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Prognostic Value of Bone Markers in Patients with Carcinoma

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Abstract

Background: We investigated the usefulness of bone markers, respectively Alkaline Phosphatase (AP) and Tartrat Resistant Acid Phosphatase 5b (TRACP 5b) for diagnosis, treatment and monitoring of patients with carcinoma of different origin. AP is a marker of bone formation, while TRACP 5b is a marker of bone resorption. The isoform 5b of the enzyme TRACP is expressed by osteoclasts and can be measured in blood.

Objectives: The aim of this study was to evaluate the prognostic value of the bone markers AP and TRACP 5b to detect bone metastasis and pathological bone metabolism.

Materials and Methods: Our study comprised 101 patients with positive tumor markers. Sera of these patients were collected and the bone markers AP and TRACP 5b were determind. TRACP 5b was measured by a colorimetric test which determines the TRACP 5b by using the phophatase activity of this enzyme by dephosphorylation of p-Nitrophenylphosphate (pNPP). The test is a two site immunoassay by Medac Diagnostika, Germany.

Results: The sensitivity of AP in our study to detect bone metastasis is 52.9%, the specificity is 53.9%. TRACP 5b shows a sensitivity of 64.7% and a specificity of 70.9%. An elevated TRACP 5b activity is associated significantly with bone metastasis in our study groups (p=0.01). In patients with chronic elevated levels of liver enzymes we could see a significant elevation of TRACP 5b (p=0.005).

Conclusion: In conclusion TRACP 5b is more sensitive and specific to detect bone metastasis and bone turnover than the Alkaline Phosphatase. In patients with multimorbidity the origin of AP is not clear due to its multiorganic appearance. The levels of TRACP 5b are elevated in patients with bone metastasis and in patients with chronical dysfunction of the liver. TRACP 5b might be helpful in the diagnostic procedure of tumor-patients to detect bone metastasis. Moreover TRACP 5b seems to be helpful to indicate oncological patients with early dysfunctions in bone metabolism and helps to induce early treatment to these patients.

Keywords: Bone marker; Tumor marker; Bone metastasis; Malignancy; Alkaline Phosphatase (AP); Tartrate Resitant Acid Phosphatase (TRACP 5b)

Introduction

Malignant diseases and metastasis induced by those diseases are topics of medical research through decades. Bone is a common site for metastasis and is often elevating pain, morbidity and mortality. Through the past years several laboratory methods and markers have been developed to assist the diagnosis of bone lesions.

The accurate diagnostic of bone metastasis and the early induced antiresorptive and cancer therapy are essential for reducing morbidity and mortality in those patients and hence an important task.

Bone is a tissue which underlies continuous resorption and formation. Malignant tumors which are spreading to bone are causing osteolytic, osteoblastic or mixed lesions. Bone is resorbed by osteoclasts rather than through the tumor cells itselves [1,2].

Under these circumstances bone turnover is elevated and some of the involved enzymes and metabolic products can be measured. Several markers of bone turnover with different sensitivity and specificity have been described so far.

The Alkaline Phosphatase is one marker of bone formation which is often used due to its wide availability as a laboratory parameter [3]. It is a membrane-bound enzyme which can be found in diverse tissues of the body, such as bone, liver, kidney and the intestine. The exact function in bone metabolism is unkown, but AP increases when mineralization of bone is in progress [4].

In a healthy adult 50% of the total amount of AP are of liver origin and 50% of bone origin. In children and growing infants up to 90% of the total amount are of bone origin due to the higher expansive bone metabolism. Is a liver disease ruled out, AP provides an impression of the osteoblastic activity [5-7].

The TRACP is an enzyme expressed in bone resorbing osteoclasts, certain tissue macrophages and alveolar macrophages of the lung. Five isoforms of TRACP have been identified so far [8]. The two isoforms identified in the circulation have been named TRACP 5a and 5b. A correlation between TRACP 5b and other markers of bone turnover or bone mineral density has been verified, but not for TRACP 5a [9]. TRACP 5b is the osteoclastic specific isoform of the Tartrat Resistant Acid Phosphatase, also called Purple Acid Phosphatase due to its colour in purified form. Its usefulness as a marker of bone turnover has been described earlier [10].

Although these markers have a potential as tools in the diagnosis of bone metastasis, further analysis of these markers has been recommended to confirm the prediction of diagnosing bone turnover

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and monitoring antiresorptive treatment. The aim of this study was to evaluate the clinical value of AP and TRACP 5b to detect bone metastasis and pathological bone metabolism in a collective of patients with positive tumor markers.

Materials and Methods

Peripheral blood samples of 101 patients with positive tumor markers have been collected. A total number of 19 patients had no malignant disease. 60 patients were suffering from a malignant disease with known metastasis but no bone metastasis. 17 patients had known bone metastasis.

Among the patients with malignant cancer diseases a total number of 11 patients had ovarial carcinoma, 14 colon carcinoma, 25 patients carcinoma of the breast, 6 pancreatic carcinoma, 8 patients carcinoma

	TRACP 5b [U/I]				AP [U/I]		
	N	Mean	Std. Dev.	Range	Mean	Std. Dev.	Range
Patients without malignant disease	19	4.22	2.37	1.87-10	171.37	114.11	59-428
Patients with known malignant disease without bone metastasis	60	5.04	2.12	1.71-10	262.80	219.47	69-1045
Patients with known bone metastasis	17	6.75	3.0	2.23-10	495.41	712.51	105-3053

Table 1: Activity of TRACP 5b and AP [U/I] in our different study groups.



Figure 1: Distribution of mean TRACP 5b in our study. Activity of TRACP 5b (U/I) against patients without a malignant disease, patients with known malignancy but without bone metastasis, patients with malignancy and bone metastasis.



Figure 2: Distribution of mean AP in our study. Activity of AP (U/I) against patients without a malignant disease, patients with known malignancy but without bone metastasis, patients with malignancy and bone metastasis.

of the liver, 4 patients neuroblastoma and 9 patients with carcinoma of other origin. In our collective 5 patients were under the age of 10, all of these patients had a TRACP 5b acticity of 10 U/l. This inverse correlation between age and TRACP 5b activity has been described earlier and these patients have been cancelled for further investigation due to the cause of expansive bone turnover in children.

The analysis of Alkaline Phosphatase has been conducted by using the Hitachi 917 Analyzer. The determination of TRACP 5b has been done by a two site immunoassay (Medac Diagnostika GmbH, Germany) with two specific monoclonal antibodies, which have been proved not to crossreact with the isoform TRACP 5a. Incubating the sera samples with p-Nitrophenylphosphate (pNPP) leads to a dephosphorylation of this agent. The product of this reaction could be measured photometrically. The colorimetric measurement to determine the TRACP 5b activity has been performed with the SLT Spectra Photometer (SLT Instruments GmbH, Austria).

Statistical Analysis

All the statistical calculations were performed with SPSS Statistics 21.0 and Microsoft Excel 2007.

Results

The results of AP and TRACP 5b activity in our different study groups are summarized in Table 1. The mean activity of AP in the group without malignancy has been 171.37 U/l, in patients with malignant disease but without bone metastasis 262.80 U/l and in patients with bone metastasis 495.41 U/l.

The serum levels of TRACP 5b activity in patients without malignancy showed a mean of 4.22 U/l. The highest activities have been found in patients with malignancy and additional bone metastasis (mean 6.75 U/l) and in patients with malignancy (mean activity of 5.04 U/l).

A significant difference between the patients without malignant disease, those with malignancy and the patients with additional bone metastasis could be shown for AP (Kruskal: p=0.009) and TRACP 5b (Kruskal: p=0.01).

The distribution of AP and TRACP 5b in our patients is shown in Figure 1 and 2.

Figure 3 and 4 are showing the categorised results of AP and TRACP 5b whether they were normal or above normal activity. For the AP we could not figure out a significant difference of AP in our study groups (Chi-square test: 0.49). We found a significant association between the occurancy of bone metastasis and elevated TRACP 5b activity in our study (Chi-square test: 0,01). In our study the sensitivity of AP to detect bone metastasis is 52.9% and for TRACP 5b 64.7%. The specificity for AP has been 53.9% and for TRACP 5b 70.9%.

Discussion

In the last years several different bone markers have been investigated to assist the diagnosis of bone turnover. However the accuracy of those markers does not allow to be the only diagnostic instrument to predict the appearance of bone metastasis. So far none of the known markers could be solely used for a screening of patients to diagnose metastasis to bone.

The measured sensitivity and specificity for AP and TRACP 5b to detect bone metastasis in our study is contrary to our expectations lower than results of earlier investigations, which is mainly due to our randomised selection of patients with positive tumor markers [11,12].



tumor 78.9 % are of normal activity, 21.1% are pathological elevated. Patients with tumor but without bone metastasis show normal activity in 68.3% and elevated levels of TRACP 5b in 31.7%. The TRACP 5b levels were normal in 35.3% of all patients with known bone metastasis and elevated in 64.7%.



The poor sensitivity and specificity for AP appeared to be caused by the multimorbidity of our patients. In those patients the elevated AP levels seemed to be caused by an origin different than bone. At least 35.3% of our patients with known malignancy and bone metastasis did not show pathological elevated serum levels of TRACP 5b, at least 9 patients of that group had been treated with bisphosphonates at the time of investigation [13]. 21.1% of the patients with no known malignancy showed elevated serum levels of TRACP 5b; 3 of these patients were pregnant and 1 patient was suffering from a cirrhosis of the liver of unknown genesis. An increasing bone turnover in pregnancy has been described previous [14]. The coincidence of a decreased bone density and liver diseases has also been formerly analyzed [15-17]. As investigated before, we found a slender ($r \le 0.5$) but high significant correlation between our measurements of AP and TRACP 5b [18]. In comparison to AP, the TRACP 5b has been the more specific bone marker to detect bone metastasis in our study.

A significant correlation between the activity of TRACP 5b and the occurancy of bone metastasis has been statistically proved (Kruskal: $p \le 0.01$, Multivariat analysis: $p \le 0.05$, Chi-square test: $p \le 0.05$). Furthermore TRACP 5b showed in our study a significant increase in patients with chronical elevated liver enzyms (Mann-Whitney-U test: $p \le 0.05$). It is known that a chronical pathological effected liver disease affects the bone metabolism and osteoporosis occurs more often. We suggest a further investigation and evaluation of TRACP 5b as a marker

J Mol Biomark Diagn ISSN:2155-9929 JMBD an open access journal of bone turnover. It seems to be a helpful diagnostic parameter of pathological elevated bone metabolism and should be used in follow up examinations of oncological patients. It seems to be not only a helpful tool to get an idea of the bone metabolism, but may be also helpful to assist an antiresorptive treatment in time to those patients with progressive affection of the bone caused by chronic liver disease.

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