Renal osteodystrophy encompasses several histologic subtypes, all of which can undergo change over time. In peritoneal dialysis (PD) patients, we studied bone histology and the factors influencing any changes over 1 year. In 44 PD patients, we collected two paired bone biopsies (at baseline and after 12 months) and biochemical and treatment data (at baseline and every 3 months).

Of the 44 original patients, 24 completed the study. Of these 24 patients, 19 were initially diagnosed with adynamic bone lesion (ABL). After 1 year, 12 still had ABL; the other 7 had changed to high turnover bone lesion (HTBL). Another 5 patients were initially diagnosed with HTBL. Among these, 4 still had HTBL at 1 year; 1 had changed to ABL. In patients who changed to HTBL from ABL, serum albumin had increased to 4.2 $\pm$ 0.3 g/dL at month 12 from 3.7 $\pm$ 0.4 g/dL at baseline ($p = 0.009$). A lower likelihood of diabetes ($p = 0.033$) and a higher serum albumin [area under the curve: 0.822; 95% confidence interval (CI): 0.651 to 0.993] identified a HTBL diagnosis at 12 months. Older age increased the probability of changing to ABL (OR: 1.2935; 95% CI: 1.03 to 1.67; $p = 0.02$).

Bone lesions can change over time, and this change is associated with age, diabetes, and serum albumin. A change to HTBL was associated with improvement in serum albumin. Protein status is possibly a factor influencing bone lesion outcome.

**Key words**
Bone biopsy, renal osteodystrophy, serum albumin

**Introduction**
Little is known about the precise factors implicated in the expression of various renal osteodystrophy (ROD) subtypes, and recently, additional factors such as nutrition have been shown to be involved (1). Moreover, we and other authors have demonstrated that individual patients can move along the spectrum of ROD over time (2,3), either spontaneously or as a result of therapeutic interventions.

The discovery of additional factors that have roles in the pathology of adynamic bone lesion (ABL) in peritoneal dialysis (PD) patients may help in the prevention and treatment of this disease and should help to ameliorate not only the progression of ABL itself, but also the morbidity and mortality resulting from...
vascular calcification in these patients. In the present study, we evaluated bone histology in PD patients during a period of 1 year and investigated the factors that influenced the development of or a shift between the various ROD subtypes in patients.

Patients and methods
In the study, we included 44 stable patients 18 years or older on chronic maintenance PD for at least 6 months, who accepted to undergo two bone biopsies and who provided informed consent. The local ethics committee approved the study protocol.

All patients were undergoing continuous ambulatory PD with three or four 2-L exchanges daily. At baseline, all patients were being dialyzed with solutions containing the same calcium concentration (1.75 mmol/L). Clinical evaluations, biochemical determinations, and doses of calcium (g), calcitriol (µg), and aluminum salts (g) were monitored at the start of the study (baseline) and every 3 months thereafter.

Intact parathyroid hormone (iPTH) was measured in plasma by immunoradiometric assay (Nichols Institute, San Juan Capistrano, CA, U.S.A.; normal range: 10 – 65 pg/mL).

An iliac crest bone biopsy was obtained at baseline and after 1 year of follow-up. Transiliac bone biopsies were obtained and processed as previously described (4). Static and dynamic histomorphometric parameters were measured by a semiautomatic image analysis system (Videoplan II: Kontron, Munich, Germany). Quantitative measurements were made on the trabecular bone area.

Histologic criteria for ABL were an osteoid volume (OV / BV) × 100 below 5%, a fibrosis volume (FbV / TV) × 100 below 0.5%, and a bone formation rate (BFR / BS) below 0.031 µm³/µm² daily (5,6) (where OV = osteoid volume in the sample; BV = volume of the bone sample; FbV = fibrosis volume in the sample; TV = trabecular volume; BFR = bone formation rate in the sample; BS = bone surface). Mild hyperparathyroidism (HPT) was defined as an osteoid volume below 15%, a fibrosis volume below 0.5%, and a bone formation rate greater than 0.031 µm³/µm² daily, and severe HPT as an osteoid volume below 15%, a fibrosis volume above 0.5%, and a bone formation rate greater than 0.031 µm³/µm² daily. High turnover bone lesion (HTBL) included both severe and mild HPT. All parameters were calculated following the recommendations of the Histomorphometry Nomenclature Committee of the American Society of Bone and Mineral Research (7).

Results are expressed as mean ± standard deviation. Differences between numerical variables were tested using the nonparametric Mann–Whitney U-test and the Wilcoxon test. Differences in categorical variables were checked with the Fisher and the McNemar tests. We used a Bonferroni correction in our analysis to reduce the probability of committing a type I error. An increase in the percentage index from baseline to final serum albumin [(ΔAlbumin: (month 12 albumin – baseline albumin / baseline albumin) × 100] was calculated in each of the principal groups. To identify the factors involved in changes in the second bone histology diagnosis, we used a univariate regression logistic analysis. The receiver operating curve (ROC) was also calculated.

Results
At baseline, 6 of the 44 patients were excluded; 5 had inadequate bone samples, and 1 had a mixed lesion. Another 14 patients were dropped from the study because of transplantation (n = 6), death (n = 2), transfer to hemodialysis (n = 2), refusing the second biopsy (n = 3), and inadequate size of the second bone sample (n = 1).

Figure 1 shows the histologic bone outcome after 12 months of follow-up. In the group of patients with an initial diagnosis of ABL who developed HTBL (n = 7), serum PTH rose significantly to 251.8 ± 128.8 pg/mL at month 12 from 90.8 ± 64.2 pg/mL at baseline (p < 0.05). In addition, serum albumin in this group rose to 4.2 ± 0.3 g/dL at month 12 from 3.7 ± 0.4 g/dL at baseline (p < 0.05). Patients who still had ABL (n = 12) showed no change in serum albumin (3.9 ± 0.4 g/dL vs. 3.8 ± 0.4 g/dL, p = nonsignificant).

Patients whose ABL status remained unchanged were older than the patients whose diagnosis changed to HTBL (62.3 ± 6.1 years vs. 50.5 ± 8.2 years, p = 0.006). This result was confirmed by the logistic regression analysis [odds ratio (OR): 1.3134; 95% confidence interval (CI): 1.03 to 1.67; p = 0.02] and the ROC analysis (area under the curve (AUC): 0.829; 95% CI: 0.662 to 1; p = 0.006). Patients with an initial diagnosis of HTBL (n = 5) also showed a significant increase in serum albumin at month 12 as compared with baseline (4 ± 0.7 g/dL vs. 3.5 ± 0.5 g/dL, p = 0.04). No other data were statistically significant.
At the end of follow-up, 13 patients were diagnosed with ABL, and 11 with HTBL (Figure 1). Table I shows the differences between the patients diagnosed with ABL and HTBL at month 12. Again, after the ROC analysis (AUC: 0.874; 95% CI: 0.735 to 1; \( p = 0.002 \)) and logistic regression analysis, older age was confirmed as a risk factor for an ABL diagnosis at second biopsy (OR: 1.2935; 95% CI: 1.03 to 1.62; \( p = 0.02 \)), and higher serum albumin levels predicted a diagnosis of HTBL (AUC: 0.822; 95% CI: 0.651 to 0.993; \( p = 0.009 \)).

With regard to treatment, patients with a diagnosis of HTBL at second biopsy showed greater accumulated intake of vitamin D over the study period (Table I)—a result of the effort to lower the higher serum PTH levels that they presented.

The study included 7 diabetic patients. Among patients with a diagnosis of HTBL on second biopsy (\( n = 11 \)), the percentage with diabetes was significantly lower than the percentage without diabetes [2/11 (18.2%) vs. 9/11 (81.8%), \( p = 0.033 \) by chi-square].

**Discussion**

The results of this prospective study of 1 year’s duration indicate that histologic bone lesion is a time-dependent status modifiable by multiple factors. Having ABL at both the start and the end of the study was associated with lower serum PTH levels and older age; a change to HTBL from ABL was associated with a lower presence of diabetes mellitus and a rising serum albumin level. In accord with the high prevalence of low turnover bone in the PD population, we found more patients with ABL than with HTBL.

The pathophysiology of ABL is poorly understood. Hypoparathyroidism has a role in the pathogenic mechanism leading to suppression of osteoblastic activity that contributes to low turnover status (8). In addition, recent studies in uremic patients have shown that a low-protein diet can induce uremic hypoparathyroidism (1,2,9). Moreover, an increase in serum PTH level has been associated with a normal serum albumin level, suggesting better visceral and somatic protein status (10). In this regard, we found that patients with initial ABL who changed to HTBL showed a significant rise in serum PTH and serum albumin. Indeed, an increase in serum albumin was associated with a diagnosis of HTBL at second biopsy.

Taken together, the foregoing findings suggest that bone resorptive activity may be influenced by protein status, and that the usual bone dynamics would be blunted in protein-deficiency states (11). In fact, some authors have speculated that the relative hypoparathyroidism observed in elderly dialysis patients (1,2,12), the PD population (12), and diabetic patients (2,4) might be attributable to their lower serum albumin. Thus, these special populations would actually be malnourished (2).

Several factors might explain this hypothesis. Bone turnover is a result of balanced osteoclastic resorption and osteoblastic formation. In advanced
chronic renal failure, protein malnutrition has been demonstrated to reduce circulating levels of important bone cell regulators, such as insulin-like growth factor I (IGF-I), with anabolic effects on the skeleton (13,14). Additionally, disturbances in circulating IGF system components have been more frequently described in PD patients than in HD patients (14). We believe that the data presented here agree with findings reported by other authors, which support the idea that low bone turnover might be a consequence of malnourishment and involutional changes (12,15).

Conclusions
Our results show that several factors can contribute to longitudinal changes between the various histologic forms of ROD. In addition to the classic phenomena such as age, diabetes, and PTH, serum albumin levels might be relevant in the outcome of renal bone disease in PD patients.

References


9 Lafage–Proust MH, Combe C, Barthe N, Aparicio M. Bone mass and dynamic parathyroid function

<table>
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<th>TABLE I Characteristics of patients diagnosed with adynamic bone lesion (ABL) and high turnover bone lesion (HTBL) at month 12 of follow-up</th>
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<tbody>
<tr>
<td><strong>ABL</strong> (n = 13)</td>
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<tr>
<td>Age (years)</td>
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<tr>
<td>Men/women</td>
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<tr>
<td>Diabetic patients [yes/no (%)]</td>
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<tr>
<td>ΔAlbumin (g/dL)</td>
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<td>P at month 12 (mg/dL)</td>
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<tr>
<td>PTH at month 12 (pg/mL)</td>
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<tr>
<td>Calcitriol intake</td>
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<td>Total dose (µg)</td>
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<td>At month 6 (yes/no)</td>
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<td>At month 9 (yes/no)</td>
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<tr>
<td>Calcium salts intake</td>
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<td>Total dose (g)</td>
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<td>Aluminum salts intake</td>
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<td>Total dose (g)</td>
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<td>Month 9 (yes/no)</td>
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* Bonferroni correction applied. NS = nonsignificant; P = serum phosphate; PTH = parathyroid hormone.
according to bone histology in nondialyzed uremic patients after long-term protein and phosphorus restriction. J Clin Endocrinol Metab 1999; 84:512–19.


Corresponding author:
M. Carmen Sánchez–González, MD PhD, Servicio de Nefrología, Hospital Universitario La Paz, Paseo Castellana 261, Madrid E-28046 Spain.
E-mail:
csanchez.hulp@salud.madrid.org