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Serum Osteocalcin in the Management of Myeloma

Adrian T. Williams, Martin J. Shearer, Joyce Oyeyi, Robin G. Aitchison, Adrian C. Newland and Stephen A. Schey

We have measured serum osteocalcin, a vitamin K-dependent glycoprotein synthesised by osteoblasts in 62 patients, 49 with myeloma, 26 at presentation and 23 previously treated, 7 with Waldenstrom's macroglobulinaemia (WM), and 6 with monoclonal gammopathy of uncertain significance (MGUS). Osteocalcin levels were normal in WM and MGUS. High values were found in 5/26 (19%) patients with myeloma at presentation. There was no relationship between serum osteocalcin and stage of disease. Osteocalcin was normal in all patients in plateau phase, falling to low levels in relapsed patients who failed to respond to further treatment. Serum osteocalcin may be a useful indicator of bone metabolism in myeloma.
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INTRODUCTION

LYTIC LESIONS, fractures, osteoporosis and hypercalcaemia are major causes of morbidity in patients with myeloma [1]. Despite increased osteoclast activity in the vicinity of myeloma cells [2], alkaline phosphatase is normal in the absence of fractures due to the lack of osteoblast response. Osteocalcin (bone Gla-protein), is a vitamin K-dependent glycoprotein synthesised by osteoblasts whose function remains unknown; circulating levels, however, are a sensitive indicator of bone turnover in a number of bone disorders [3, 4]. In myeloma, an inverse correlation between serum osteocalcin and stage has been reported [5]. We have measured serum osteocalcin in paraproteinaemias to assess its relationship to disease activity.

PATIENTS AND METHODS

Patients

62 patients with paraproteinaemia were studied, 49 with myeloma (26 at presentation and 23 previously treated), 7 with Waldenstrom's macroglobulinaemia (WM) and 6 with monoclonal gammopathy of uncertain significance (MGUS). 12 patients were stage I, 14 stage II and 23 stage III. The paraprotein was IgG in 40, IgA in 5 and IgD in 1 patient, and there were 3 light chain myeloma cases. Patients were treated with various

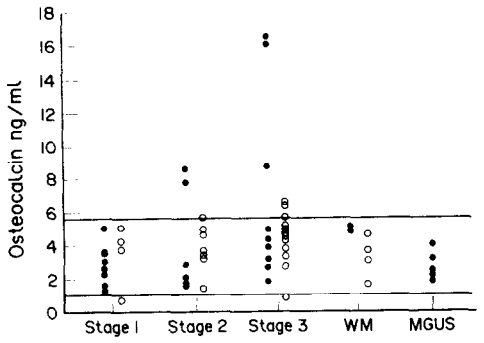

Fig. 1. Serum osteocalcin values in 62 patients with paraproteinaemia according to disease type and status. The horizontal lines represent the normal range. Stage 1, 2 and 3, Myeloma stage according to Durie and Salmon [9]. WM = Waldenstrom's macroglobulinaemia; MGUS = Monoclonal gammopathy of uncertain significance. ● = Untreated; ○ = treated.

chemotherapeutic regimens and local radiotherapy if appropriate. The study included 1 patient with stage I myeloma, previously treated and receiving long-term warfarin therapy for recurrent deep vein thrombosis, and 2 patients with osteosclerotic myeloma. Response to treatment was defined as good when the paraprotein fell by > 50% of the presentation value and partial when this was < 50%, but > 25%. Relapse with progressive disease was defined as a rise of > 25% in paraprotein on two occasions separated by at least 3 weeks. Patients in renal failure which raises serum osteocalcin [6] were excluded.

Methods

Serum osteocalcin was measured by radioimmunoassay ("Incstar", Stillwater, Minnesota, USA). Blood samples were obtained between 0900 and 1200 h and serum aliquots stored at −20°C within 4 h of collection. Serum osteocalcin did not deteriorate over a 6-h period at room temperature (data not shown).

Plasma calcium, alkaline phosphatase and total protein were measured by a Hitachi multi-channel analyser. Paraprotein was determined by modifying a method previously described [7]. Urinary hydroxyproline was measured in early morning samples [8] and urinary calcium and creatinine in 24-h collections. Staging was according to the criteria of Durie and Salmon [9]. Results were analysed by multiple analysis of variance for correlations and by *t*-tests for comparisons between stages.

RESULTS

The normal range (1.1–5.5 ng/ml; mean 3.3 ng/ml) for serum osteocalcin was determined in 50 healthy adults (21–62 years) and followed a normal distribution.

A wide range of serum osteocalcin levels was found in myeloma (0.7–16.4 ng/ml) (Fig. 1). Raised levels were seen in 5/26 (19%) at diagnosis and in 4/23 (17%) of previously treated patients; in both groups there was a trend (not significant) for osteocalcin to rise with advancing stage. 2 patients with osteosclerotic myeloma had very high serum osteocalcin levels of 8.6 and 13.6 ng/ml.

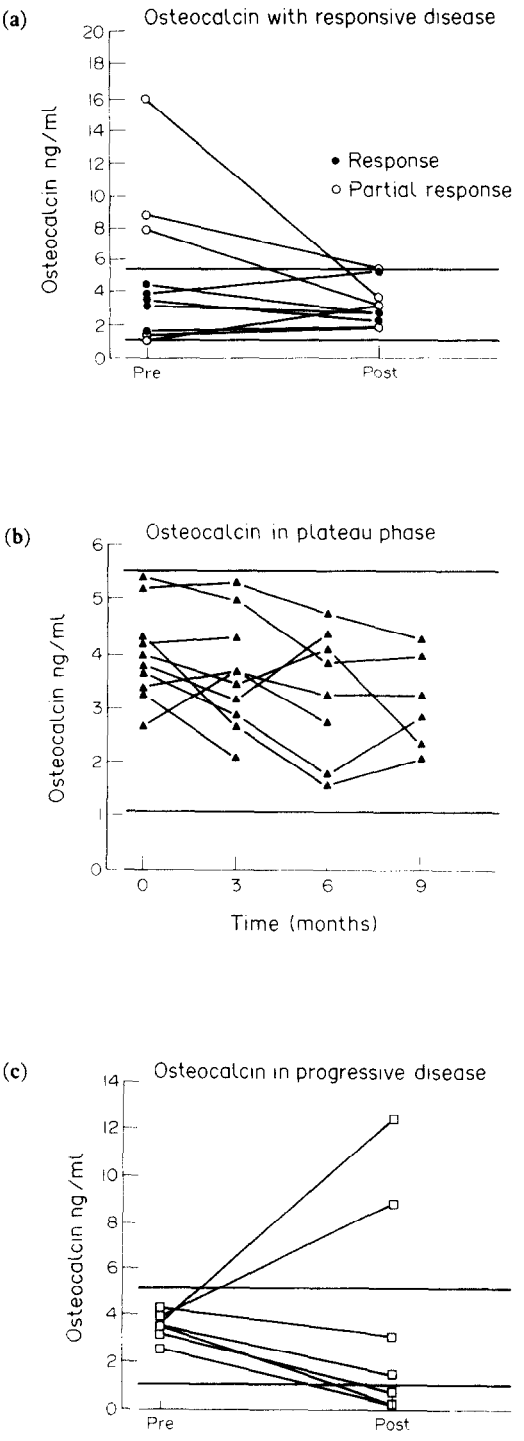

Fig. 2. Serial studies of serum osteocalcin in patients with multiple myeloma. (a) Patients who were treated and exhibited a good (> 50%) or partial (> 25%–<50%) reduction in paraprotein value. (b) Patients in plateau phase who demonstrate a stable paraprotein value. (c) Patients showing progressive disease from plateau with a rising paraprotein value.

The former maintained a stable paraprotein without treatment and serum osteocalcin remained elevated. The latter was lost to follow-up. The patient on long-term warfarin therapy had a low serum osteocalcin, which remained low despite response to chemotherapy.

Serial osteocalcin measurements were made in 10 myeloma patients followed from diagnosis. 5 of these had a good response to treatment and normal osteocalcin levels which remained

Correspondence to A.T. Williams.
A.T. Williams, M.J. Shearer, J. Oyeyi and S.A. Schey are at the Department of Haematology, Guy's Hospital, London SE1 9RT; and R.G. Aitchison and A.C. Newland are at the Department of Haematology, Royal London Hospital, Whitechapel, London E1, U.K.
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normal in 4 but rose in one before falling back to normal (Fig. 2a). Of the other 5 patients who had a partial response, 3 had high osteocalcin levels which again fell to normal as the patients responded to treatment (Fig. 2a).

Serial osteocalcin measurements were made in 10 patients in plateau phase over 3–9 months; all were within the normal range (Fig. 2b). In 7 patients who relapsed, serum osteocalcin fell below the normal range in 3, rose above normal in 2 and remained within the normal range in the other 2 (Fig. 2c). The 4 patients with rising or normal serum osteocalcin levels exhibited a response to second line treatment. The response was accompanied by a fall in serum osteocalcin to normal in the 2 with high levels and remained normal in the 2 who had been normal. Survival times from progression for these 4 patients were 11, 11, 32 and >32 months. The 3 relapsed patients whose serum osteocalcin fell below normal did not respond to second line treatment and died of progressive disease at 3, 4 and 12 weeks.

No correlation was found between serum osteocalcin and either serum paraprotein, total protein, alkaline phosphatase, calcium, haemoglobin, urinary hydroxyproline or urinary calcium excretion (data not shown).

DISCUSSION

Normally, when bone is remodelled, e.g. following a fracture, the increase in osteoclast activity results in a balanced increase in osteoblast activity, a coupled response. In myeloma, plasma cells produce a lymphotoxin [10], previously known as osteoclast activating factor (OAF), which stimulates osteoclasts with loss of the normal balance between bone resorption and formation. This in turn may lead to osteoporosis or lytic lesions [11] (an uncoupled response).

Patients with extensive lytic lesions are classified as having stage III myeloma [9] but fractures may occur in any stage. In our study, contrary to a previous report [5], there was no correlation between serum osteocalcin at presentation and stage of disease. This difference may be due to the absence in our study of patients who had fractures when they presented. Alkaline phosphatase, usually normal in myeloma in the absence of fractures, was not correlated with serum osteocalcin and this is not yet explained.

Abnormally high osteocalcin levels at presentation were seen in only 9/49 patients (18%). 2 of these patients had histologically and radiologically proven osteosclerotic myeloma, indicating increased osteoblast activity. Of the others, 3 patients were followed serially from diagnosis. Their response to treatment with a corresponding fall in osteocalcin supports the concept that a coupled response occurs in only a minority of myeloma patients. 1 patient showed a rise in serum osteocalcin to > 25 ng/ml as she responded to chemotherapy, suggesting release from an inhibitory effect on osteoblast activity.

All patients in plateau phase had normal serum osteocalcin levels and a change outside the normal range appears to reflect disease progression. As other factors, e.g. vitamin K antagonists, are known to affect osteocalcin levels, it is of interest that the patient receiving long-term warfarin had a low serum osteocalcin. This suggests that gamma-carboxylation may be important for functional activity and/or secretion into the circulation [12, 13].

In conclusion, we suggest that serum osteocalcin has a limited value in the management of multiple myeloma. If elevated at presentation, a fall gives additional evidence of response to treatment. More importantly, in plateau phase, normal serum osteocalcin levels provide further evidence for plateau and a change outside normal indicates relapse. Although the number of patients is too small to draw a firm conclusion, a fall in serum osteocalcin to a low level at relapse suggests a poor prognosis and supports a previous study [14].

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