Diagnosis and treatment of renal bone disease

G. B. Spasovski

Department of Nephrology, University Clinical Center, University of Skopje, Republic of Macedonia

Abstract

The abnormalities in bone histology in patients with chronic renal failure (CRF), known as renal osteodystrophy (ROD), can be observed early in the course of the disease. Patients with mild to moderate degrees of CRF rarely experience symptoms, although skeletal changes may occur years before the symptoms arise. In end stage renal failure (ESRF) when patients require chronic maintenance dialysis, nearly all of them have abnormal bone histology. Moreover, survival rates of patients on dialysis have increased because of therapeutic improvement and the resultant increase in duration of dialysis has led to a further rise in renal osteodystrophy. Because metabolic bone disease can produce fractures, bone pain, and deformities late in the course of the disease, diagnosis, prevention and early treatment are essential.

To date, bone biopsy is the most powerful and informative diagnostic tool to provide precise information on the type and severity of renal osteodystrophy and also useful in research to assess the effects of therapies on bone. Alternatives to the bone biopsy continue to be searching for, but the non-invasive bone markers have not been proven to hold sufficient diagnostic performance. Hence, transiliac bone biopsy remains the golden standard for the diagnosis of renal osteodystrophy.

The therapy of renal bone disease depends on the particular type of ROD. However, some therapies (aluminum hydroxide and calcium carbonate) can exacerbate mineral balance and lead to the development of low-turnover bone diseases (osteomalacia or adynamic bone) and increased levels of vascular calcifications. Nowadays, phosphate control has been achieved with alternative phosphate binders that are not associated with these side effects (Sevelamer hydrochloride - RenaGel® and Lanthanum carbonat - Fosrenol®).

Key words: renal failure, renal osteodystrophy, bone biopsy, bone markers, calcium carbonate, lanthanum carbonate.

Bone biopsy

Double tetracycline labelling is the first prerequisite for an informative bone biopsy with an interval of 8 to 12 days (1). Phosphate binding treatment is stopped at the time of labeling and transiliac bone biopsy is then performed 2 to 6 days after the second label, under local anesthesia.

The possible complications from bone biopsies can include pain, haematoma, wound infection, and rarely neuropathy. However, studies show that the biopsies of the anterior iliac crest result in very small morbidity and no mortality as a result of procedure (2-4). The operator's experience is important in minimizing morbidity and in obtaining an adequate specimen. Based on histomorphometric findings, two main groups of renal bone disease can be classified: low (LTO) and high bone turnover (HTO) (3,5). Adynamic bone disease is characterized by a decreased number of osteoblasts and osteoclasts with a low bone formation rate (BFR). The second type of LTO, osteomalacia (OM), has a superimposed mineralization defect producing a great amount of unmineralized osteoid. HTO bone disease includes mild and severe hyperparathyroid bone disease (HPTH) or osteitis fibrosa, characterized by an excessive number of osteoclasts and osteoblasts and a high rate of bone formation and resorption. Mixed uremic osteodystrophy (Mx) possesses the combined features of both HPTH and OM.

Alternatives to the bone biopsy continue to be searching for, but the non-invasive bone markers have not been proven to hold sufficient diagnostic performance (6). Hence, transiliac bone biopsy remains the golden standard for the diagnosis of renal osteodystrophy.

Clinical application - Because bone biopsies more accurately determine the type of renal osteodystrophy and can indicate potential aluminum, strontium and lanthanum accumulation in dialyzed patients, they also allow tailoring of therapeutic measures. Additionally, bone biopsies could be performed at an interval of 6-12 months, sufficient for recognition of the specific changes of bone remodeling and mineral metabolism.

The biopsy shows the degree of bone turnover helping the practitioner to determine the route, aggressiveness, and length of phosphate binding and calcitriol therapy. Severe hyperparathyroidism with marked bone marrow fibrosis is an indication for high doses of calcitriol if the calcium-phosphorus product can be controlled. In patients with mild to moderate increase in bone turnover with or without mineralization defect, doses of intravenous or preoperative calcitriol and duration of therapy may be adjusted to avoid the development of ABD.

In case of ABD, calcitriol therapy is not desirable because of the risk of inducing hypercalcemia, extraosseous calcifications and further suppression of parathyroid glands' activity. Moreover, the use of a low calcium dialysate is recommended, as well as a lesser daily intake of calcium in the diet, ommiting the treatment with calcium containing phosphate binding agents.

Clinical experience

Our bone biopsy study in 84 ESRD patients revealed that

Correspodence to: G. B. Spasovski, Department of Nephrology, University Clinical Center, Vodnjanska 17, 1000 Skopje, Macedonia; Telephone: + 389 70 268 232; Fax: + 389 2 3231 501; E-mail: gspas@sonet.com.mk

62% of a predialysis population had abnormal bone histology (3). ABD was found to be the most frequent bone lesion observed in 23%, while HPTH (mild form) was diagnosed in only 9% of the patients. The majority of patients (38%) in our study presented with a normal bone histology. Hence, this finding differs considerably from the ROD spectra reported previously in non-dialysed renal failure patients where none of the patients was reported to have normal bone histology (7,8). Furthermore, our study revealed that serum calcium levels in 15 out of 19 (79%) patients with ABD appeared to be > 2.1 mmol/l; 4 of them were hypercalcemic >2.5 mmol/l and 12 (63%) presented with calcium x phosphorus product > 4.4 mmol/l (55 mg^2/dl^2). These findings were in agreement with the afore-mentioned treatment for ABD patients.

A recent study with lanthanum carbonate (LC) as a new phosphate binder, has shown its safety and effectiveness in phosphate binding (9). Additionally, we evaluated plasma and bone lanthanum levels in 20 incident dialysis patients at baseline, after 1 year of LC (n=10) and calcium carbonate treatment (CC=10) and after a 2-year of follow-up period during which the lanthanum treatment was replaced by CC (n=19) (4).

Baseline plasma lanthanum levels were below 0.03 ng/ml in most of the patients of both groups. During lanthanum carbonate treatment lanthanum levels increased reaching a maximal level of 1.26 ± 1.24 ng/ml at 24 weeks, after which they stabilized at a value varying around 0.60 ng/ml. Compared to the values noted at cessation of lanthanum treatment a significant decline of plasma lanthanum levels was noted at 6 weeks of follow-up (0.59 ± 0.52 *vs.* 0.17 ± 0.12 ng/ml; $P < 0.05$). There was no further significant decrease in mean plasma lanthanum concentration during the further 2-year follow-up (0.09 ± 0.03 ng/ml).

The mean bone concentration in patients receiving LC increased substantially from 0.05±0.03 to 2.3±1.6 mg/g ($P<0.05$) after 1 year and slightly decreased at the end of the study to 1.9±1.6 mg/g ($P<0.05$). Plasma and bone lanthanum levels did not correlate with the average lanthanum dose at any time point. At 1-year biopsy none of the patients in the LC group developed low bone turnover, this in contrast to the CC group in which three patients had developed adynamic bone. The moderate increase in the number of osteoblasts from 14.45 ± 7.92 % at baseline up to 21.23 ± 15.88 % (P = 0.19) after 1-year of lanthanum carbonate treatment, remaining unchanged after 2-year follow-up (20.27 ± 15.70%), further supported the hypothesis that bone lanthanum deposition was not associated with aluminum-like bone toxicity.

We concluded that lanthanum treatment resulted in a limited deposition of the element in bone with its slow release 2 years after arrest of the treatment and was no associated with aluminum-like bone toxicity. Morover, bone lanthanum deposition was not related to the dose administered, indicating patient-related differences in gastrointestinal absorption.

Conclusions

Bone biopsies are presently more widely used for diagnosis and research than they have been in the past although alternatives to bone biopsy continue to be pursued. However, these alternatives have not proven yet to be specific or sensitive enough to effectively replace the golden standard of bone biopsy.

Our experience on more than 150 transiliac bone biopsies showed no evidence of serious complications except for a few episodes of a moderate pain at the site of bone biopsy. Hence, this method can be considered as a safe and valuable diagnostic tool in the diagnosis and follow-up of the treatment of renal osteodystrophy.

ABD was found to be the most frequent bone lesion in patients with end stage renal failure and over the years on calcium carbonate treatment. Lanthanum carbonate was shown to be a safe and efficient phosphate binder which was not associated with aluminum-like bone toxicity.

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