

MANUEL ANIBAL FERREIRA, MD

LISBON, PORTUGAL

TOPIC: EVALUATION OF RENAL OSTEODYSTROPHY

Manuel Anibal Ferreira, MD
Lisbon, Portugal

About a decade ago I started to perform bone biopsies in uremic patients from Portugal. Until now I performed more than 470 bone biopsies, and the majority of them were analyzed by me, in our laboratory (Nephrol Dial Transplant 1998;13:41-45). Usually we give to the clinician a qualitative evaluation of the bone and only for research protocols we perform the histomorphometric evaluation. We optimized the acid phosphatase staining to obtain a better differentiation of osteoclasts cells.

Some years ago, we demonstrate, for the first time, that serum Pyridinoline (Pyr) cross-links concentrations can be reliably measured with an accurate competitive enzyme immunoassay (J Bone Min Res 1995;10(6):932-939) in dialysis patients, and that these patients had markedly increased serum Pyr levels compared with normal individuals. In our 37 haemodialysis patients, the highest values of serum Pyr were found in patients with the highest rate of bone resorption. We observed a good correlation between serum Pyr levels and the number of osteoclasts/mm² and the percentage of bone covered by osteoclasts.

We also had the opportunity to show, in 42 haemodialysis patients, that plasma bone alkaline phosphatase (bAP) levels correlated better with bone formation and bone resorption histomorphometric parameters than iPTH or total AP levels (J Am Soc Nephrol 1994;5:858). Values of bAP higher than 20 ng/ml had a sensitivity of 100% and a specificity of 100% for the diagnosis of high turn-over bone disease (HTBD) and there was an excellent correlation between plasma bAP levels and the bone formation rate (BFR). When these limits of bAP values were associated with iPTH serum levels > 200 pg/ml the positive predictability value for the diagnosis of HTBD, increased from 84% to 94% (J Am Soc Nephrol 1996;7:506-512).

We also had the opportunity to show that chronically haemodialysed patients with polyacrilnitrile dialyzers have less osteoblastic and osteoclastic activation than patients dialyzed with cuprofan membranes (the levels of iPTH are similar in both groups) (Nephrol Dial Transplant 1996;11:399-400). These results suggest less bone turnover activation when more biocompatible and/or more permeable haemodialysis membranes are used, which may be related to the ultra-filtration of cell activation mediators (such as beta-2-microglobulin, which is significantly less higher in these patients) or with the lesser activation of bone turnover stimulating mechanisms, on behalf of these membranes (Nephrol Dial Transplant (2001) 16: 1230-1238).

To study the role of some cytokines in bone turnover process, we measured the circulating levels of different cytokines and of their specific inhibitors by Elisa, using serum of 17 chronically haemodialyzed patients. In this study we established the presence of increased levels of Interleukin-1, Interleukin-1 receptor antagonist, Interleukin-6 and Interleukin-6 soluble receptor.

In a more recent study, a transiliac bone biopsy was performed after double tetracycline labelling in 47 patients on hemodialysis treatment for >6 months (mean 81.4 ± 52.5 months). Static and dynamic histomorphometric analyses were performed. Serum levels of intact PTH (iPTH 1-84; Nichols), total alkaline phosphatase (tAP), calcium, phosphate, and aluminum (Al) were evaluated. Circulating levels of interleukin-6 (IL-6), interleukin-1 receptor antagonist (IL-1Ra), and soluble interleukin-6 receptor (sIL-6r) (Elisa; Medgenix) were determined. Interleukin

1 β (IL-1 β), IL-6, interleukin 8 (IL-8), interleukin 10 (IL-10); interleukin 12p70 (IL-12p70) and Tumor Necrosis Factor (TNF) were quantified simultaneously by flow cytometry (BD Cytometric Bead Array).

Significant associations were found between several circulating cytokines and bone histomorphometry data, including correlations of IL-1-Ra, sIL-6r and IL-10 with Bone Area (B.Ar). Multiple regression analysis indicated that IL-1-Ra and IL-10 were independently predictive of B.Ar., that IL-6 and IL-12p70 were predictive of Mineral Apposition Rate (MAR; $\mu\text{m}/\text{day}$), and that IL-12p70 levels were predictive of BFR ($\mu\text{m}^2/\text{mm}^2/\text{day}$). These results will be presented to the next ASN meeting.

