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Biochemical markers for the detection of bone metastasis in patients with prostate cancer: diagnostic efficacy and the effect of hormonal therapy

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Abstract In the present study, we investigated the diagnostic effectiveness of biochemical markers of bone turnover for the detection of bone metastasis from prostate cancer and changes in the levels of these markers caused by hormonal therapy. Ninety-five patients with prostate cancer were divided into one of three groups: 26 patients with bone metastasis (BM(+)), 35 patients without bone metastasis on nonhormonal therapy (BM(−)HT(−)) and 34 patients without bone metastasis on hormonal therapy (BM(−)HT(+)). All patients in the BM(+) group had received hormonal therapy. Serum or urinary levels of the following biochemical markers of bone turnover were examined: bone-specific alkaline phosphatase (B-ALP), osteocalcin (OC), type I procollagen C-propeptide (PICP), type I collagen cross-linked C-telopeptide (ICTP), C-telopeptide fragment (CTx), N-telopeptide fragment (NTx), total pyridinoline (T-Pyr), total deoxypyridinoline (T-D-Pyr) and free deoxypyridinoline (F-D-Pyr). The BM(+) group showed significantly higher values than the BM(-)HT(-) group for B-ALP, PICP, NTx, CTx, T-Pyr, T-D-Pyr, and F-D-Pyr. Compared with the BM(−)HT(+) group, the BM(+) group showed significantly higher values for B-ALP, ICTP, NTx, T-Pyr and T-D-Pyr. The levels of B-ALP, NTx, CTx, T-D-Pyr and F-D-Pyr were significantly different between the BM(−)HT(−) and BM(−)HT(+) groups. All markers, except OC and CTx, significantly were correlated with the extent of bone metastasis on bone scintigraphy. Of all markers, receiver operating characteristic (ROC) analyses revealed B-ALP and F-D-Pyr to be the most sensitive and specific for differentiation between the BM(+) and BM(−)HT(−) groups with regard to bone formation and resorption, respectively. In contrast, B-ALP and ICTP were most sensitive and specific for differentiation between the BM(+) and BM(−)HT(+) groups. The results suggest that hormonal therapy greatly affects the efficacy of PICP, CTx and F-D-Pyr in the diagnosis of bone metastasis, whereas its effects on ICTP are small. Although bone metabolic markers would be useful in the diagnosis of bone metastasis from prostate cancer, the effects of hormonal therapy on bone metabolism should be kept in mind in their evaluation.

Key words prostate cancer · bone metastasis · biochemical markers of bone turnover · antiandrogen · luteinizing hormone-releasing hormone analog

Introduction

Bone is one of the most common sites of metastasis from prostate cancer, and bone metastasis greatly affect the quality of life and prognosis of patients with prostate cancer. Although bone scans have been widely used for the assessment and monitoring of bone metastasis, they have several shortcomings, such as nonspecificity and limited availability. Recently, various biochemical markers have been developed and used as indicators of bone formation or resorption. The efficacy of these bone metabolic markers for assessing bone metastasis in patients with prostate cancer has been evaluated in several studies [1–17]. The results have demonstrated that serum levels of total alkaline phosphatase (ALP) [1,3,4], bone-specific ALP (B-ALP) [6,12,17] and type I procollagen C-propeptide (PICP) [1,5–7,9,10,15] as bone formation markers, serum levels of type I collagen cross-linked C-telopeptide (ICTP) [1,2,5,9,10,13–15] and urinary levels of pyridinium cross-links [8,9,11,16] as bone resorption markers were useful for the assessment of the progression or regression of bone metastasis in patients with prostate cancer. Overall, both bone formation and resorption markers, except osteocalcin (OC), are thought to be effective in the diagnosis of bone metastasis from prostate cancer. However, the precise order of the diagnostic reliability of these markers varies among reports.

Hormonal therapy is often used in the management of prostate cancer patients. The effects of sexual hor-

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mone may be different depending on the type of bone markers. Indeed, in women, the magnitude of elevation after menopause is small for ICTP and large for urinary pyridinium cross-links [18]. Because the effects of hormonal therapy on the diagnosis of bone metastasis of prostate cancer have not been examined thoroughly in previous studies, the variability of the endocrine state as a result of hormonal therapy may cause different results in the order of diagnostic reliability of bone markers. In the present study, we evaluated the diagnostic efficacy of biochemical markers of bone turnover for the detection of bone metastasis from prostate cancer and investigated the effects of hormonal therapy on these markers and, thus, the diagnosis of bone metastasis.

Materials and methods

Subjects

Between October 1997 and March 1998, 95 patients with pathologically confirmed prostate cancer at our hospital underwent bone scintigraphy for the assessment of bone involvement. Subjects were divided into two groups: 26 patients with bone metastasis (BM(+); mean age 71.6 ± 8.5 years), and 69 patients without bone metastasis (BM(−)). The latter group was further divided into 35 patients on nonhormonal therapy (BM(−)HT(−); mean age 71.7 ± 6.8 years) and 34 patients on hormonal therapy (BM(−)HT(+); mean age 75.1 ± 7.8 years). Patients in the BM(−)HT(+) group received a luteinizing hormone-releasing hormone (LH-RH) analog (gosereline acetate; 3.6 mg; s.c., every 4 weeks) alone or combination therapy with an antiandrogen (flutamide; 375 mg daily) and an LH-RH analog as hormonal therapy. The administration period of the drugs was from 1 to 88 months (mean 20.53 months). All patients in the BM(+) group had received hormonal therapy. The diagnosis of bone metastasis was made using conventional radiography, bone scintigraphy, computed tomography and magnetic resonance imaging. The details of the study were explained to all subjects and their written consent to participate was obtained.

Bone scintigraphy

The extent of bone metastasis was classified into five grades according to the extent of disease (EOD) score formulated by Soloway et al. [19]: 0, normal or abnormal due to benign bone disease; 1, bone metastases fewer than 6; each of which is less than 50% of the size of a vertebral body (one lesion approximately the size of a vertebral body would be counted as two lesions); 2, bone metastases between 6 and 20; 3, the bone metastases more than 20 but less than a superscan; and 4, a superscan or its equivalent (i.e. more than 75% of the ribs, vertebrae, and pelvic bones).

Measurement of biochemical markers

Urine and blood samples were obtained from 0800 to 1030 h, and were kept frozen at −40°C until assay. Bone formation markers (i.e. PICP, B-ALP, and OC), and bone resorption markers (i.e. ICTP, C-telopeptide fragment (CTx), N-telopeptide fragment (NTx), total pyridinoline (T-Pyr), total deoxypyridinoline (T-D-Pyr), and free deoxypyridinoline (F-D-Pyr)), were analyzed. Serum PICP and ICTP were measured by radioimmunoassay (Procollagen PICP and Pyridinoline ICTP, respectively; Chugai Pharmaceutical, Tokyo, Japan). Serum B-ALP was determined by enzyme immunoassay (Alkphase-B; Metra Biosystems, Palo Alto, CA, USA). Serum OC was measured by a two-site immunoradiometric assay (Mitsubishi BGP-IRMA; Mitsubishi Chemical, Tokyo, Japan). Urinary NTx and CTx were determined by enzyme-linked immunosorbent assays (ELISA; Osteomark; Mochida Pharmaceutical, Tokyo, Japan and CrossLaps ELISA; Osteometer, Rodovre, Denmark, respectively). Urinary T-Pyr and T-D-Pyr were measured by high-pressure liquid chromatography (HPLC) as described by Fujimoto et al. [20]. Urinary F-D-Pry was determined by ELISA (Pyrinks-D; Metra Biosystems). Results for NTx, CTx, T-Pyr, T-D-Pyr and F-D-Pry are expressed relative to urinary creatinine.

Statistical analysis

Marker data are expressed as the mean ± SD. The significance of differences between groups of patients was assessed by the Student's *t*-test. The ability of biochemical markers to discriminate between subjects in different groups was evaluated by using receiver operating characteristic (ROC) analysis. The areas under the ROC curves were calculated using the ROCKIT program of Metz [21]. The correlation between the EOD score and biochemical markers was determined with the Spearman rank correlation test by assigning an EOD sore of 0 to cases in the BM(−)HT(+) group. $P < 0.05$ was considered to indicate statistically significant differences or relationships.

Results

Comparison of nonmetastatic and metastatic patients

Subjects in the BM(+) group showed significantly higher values than those in the BM(−)HT(−) group for PICP, B-ALP and five bone resorption markers (NTx, CTx, T-Pyr, T-D-Pyr, and F-D-Pyr). However, compared with subjects in the BM(−)HT(+) group, those

Table 1. Biochemical bone markers measurements in patients with prostate cancer (mean ± SD)

	BM(+)	BM(−)HT(−)	BM(−)HT(+)
No. Subjects	26	35	34
Age (years)	71.6 ± 8.5	71.7 ± 6.8	75.1 ± 7.8
Bone formation markers			
PICP (ng/ml)	136.5 ± 35.2[a]*	112.0 ± 30.3	127.7 ± 40.3
B-ALP (U/l)	33.3 ± 20.5[a]***,[b]**	18.5 ± 6.4	24.6 ± 9.4[c]**
OC (ng/ml)	9.1 ± 5.9	7.2 ± 4.5	8.0 ± 5.1
Bone resorption markers			
ICTP (ng/ml)	5.5 ± 2.2[b]**	4.5 ± 1.8	4.2 ± 1.5
NTx (nM BCE/mM Cr)	83.9 ± 45.3[a]***,[b]**	42.9 ± 21.7	60.1 ± 27.3[c]**
CTx (mg/M Cr)	404.2 ± 227.8[a]***	187.6 ± 146.4	352.2 ± 192.1[c]***
T-Pyr (pM/μM Cr)	52.6 ± 17.0[a]***,[b]**	39.3 ± 17.8	44.0 ± 17.8
T-D-Pyr (pM/μM Cr)	9.2 ± 3.1[a]***,[b]**	5.8 ± 2.5	7.6 ± 2.8[c]**
F-D-Pyr (pM/μM Cr)	7.6 ± 2.4[a]***	5.0 ± 2.1	6.4 ± 2.2[c]**

Data are the mean ± SD
BM(+), with bone metastasis; BM(−)HT(−), without bone metastasis on nonhormonal therapy; BM(−)HT(+), without bone metastasis on hormonal therapy; B-ALP, bone-specific alkaline phosphatase; OC, osteocalcin; PICP, type I procollagen C-propeptide; ICTP, type I collagen cross-linked C-telopeptide; CTx, C-telopeptide fragment; NTx, N-telopeptide fragment; T-Pyr, total pyridinoline; T-D-Pyr, total deoxypyridinoline; F-D-Pyr, free deoxypyridinoline; Cr, creatinine; BCE, bone collagen equivalent
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$
[a] BM(+) vs BM(−)HT(−)
[b] BM(+) vs BM(−)HT(+)
[c] BM(−)HT(−) vs BM(−)HT(+)

in the BM(+) group showed significantly higher values for B-ALP and four bone resorption markers (ICTP, NTx, T-Pyr, and T-D-Pyr; Table 1).

Comparison of patients with and without hormonal therapy

A comparison between subjects in the BM(−)HT(−) and BM(−)HT(+) groups showed significantly higher values for B-ALP and four bone resorption markers (NTx, CTx, T-D-Pyr, and F-D-Pyr) in the latter group (Table 1).

Comparison of patients with combination therapy (antiandrogen + LH-RH analog) and LH-RH analog alone

A comparison of the 23 patients receiving a LH-RH analog alone and the 11 patients on combination therapy among the BM(−)HT(+) group revealed significantly higher values in the latter group for B-ALP and four bone resorption markers (ICTP, NTx, T-Pyr, and T-D-Pyr; Table 2).

Biochemical markers and the EOD score

There were 69 patients with EOD 0, 10 patients with EOD 1, nine patients with EOD 2, five patients with EOD 3 and two patients with EOD 4. Thirty-four patients in the EOD 0 group had received hormonal therapy. All markers, except OC and CTx, were significantly correlated with EOD scoring, B-ALP and T-Pyr showing the highest correlation among formation and resorption markers, respectively (Fig. 1).

ROC analysis in metastatic and nonmetastatic patients

The results of ROC analysis are shown in Table 3. B-ALP as a bone formation marker and F-D-Pyr as a bone resorption marker were most efficient for differentiation between subjects in the BM(+) and BM(−)HT(−) groups. In contrast, B-ALP as a bone formation marker and ICTP as a bone resorption marker were most efficient for differentiation between subjects in the BM(+) and BM(−)HT(+) groups.

Discussion

The present study has demonstrated that hormonal therapy greatly affects the efficacy of diagnosis of bone metastasis. The levels of CTx and F-D-Pyr were significantly different between the BM(−)HT(+) and BM(−)HT(−) groups, and their increase in BM(+) patients was significant only compared with the BM(−)HT(−) group and not with BM(−)HT(+) pa-

Table 2. Comparison of biochemical bone markers in nonmetastatic patients with hormonal therapy

	Combination therapy	LH-RH analog alone	*P*
No. Subjects	11	23	
Age (years)	72.2 ± 8.2	76.4 ± 76.4	0.141
Bone formation markers			
PICP (ng/ml)	132.6 ± 31.1	125.4 ± 44.6	0.636
B-ALP (U/l)	32.5 ± 10.1	20.8 ± 6.4	<0.001
OC (ng/ml)	9.4 ± 6.2	7.3 ± 4.4	0.274
Bone resorption markers			
ICTP(ng/ml)	5.2 ± 1.8	3.7 ± 1.1	0.004
NTx (nM BCE/mM Cr)	73.7 ± 26.6	53.6 ± 25.6	0.042
CTx (mg/M Cr)	444.6 ± 179.8	308.0 ± 185.3	0.051
T-Pyr (pM/μM Cr)	55.1 ± 20.3	38.6 ± 13.2	0.009
T-D-Pyr (pM/μM Cr)	9.6 ± 2.8	6.7 ± 2.3	0.003
F-D-Pyr (pM/μM Cr)	7.2 ± 2.1	6.0 ± 2.2	0.172

Data are the mean ± SD. LH-RH, luteinizing hormone-releasing hormone; other abbreviations are as given for Table 1

Table 3. Areas under the receiver operating characteristic curves and 95% confidence intervals in parentheses for biochemical bone markers

	BM(+)/BM(−)HT(−)	BM(+)/BM(−)HT(+)
Bone formation markers		
PICP	0.695 (0.552–0.813)	0.583 (0.435–0.720)
B-ALP	0.811 (0.680–0.902)	0.609 (0.458–0.745)
OC	0.612 (0.462–0.747)	0.568 (0.420–0.708)
Bone resorption markers		
ICTP	0.642 (0.498–0.769)	0.674 (0.529–0.796)
NTx	0.809 (0.677–0.902)	0.657 (0.511–0.782)
CTx	0.810 (0.680–0.901)	0.552 (0.407–0.690)
T-Pyr	0.708 (0.569–0.822)	0.657 (0.514–0.781)
T-D-Pyr	0.797 (0.667–0.890)	0.632 (0.486–0.761)
F-D-Pyr	0.812 (0.689–0.900)	0.661 (0.516–0.785)

Abbreviations are as given in Table 1

tients. PICP in BM(+) patients was also significantly higher only in comparison with the BM(−)HT(−) group and not the BM(−)HT(+) group, although the difference in PICP between the BM(−)HT(+) and BM(−)HT(−) groups did not reach statistical significance. B-ALP, NTx and T-D-Pyr also demonstrated effects of hormonal therapy, but these markers in the BM(+) group showed higher levels in comparison with both the BM(−)HT(−) and BM(−)HT(+) groups. The levels of ICTP were slightly higher in the BM(−)HT(−) group compared with the BM(−)HT(+) group, but were significantly different between the BM(+) and BM(−)HT(+) groups. Taken together, these results suggest that hormonal therapy greatly affects the efficacy of PICP, CTx and F-D-Pyr in the diagnosis of bone metastasis, whereas its effect on ICTP is small.

Recent studies have demonstrated that patients with prostate cancer treated by either orchiectomy or with androgen blockade will experience hypogonadal symptoms and may be at risk for developing high turnover osteoporosis [22–24]. Diamond et al. [25] have reported that combined androgen blockade leads to increases in serum OC and urinary D-Pyr. In the present study, the effect of hormonal therapy on the levels of biochemical bone markers was more evident in combination therapy compared with therapy with a LH-RH analog alone. Because antiandrogen suppresses adrenal androgen as well as testosterone, combination therapy could be considered to have a stronger effect on bone metabolism than the LH-RH analog alone.

All markers, except OC and CTx, were significantly correlated with the extent of bone metastasis on bone scintigraphy. This result is inconsistent with the findings of Nguyen-Pamart et al. [8], who showed a high sensitivity of CTx for the diagnosis of bone metastasis from prostate cancer. In the present study, urinary levels of

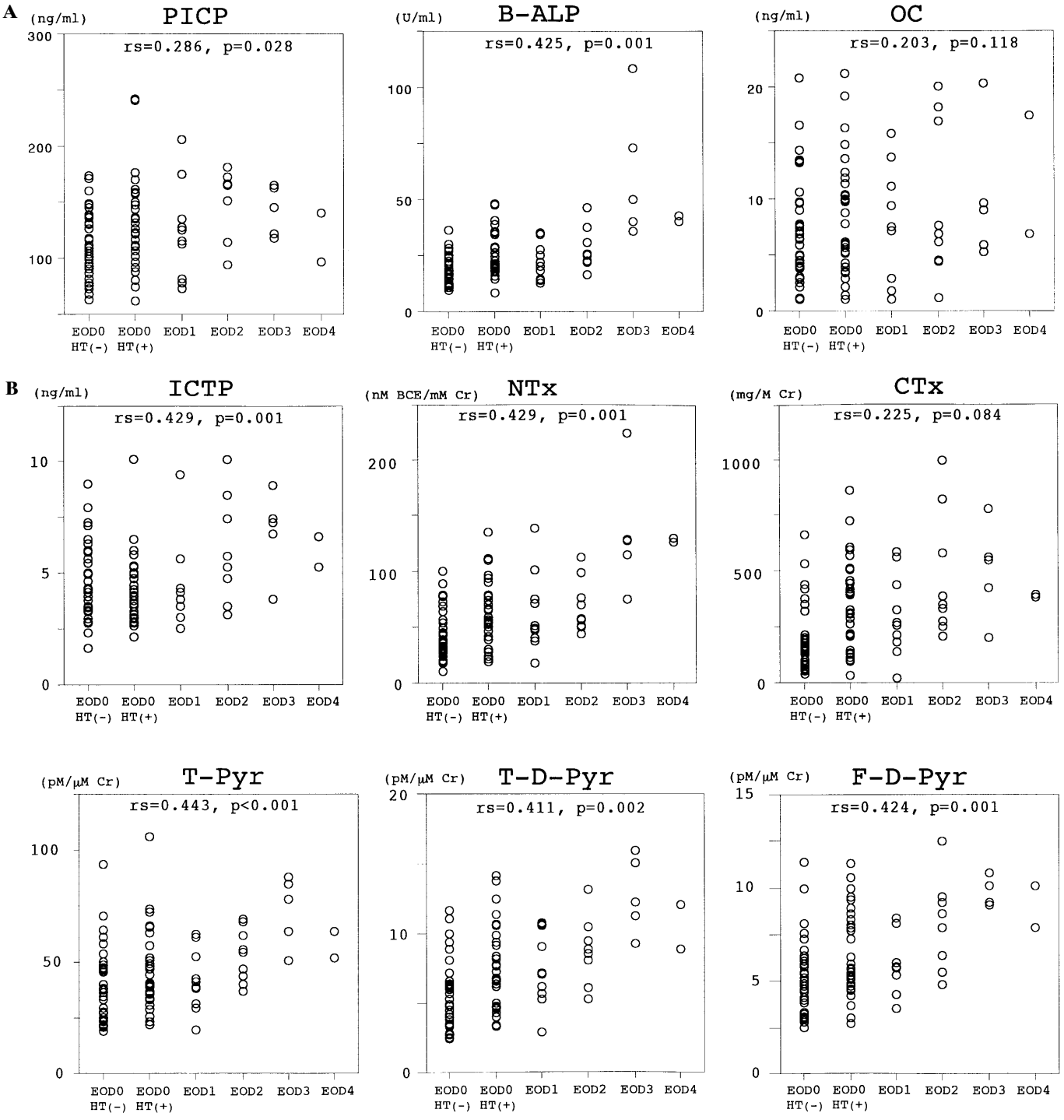

Fig. 1. Levels of bone formation (**A**) and resorption markers (**B**) as a function of the extent of disease (EOD) score in patients with prostate cancer. BM(+), with bone metastasis; BM(−)HT(−), without bone metastasis on nonhormonal therapy; BM(−)HT(+), without bone metastasis on hormonal therapy; B-ALP, bone-specific alkaline phosphatase; OC, osteocalcin; PICP, type I procollagen C-propeptide; ICTP, type I collagen cross-linked C-telopeptide; CTx, C-telopeptide fragment; NTx, N-telopeptide fragment; T-Pyr, total pyridinoline; T-D-Pyr, total deoxypyridinoline; F-D-Pyr, free deoxypyridinoline; Cr, creatinine; BCE, bone collagen equivalent. Spearman's rank correlation coefficient (*rs*) among EOD scores was calculated by assigning an EOD sore of 0 to cases in the BM(−)HT(+) group

CTx were markedly increased in patients on hormonal therapy. Although Nguyen-Pamart et al. [8] did not mention the treatment their patients were on, differences in hormonal therapy may account for the apparent discrepancy between their results and the results of the present study.

Of the bone formation markers evaluated in the present study, only B-ALP was significantly different between the BM(+) and BM(−)HT(+) groups. Koizumi et al. [6] reported that patients with prostate cancer showed statistically significant increases in B-ALP and PICP, but not OC. B-ALP, PICP and OC are considered to be markers of proliferation (early phase), matrix maturation (middle phase) and mineralization (late phase), respectively, in the phenotypic developmental sequence of osteoblasts [26–28]. The results may suggest the abnormality of bone formation in its early and/or middle stage in the progression of bone metastasis from prostate cancer.

Although bone metastasis of prostate cancer is mostly osteoblastic in its radiographic appearance, all six bone resorption markers evaluated in the present study showed higher levels in patients with bone metastasis. This result is in accordance with previous findings demonstrating an elevation of both bone formation and resorption markers in bone metastasis of prostate cancer [2,5–14]. The acceleration of bone resorption was also evidenced by bone histomorphometry and the presence of lytic bones on radiographs [29–31]. Furthermore, osteoblastic metastasis may lead to calcium entrapment in bone and a subsequent increase in parathyroid hormone secretion as a response to lowered levels of calcium [32,33]. This mechanism may also be responsible for a generalized increase in bone resorption.

In summary, our results suggest the importance of metabolic effects of hormonal therapy when using biochemical bone markers for the assessment of bone metastasis from prostate cancer. The diagnostic efficacy of each marker was affected by the condition of hormonal therapy; B-ALP and F-D-Pyr were most efficient in patients on nonhormonal therapy, whereas B-ALP and ICTP were most efficient in patients on hormonal therapy. The effect of hormonal therapy on the levels of biochemical markers was larger in combination therapy than when a LH-RH analog was used alone.

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