

Evaluation of Circulating Type I Procollagen Propeptides in Patients with Paget's Disease of Bone

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We evaluated circulating aminoterminal and carboxyterminal propeptides of type I procollagen and total alkaline phosphatase levels in eighty consecutive patients affected by Paget's disease of bone. We compared the biochemical data with the extent of bone disease calculated on the basis of the bone scintigraphic indices.

Serum aminoterminal propeptide of type I procollagen levels were high in 77% of patients, serum carboxyterminal propeptide of type I procollagen levels in 22% and serum total alkaline phosphatase levels in 76%. We found significant correlations between the three markers studied. The three biochemical markers correlated significantly with the bone scintigraphic activity indices, but the highest correlation coefficient was between the aminoterminal propeptide and total alkaline phosphatase.

We conclude that there is a discrepancy between serum levels of the propeptides studied in relation to Paget's disease of bone. The sensitivity of the carboxyterminal propeptide of type I procollagen in this disease is low. In contrast the aminoterminal propeptide may be as sensitive a marker for the evaluation of this disorder as total alkaline phosphatase, and in addition may be more specific.

Key words: Biochemical bone markers; Paget's disease of bone; Type I procollagen propeptides.

Introduction

The carboxyterminal propeptides of type I procollagen (PICP) and the aminoterminal propeptides of type I procollagen (PINP) arise from the cleavage of a large precursor of type I collagen by two specific proteolytic enzymes (1). These two peptides have different molecular weights and are delivered into the circulation in a 1/1 molar ratio. They are rapidly cleared from the blood by different receptors via endocytosis in the liver (2,3). Their values may be considered as indices of the rate of synthesis of type I collagen, the major protein in the organic matrix of bone.

Paget's disease of bone is a metabolic bone disorder,

characterized by increased bone turnover (4). Traditionally total alkaline phosphatase (TAP) and urinary hydroxyproline, considered markers of bone formation and resorption respectively, have been used as indices of bone activity in the study of this disorder (5). Other biochemical markers of bone metabolism have been studied and have presented varying diagnostic sensitivity. Serum concentrations of the PICP and PINP may be more specific markers of bone turnover than TAP. Nevertheless, the sensitivity of the PICP in Paget's disease of bone has been reported to be relatively low (6).

Recently, a method for measuring serum concentrations of the intact trimeric form of circulating PINP has become commercially available (7).

The aim of the present study is to compare serum concentrations of PICP and PINP in a group of patients with Paget's disease of bone. We analyse the correlation between biochemical data and the extent of the disease.

Materials and Methods

Subjects

Eighty consecutive patients (50 males and 30 females, mean age 69 years, range 46–88 years) affected by Paget's disease of bone, were included in a cross sectional prospective study. Paget's disease was diagnosed by radiography and bone scan with 99m-Tcnetium. The mean duration of disease was 85.8 ± 65.5 months since diagnosis. Disease activity was evaluated by three methods:

1. The condition was considered polyostotic when 2 or more bones were affected, and monostotic when only a single bone was involved.
2. Sites affected were divided into four categories: pelvis, head, axial skeleton and limbs. The patients were classified according to the number of regions affected (one, two, three or four) (8).
3. Scintigraphic indices of disease activity:

The scintigraphic disease activity index (AI) in all patients was calculated using the following calculation:

$$AI = \text{bone extent} \times \text{uptake coefficient}$$

for all the bones affected.

The extent of the disease was measured using the coefficient given by Coutris *et al.* (9). The scintigraphic uptake coefficient was obtained for each bone on a 6-point scale (10). The scintigraphic index of disease activity for each patient was obtained as the sum of the indices of activity for the affected bones.

Blood samples were obtained from each patient between 8:00 a.m. and 10:00 a.m. Serum samples were kept frozen at –80 °C until analysis. We measured TAP, PINP and PICP.

Analytical methods

Serum concentrations of TAP were routinely determined on a BM/Hitachi 717 analyser using Boehringer Mannheim kits. Inter-assay coefficient of variation (CV) was 5 %.

Serum PINP and PICP were assayed by radioimmunoassay (Orion Diagnostica, Finland). Intra-assay CVs were 11 % and 10.8 % respectively.

Statistical analysis

Between-group comparisons were done by the Mann-Whitney test. The correlation coefficients were obtained from the non-parametric Spearman's rank test. As regards affected sites, differences between the results were evaluated by the Kruskal-Wallis test.

Results

Skeletal involvement

The disease was polyostotic in fifty patients (62.5 %) and monostotic in thirty patients (37.5 %). As regards the number of regions affected, 40 % of patients presented with one site affected, 32.5 % with two, 20 % with three and 7.5 % with four.

Bone scintigraphic index

Values for the activity index ranged from 1.2 to 220. Monostotic patients had lower values than polyostotic (17.49 ± 11.55 vs. 52.94 ± 41.5 , $p < 0.001$).

Biochemical markers

Serum TAP levels were high in 61 patients (76 %). Serum concentrations of PICP were increased in 18 patients (22 %). Serum concentrations of PINP were high in 62 patients (77 %). Table 1 shows mean absolute values of the three bone markers studied, and the bone scintigraphic index in monostotic and polyostotic patients.

Tab. 1 Biochemical markers of bone turnover and scintigraphic index in patients with monostotic and polyostotic Paget's disease of bone.

	Monostotic (n=30)	Polyostotic (n=50)	Normal range
AI	17.5 ± 11.5	52.9 ± 41.5	
TAP mkat/l	3.8 ± 2.9	8.9 ± 11.6	0.6-2.1
PINP mg/l	80.7 ± 224.3	382.4 ± 385.5	19-84
PICP mg/l	144.0 ± 36.8	261.6 ± 309	38-202

Values are mean \pm SD. AI = Bone scintigraphic index. TAP = total alkaline phosphatase; PINP = aminoterminal propeptide of type I procollagen; PICP = carboxyterminal propeptide of type I procollagen.

In patients with polyostotic disease significantly higher values were found for TAP ($p = 0.006$) and PINP ($p = 0.001$), but not for the PICP ($p = 0.06$). All data are shown in figure 1.

If we separate the patients by specific areas of involvement significant differences appear between all the groups as regards serum TAP ($p = 0.001$) and serum PINP ($p = 0.001$) but not for levels of serum PICP ($p = 0.06$). Results are shown in table 2.

Correlation study

The three biochemical markers studied were significantly correlated with the bone scintigraphic indices, but serum TAP and serum PINP showed the highest correlation coefficients ($r = 0.63$, $p < 0.001$ and $r = 0.60$, $p < 0.001$, respectively). The correlation coefficient between PICP and the scintigraphic indices was $r = 0.28$, $p = 0.01$.

We observed significant correlations between PINP and TAP ($r = 0.80$, $p < 0.001$), PICP and TAP ($r = 0.37$, $p = 0.001$), and PINP and PICP ($r = 0.52$, $p < 0.001$).

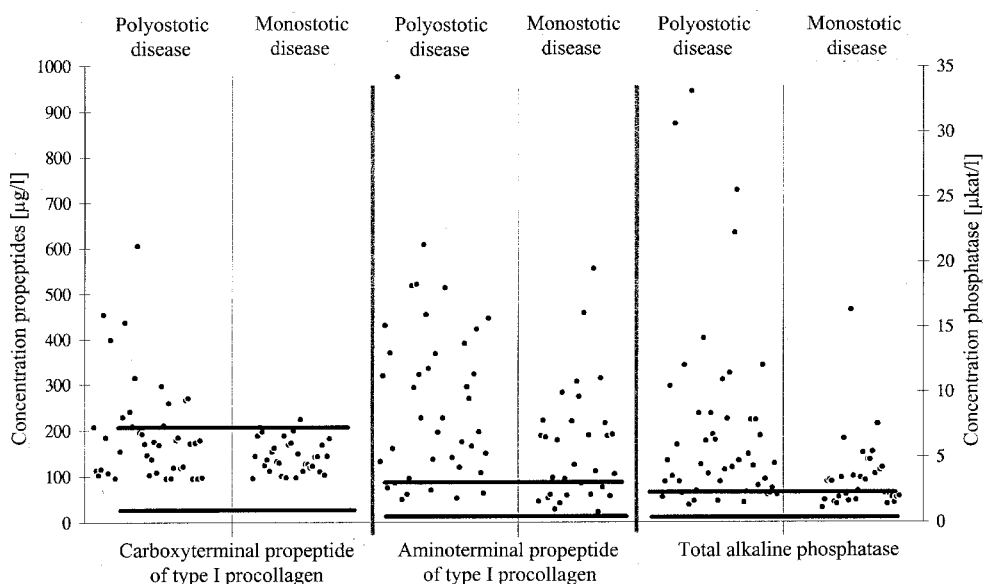


Fig. 1 Individual levels of serum propeptide carboxyterminal of type I procollagen, propeptide aminoterminal of type I procollagen and total alkaline phosphatase in polyostotic and

monostotic patients. Areas between horizontal lines represent normal ranges.

Tab. 2 Biochemical markers of bone turnover according to the number of regions affected.

Bone marker	Number of regions affected			
	1 (n=32)	2 (n=26)	3 (n=16)	4 (n=6)
TAP mkat/l	3.7±2.8	7.5±11.5	8.2±7.5	19.0±18.5
PINP mg/l	187.0±222.8	296.8±326	344.0±306	889.5±524
PICP mg/l	139.5±35.3	218.8±210	293.9±349	424.5±538

Values are mean ± SD. Definitions are in Table 1.

Discussion

Total alkaline phosphatase, PINP and PICP are considered to be biochemical markers of bone formation (11). Alkaline phosphatase is a marker of enzyme activity of osteoblasts. The propeptides are released by osteoblasts during bone formation. Although type I collagen is found in other tissues, the rate of turnover for these tissues is lower than that for bone. Total alkaline phosphatase is still the most widely used bone marker in the clinical setting but it is also produced in other tissues (12).

In the present study the three markers of bone formation studied correlated with the activity and extent of the disease; however they present a number of differences.

Serum alkaline phosphatase and PINP show a similar proportion of high values in the Paget's patients. In contrast, concentrations of serum PICP were in the normal range in both monostotic and polyostotic patients. On separating patients by specific areas of involvement we found significant differences between each group for TAP and PINP values but not for PICP. These results, similar to data reported previously (13), show that serum PICP is relatively insensitive as a marker of activity in Paget's disease of bone.

This discrepancy between values of serum PICP and PINP in active Paget's disease may be due to differences in the clearance of the propeptides from the circulation, or to the existence of different circulating forms of type I procollagen (14).

The significant correlations between the biochemical markers studied and the scintigraphic indices show the usefulness of both determinations for assessing Paget's disease activity.

We conclude that the sensitivity of PINP as a marker of activity in the study of patients with Paget's disease of bone is comparable to that of TAP. It may also be a more specific marker of bone turnover directly related to collagen synthesis.

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