, B-ALP and PSA and urinary DPD levels by the method of Soloway et al. for grading bone scintigrams. Serum T-ALP and B-ALP levels and urinary excretion of DPD were significantly correlated with the Soloway score ( $p = 0.03$ ,  $p = 0.01$  and  $p = 0.01$  respectively Table 2). However, serum PSA was not correlated with the bone scintigram score ( $p = 0.17$ ).

**Discussion**

Prostate cancer affects mostly elderly men and bone metastases are the most common form of prostate cancer metastasis, the presence of which affects the prognosis of such patients. Radioisotopic bone scans have a remarkable sensitivity for detecting metastases, but bone scans may not correlate with actual disease activity (7). In addition, bone scans are expensive and incapable of detecting bone degradation. Thus a biochemical marker with the ability to discriminate between patients with and

	BPH (n=20)	LPC (n=12)	MPC (n=11)
Age	60.5±6.52	61.75±7.82	65.36±7.50
DPD	3.73±1.60	5.19±2.32	14.49±6.95*
T-ALP	148.85±32.34	179±44.27	655.27±360.83*
B-ALP	39.30±18.74	46.75±28.66	476.54±302.22*
PSA	3.57±2.70	8.09±4.43**	197.65±107.57*

Table 1. Median age and distribution of values of biochemical markers in the three groups of patients.

\*  $p < 0.001$ : MPC versus LPC and BPH; \*\*  $p < 0.01$ : LPC versus BPH; BPH, benign prostate hyperplasia; LPC, localised prostate cancer; MPC, metastatic prostate cancer.

Table 2. Spearman's rank correlation coefficients for the correlation between Soloway grading and parameters in patients with bone metastases.

	Correlation coefficient ( r )	p
DPD	0.79	0.01
T-ALP	0.66	0.03
B-ALP	0.81	0.01
PSA	0.43	0.17

without metastatic bone involvement would be important for the early diagnosis of advanced prostate cancer.

It is known that PSA in serum has a high diagnostic value in the early diagnosis of prostate cancer, and it is possible to differentiate almost completely between patients with or without prostate cancer on the basis of PSA measurements, but there is a considerable overlap of PSA values between various stages of prostate cancer (10), and decreasing levels cannot be used to evaluate treatment efficacy in individual patients (11).

Collagen is a triple helical structure that contributes to the strength and integrity of the bony matrix. Degradation products of collagen are excreted in the urine and are not reused in collagen synthesis. Recent evidence suggests that urinary excretion of these cross-

links is not affected by dietary habits (4). Therefore, analysis of collagen metabolites in urine has been used to monitor bone collagen metabolism in physiological and pathological conditions. We found that patients with bone metastases had significantly higher mean concentrations of urinary DPD than those of cancer patients without clinical evidence of bone involvement. Our results demonstrate that urinary DPD may be a clinical marker of bone metastasis in prostate cancer, as has also been reported by other investigators (7,12). DPD is an analogue of pyridinoline and has a greater specificity for bone than does pyridinoline (13).

In the present study, it was observed that T-ALP and B-ALP can be used in diagnosing advanced prostate cancer. The prostate cancer-related increase in serum ALP activity is considered to reflect accelerated bone turnover after bone metastatic prostate cancer. Our results support the previous reports (7,12,14). In conclusion, urinary DPD and serum B-ALP and T-ALP may provide useful information supplementing PSA and bone-scan results in evaluating the bone-metastatic activity.

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