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Serum osteocalcin levels in breast cancer patients

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Summary. The serum levels of osteocalcin, a 49-amino-acid bone-matrix protein, which is a biochemical parameter of bone formation, were measured in 61 patients with breast cancer. Breast cancer patients were subdivided as follows: (a) Patients in complete remission; (b) patients with visceral metastases (without bone metastases); (c) patients with bone metastases (with or without visceral metastases). Serum osteocalcin levels were significantly higher in patients with bone metastases than in patients in complete remission ($P<0.005$). When osteocalcin levels of patients with bone metastases were compared with those of an age-matched control group, serum osteocalcin levels were higher in the patients with bone metastases; however, the differences did not reach statistical significance. Serum osteocalcin levels of patients with visceral metastases (without bone metastases) were significantly lower than in control subjects ($P<0.02$). Our data demonstrate that serum osteocalcin levels are higher in breast cancer patients with bone metastases than in patients in remission. Bone formation, as reflected by serum osteocalcin levels, is decreased in breast cancer patients with visceral metastases.

Key words: Osteocalcin – Bone GLA protein – Bone formation – Breast cancer – Bone metastases

Introduction

Osteocalcin [bone γ-carboxyglutamic-acid-containing (GLA) protein] is a noncollagenous 49-amino-acid bone-matrix protein, which is released into the circulation. The serum levels of osteocalcin, as measured by radioimmunoassay, have been found to be specific biochemical parameters of bone formation (Price et al. 1980; Brown et al. 1984). As this is of particular interest in disease leading to bone destruction, we have investigated serum osteocalcin levels in patients with breast cancer, where the occurrence of bone metastases is relatively frequent.

In the evaluation of patients with bone metastases, the determination of serum levels of alkaline phosphatase is frequently applied although this assessment is not specific and relatively insensitive. In the present paper, we report the results of determinations of serum osteocalcin levels in patients with various stages of breast cancer.

Patients and methods

We studied 61 patients with histologically confirmed breast cancer. All patients were regularly seen at the oncological outpatient clinic of the Department of Medicine II, University of Vienna. Patients with bone disorders unrelated to breast cancer were not included in our study. In all patients, a detailed physical examination, chest X-rays, mammography, abdominal ultrasonic examination, and bone scan were performed. If a bone scan revealed suspected bone lesions, the presence or absence of bone metastases was confirmed by bone X-rays of the relevant area. In all patients, blood for the determination of routine blood chemistry, carcinoembryonic antigen and osteocalcin was sampled in the fasting state between 8.00 and 9.00 a.m. Breast cancer patients were subdivided as follows: group A: patients in complete remission ($n=24$, mean age 59 ± 2 years); group B: patients with visceral metastases but without bone metastases ($n=10$, mean age 54 ± 4 years); group C: patients with bone metastases with and without visceral metastases ($n=27$, mean age 59 ± 3 years).

The majority of the patients of groups B and C were treated by cytotoxic chemotherapy and/or hormonal therapy. Of the patients, in complete remission 15 were untreated, 7 were treated by hormonal therapy (mostly tamoxifen 20 mg/day), and 2 were treated by adjuvant chemotherapy; 19 healthy women (mean age 51 ± 2 years) were studied as a control group. The control subjects had no history of malignant disease, diabetes mellitus, endocrine or bone disorders. In all controls, liver and renal function, assessed by routine blood chemistry, were normal.

In all patients and controls, serum osteocalcin levels were determined by radioimmunoassay, as described in detail earlier (Pietschmann et al. 1988). The minimal detectable concentration of osteocal-

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cin was 0.2 ng/ml, the intraassay coefficient of variation in the useful range of the assay was less than 8%, the interassay coefficient less than 14%. Routine blood chemistry, including calcium, creatinine and alkaline phosphatase, was measured by an American Monitor Parallel Analyzer (Richmond, USA) in the breast cancer patients serum levels of carcinoembryonic antigen (CEA) were determined by enzyme immunoassay (Abbott CEA-EIA Monoclonal One-Step, Abbot Diagnostic products, FRG.

All the data in the text and the table are given as the means ± SEM. The Mann Whitney test and Kendall's correlation coefficient were used for statistical analysis.

Results

The serum levels of osteocalcin, alkaline phosphatase, calcium and carcinoembryonic antigen are shown in Table 1. The serum osteocalcin levels were significantly higher in breast cancer patients with bone metastases than in patients in complete remission ($P<0.005$) or in patients presenting with visceral metastases alone ($P<0.005$). Serum osteocalcin levels were higher in patients with bone metastases than in control subjects, although the differences did not reach statistical significance; when serum osteocalcin levels in breast cancer patients with visceral metastases (without bone metastases) were compared to those of control subjects, serum osteocalcin levels in patients with visceral metastases were found to be significantly decreased ($P<0.02$). The serum osteocalcin levels in patients in complete remission and in control subjects were not statistically different.

The serum levels of alkaline phosphatase were significantly higher in patients with bone metastases than in patients in complete remission ($P<0.0001$) or in control subjects ($P<0.0003$). Serum levels of both creatinine and calcium were in the normal range in all breast cancer patients and in control subjects. When the data from breast cancer patients were combined, a significant positive correlation between serum osteocalcin levels and the levels of alkaline phosphatase was established ($\tau=0.22$; $P<0.01$), whereas no significant correlation between serum osteocalcin levels and serum levels of carcinoembryonic antigen could be found ($\tau=0.001$; n.s.).

Table 1. Serum levels of osteocalcin (OC), alkaline phosphatase (AP), calcium (C) and carcinoembryonic antigen (CEA) in the control subjects, the breast cancer patients in complete remission (REM), in patients with visceral metastases alone (VIS) and in patients with bone metastases (OSS)

Subjects	OC (ng/ml)	AP (U/l)	C (mmol/l)	CEA (ng/ml)
Control	6.6±0.4	113± 9	2.4±0.02	–
REM	5.2±0.5	110± 6	2.4±0.02	1.1± 0.2
VIS	4.2±0.7	149±19	2.4±0.02	34 ±19
OSS	7.7±0.6	278±41	2.4±0.03	45 ±27

Discussion

Our data indicate that serum osteocalcin levels are higher in breast cancer patients with bone metastases than in patients with visceral metastases alone or in patients in complete remission. In bone biopsy studies of both patients with postmenopausal osteoporosis and in normal subjects a significant correlation between serum osteocalcin levels and the histomorphometric parameters of bone formation has been found (Brown et al. 1984; Carrasco et al. 1988). In diseases with increased bone formation, such as in primary hyperparathyroidism and hyperthyroidism, serum osteocalcin levels are increased (Price et al. 1980; Garret et al. 1986), whereas in conditions with decreased bone formation, such as in glucocorticoid-treated patients, serum osteocalcin levels are decreased (Luckert et al. 1986). Our data thus give evidence that bone formation is higher in patients with bone metastases than in patients presenting merely with visceral metastases or in patients in complete remission. Breast cancer patients with skeletal metastases have an increased urinary excretion of hydroxypyroline, which is considered as a marker of bone resorption (Niell et al. 1983). Thus, the presence of skeleton metastases in patients with breast cancer is associated with a state of high bone turnover, an increased bone formation and an increased bone resorption.

Conflicting data have been reported about serum osteocalcin levels in cancer patients with bone metastases: Deftos et al. (1982) and Slovik et al. (1984) found increased serum osteocalcin levels in patients with bone meatastases in general, which was corroborated by Coleman et al. (1988), who showed increased serum osteocalcin levels in breast cancer patients with skeletal metastases. In contrast, Delmas et al. (1986) described normal serum osteocalcin levels in normocalcemic breast cancer patients with skeletal metastases, but decreased serum osteocalcin levels in hypercalcemic breast cancer patients. In our study of normocalcemic breast cancer patients with bone metastases, serum osteocalcin levels were higher than in control subjects; however, the differences did not reach statistical significance. These data indicate that serum osteocalcin levels are not a very sensitive marker for bone metastases in breast cancer. Furthermore, as we have found a significant positive correlation between the serum osteocalcin levels and the levels of alkaline phosphatase, it is not our view that serum osteocalcin levels might substitute for the determination of serum alkaline phosphatase in the evaluation of bone involvement in breast cancer patients.

Unexpectedly, serum osteocalcin levels in breast cancer patients with visceral metastases without any evidence of bone involvement were significantly lower

than in control subjects. These data suggest that bone formation might be decreased in breast cancer patients presenting with visceral metastases. At present we can neither explain how the presence of visceral metastases might decrease bone formation nor exclude the possibility that side-effects of antitumor treatment might contribute – at least in part – to these findings.

In conclusion, our data demonstrate that serum osteocalcin levels in patients with metastastic breast cancer are influenced by the presence of bone and possibly visceral metastases.

References

Brown JP, Delmas PD, Malaval L, Edouard C, Chapuy MC, Meunier PJ (1984) Serum bone GLA-protein: a specific marker for bone formation in postmenopausal osteoporosis. Lancet 1:1091

Carrasco MG, Gruson M, De Vernejoul MC, Denne MA, Miravet L (1988) Osteocalcin and bone morphometric parameters in adults without bone disease. Calcif Tissue Int 42:13–17

Coleman RE, Mashiter G, Fogelman I, Whitaker KD, Caleffi M, Moss DW, Rubens RD (1988) Osteocalcin: a potential marker of metastatic bone disease and response to treatment. Eur J Cancer Clin Oncol 24:1211–1217

Deftos LJ, Parthemore G, Price A (1982) Canges in plasma bone GLA protein during treatment of bone disease. Calcif Tissue Int 34:121–124

Delmas PD, Demiaux B, Malaval L, Chapuy MC, Edouard C, Meunier PJ (1986) Serum bone gamma carboxyglutamic acid-containing protein in primary hyperparathyroidism and in malignant hypercalcemia. J Clin Invest 77:985–991

Garrel DR, Delmas PD, Malaval L, Tourniaire J (1986) Serum Bone GLA protein: A marker of bone turnover in hyperthyroidism. J Clin Endocrinol Metab 62:1052

Lukert BP, Higgins JC, Stoskopf MM (1986) Serum osteocalcin is increased in patients with hyperthyroidism and decreased in patients receiving glucocorticoids. J Clin Endocrinol Metab 62:1056

Niell HB, Neely CL, Palmieri GM, McDonald MW (1983) The postabsorptive hydroxyproline in the long-term evaluation of patients with breast cancer. Am Cancer 52:1442–1447

Pietschmann P, Woloszczuk W, Panzer S, Kyrle P, Smolen J (1988) Decreased serum osteocalcin levels in phenprocoumon-treated patients. J Clin Endocrinol Metab 66:1071–1074

Price PA, Parthemore JG, Deftos LJ (1980) New biochemical marker for bone metabolism. Measurement by radioimmunoassay of bone GLA protein in the plasma of normal subjects and patients with bone disease. J Clin Invest 66:878

Slovik DM, Gundberg CM, Neer RM, Lian JB (1984) Clinical evaluation of bone turnover by serum osteocalcin measurements in a hospital setting. J Clin Endocrinol Metab 59:228

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