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NEPHROLOGY FORUM

Hypokinetic azotemic osteodystrophy

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CASE PRESENTATION

A 61-year-old male dialysis patient was referred from another center to the Bone and Mineral Research Unit of the Hospital Central de Asturias for evaluation. At age 24, renal tuberculosis had necessitated a left nephrectomy; at age 42 nephrolithiasis in the right kidney had prompted surgical intervention. Four years later, moderate renal failure presumably due to chronic interstitial nephritis was diagnosed; 7 years later, at age 53, he entered the dialysis program. He received treatment in a dialysis unit equipped with a reverse osmosis (RO) system for water treatment. Renal osteodystrophy had been present since the beginning of dialysis, and the thoracic and lumbar spine showed demineralization.

During the first 5 years of hemodialysis, symptoms and radiologic signs of hyperparathyroidism, including multiple vascular calcifications, worsened. The serum calcium (Ca^+) level progressively increased, reaching 10.5 mg/dl. The serum phosphorus (P) level was high, although the patient had received long-term treatment with aluminum hydroxide. During that period, parathyroid hormone (PTH) levels (carboxy terminal) had remained 40 to 50 times higher than the upper limit of normal. Total alkaline phosphatase measurements had stayed in the low-normal range. The patient needed frequent red cell transfusions to avoid symptoms of anemia. Five years after beginning dialysis, he had a non-traumatic radial fracture coincident with worsening of the radiologic signs and his symptoms. A subtotal parathyroidectomy was performed.

During the 2 years after the subtotal parathyroidectomy, his symptoms mildly improved, and the carboxy terminal PTH level decreased, stabilizing in the upper limit of normal. Total alkaline phosphatase fell to lower than normal, and the serum P was kept at acceptable values by aluminum hydroxide and calcium carbonate. Oral calcitriol (1.5–3.5 μg/week) maintained serum Ca^+ levels in the range of 10.0 mg/dl–10.5 mg/dl. Two years after the parathyroidectomy, bilateral carpal tunnel syndrome was detected and surgically relieved. Amyloid was detected in the surrounding fat tissue, serum beta-2 microglobulin was elevated; dialysis with highly permeable membranes (PAN) was prescribed.

Three years after the parathyroidectomy, PTH levels, measured several times using a PTH intact assay, revealed very low values (from undetectable to 13.5 pg/ml) and total alkaline phosphatase had returned to pre-surgery values (in the low-normal range). Basal serum aluminum (Al) was 96 μg/liter, increasing to 234 μg/liter after the infusion of 40 mg/kg of deferoxamine. Because Al-induced bone disease was suspected, a bone biopsy with tetracycline labeling was performed. The main histologic and histomorphometric findings of the bone biopsy were reduction in trabecular bone volume (11%), a slight increase in relative osteoid surface (20%), a decrease in osteoid volume (1.3%), low osteoblast surface (0.12%), low osteoclast surface (0.59%), positive Al surface staining (aluminum 16%; solochrome of azurine, 47%), and negative iron (Fe) staining (Perls). Bone Al and Fe concentration, measured by atomic absorption spectrometry, were 28 μg/g and 405 μg/g, respectively (normal, 3 μg/g and 300 μg/g, respectively). The tetracycline study showed only a single and diffuse labeling. Aluminum-induced adynamic bone disease was diagnosed.

After the bone biopsy, therapy with deferoxamine (40 mg/kg/week) was prescribed (18 months of intermittent treatment over 3 years). During deferoxamine therapy, repeated basal serum Al levels were 50–85 μg/liter; these values doubled after the deferoxamine tests performed during that period. At the end of deferoxamine treatment, the serum Al remained at the same level, but intact PTH and alkaline phosphatase levels progressively increased, reaching 150 pg/ml and 219 U/liter, respectively (normal, 10–65 pg/ml and 70–280 U/liter). Before and after the deferoxamine treatment, serum transferrin, serum Fe, and Fe-transferrin saturation were always in the normal range. Two years after the bone biopsy, when the patient was 62 years old, he suffered a fracture of the right femoral neck; one year later, he fractured the left femoral neck. Both were treated with standard surgical techniques.

During the following 4 years, the patient was admitted to the hospital several times with diagnoses of diabetes mellitus type II, diverticulitis, ventricular tachycardia, and congestive cardiac failure. Also, severe vascular obstruction of the left leg necessitated amputation of the second toe of the left foot. During the last year (7 years after the bone biopsy), he has maintained a serum calcium ranging between 9.0–9.5 mg/dl; serum phosphorus, 4.7–6.5 mg/dl; serum aluminum, 73.0–90.8 μg/liter; normal serum iron parameters; intact PTH levels of 314–415 pg/ml; and an alkaline phosphatase of 125–139 U/liter.

DISCUSSION

DR. JORGE B. CANNATA-ANDÍA (*Head, Bone and Mineral Research Unit, Professor of Nephrology, Instituto Reina Sofía de Investigación, Hospital Central de Asturias, Universidad de Oviedo, Oviedo, Spain*): This man had long-standing, slowly progressive renal failure. When he entered the dialysis program, his renal osteodystrophy was symptomatic. Most of his signs and symptoms were interpreted as due to secondary hyperparathyroidism (osteitis fibrosa), even

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though the total alkaline phosphatase levels were not in the range of the severe forms of high bone remodeling. The possibility of his having aluminum overload was not investigated. The first non-traumatic bone fracture, in association with the worsening of his clinical symptoms, was attributed to secondary hyperparathyroidism and prompted subtotal parathyroidectomy; other diagnostic possibilities were not considered.

Although osteitis fibrosa due to hyperparathyroidism is the most frequent form of renal osteodystrophy in patients entering a dialysis program, different factors can influence bone remodeling and facilitate the appearance of low-bone-remodeling lesions in patients with the slowly progressive forms of renal disease. A large proportion of patients thus do not have a high-bone-remodeling lesion. While symptoms and signs of renal osteodystrophy sometimes can indicate the diagnosis, just as often they provide little help in distinguishing the type of bone lesion. In addition, physicians at dialysis centers with adequate water treatment systems (for example, RO) frequently underestimate the possibility of aluminum exposure contributing to renal osteodystrophy.

In this patient, parathyroidectomy apparently improved his signs and symptoms somewhat, but it is highly likely that this operation adversely affected his subsequent course, including the histologic bone pattern found 3 years later, the bone fractures, and the persistent relative hypoparathyroidism. After long-term treatment with deferoxamine, biochemical markers indicated slow but progressive improvement in bone remodeling. However, not until 10 years after parathyroidectomy did his bone remodeling return to acceptable levels.

The type of bone lesion and the concentrations of aluminum and iron in this patient merit special comment. While this patient received multiple red cell transfusions, he apparently did not have a heavy aluminum load in his dialysate. Moderate aluminum load from intermittent aluminum hydroxide treatment was present in this patient with relative hypoparathyroidism, and he developed adynamic bone disease instead of osteitis fibrosa. In this Forum, I will review the importance of the association of iron load, aluminum load, and relative hypoparathyroidism in producing the various bone remodeling lesions.

Bone remodeling and renal osteodystrophy

Bone disease in patients with renal failure is not a uniform metabolic disorder [1, 2]. As renal failure progresses, the disordered patterns of bone metabolism differ greatly among patients [2–5]. Decreased serum calcium and 1,25 vitamin D synthesis plus retention of phosphate trigger secondary hyperparathyroidism, but several factors modulate the severity and final outcome of this disorder. Two main factors can modify the pattern and form of presentation of renal osteodystrophy. (*1*) The first group of factors is related to the underlying renal disease, for example, diabetes or rapidly progressive glomerulonephritis. In these cases, the disease itself and/or the treatment prescribed (for example, corticosteroids) as well as the age of the patient result in particular forms of bone lesions. When the patient presents with severe renal failure, there is little we can do to modify or influence these underlying factors. (*2*) The other set of factors is related to the medical management of secondary hyperparathyroidism and to the dialysis treatment itself. In these two circumstances, the type and modality of treatment (hemodialysis or CAPD), and also the use of different therapeutic approaches (phosphate binders, vitamin D metabolites, etc.) can introduce changes that affect the presentation and evolution of the metabolic bone disorders of chronic renal failure. As a result of the interactions of these several factors, renal osteodystrophy can present with a wide spectrum of bone derangements, ranging from high bone remodeling—the classic pattern of disordered bone metabolism in chronic renal failure—to low bone remodeling. I will focus my attention here on the latter, because recent reports indicate a likely increase in its incidence and prevalence in patients with chronic renal failure [3–9].

The literature contains several histologic classifications of renal osteodystrophy [3, 5, 9]. It is beyond the scope of this review to compare and analyze them. However, I believe it useful to categorize the bone changes found in uremia into high- or low-bone remodeling lesions. This conceptual division offers an understandable framework of the different forms of renal osteodystrophy, making easier the application of different therapeutic strategies.

The concept of high- and low-bone-remodeling lesions involves two main aspects: a difference in the number of active bone remodeling units, and a difference in the level of activity of each bone remodeling unit. The end product of these two factors results in great differences in bone formation rate, accounting for the wide spectrum of renal osteodystrophy.

Low-bone-remodeling hypokinetic osteodystrophy, by definition characterized by a low formation rate of bone, essentially reflects the body's lack of ability to form normal bone matrix, mainly because of low cellular activity, and also the body's inability to mineralize bone adequately. The two main histologic forms of low-bone-remodeling disease are osteomalacia and adynamic bone disease. Both entities present clear and objective pathophysiologic and histologic differences. In osteomalacia, both osteoid deposition (osteoblast activity) and the rate of mineralization are reduced, but the reduction in mineralization is by far greater than the reduction in osteoid formation [1, 5, 10]. The reduced mineralization leads to an increase in non-mineralized osteoid (osteoid accumulation) and consequently to an increase in osteoid volume. By contrast, adynamic bone is characterized by low osteoid formation (osteoblast activity) and by a proportional reduction in bone mineralization,

there being no specific impairment in the mineralization process [1, 5, 7, 11].

Has the prevalence of the different forms of renal osteodystrophy changed? Throughout the last 20 years, our knowledge of renal osteodystrophy has expanded greatly. Before, the pathogenetic mechanisms were poorly understood, and we had less-accurate diagnostic methods and fewer therapeutic possibilities [12, 13]. Over the last decade, new therapeutic approaches have been introduced [1, 2, 4, 14]. As a result, we might expect to find differences in the prevalence of the different types of renal osteodystrophy from that found in earlier studies [3–5, 6–9, 12, 13].

Unfortunately, the early studies of renal osteodystrophy did not evaluate non-selected patients. Nevertheless, we know that high bone remodeling (from mild to severe) was the most common diagnosis, two to three times more frequent than low bone remodeling [7, 13]. Thus, several years ago, the predominant bone lesion in patients in whom bone biopsy was performed was probably due to hyperparathyroidism. The second most common diagnosis was aluminum-induced osteomalacia [5, 7, 8, 15]. The incidence of this diagnosis varied greatly among centers, regions, and countries [10].

By contrast, recent reports in non-selected patients [3, 4, 6, 8] as well as in patients in whom bone biopsy was performed for specific medical reasons [5, 7] reveal that low-bone-remodeling lesions are quite frequent, accounting in some series for almost one-half the lesions observed [3, 4, 8]. This increase in the incidence of low-bone-remodeling lesions seems to be due to the increase in adynamic bone disease. On the other hand, the frequency of the previously most common form of low bone turnover, aluminum-induced osteomalacia, seems to have diminished [4, 5]. Still, this assertion has a major limitation: the criteria used to define adynamic bone have not been uniform. To distinguish osteomalacia from adynamic bone disease, one must have consistent cut-off levels to define normal, low, and high osteoid volume. Although the upper limit of osteoid volume in a normal population is considered to be approximately 5% of bone volume, the most quoted studies have used different limits to define low or high osteoid volume. These limits have ranged between 5% in the first studies [10] to 15% in the most recent publications [3, 4, 6–8]. Using the lower threshold (5%), more patients are diagnosed with osteomalacia, but if higher limits are used (12% to 15%), more patients are diagnosed as having an adynamic bone disease, without real changes in the incidence or the prevalence of these entities. The most recent papers, which use limits for osteoid volume of 12% to 15%, classify only the most severe cases of osteoid accumulation as osteomalacia. This fact might well contribute to the increased prevalence of adynamic bone disease compared with osteomalacia [3, 4, 6, 8, 10], but it cannot account entirely for the change observed in the frequency of the two diseases. Although the criteria haven't changed for either osteomalacia or adynamic bone disease since 1983 [5, 7], some authors have reported a decrease in osteomalacia and an increase in adynamic bone disease. However, these changes have occurred without an overall increase in the aggregate number of the two low-bone-remodeling lesions; the cumulative incidence has remained stable at approximately 25% of all bone biopsies throughout the last 12 years [5].

Aluminum toxicity, the main cause of low-bone-turnover osteomalacia in the 1970s and 1980s, is now better managed in most developed countries [16]. In other areas of the world [17–19], however, aluminum toxicity remains a major challenge. The change in the pattern of aluminum exposure alone cannot explain the increase in the prevalence of adynamic bone disease. Other factors likely have contributed to its increase. The type of patients undergoing dialysis clearly has changed. Diabetics and older patients now comprise a major segment of the dialysis population [20, 21]. Diabetes as well as age have been indicted as independent factors that can induce a decrease in bone remodeling [4, 8, 22, 23]. The management of renal patients also has changed. New therapeutic approaches keep secondary hyperparathyroidism under control, such as the increasing use of calcium carbonate, calcium acetate, and vitamin D metabolites [24, 25]. Bicarbonate has almost replaced acetate as a buffer in hemodialysis [26]. All these factors might have contributed to a greater suppression of PTH function and to better control of metabolic acidosis, with a consequent decrease in bone resorption [27, 28]. Similarily, in peritoneal dialysis patients, the stability in the serum calcium and acid-base balance also has been implicated in explaining the higher incidence of low bone remodeling in these patients [9].

In chronic renal failure, our goal should be to achieve the more adequate ("normal") bone turnover. Therefore, before going further, it is important that we define the limits between high, "normal," and low bone turnover. Clinicians generally agree that uremia results in a multifactorial resistance to the action of PTH in bone; this concept is known as "skeletal resistance to PTH." In practical terms, uremia necessitates a higher level of circulating PTH to obtain adequate ("normal") bone turnover. Although this concept is rather old [18–20], accurate PTH assays, and thus reliable serum values of PTH that precisely define the concept of "skeletal resistance to PTH," were not available until recently [3, 4, 6].

To maintain a normal osteoblast surface, dialysis patients require PTH levels in the range of 70–260 pg/ml; to obtain a normal bone formation rate, they require PTH levels between 100–170 pg/ml (reference values in subjects with normal renal function, 10–65 pg/ml) [4]. Recent studies suggest that because dialysis treatment only partially corrects this skeletal resistance to PTH, predialysis patients require higher parathyroid hormone levels (up to 375 pg/ml) to maintain a normal osteoblast surface and bone

formation rate [4]. Therefore, the optimal PTH range that we consider "normal" in chronic renal failure is 125–250 pg/ml in dialysis patients, and 300–375 pg/ml in predialysis patients with advanced renal failure [4]. Values below 120 pg/ml provide a positive predictive value of 83% and 90% for the diagnosis of low bone remodeling, in predialysis and dialysis patients, respectively [4].

These figures are valid only for patients not receiving vitamin D pulse therapy with calcitriol, which can directly suppress bone formation. Therefore, particularly in severe forms (diffuse or nodular hyperparathyroidism), calcitriol pulse therapy does not always suppress PTH synthesis, but it can reduce bone formation. Under these circumstances, PTH levels will not reflect what is happening in bone [29, 30].

Parathyroid function in low bone remodeling. The forms of renal osteodystrophy involving low bone remodeling are associated with "relative" basal PTH deficiency [31, 32]. In basal conditions, the circulating absolute levels of PTH are normal or insufficiently increased to maintain adequate bone turnover. The value of measuring basal PTH levels in dialysis patients is limited because serum calcium, a major regulator of PTH production and release, can induce a wide range of intra- and extradialytic changes [33], making comparison of PTH function among these patients difficult. In addition, analysis of a single determination of calcium and PTH provides information limited to only one point in time.

More recently, new dynamic tests that assess parathyroid function have helped us better understand the function of the parathyroid gland in the different forms of renal osteodystrophy [31, 34]. Analysis of the sigmoidal curve, which relates serum calcium and PTH changes, tells us about the sensitivity of the gland (slope of the curve and set point), and dynamic tests help us judge the secretory reserve capacity of the parathyroid cells [31, 34–36]. Unfortunately, the studies reported have not used similar methods and therefore cannot be directly compared. Important factors such as phosphorus, pH (use of acetate or bicarbonate), glucose, and magnesium have not been taken into account. Another important factor, age of the patient, has been consistently ignored; comparisons of studies conducted in young people [53] with studies carried out in older people [31–35], in whom the parathyroid gland is less active, have limited value. Despite all these limitations, we have gathered enough information to allow us to analyze the responsiveness of the parathyroid gland in low bone remodeling.

The first clinical studies of parathyroid gland responsiveness in low bone turnover were carried out in the early 1980s and compared patients with aluminum-induced osteomalacia with patients with high bone turnover (osteitis fibrosa) [37, 38]. In both studies, patients with osteitis fibrosa had, in absolute terms, a significantly greater response to hypocalcemia than did the patients with osteomalacia. However, if we analyze the changes in PTH response as a percentage of the basal values, we find that both groups behaved in a similar way, with no differences in the percentage increments. In other words, the larger the gland, the greater the magnitude of the response [36–38].

Further studies inducing hypo- and hypercalcemia during hemodialysis showed similar results. Lower absolute increments from hypocalcemia were found in patients with low bone remodeling (with and without aluminum) than in patients with high bone remodeling [31]. Adjustment of the curves to show the maximal PTH (100%) of each group demonstrated that the set point and the slope of the curve, independent of the presence of aluminum, were lower in patients with low bone remodeling. In another study, the same group found that one year of treatment with deferoxamine did not increase the maximal absolute values of PTH, but did shift the calcium-PTH curve to the right, and the curve also had a slightly steeper slope [39]. This result suggested that the removal of aluminum partially restores the gland's sensitivity. This finding is also supported by another clinical study carried out after 6 months of continuous deferoxamine administration [19].

More recently, another study investigated the maximal and minimal PTH response in normal volunteers, in patients with adynamic bone disease, and in osteitis fibrosa in CAPD patients [35]. As in previous studies, hypocalcemia was followed by a lower absolute response in PTH levels in CAPD patients with adynamic bone. When the results were expressed as a percentage increase over basal PTH values, however, the increments of PTH in adynamic patients were in the same range as those in normal volunteers and were even higher than those in patients with osteitis fibrosa. The maximal PTH was reached slowly in the adynamic group compared with the other two groups, but PTH levels remained high for a longer period in patients with adynamic bone. This persistence demonstrated an adequate secretory reserve in this group. On the other hand, after calcium infusion, patients with adynamic bone demonstrated, as in other studies [40], a lack of capacity to handle calcium loads, and they had a more sustained hypercalcemia after the calcium infusion [35].

Another parameter used to investigate changes in the sensitivity of the parathyroid gland has been the set point, defined in clinical studies by the serum calcium concentration at which the maximal PTH is suppressed by 50%. Although some studies have found a lower set point in low bone remodeling, other studies have found no differences in the set point in high, normal, or low bone remodeling [35]. Thus, the value of the set point in these (and other) circumstances remains controversial [39, 40]. I personally believe that analysis of the slope of the calcium PTH curve and its shift to the right or left gives better information about the sensitivity of the parathyroid gland. The usefulness of the set point is more controversial; its value, which

after all is a single measurement of the sensitivity of the gland, likely has been overestimated.

In summary, the magnitude of change in PTH per unit of change of serum calcium is lower in low bone remodeling. This alteration indicates a reduction in the sensitivity of parathyroid cells, independent of the presence of aluminum. Nevertheless, the maximal and minimal capacities of the gland remain in a normal range. Overall, the information available indicates that in low bone remodeling, the parathyroid gland probably is slower to respond but its secretory reserve is preserved.

Pathogenesis of low bone remodeling

I already have set forth the most frequent causes of low bone remodeling in uremia. Now we will analyze in detail the factors and likely mechanisms involved in the pathogenesis of low bone remodeling. Among all causes of low bone remodeling, the first cause described and the most studied is aluminum-induced bone disease. In addition, aluminum-induced bone disease is the only form of low-bone-turnover producing symptoms and ultimately death [3, 5, 8, 10, 15, 18, 41].

For this reason, some investigators classify low-bone-turnover disease into two main types: aluminum-induced and non-aluminum-induced low bone remodeling. This classification allows us to recognize when aluminum is the likely cause of the disease, when aluminum is not implicated, and when aluminum is merely an "innocent bystander." This important topic has practical consequences, but unfortunately we do not have definitive answers.

Aluminum-induced low bone remodeling. Aluminum toxicity produces two alterations in bone: osteomalacia and adynamic bone disease. Controversy remains, however, regarding whether aluminum is responsible for the adynamic lesion. In this review, I prefer to use the term aluminum-induced adynamic bone disease, because the clinical [3, 5, 10, 15] and experimental evidence [42–44] suggests that in many cases aluminum is responsible for the lesion rather than an innocent bystander.

Reports indicate that the incidence of aluminum-induced toxicity has decreased over the last decade [3, 5, 8], but this is not true for many developing countries [18, 19], in which aluminum still is implicated in a high percentage of low-bone-remodeling lesions. Furthermore, recent series from Europe and North America reveal that bone biopsies with substantial amounts of stainable aluminum still are frequent [5, 45, 46]. Even though the finding of aluminum in the mineralization front does not necessarily mean that aluminum is the cause of the disease, there is no doubt that the presence of aluminum, either in the mineralization front or inside the trabeculae, represents a potential hazard, particularly in patients who undergo parathyroidectomy [47–49], like the patient presented in this Forum.

The presence of aluminum in bone may or may not be associated with aluminum-induced toxicity. If histochemical staining techniques reveal that the trabecular bone surface is covered at least 25% to 30% with aluminum [3, 10], most investigators would attribute low bone remodeling to the aluminum. I am unsure about aluminum's responsibility, however, because I view this threshold of bone surface covered by aluminum as rather empiric. Further, I believe that the staining technique, such as the aurin tricarboxilic acid (aluminon), is not sensitive enough.

Ascribing low-turnover-bone disease either to aluminum or to non-aluminum factors comes from early studies [50, 51], performed when the amount of aluminum exposure was very high. Aluminum-induced osteomalacia was the most common, and almost the only, form of low-bone-turnover disease. Then, the mean percentage of aluminum covering the mineralization front, measured by histochemical techniques, correlated better with the histomorphometric parameters than did the amount of aluminum in bone, measured by atomic absorption spectrometry [50, 51]. Currently, the amount of aluminum available for deposition in the mineralization front is lower, and the value of histochemical staining in the diagnosis of aluminum toxicity should be reconsidered. The stain currently used most to detect aluminum is aluminon, which has a low sensitivity. By contrast, other stains, such as solochrome of azurine, have performed significantly better, and the latter can obtain more reliable results in the presence of low aluminum concentrations [51, 52].

Because of the reduction in aluminum exposure, we need more sensitive methods to detect lower concentrations of aluminum in the mineralization front and also in the depth of the trabeculae [52]. Unfortunately, most of the recent series showing a high prevalence of non-aluminum-induced adynamic bone disease still use only the less-sensitive aluminon technique to rule out aluminum as the cause [3, 4, 8]. Thus, the prevalence of adynamic bone disease induced by aluminum might be underestimated.

Aluminum may negatively influence bone metabolism directly by acting on bone or indirectly by depressing parathyroid function. One of the first reasons for aluminum being considered toxic to bone is that aluminum can be deposited in the mineralization front. The presence of aluminum in this specific location, between the osteoid and the mineralized bone, was thought to be a physicochemical obstacle for calcium deposition [45, 53, 54].

The assumption that osteomalacia resulted mainly from a defect in bone mineralization was confirmed in experimental studies, which also determined that aluminum's toxicity in bone is multifactorial, impairing not only the mineralization process, but also proliferation and activity of parathyroid and bone cells. Dissociating aluminum's effect on bone from its effect exerted in vivo on the parathyroid gland (and other endocrine and paracrine influences) is difficult. But in-vivo experiments confirmed an independent and direct effect of aluminum on bone cells. High doses of aluminum given to azotemic rats decreased both

osteoblast activity (osteoblast surface) and bone formation rate (mineralized bone) [44, 45]. However, the decrease in bone formation rate is much more pronounced than is the effect on osteoblasts. Thus, the overall effect of heavy aluminum loads is a greater reduction in mineralized bone compared with its negative effect on osteoid formation (osteoblast activity), and the resulting increments in nonmineralized osteoid (increased osteoid volume). In summary, high doses of aluminum induce the typical lesions of osteomalacia, and a high percentage of the osteoid surface is covered by aluminum [10, 15, 44, 46].

Infusion of PTH partly reverses the toxic effect of aluminum on bone cells, increasing their number and activity, but PTH supplementation does not improve the defect in mineralization caused by aluminum [55]. Evidence from in-vitro studies demonstrates that calcium influx and efflux from bone cells is altered [43] and also that calcium uptake from bone cells might be decreased [42, 56]. Both these changes impair calcium apposition, crystallization, and consequently bone mineralization.

What happens in bone when moderate but long-term aluminum exposure occurs? The answer is unclear and awaits studies using experimental models in which aluminum is administered in a fashion comparable to the current aluminum exposure in dialysis patients.

Apart from the just-described direct effects of aluminum on bone turnover, aluminum also might have an additive effect on bone metabolism: it interferes with PTH function and in turn influences bone remodeling. Aluminum can reduce serum levels of PTH via two main pathways: acting directly on parathyroid synthesis, degradation, or release, and indirectly by elevating serum calcium, which in turn suppresses parathyroid activity [53, 57–60].

Several clinical and experimental studies have shown that aluminum can directly reduce PTH [37, 38, 55, 58, 59–61]. A series of experiments, carried out by our group some years ago, gave support to the hypothesis that aluminum interferes mainly with PTH release and/or degradation [61, 62] rather than with PTH synthesis. Nevertheless, high doses of aluminum were needed to suppress PTH release [61]. We proposed that aluminum (AL^{3+}) produces a prompt and direct response—within a few minutes—likely acting at ionic levels [59, 61], as calcium does, possibly influencing the calcium-sensing mechanism. The recent demonstration that the calcium-sensing receptor is sensitive to other bi- and trivalent ions [63] makes our hypothesis quite possible [59].

More recently, preliminary studies have suggested a reduction in RNA messenger of PTH in rats with acute aluminum loads; these early data suggest that aluminum reduces PTH synthesis [64]. Recent preliminary experimental results suggest that aluminum is taken up by the gland via the transferrin receptor [65].

In addition to aluminum's direct effect on the parathyroid gland, it might exert a suppressor effect on PTH indirectly by elevating the serum calcium level [53, 60]. Patients with low bone remodeling, either with osteomalacia or adynamic bone disease, have a decreased ability to buffer calcium loads [40]. Since the first descriptions of aluminum-induced bone toxicity, we now know that these patients are more likely to have serum calcium elevations and to develop hypercalcemia [5], either spontaneously or when receiving calcium salts or vitamin D therapy.

The mechanisms by which aluminum indirectly decreases PTH release by elevating serum calcium are easily explained when one considers where and how aluminum accumulates. When the aluminum load is high, a large amount of aluminum is deposited in the mineralization front. This deposition interferes with the incorporation of calcium into osteoid. The prevention of calcium deposition in bone changes the normal calcium equilibrium between extra- and intracellular compartments; this situation, characterized by an increase of calcium in the extracellular pool, results in elevated serum calcium levels, in turn suppressing the synthesis and release of PTH [54, 60].

Aluminum's suppressive effect on parathyroid function, no matter what the mechanism, is extremely important for several reasons. As has been known for decades, chronic renal failure is characterized by a skeletal resistance to PTH; thus one needs higher levels of PTH to maintain adequate bone remodeling. In addition, however, a higher PTH level is desirable whenever aluminum overload exists. Evidence suggests that aluminum's toxic effect on bone is modulated via serum PTH levels. When enough PTH is present, that is, when high bone remodeling is the background, the toxic effect of this metal in bone decreases despite high bone concentrations of aluminum, and the likelihood of low bone remodeling is lower.

This phenomenon occurs even though high PTH levels can increase aluminum uptake in different tissues [59] without affecting bone remodeling. Thus, a paradoxical situation might exist in which high PTH levels favor aluminum accumulation in tissues but the toxic effect of aluminum on bone is lessened, probably because of high bone turnover induced by PTH. Adequate PTH levels thus seem to provide significant protection against aluminum toxicity in bone. The protective role of PTH is apparent from clinical and experimental studies [47, 48, 56], which demonstrate the high risk of aluminum-induced low-bone-turnover disease after parathyroidectomy. The case presented in this Forum is a good example of that risk.

In summary, I would suggest that aluminum's effect on mineral metabolism, and ultimately on bone, differs according to the timing and amount of aluminum exposure. With heavy aluminum loads, the predominant effect is a defect in mineralization that produces osteomalacia. However, low-moderate aluminum exposure, as in the range of dialysis patients today, together with reduced levels of PTH because of the widespread use of vitamin D metabolites and/or calcium salts, produce a different effect on mineral

metabolism. These less-severe exposures induce a pattern of bone damage similar to that in adynamic bone disease. Because aluminum has an independent effect on the parathyroid gland, I don't think we can eliminate a role for aluminum in the pathogenesis of adynamic bone disease.

One can reasonably speculate that changes in the pattern of aluminum toxicity in bone are partly due to the changes in the pattern of aluminum exposure. In the late 1970s and early 1980s, dialysis patients were heavily aluminum overloaded. Fortunately, apart from sporadic episodes of aluminum exposure [66, 67], in most centers massive aluminum loads have given way to moderate loads. We and others have stressed that the widespread use of adequate water treatment systems and the reduction in the consumption of aluminum hydroxide have dramatically reduced aluminum overload in patients with chronic renal failure [16, 67]. However, aluminum exposure has not disappeared, and many patients are still permanently exposed to moderate loads of aluminum both via dialysis fluids and through oral aluminum hydroxide intake [16].

In the field of prevention of aluminum toxicity, we are still using the conceptual framework we adopted nearly 15 years ago, when heavy aluminum exposure occurred. Various governments still accept 10 μg/liter as a safe limit for aluminum concentration in dialysis fluid. This figure derives from the early 1980s, when many dialysis patients had serum aluminum values in the range of 100 μg/liter to 200 μg/liter. Considering that only 10% to 15% of aluminum is dialysable (the remaining 85%–90% is protein bound), the figure of 10 μg/liter seems a reasonably safe upper limit. However, in almost all countries, mean basal serum aluminum levels of patients on dialysis have fallen significantly. In Spain, this figure is close to 20 μg/liter; thus, the aluminum concentration in the dialysate should not exceed 2–3 μg/liter. Yet even in recent reports, the figure of 10 μg/liter of aluminum in dialysis fluids is still perceived as safe.

The other important source of aluminum exposure, aluminum hydroxide intake, also has been reduced. Even though other aluminum-free phosphate binders such as calcium acetate, calcium carbonate, and others are widely used, a high percentage of patients, at least in Europe (42% to 75%), still receive aluminum hydroxide alone or in combination with calcium salts [24].

Bone biopsy specimens from patients who started dialysis during the last decade in Europe, in centers that have used adequate water treatment systems and low doses of aluminum-containing phosphate binders for more than 15 years, still reveal aluminum concentrations in bone 20 to 50 times higher than normal values [5, 58]. Despite these high concentrations of aluminum in bone, however, the distribution of aluminum into the bone has changed, and its concentration in the mineralization front is lower.

As I mentioned earlier, aluminon, the most widely used staining method for aluminum detection, has a low sensitivity and thus leads to negative or weakly positive results in contrast to positive results using solochrome of azurine [52]. This technical error contributes to the widespread, erroneous concept that aluminum exposure and toxicity no longer occur. We still do not know the significance and the toxic role of this different distribution of aluminum in bone, but if we are to indict or eliminate aluminum as toxic to bone in an individual patient, we cannot use the same rules that we used to diagnose osteomalacia in the past.

Aluminum and iron have some similar biochemical properties, and they share important biologic pathways [68]. For example, they compete for the same mechanisms of gastrointestinal absorption and cellular uptake [69], are carried by the same serum proteins, are chelated by the same drugs [68], are stained in bone with the same compounds (aluminon and solochrome of azurine), and both have been implicated in the pathogenesis of low bone remodeling [53, 70, 71]. Therefore, iron toxicity must be considered when evaluating patients with low bone turnover.

It is beyond the scope of this Forum to discuss in detail the aluminum-iron interaction [69–71], but I shall briefly summarize the most relevant aspects of this relationship and its likely links with low bone turnover. Iron overload has negative effects on bone [71, 72]. In acute experimental studies, iron overload did not affect bone mineralization, but did decrease osteoblast number and activity [72]. Experimental studies did not demonstrate any effect of iron overload on PTH, but the assay used in these experimental studies lacks sensitivity [72]. Clinical studies in patients with hemochromatosis [73] and in patients with renal failure and iron overload demonstrated a decrease in bone mineral density and the presence of adynamic bone, respectively.

On the other hand, although a recent study failed to show any influence of iron stores on aluminum metabolism [74], several studies from different groups have found an inverse and competitive relationship between iron and aluminum metabolism [69, 75–77]. Iron overload decreases aluminum absorption (thus decreasing the changes of aluminum overload), aluminum binding to transferrin, and aluminum cellular uptake. On the other hand, iron depletion (frequently present when patients are treated with both erythropoietin and deferoxamine) facilitates the development of mild to moderate aluminum toxicity and with it the risk of low bone turnover. Therefore, the two extremes of this spectrum—high aluminum-low iron, and high iron-low aluminum—can be implicated in the pathogenesis of low-bone-remodeling lesions. In addition, recent preliminary findings suggest that strontium induces low bone remodeling [78].

Non-aluminum-induced adynamic bone disease. I have extensively discussed the association of relative PTH deficiency with low bone remodeling. I previously used the term "aluminum-induced bone disease" to refer to the low-bone-remodeling disorder induced by aluminum. By contrast, in the analysis of other causes of adynamia, I will

use the term "adynamic bone." As I have already stressed, the factors to be discussed can cause adynamic bone, but not necessarily a disease.

Calcium loading decreases PTH synthesis and release by a direct effect, but calcium loading also might have a direct negative effect on bone. Some authors have speculated that excess calcium saturates the sites of bone calcium exchange, increasing the risk of adynamic bone [40].

In addition, while first reports on the existence of adynamic bone unrelated to aluminum failed to show any influence of calcium, more recent reports have found higher levels of serum calcium and a much higher intake of calcium carbonate in patients with adynamic bone [3, 5, 8, 9, 79]. Hypophosphatemia also can reduce PTH secretion, and thus it can be involved in the pathogenesis of low bone turnover. In several reports, particularly involving CAPD patients, lower serum phosphate levels have been linked with adynamic bone [5, 9, 79]. Calcitriol can suppress PTH indirectly (by raising serum calcium) and directly through its action on vitamin D receptors in the parathyroid gland [16, 80, 88]. In addition, as previously discussed, intermittent pulses of calcitriol have a direct suppressive effect on bone [29, 30]. This direct inhibitory effect of calcitriol on bone cannot be detected with sequential PTH measurements, because this effect is independent of PTH levels, which can remain high [29]. New vitamin D metabolites, with a likely lower direct inhibitory effect on bone, are undergoing experimental and clinical investigation [82].

The way in which calcitriol directly depresses bone activity is not fully understood. Calcitriol, an important regulator of osteoblastic activity, promotes the differentiation of osteoblastic precursors into mature osteoblasts, enhancing alkaline phosphatase and osteocalcin activity [29, 83]. By contrast, calcitriol also can reduce collagen synthesis by osteoblasts [83]. Lastly, during high and intermittent doses of calcitriol, changes in the expression of vitamin D receptor (VDR) in bone occur [29]. I believe that the scant human data available suggest that intermittent calcitriol therapy reduces the activity of differentiated osteoblasts and chondrocytes [84].

The complex interrelationship among calcium, phosphorus, and calcitriol, and the effect of this triad on bone metabolism, seems best expressed in CAPD patients. In the most recent series, the prevalence of patients with adynamic bone is higher in CAPD compared with hemodialysis, ranging from 22% to 61% [3, 4, 9, 84]. The frequency of adynamic bone disease in CAPD also was reported higher in two large series that analyzed 2248 bone biopsy specimens from North America [5, 6] and 1429 bone biopsies from Italy [46]. This higher incidence of adynamic bone in CAPD patients likely results from continuous exposure to high calcium levels in the dialysate, stabilizing serum calcium at higher levels and, in turn, leading to more marked PTH suppression. The dialysance of PTH in CAPD patients also leads to a greater reduction in PTH levels in this population of patients. Similarly, the higher clearance of phosphorus observed in CAPD, leading to lower serum phosphate levels, also would lead to a higher incidence of adynamic bone disease in this setting [79]. Since CAPD patients frequently are older [3, 8] and more likely to be diabetic, these two factors also might play a role. Let me turn to this issue and to the important effect of acidosis on bone metabolism.

The growing incidence of patients with adynamic bone temporally coincides with the increasing use of bicarbonate (instead of acetate) as a buffer in hemodialysis patients. The resulting more stable control of acid-base balance is likely to be one of the factors responsible for the higher incidence of adynamic bone. Acidosis inhibits osteoblastic, and stimulates osteoclastic, activity in vitro [27], and stimulates bone resorption in animals [85] and in patients on dialysis [26]. Therefore, the widespread use of bicarbonate as the dialysate buffer (along with more widespread use of oral calcium carbonate) likely has contributed to decreasing the incidence of the high-bone-remodeling disorder [86].

Studies in the 1980s and 1990s showed that diabetic patients have a lower incidence of hyperparathyroidism than do non-diabetic patients; they also have only a moderate increase in bone activity [22, 23]. These observations, coupled with the growing number of diabetic patients in CAPD and hemodialysis programs, may partly explain the increase in low bone remodeling now seen [20, 21]. The major explanation for the low bone remodeling in diabetics seems to be the lower PTH levels. The factors possibly responsible for relative hypoparathyroid function in diabetes are: vascular disease of the parathyroid gland [22] and the effects on bone of the metabolic derangement of diabetes per se [87, 88]. Vascular disease of the parathyroid gland is a reasonable and convincing explanation. Diabetic patients often have widespread and severe vascular disease; thus one might speculate that the parathyroid gland also might sustain vascular damage.

Insulin and hyperglycemia inhibit PTH secretion [88], but also can have a direct effect on bone. Recent experimental studies in rats suggest that poor control of diabetes results in a decreased osteoblast surface and bone formation rate, independent of PTH levels [87]. Moreover, serum from patients with poorly controlled diabetes inhibits human osteoblast growth in vitro [89].

Age is another independent factor involved in the pathogenesis of low bone remodeling. Most regular dialysis programs no longer impose age restrictions. As a result, the dialysis population is aging, especially the CAPD population. Thus it is difficult to separate the effects of age from those of CAPD. Nevertheless, age seems to be an independent risk factor for the development of adynamic bone [5, 8]. The observation that age affects bone metabolism is not new. Bone turnover decreases with age. Thus, not too surprisingly, the quality and quantity of bone remodeling

differ markedly at age 30 or 70. It seems reasonable to expect a higher incidence of adynamic bone as the age of the dialysis population rises. Whether adynamic bone in the aged is a disease or simply part of the physiologic response of the aging skeleton is not clear.

Low levels of estrogens, androgens, and thyroid hormones can cause low bone turnover [28], but these disorders need to be considered only in specific cases. Of greater importance in causing low bone remodeling are corticosteroids and other immunosuppressors. Renal transplant patients receive corticosteroids and immunosuppressors such as cyclosporine for years. Both groups of drugs have clear negative effects on bone metabolism, as recently reviewed in a Nephrology Forum [18]. I need not review this subject in detail. However, it is important to emphasize that the evolution of bone lesions after successful renal transplantion is greatly affected by the type of bone lesions present at the time of transplantation [18, 90–93]. Additional factors such as cytokines, the polymorphisms of genes, and changes in the expression of different receptors involved in bone metabolism recently have been implicated in the pathogenesis of the different forms of renal osteodystrophy and in the response to therapy [2, 92–95].

All these factors might contribute to the increasing frequency of adynamic bone in chronic renal failure. In some circumstances—for example, aging—low bone remodeling might not represent a disease, but in other circumstances, low bone remodeling definitely should be considered a disease.

Diagnosis

Low bone turnover can manifest as fatigue and lack of bone strength; it also increases the risk of fracture. However, expression of these signs and symptoms is confined for the most part to the aluminum-induced form of this disorder. In contrast, the majority of patients with low bone remodeling we see now are free of symptoms, and many of them should not be considered as having disease. Most of the evidence in patients with low bone remodeling indicates that the incidence of bone pain, hypercalcemia, and bone fractures is related to the presence of more than 20% of bone surface covered by aluminum [3, 37]. It remains a matter of debate whether moderate aluminum-induced or non-aluminum-induced adynamic bone will become symptomatic in the long term. In any case, signs and symptoms appear late in the development of low-bone-turnover disease, and more sensitive and precise markers need to be used for early diagnosis.

Among the non-invasive markers, the most widely used is the basal serum PTH level, which I already discussed. To summarize, basal serum PTH levels lower than 200 pg/ml should alert us to the possibility of low bone remodeling. Values in dialysis patients lower than 125 pg/ml have a positive predictive value for low bone remodeling of approximately 90% [4]. In predialysis patients with advanced renal failure, a PTH value of approximately 300–375 pg/ml is needed to achieve adequate "normal" bone turnover.

To determine whether aluminum is involved in low bone remodeling, direct measurement of serum aluminum should be carried out. Over the last two decades, the levels of "normal, acceptable, and safe" serum aluminum values in dialysis patients have been dramatically reduced. At present, I consider acceptable serum aluminum values lower than 20 μg/liter (reference values in controls with normal renal function: 2 μg/liter); values from 20 to 60 μg/liter raise the possibility of aluminum overload. Repeated values higher than 60 μg/liter are indicative of aluminum toxicity.

Even though serum aluminum levels better reflect acute rather than chronic aluminum exposure, serial measurements of serum aluminum concentration correlate with aluminum concentration in tissues. If the serum aluminum values vary or are always in the borderline area (20 to 60 μg/liter), the deferoxamine challenge test can help in the evaluation of the total-body burden of aluminum. While controversy remains regarding what level of response is positive [16, 41, 96], in general terms, any increment in serum aluminum after infusion of deferoxamine indicates an excess of aluminum in tissues. Depending on the dose (5–15 mg/kg) of deferoxamine used [20], a rise in serum aluminum of 50 μg/liter to 100 μg/liter, or simply a twofold increase from serum basal aluminum values, strongly suggests an excess of aluminum in tissues.

The deferoxamine test has several limitations in its interpretation, such as a high number (up to 45%) of false-negative results [17, 97]. Difficulties in comparing the results of deferoxamine tests are due to differences in doses, method of administration, and differences in iron status of the patients [97]. In general, patients with iron depletion are more likely to have greater increments in serum aluminum after deferoxamine infusion, compared with iron-replete patients [97].

Osteocalcin, total alkaline phosphatase, and bone alkaline phosphatase also are useful in the non-invasive diagnosis of low bone turnover; the last seems to be the most promising among these biochemical markers [98]. These markers directly reflect bone activity and are of particular interest in patients receiving calcitriol by pulse therapy. Since pulse calcitriol inhibits bone turnover without necessarily reducing PTH measurements [29, 30], markers other than PTH must be utilized. Serum pyridinoline might have a place in the assessment of low bone remodeling [99], but further studies are required. In general, the available serum markers have their greatest utility in separating high- from low-bone-turnover forms, as well as identifying the degree of high bone turnover. However, they do not at present allow us to recognize different types and degrees of low bone turnover.

The different imaging techniques, radiology, ^{99m}technetium bone scans, and bone mass measurement with quantitive computerized tomography (QCT) or dual energy x-ray absorptiometry (DEXA), unfortunately remain of limited value in the evaluation of low bone remodeling. Radiologic changes appear too late in the development of low bone remodeling. Bone scans are not better than biochemical markers in separating high and low bone remodeling; DEXA or even QCT can help in the demonstration that low-bone turnover is associated with low bone mass. The main value of imaging techniques resides in their utility in long-term followup.

To accurately diagnose low bone remodeling, and to determine whether aluminum is involved in this disorder, a bone biopsy is required. It is beyond the scope of this review to analyze the histologic findings of osteomalacia or adynamic bone; these entities are discussed extensively elsewhere [3, 4, 8, 10]. By definition, low bone remodeling implies a reduction in bone formation rate; thus, given the limitations of the noninvasive tests discussed, bone biopsy is the only method that can provide a definitive diagnosis.

Management

In managing patients with low bone turnover, it is essential that one start from the basic concept that two main forms of low bone remodeling exist: aluminum-induced and non-aluminum-induced low bone remodeling. By definition, both forms (independently of the presence or absence of symptoms) have low bone formation rates and excessively low PTH levels. Thus, in both forms of low bone remodeling, excessive PTH suppression must be avoided. Maintenance of an appropriate PTH level requires avoidance of high calcium dialysate or inappropriate amounts of calcium supplements and vitamin D metabolites. Using a normal-low calcium dialysate concentration of 1.25 mM for long periods results in significant rises in PTH [100, 101]. This active approach designed to increase PTH levels from excessively suppressed values and, in turn, bone turnover is useful in selected patients with low bone remodeling. I do not believe it is advisable to use this approach as a general strategy for all dialysis patients because, in many, PTH values rise to excessively high levels and cause high-bone-remodeling disease [101].

If aluminum is responsible for low bone remodeling, the aluminum overload must be reduced. The first goal in such patients must be to avoid further aluminum exposure, either via dialysate or orally. Using even the most effective techniques to remove aluminum, the total amount of aluminum eliminated via dialysis is very low, on the order of micrograms per dialysis session. Similar amounts of aluminum can enter the patient if oral aluminum hydroxide is used, or if the dialysate contains a few μg/liter of aluminum more than the "dialyzable aluminum" of the patient (10%–15% of total serum aluminum). An aluminum concentration of 2 μg/liter in the dialysate is the best guarantee of successful removal of aluminum. Second, to augment aluminum removal, the use of highly permeable membranes or techniques that combine more than one method of blood cleansing (for example, paired filtration dialysis or charcoal cartridges) is required. However, the beneficial effect of a highly permeable membrane or a more effective dialysis technique is overridden if the aluminum concentration in the dialysate exceeds 5 μg/liter.

The third step involves the use of deferoxamine to increase the gradient of ultrafiltrable (dialysable) aluminum between patient and dialysate. Deferoxamine draws aluminum from tissues; thus it raises the serum aluminum levels, increasing the gradient. Over the last decade, we have reduced the dose of deferoxamine used to treat aluminum overload. We also have employed different schedules of deferoxamine administration to decrease its major side effects [102, 103]. Even though 5 mg/kg is the current recommended dose, recent studies suggest that doses as low as 2.5 mg/kg, or even 0.5 mg/kg, are effective in removing aluminum [104].

Finally, several studies have shown that successful renal transplantion is probably the most effective way to treat aluminum-induced low bone remodeling [18, 105]. This also might be the case with non-aluminum-induced low bone remodeling, but little information is available. A recent report demonstrated the presence of adynamic bone 7 years after renal transplantation in as many as 80% of patients [106]. By contrast, another preliminary report found a normal bone formation rate in non-aluminum-induced low bone remodeling one year after transplantation in 23 patients [107]. Differences in the bone microenvironment, in PTH levels, and in the responsiveness of bone receptors to PTH might help explain these contradictory preliminary results.

Final remarks

In conclusion, the low-bone-remodeling form of azotemic osteodystrophy does not represent a single entity. Rather, it represents a useful concept for grouping the various mechanisms that can result in this particular response of the skeleton during azotemia. While noninvasive diagnostic tests can help separate this entity from the high-bone-remodeling form of azotemic osteodystrophy, bone biopsy is the only sure way to diagnose this histologic syndrome.

Some patients with low bone remodeling, especially those with aluminum-induced disease, need more active medical management; other patients need only preventive methods to avoid unnecessary suppression of parathyroid hormone and bone turnover. The evolution of this bone lesion depends heavily on aluminum, first by its direct effect on bone, and second by its suppressive effect on the parathyroid gland.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (*Dean of Medicine, Tufts University School of Medicine, Boston, Massachusetts, USA*): Given the high prevalence of the various forms of metabolic bone disease in chronic renal failure, would it not make sense to perform a bone biopsy early in the course of renal osteodystrophy, or at least in patients with suspected aluminum intoxication? I understand that the procedure is relatively simple and that the morbidity and mortality are extraordinarily low. Should we be more active in suggesting bone biopsies to our patients?

Dr. Cannata: I do not think we should perform a bone biopsy in all patients with chronic renal failure. This policy should be followed only by specialized groups under specific research protocols for the purpose of learning more about metabolic bone diseases at different stages of chronic renal failure. For clinical purposes, I do think that nephrologists should obtain more bone biopsies than they do. There is no reason to be afraid of bone biopsy. There is more risk in treating a patient for a long time with an unclear diagnosis than in establishing the diagnosis with a bone biopsy, and then treating the patient using more objective data. Bone biopsy is particularly helpful in patients in whom the biologic markers suggest a low-bone-modeling state and in whom we have reasonable doubts about the participation of aluminum in the bone lesion. Bone biopsies also are warranted in some patients with hyperparathyroidism who have been treated with vitamin D metabolites and in whom the PTH levels might not reflect what is happening in the bone. I also advise bone biopsy for any symptomatic patient. From the clinical point of view, bone biopsy should be used whenever the diagnosis is not clear.

Dr. Harrington: Have any of your patients died as a result of a bone biopsy? What is the worst outcome of bone biopsies in your own institution?

Dr. Cannata: Bone biopsy is a very safe procedure. We have not had any important complication, either in patients with osteoporosis or in patients with renal osteodystrophy. The main complication of the bone biopsy is hematoma, which occurs in not more than 3% of patients [108]. Some patients experience discomfort or pain, but these symptoms can be easily resolved with analgesic medications.

Dr. Manuel Martinez-Maldonado (*Emory University School of Medicine, Atlanta, Georgia, USA*): I want to talk a little bit about the role of acidosis. Many years ago, it was demonstrated that bone participates in buffering acidosis but suffers demineralization in the process [109]. You mentioned that correction of acidosis with bicarbonate and calcium carbonate has increased the incidence of bone disease. Would you please explain how that occurs?

Dr. Cannata: It is well known that acidosis has a negative effect on bone because it induces bone loss. Therefore, if you correct acidosis, you might expect a change in bone metabolism but not an increase in the overall incidence of bone disease. With the correction of acidosis, we should expect a decrease in bone turnover and possibly a change in the pattern of the bone disease. The increasing use of bicarbonate as a buffer in dialysate, instead of acetate, has led to a better correction of acidosis, and this fact might partly explain the increased incidence of low bone remodeling in dialysis patients. I do not imply that correction of acidosis is a problem; on the contrary, better correction of acidosis might contribute to a decrease in bone resorption. In addition, data in hemodialysis patients demonstrate a reduction in the serum levels of biochemical markers of bone resorption when you change acetate for bicarbonate [86].

Dr. Martinez-Maldonado: Are there any data suggesting that extracellular or intracellular pH is significantly altered in either low or normal bone remodeling? Has anybody used biopsies to determine whether control of the intracellular pH induces either low or high bone remodeling?

Dr. Cannata: To my knowledge there are no data on bone biopsies and intracellular pH. However, experimental evidence from cultured neonatal mouse calvariae suggests that metabolic acidosis inhibits osteoblastic, and stimulates osteoclastic, activity, whereas metabolic alkalosis increases osteoblastic collagen synthesis [27].

Dr. Martinez-Maldonado: What is the incidence of adynamic bone disease in areas where aluminum toxicity has been controlled? Is the incidence related to alterations in acid-base status? How might acidosis contribute to this bone disease?

Dr. Cannata: Before answering your question, I want to emphasize one important concept that technically is not related to the effect of acid-base balance on bone but is related to the concept of how to elucidate the role of aluminum in bone disease. There is a tendency among some nephrologists (which I do not share) to exclude the participation of aluminum in bone disease, simply if the concentration of aluminum in the dialysate is below 10 μ/liter or 15 μg/liter, or if less than 15% or 25% of the bone surface is covered by aluminum, using aluminon as a marker. I have emphasized that, at present, I do not believe this is the right way to exclude the participation of aluminum in bone lesions. Over the last 10 years, we have analyzed many bone biopsies from patients who had been previously classified as having had bone lesions not due to aluminum. We have found a high percentage of the surface covered by aluminum (using solochrome of azurine), and we also have found very high aluminum concentrations in bone measured by atomic absorption spectrometry, in some patients an aluminum level as high as 50–70 μg/g. The normal value of aluminum in bone can reach 2–3 μg/g.

Now let me address the first part of your question. In places where aluminum exposure seems to not be a common clinical problem, the prevalence of adynamic bone

disease still seems high. It is very likely that other factors that I mentioned explain the decrease in high bone turnover disease and the increase in low-bone-turnover disease. In regard to your followup question on acidosis, as I mentioned, better control of acidosis has led to a decrease in bone resorption. Consequently, this change must be considered one of the factors responsible for the increment in the prevalence of low bone turnover in dialysis patients.

Dr. Pablo Massari (*Nephrology Chief, Hospital Privado, Universidad Católica, Córdoba, Argentina*): It has been suggested that adynamic bone disease is a marker of poor survival on hemodialysis, even if you correct for age and diabetes. Could you comment on the mechanism and the possible cause of death in these patients?

Dr. Cannata: The information I am aware of demonstrates that the morbidity of adynamic bone disease is directly related to the presence of aluminum. The higher the aluminum in bone, the greater the presence of symptoms. In the preliminary results of the 5-year followup from the Toronto study, it seems that there is an increase in morbidity, mainly fractures, and in mortality in patients with adynamic bone disease in whom aluminum exposure is mild. As patients with adynamic bone disease are older than patients with high bone turnover, the increment in mortality has been partly attributed to this factor. However, we cannot rule out the possibility that the presence of low bone remodeling itself is, in some circumstances, a marker of poor health.

Dr. Massari: Is there any study looking at the time it takes for aluminum to completely disappear from the bone with different deferoxamine doses?

Dr. Cannata: Deferoxamine removes aluminum from different tissues, including bone, but unfortunately, the total amount removed by deferoxamine is small (measured in micrograms). You can reduce the aluminum concentration in bone (a few μg/g of tissue), but we are far from totally eliminating aluminum from bone. A great part of the benefit to bone metabolism that we gain by using long-term deferoxamine administration is related not only to the removal of aluminum from the bone mineralization front, but also is related to the removal of aluminum from the parathyroid gland. The improvement of bone remodeling correlates more with the increments in circulating PTH levels than with the reduction of aluminum in bone. This is why I stress the prevention of aluminum exposure; aluminum removal is not easy, and it sometimes is insufficient.

Dr. Nestor Schor (*Professor of Medicine, University of São Paulo, Brazil*): All of us know that the number of renal patients with tuberculosis is increasing. If you have a patient with tuberculosis, a renal stone, and interstitial nephritis, do you measure calcitriol or 1-alpha-hydroxylase? Do you also measure angiotensin-converting enzyme? Could this granulomatous disease participate in adynamic bone disease?

Dr. Cannata: The patient we described suffered from tuberculosis, but this occurred many years before the diagnosis of adynamic bone disease. Thus, I do not believe that tuberculosis was involved in this patient's bone disease. Nevertheless, your speculation is correct. Patients with any active granulomatous disease can have increased production of 1-alpha-hydroxylase from the granulomas. Thus the levels of calcitriol are high, and consequently PTH can be further suppressed. This scenario would more plausible if the patient also were receiving calcitriol. In such a circumstance, I think measuring calcitriol levels would be enough.

Dr. J. Carlos Ayus (*Baylor College of Medicine, Houston, Texas, USA*): In our unit, one of the most common causes of renal failure these days is diabetes. The mean age of our population is about 60 years, and many of the patients who come to our unit are malnourished. We have followed these patients for 5 years; the vast majority were females. At the beginning, PTH levels were very low—in the range of values able to induce low bone remodeling. When these patients started to eat better, received more protein and thus more phosphorus, and also when they received more-efficient dialysis, their PTH levels rose. At first, we thought the increase was due to the hyperphosphatemia, but when we analyzed the serum phosphate levels, we realized that none of the patients had become severely hyperphosphatemic. Nevertheless, the PTH levels of these patients rose. There was no aluminum exposure, either through dialysate or oral sources. What do you think is the reason for that?

Dr. Cannata: It is extremely difficult to explain the situation of this particular group of malnourished patients. It looks like a positive effect of the efficient dialysis on the general condition of health. If you isolate the data on the increment of phosphorus, it could explain, together with the better nutrition, the increments in PTH. Experimental studies have demonstrated that a diet rich in phosphorus can induce increments in PTH without inducing increments in serum phosphorus [110]. This could be at least a partial explanation; however, your example is quite specific, and many other factors could be involved.

Dr. Fernando Valderrábano (*Professor of Medicine, Head, Department of Nephrology, Hospital General Universitario Gregorio Marañón, Madrid, Spain*): Aluminum interferes with gastrointestinal absorption of iron, its binding to proteins, and its storage. On the other hand, aluminum intoxication produces microcytic anemia and also causes resistance to erythropoietin. Do you think that the resistance to erythropoietin treatment and the microcytic anemia in aluminum intoxication are the consequence of decreased bioavailability of iron to the bone marrow?

Dr. Cannata: You are correct in suspecting a likely role in iron bioavailability in aluminum intoxication. As you know, there is a two-way relationship between iron and aluminum. It is reasonable to speculate that if iron metabolism partially modulates aluminum uptake, the reverse also is possible. Therefore, in cases of aluminum overload,

the saturation of extra- and intracellular binding sites with aluminum might decrease the chances to bind iron. In these circumstances, iron metabolism might be influenced by aluminum intoxication. This mechanism could be involved in the resistance to erythropoietin treatment. One of our recent goals has been to prove this hypothesis. We have observed reduced iron absorption in animals with aluminum intoxication [77]. Also, in cell culture models, the iron uptake by intestinal and bone cells is reduced if the cells have been preloaded with aluminum [77]. These findings support the hypothesis that in aluminum intoxication, at least part of the resistance to erythropoietin treatment is indirectly due to reduced bioavailability of iron.

Dr. Harrington: First, are bone fractures equally likely in patients with high- or low-bone-turnover disease? Second, in patients with low-bone-remodeling disease, what histologic or histomorphometric finding best correlates with fractures?

Dr. Cannata: High- as well as low-bone-remodeling diseases can be symptomatic. In addition, they can have similar symptoms, but the prevalence of bone fractures is higher in patients with low bone turnover induced by aluminum. The patient discussed in this Forum is a good example. It is also likely that the forms of low bone remodeling in which aluminum participation is null, mild, or moderate also can have a higher incidence of bone fractures over the long term. However, the preliminary data in this field indicate that age also plays a role. It is well known that the fracture rate due to osteoporosis increases with age, and patients on dialysis are not excluded from this group.

Regarding your second question, I am not aware of specific data relating the incidence of fractures and selected histologic or histomorphometric parameters. However, most of the series attributing bone morbidity to aluminum use the percentage of bone surface covered by aluminum as the best differentiating marker. Other markers could also be useful, for example, bone formation rate, but the problem with this measurement is that when bone remodeling is low, it is difficult to establish significant differences among the biopsies, in turn making it difficult to correlate this measure with clinical outcomes.

Dr. Joao Frazao (*Visiting Assistant Professor, University of California, Los Angeles, California, USA*): My first question relates to the first part of your talk. You mentioned, and I agree, that there is a different limit in the amount of osteoid volume for the diagnosis of aplastic bone—5% in Dr. Llach's series, 15% in the Sherrard series. Many of the patients from Dr. Llach's series considered to have osteomalacia would have aplastic bone in the Sherrard series. What should be the threshold for osteoid volume in diagnosing adynamic bone disease?

Dr. Cannata: As a nephrologist, it is difficult for me to define an upper limit for normal osteoid, especially when the experts in this field did not reach agreement on that point. My feeling is that 5% of osteoid volume is an extremely low limit, but at the same time, 15% is a rather high limit. Maybe a figure of around 10% to 12% would be better, but again this is a speculation; I do not have data to support it.

Dr. Frazao: Hypercalcemic episodes are seen more often in patients with low-bone-turnover disease, even in the cases not related to aluminum. Given this high incidence of hypercalcemia, shouldn't we always consider low bone turnover a disease?

Dr. Cannata: You have brought up a very important issue. It is difficult to know whether we should always consider low bone turnover a disease. The message I tried to give in my talk is that we have to put our efforts toward identifying the cases of low bone remodeling that feature specific disabling characteristics; these cases need to be considered a disease. The extremes of the spectrum of low-bone-remodeling conditions are easy to classify: on one side, we have the classic examples of low bone turnover as a disease (that is, aluminum toxicity). On the other side, we have the cases in which the low bone remodeling is almost a physiologic condition (that is, age). I believe the appearance of fractures, symptoms, or even hypercalcemia in any patient with the suspicion of low bone turnover gives us justification for considering the condition a disease. Even though we tend to consider hypercalcemia a minor problem, I don't believe we should, because the presence of spontaneous hypercalcemia means a lack of ability to handle calcium. Patients with this problem will have a higher risk of developing extraosseous and vascular calcifications.

Dr. Jack W. Coburn (*Professor of Medicine, UCLA School of Medicine, VA Medical Center, Los Angeles, California, USA*): Even though we do not prescribe aluminum gels in our dialysis units, aluminum gels are still used in many places. As you discussed, the use of aluminum gels is dangerous because the bone is more susceptible to aluminum toxicity if low bone turnover is present. This is an added reason why this condition, even though sometimes it is not a disease, could easily become a disease if aluminum exposure were high. Thus, in the presence of low bone remodeling, we unequivocally have to reduce the chances of aluminum exposure.

I have another comment. Let's look at patients with very high parathyroid hormone levels who have either high serum aluminum levels (above 40 or 50 μg/liter) or who have been taking aluminum gels. If they have a parathyroidectomy for histologically proved osteitis fibrosa, they have a high likelihood of developing aluminum-induced bone toxicity. This is the kind of patient in whom a bone biopsy is warranted before parathyroidectomy.

My question addresses the different responses among patients. Why is there so much heterogeneity among patients with regard to aluminum inhibiting parathyroid hormone? Even in days gone by in Newcastle, where there was

aluminum in the water and all the patients were exposed, still only a small fraction developed hyperparathyroidism. In this experiment of nature, some patients' parathyroid glands were insensitive to suppression of PTH. Do you have any ideas as to the mechanism?

Dr. Cannata: I do not have a definitive answer. It is easy to assume that when the source of aluminum exposure is oral, differences in aluminum uptake observed in different tissues, including the parathyroid gland, can be at least partly explained through the different degree of gastrointestinal aluminum absorption observed in dialysis patients. However, when the aluminum exposure is through dialysis fluids, there is no barrier of protection, such as the gastrointestinal tract, and the differences must be explained using other arguments. The different carriers of aluminum in serum and its ability to be incorporated in the cells by receptors might partly explain this phenomenon. We are now learning about the influence of the different receptors and their polymorphisms in bone metabolism. It is highly likely that aluminum uses different receptors when it is incorporated into cells. Differences in density, affinity, or characteristics of this active transfer might in the future give a clue to the individual susceptibility found in some patients.

Dr. José R. Weisinger (*Professor of Medicine, Head, Division of Nephrology, Hospital Universitario de Caracas, Universidad Central de Venezuela, Venezuela*): You mentioned that age is a factor related to low bone remodeling. Many female patients with early menopause and also male patients with low sexual hormones do not get hormone replacement. Do you think this situation could be a factor precipitating low bone remodeling? Should we treat our ESRD patients who have early menopause with hormone replacement?

Dr. Cannata: I do not know whether the lack of sex hormones can precipitate low bone remodeling, but I am sure that the lack of sex hormones plays a role in the pathogenesis of bone disease in dialysis patients, as it does in the general population, particularly in women. If you consider the mechanism of action of estrogens, the decrease in serum levels might favor bone turnover and high bone resorption; on the other hand, the lack of estrogens might influence the necessary secretion of PTH. It is also likely that estrogens change the sensitivity of bone to PTH. There are no solid data in this field, but I believe that in the following years we will have an answer to this question. In Spain we are now setting up a multicenter trial in women on dialysis to find out the effect of hormone replacement therapy.

Dr. Harrington: Has anyone begun using alendronate in elderly dialysis patients with known metabolic bone disease?

Dr. Cannata: Preliminary data presented by Dr. Weisinger and Dr. Heilberg at the recent renal osteodystrophy meeting in Oviedo showed some benefit in using biphosphonates in dialysis patients. I do not think this approach will have benefit in patients with low bone remodeling, but it will benefit some forms of bone disease, particularly if bone resorption is high. Biphosphonates also could be used in cases of high bone remodeling in patients who refuse parathyroidectomy or in whom a previous aluminum load makes it inadvisable to remove parathyroid tissue.

Dr. I. P. Heilberg (*University of São Paulo, Brazil*): You mentioned the direct effect of vitamin D on bone formation rate. Would you speculate on this mechanism? Do you think this effect is related to the administered dose or to the blood level of vitamin D?

Dr. Cannata: Calcitriol suppresses PTH, but it also has a direct effect on bone cells. This direct effect has been observed using intraperitoneal and intravenous calcitriol, but the effect has not been observed using low doses of oral calcitriol [29]. Considering that you achieve a higher peak of calcitriol with the parenteral injections, we can speculate that, at least, this is partly a dose-related effect. Growth plate and mature bone have a great density of vitamin D receptors. It appears that if you fully block the receptors, you obtain undesirable effects in both cartilage and bone. This is one of the reasons why efforts are in progress to synthesize new vitamin D metabolites able to act on PTH but without a marked effect on bone.

Dr. Anibal Ferreira (*Curry Cabral Hospital, Lisbon, Portugal*): What is your opinion about the role of β-2-microglobulin and the type of dialysis membrane? Do you think this factor could play a role in bone cell activation and bone remodeling and that it might account for the increase of adynamic bone disease in recent years?

Dr. Cannata: The use of more biocompatible membranes decreases the production of local factors that stimulate bone resorption, such as various cytokines (interleukins, TNFα, etc.). In effect, by using this approach, we are decreasing the production of substances that negatively affect bone metabolism, and maybe we are approaching a more adequate bone remodeling.

Dr. Harrington: Given that we can administer hormones like insulin, calcitriol, and erythropoietin, do you think that in the future we will use parathyroid hormone for patients who have low PTH levels and also for those who have had parathyroidectomy?

Dr. Cannata: Thank you for your interesting comment. This is an open field for research. Several pharmaceutical companies are investigating new active fragments of PTH to be used mainly in some forms of osteoporosis, with the aim of stimulating bone remodeling. These drugs would be applicable to forms of low bone remodeling observed in chronic renal failure. If we had the opportunity to administer PTH, we could increase bone activity with more precision and also at the level we desire. In addition, we could use pulses of PTH to obtain a more controlled activation of bone turnover. This form of therapy would allow us to avoid the indirect approach of treatment we are

using now, for example, lowering the calcium level in the dialysate, with the aim of increasing PTH. Also, PTH therapy would be useful in patients with PTH suppression due to aluminum toxicity; increasing PTH levels in turn would protect bone from the toxic effect of aluminum.

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