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Increased bone strontium levels in hemodialysis patients with osteomalacia

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Background. In this study, we report on the association between increased bone strontium levels and the presence of osteomalacia in end-stage renal failure patients treated by hemodialysis.

Methods. We performed a histologic examination and determined the strontium content and strontium/calcium ratios in bone biopsies of 100 hemodialysis patients recruited from various centers all over the world. Aside from the bone strontium concentration, the bone aluminum content was assessed. The bone zinc concentration, a nonrelevant element for bone toxicity, was also measured.

Results. Bone strontium levels and bone strontium/calcium ratios were increased in subjects with osteomalacia when compared with those with the other types of renal osteodystrophy. Bone strontium and bone calcium levels correlated with each other. The slope of the linear regression curve correlating these parameters was much steeper in the osteomalacic group ($Y = 2.22X - 120$) as compared with the other types of renal osteodystrophy ($Y = 0.52X - 5.7$). Within the group of patients with osteomalacia, bone strontium levels also significantly correlated with the bone aluminum content ($r = 0.72$, $P = 0.018$). No such correlation was found for the other types of renal osteodystrophy. The bone zinc concentration of subjects with normal renal function did not differ significantly from the values noted for the various types of renal osteodystrophy taken as separate groups, nor could increased bone zinc concentrations be associated with a particular bone lesion.

Conclusions. Our data demonstrate an association between osteomalacia and increased bone strontium concentrations in dialysis patients. Further studies are warranted to establish whether strontium plays either a primary, secondary, or contributive role in the development of the latter type of renal osteodystrophy.

End-stage renal failure (ESRF) patients, especially those treated by chronic maintenance dialysis, exhibit marked metabolic disturbances that result in the development of renal osteodystrophy, the spectrum of which covers two general types of bone disease: a high turnover disease exemplified by either osteitis fibrosa or mild secondary hyperparathyroidism, and the low turnover lesions characterized by osteomalacia and adynamic bone disease. Mixed or transitional disorders displaying the histologic features of both low and high turnover lesions may also be present. The mechanisms underlying the development of these bone diseases are multifactorial and still controversial [1, 2]. The initial derangements induced by the failing endocrine and excretory functions of the kidney are rather uniform among chronic renal failure patients. However, other factors such as the prominence of vitamin D deficiency, medication, exposure to aluminum, and dialysis modalities influence the bone abnormalities that develop in ESRF patients who require maintenance dialysis [3–5]. In a distinct number of chronic renal failure patients, the etiology of their bone disease remains unknown.

Because of the impaired renal function, medication, and the use of contaminated dialysis and parenteral fluids, trace elements may accumulate in dialysis patients [6]. The association between bone aluminum accumulation and the development of osteomalacia and to a less extent adynamic bone disease has been established in these subjects [3, 7, 8]. The extent to which other trace elements may also interfere with the bone metabolism of dialysis patients is unknown.

In view of (*1*) the striking physicochemical similarities of strontium with calcium, (*2*) the element's potential to accumulate in dialysis patients [9, 10], (*3*) the reported interference of strontium with the biosynthesis of $1\alpha,25\text{-}(OH)_2D_3$ and calcium absorption [11, 12], and (*4*) the previously described effects on bone formation, mineralization, and resorption, as evidenced in experimental studies [13–15], the lack of information on the potential effects of strontium on bone metabolism in humans, particularly in dialyzed patients, is surprising.

Key words: renal osteodystrophy, bone histology, mineralization, trace metal, dialysis.

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By means of a recently developed analytical electrothermal atomic absorption spectrometric method [16], we determined the bone strontium levels in 100 biopsies of hemodialysis patients from various centers in several countries and correlated these with the different types of renal osteodystrophy.

METHODS

Patients

Transiliac bone biopsies were taken in 100 dialysis patients from different centers in various geographic areas: Belgium ($N = 46$), Greece ($N = 39$), Czechia ($N = 7$), Argentina ($N = 3$), and Egypt ($N = 5$). Bone biopsies were taken within a period of two years in the frame of studies on the noninvasive diagnosis of adynamic and aluminum-related bone disease [17, 18]. There were 48 males (48%) and 52 females with a mean ± SD age of 58.8 ± 13.2 years and a mean ± SD time on dialysis of 5.19 ± 4.17 years. Data on phosphate-binding therapy were available for 89 patients and consisted of $CaCO_3$ in 33 patients, 31 patients received $Al(OH)_3$, while 21 patients took a combination of $CaCO_3$ and $Al(OH)_3$. Four patients did not receive any phosphate binder at all. Some (44.2%) of the patients received vitamin D. No differentiation was made between the various vitamin D analogues.

The indications for performing a bone biopsy were diverse: suspicion of aluminum intoxication, abnormal levels of parathyroid hormone (iPTH; either high or low), diagnostic work-up before parathyroidectomy, a low bone-alkaline phosphatase level, or a combination of either of these pathologies. To determine the bone formation rate (BFR) and to perform histologic classification, a double tetracyclin labeling was performed prior to biopsy that followed a standardized procedure [19]. Criteria for classification of the different types of bone disease are outlined later in this article.

Bone samples were also taken postmortem in 10 subjects known to have had a normal renal function and no history of bone disease or endocrine or metabolic disease or drug intake interfering with bone metabolism. Their mean age was 56.9 ± 23.7 years and was not significantly different ($P = 0.75$) from that of the dialysis population. Two out of the 10 normal patients were female. All of these subjects presented a normal bone histology.

Bone biopsy

Bone biopsies of dialysis patients were taken under local anesthesia using a Bordier-Meunier needle. To reduce the risk for contamination, the use of reagents was kept minimal, and every item used from the moment of sampling until analysis was regarded as a potential source of contamination and was checked to verify that it did not to contain or leach any detectable amount of the elements under study. Only plastic material was used for sample storage and preparation [20]. Bone samples of subjects with normal renal function were taken at autopsy following the same procedure.

All bone samples were divided in two pieces. One part was put in Burkhardt's solution for 24 hours, and it was then transferred to 70% ethanol and stored at 4°C until further processing for histologic/histochemical examination. The second part was weighed directly after sampling and stored at −20°C until chemical analysis, that is, strontium, aluminum, zinc, and calcium measurement.

Laboratory analyses

Bone analysis. Before measurement for chemical analysis, 20 to 500 mg of the human transiliac bone biopsies were digested at 90 to 100°C in 1 to 2 mL of nitric acid (Suprapur®; Merck, Darmstadt, Germany) in stoppered polytetrafluoroethylene test tubes for at least three to four hours until a clear digest was obtained [21]. According to the sample weight, the clear digest was adjusted to either 10, 25, or 50 mL with doubly distilled water in polypropylene volumetric flasks and subsequently transferred to stoppered polystyrene test tubes for storage at −20°C until analysis. The elements under study were determined in the same bone digestion liquid by atomic absorption spectrometry. For the determination of calcium, we used flame atomic absorption spectrometry (Perkin-Elmer Model 3110; Perkin-Elmer, Norwalk, CT, USA). With this method, bone digestion liquids were diluted 1/500 in doubly distilled water containing 1 g/L of lanthanum, which was added to overcome ionization and phosphate interferences. Strontium, aluminum, and zinc were measured by means of electrothermal atomic absorption spectrometry with Zeeman background correction (Perkin-Elmer Model 3030; Graphite Furnace HGA 600) using or adapting previously described methodologies [16, 21, 22].

Histologic data as well as dynamic parameters are reported according to the standardized nomenclature and definitions [23]. Undecalcified, 4 μm thick human bone sections were stained according to Goldner for descriptive histology and with Aluminon® for aluminum staining. Aluminum staining was not performed in three patients with adynamic bone disease (ABD), one with mixed lesion, and two with hyperparathyroidism. Ten micrometer sections were mounted unstained in 10% glycerol and examined by fluorescence microscopy for the evaluation of tetracyclin labels [24].

The following histologic variables were determined for trabecular bone: (*1*) total bone area (%), the area of trabecular bone, including both mineralized bone and unmineralized bone matrix (osteoid), expressed as a percentage of the total tissue area; (*2*) osteoid area (%), the area of unmineralized bone matrix expressed as a percentage of the total bone area; (*3*) osteoid surface (%),

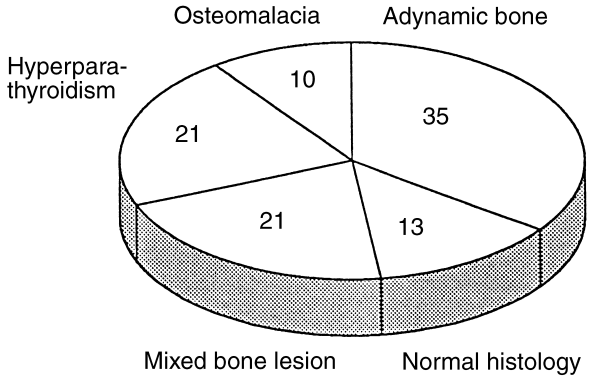

Fig. 1. Distribution of the various types of renal osteodystrophy of the dialysis population under study.

the percentage of the trabecular bone surface covered by osteoid; (*4*) osteoid thickness (μm), the mean width of surface osteoid seams obtained by dividing the measured osteoid area, in mm^2, by the length in mm, of trabecular surface covered by osteoid; (*5*) eroded surface (%), the percentages of trabecular bone surface characterized by the presence of scalloped bone resorptive lacunae; (*6*) double tetracyclin-labeled surface (%), the percentage of trabecular bone surfaces that exhibited double bands of tetracyclin fluorescence; (*7*) mineral apposition rate (μm/day), determined by dividing the width of separation of double tetracyclin labels by the time interval between the administration of the two labels; (*8*) BFR ($\mu m^2/mm^2$/day), defined as the area of bone formed per unit area of existing trabecular bone per day; and (*9*) mineralization lag time (days), calculated by dividing the mean osteoid thickness by the mineral bone apposition rate.

The different types of renal osteodystrophy were diagnosed according to the amount of osteoid, the presence of fibrosis, and the BFR [19]. Normal histology was defined as an osteoid area of <12%, no fibrosis, and BFR in 97 to 613 $\mu m^2/mm^2$/day range. Hyperparathyroidism was an osteoid area of <12%, no fibrosis (mild) with fibrosis (osteitis fibrosa), and BFR >613 $\mu m^2/mm^2$/day; in the present study, osteitis fibrosa and mild hyperparathyroidism were considered as one group. Osteomalacia was an osteoid area of >12%, no fibrosis, BFR <97 $\mu m^2/mm^2$/day. Adynamic bone disease was an osteoid area of <12%, no fibrosis, BFR <97 $\mu m^2/mm^2$/day. Mixed lesion was an osteoid area >12%, with fibrosis.

Biochemical serum analysis. Serum iPTH levels were determined by means of a two-side immunoradiometric assay (IRMA; Nichols Institute, San Juan Capistrano, CA, USA). For the measurement of serum osteocalcin (OC), the radioimmunoassay from Incstar (Stillwater, MN, USA) was used. Bone alkaline phosphatase was determined by an agarose gel electrophoretic method described by Van Hoof et al [25].

Table 1. Clinical/personnel data of the various study groups

Lesion	*N*	Age *years*	Sex *M/F*	Time in dialysis *years*	Vitamin D intake %
ABD	35	62.4 ± 9.2	18/17	3.7 ± 3.3	41
MX	21	60.0 ± 12.4	8/13	5.5 ± 5.6	45
N	13	64.3 ± 12.8	5/8	5.7 ± 3.0	31
HPTH	21	51.2 ± 15.9[a]	11/10	7.3 ± 4.2[b]	29
OM	10	53.0 ± 12.9	6/4	4.1 ± 2.4	70[c]

Abbreviations are: ABD, adynamic bone disease; MX, mixed lesion; N, normal histology; HPTH, hyperparathyroidism; OM, osteomalacia.
[a] $P < 0.05$ vs. ABD and N
[b] $P < 0.05$ vs. ABD
[c] $P < 0.05$ vs. all other groups

Statistics

A comparison between groups of the various parameters under study assessed in bone or serum was done by means of either Kruskal-Wallis or one-way analysis of variance (ANOVA), followed by the Bonferroni test when more than two groups were considered. A comparison of the bone strontium concentration in patients taken vitamin D versus patients without vitamin D intake and males versus females was done by means of the Mann–Whitney rank sum test. A comparison of the percentage of patients taking vitamin D in the various study groups was done by chi-square analysis. A P value < 0.05 was considered to be significant at a two-tailed level. The SPSS statistical software was used. Bone analyte concentrations are expressed in μg/g wet weight. As a general rule, to compare wet weight measurements of the present study with literature data using dry or ash weight measurements, the conversion of 10 g wet = 6 g dry = 3 g ash should be used. Results are expressed in either mean ± SD or median (range; Box-Whisker plots, serum biochemistry). The analyte/Ca ratio was calculated to allow correction for bone density. Relationships between variables were assessed by linear regression analysis.

RESULTS

Histologic and histomorphometric examination of 100 bone biopsies revealed that our study patients represented various types of renal osteodystrophy (Fig. 1). Clinical and biochemical data corresponding with the different bone lesions are presented in Tables 1 and 2.

Chemical bone analysis by Zeeman atomic absorption spectrometry indicated the bone strontium/calcium ratio in the overall dialysis population to differ significantly from that noted in subjects with normal renal function ($0.49 \times 10^{-3} \pm 0.27 \times 10^{-3}$ vs. $0.29 \times 10^{-3} \pm 0.08 \times 10^{-3}$, $P = 0.0048$). Within the dialysis population, both bone strontium levels and strontium/calcium ratios in patients with osteomalacia (mean ± SD; 91 ± 51 μg/g, $0.92 \times 10^{-3} \pm 0.41 \times 10^{-3}$) were significantly ($P < 0.0001$) higher than the values noted in all other types of renal

Table 2. Biochemical data [median (range)] of the various study groups

Type of bone lesion	Serum		
	iPTH *pg/mL*	BAP *U/L*	OC *ng/mL*
ABD	91 (1–367)	20 (9–636)	7.3 (1.5–20.8)
MX	353 (91–1152)[a]	125 (22–1919)[c]	17.1 (3.2–34.3)[d]
N	200 (31–650)	34 (12–119)	10.0 (6.9–21.3)
HPTH	797 (180–2240)[b]	184 (30–1604)	19.0 (5.6–58.3)[e]
OM	109 (8–318)	50 (11–715)	11.5 (3.4–23.1)

Abbreviations are: ABD, adynamic bone disease; MX, mixed lesion; N, normal histology; HPTH, hyperparathyroidism, OM, osteomalacia; BAP, bone alkaline phosphatase; OC, osteocalcin; iPTH, intact parathormone.

[a] $P < 0.005$ vs. ABD

[b] $P < 0.001$ vs. ABD, MX, N, OM

[c] $P < 0.05$ vs. ABD

[d] $P < 0.005$ vs. ABD

[e] $P < 0.005$ vs. ABD, N; $P < 0.05$ vs. OM

osteodystrophy considered as a single group (45 ± 31 μg/g, $0.45 \times 10^{-3} \pm 0.22 \times 10^{-3}$; Fig. 2A). Taking all types of renal osteodystrophy separately, it was found that both the strontium concentration and strontium/calcium ratio in osteomalacic bone were significantly increased ($P < 0.05$) as compared with all other types of renal osteodystrophy: normal histology (30 ± 24 μg/g, $0.33 \times 10^{-3} \pm 0.13 \times 10^{-3}$), hyperparathyroid bone disease (48 ± 32 μg/g, $0.44 \times 10^{-3} \pm 0.28 \times 10^{-3}$), adynamic bone disease (48 ± 25 μg/g, $0.44 \times 10^{-3} \pm 0.14 \times 10^{-3}$), and mixed bone lesion (45 ± 42 μg/g, $0.47 \times 10^{-3} \pm 0.28 \times 10^{-3}$; Fig. 2B).

As expected, the bone aluminum/calcium ratio in the dialysis patients ($0.34 \times 10^{-3} \pm 0.50 \times 10^{-3}$) significantly differed from the values noted in the subjects with normal renal function ($P < 0.0001$; $0.018 \times 10^{-3} \pm 0.009 \times 10^{-3}$). Considering the hemodialysis population, the bone aluminum/calcium ratios of the various groups behaved in a less specific way compared with what was noted for strontium. Indeed, whereas an increased strontium/calcium ratio could be associated with a single type of renal osteodystrophy, that is, osteomalacia, the bone aluminum/calcium ratio differed significantly ($P < 0.05$) only between the patients presenting the mixed lesion ($0.58 \times 10^{-3} \pm 0.93 \times 10^{-3}$) versus those having adynamic bone disease ($0.17 \times 10^{-3} \pm 0.21 \times 10^{-3}$; Fig. 3A). Positive staining (>0%) for aluminum was not only associated with osteomalacia (6 out of 10 patients; range of bone surface stained positive 0 to 93.4%) but also with the other types of renal osteodystrophy: adynamic bone (11 out of 32; 0 to 45%), mixed lesion (9 out of 20; 0 to 34.3%), normal histology (8 out of 13; 0 to 31.0%), and hyperparathyroidism (4 out of 19; 0 to 29.7%).

As a nonrelevant element for bone toxicity and to check whether the observations for strontium were not mainly due to the patients' uremic state, the bone zinc concentration was also assessed. The bone zinc concentration and zinc/calcium ratios of subjects with normal renal function did not differ significantly from the values found for the various types of renal osteodystrophy taken as separate groups, nor could increased bone zinc concentration be associated with any type of renal osteodystrophy (Fig. 3B).

Within the group of patients with osteomalacia, bone strontium levels significantly correlated with the bone aluminum content ($Y = 0.88X + 41.6$, $r = 0.721$, $P = 0.018$), while this was not the case for the other types of renal osteodystrophy. Within the dialysis population, both strontium and aluminum significantly correlated with the osteoid area [$r = 0.300$, $P = 0.003$ (strontium); $r = 0.561$, $P < 0.0001$ (aluminum)], whereas strontium (not aluminum) also correlated with the mineralization lag time ($r = 0.285$, $P = 0.006$).

In the patients with osteomalacia, as well as in those presenting the other types of renal osteodystrophy, a significant association was found between the bone strontium and bone calcium content ($r = 0.78$, $P = 0.008$, and $r = 0.68$, $P < 0.0001$, respectively; Fig. 4). However, when the slopes of the linear regression curves correlating bone strontium (Y) and bone calcium (X) concentrations were compared with each other, the curve was much steeper in the osteomalacic group ($Y = 2.22X - 120$; Fig. 4A) than noted for the patients presenting the other types of renal osteodystrophy ($Y = 0.52X - 5.7$; Fig. 4B).

Patients with osteomalacia came from various regions, that is, Belgium ($N = 3$), Egypt ($N = 4$), Argentina ($N = 2$), and Greece ($N = 1$). Furthermore, it was noted that the bone strontium (r −0.28, $P = 0.009$) and strontium/calcium ratio (r −0.31, $P = 0.003$) decreased with age when calculated for the entire study population. No relationship was found between the bone strontium content or strontium/calcium ratio with sex or vitamin D intake. With regard to the latter, it should be mentioned, however, that the percentage of patients taking vitamin D differed between groups ($P = 0.033$) and was significantly ($P < 0.05$) higher in the osteomalacic group as compared with all other types of renal osteodystrophy (Table 1).

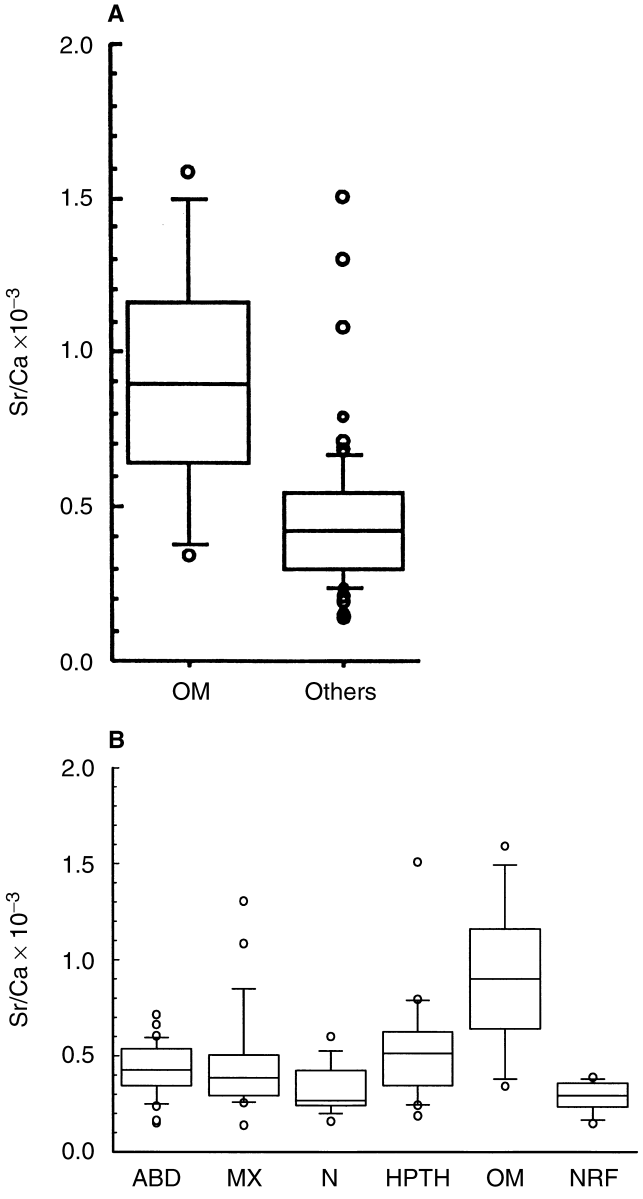

Fig. 2. (*A*) The bone strontium/calcium ratio in dialysis patients with osteomalacia (OM) versus the total group of patients presenting the other types of renal osteodystrophy ($P < 0001$). (*B*) Bone strontium/calcium ratio of dialysis patients with osteomalacia versus the other types of renal osteodystrophy and the ratio noted in subjects with normal renal function. Statistical analysis revealed the bone strontium/calcium ratio in patients with osteomalacia to be significantly ($P < 0.05$) elevated as compared with all other groups. From left to right, adynamic bone disease, mixed disease, normal histology, hyperparathyroidism, osteomalacia, and normal renal function are shown.

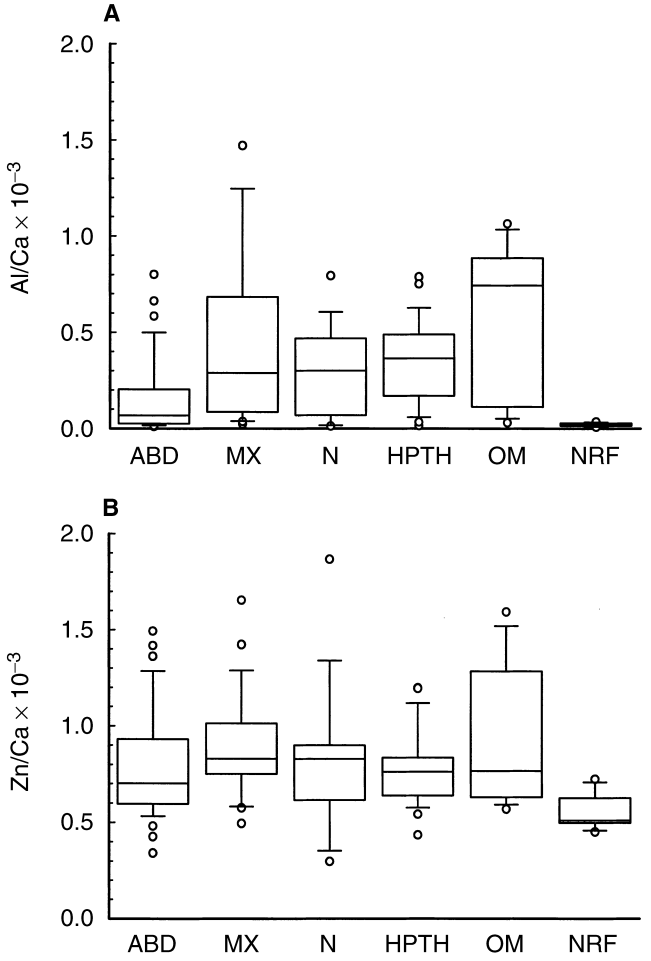

Fig. 3. (*A*) Bone aluminum/calcium ratio in function of the various types of renal osteodystrophy in the dialysis population and subjects with normal renal function. Statistical analysis revealed the bone aluminum/calcium ratio to be significantly ($P < 0.05$) elevated as compared with subjects with normal renal function ($P < 0.05$). Within the dialysis population, the bone aluminum/calcium ratio significantly ($P = 0.019$) differed between the various types of renal osteodystrophy. Post hoc pair-wise comparison only revealed significant differences between the mixed lesion and adynamic bone ($P < 0.05$). From left to right, adynamic bone disease, mixed disease, normal histology, hyperparathyroidism, osteomalacia, and normal renal function are shown. (*B*) The bone zinc/calcium ratio did not differ significantly between the various types of renal osteodystrophy and individuals with normal renal function. Also, there was no association between the bone zinc/calcium ratio and any type of renal osteodystrophy.

DISCUSSION

In the geosphere, strontium occurs in relatively high amounts. Its concentration in the earth crust varies around 450 p.p.m., ranking as the 15th element in the order of crustal abundance [26]. Although there are some indications for strontium to be an essential element for bone calcification, clear-cut evidence is still lacking. Gastrointestinal absorption represents the main route of entry of strontium in nondialyzed individuals. As for calcium, the fractional absorption of this "bone seeking" element seems to depend strongly on vitamin D status [15, 27].

Although a substantial amount of data have been published in the 1960s in connection with protective measures against radiostrontium [28–30], information on the element's metabolism in ESRF patients is lacking. It is clear that strontium, which is mainly excreted by the kidney, might accumulate and perhaps exert some adverse effects in these subjects.

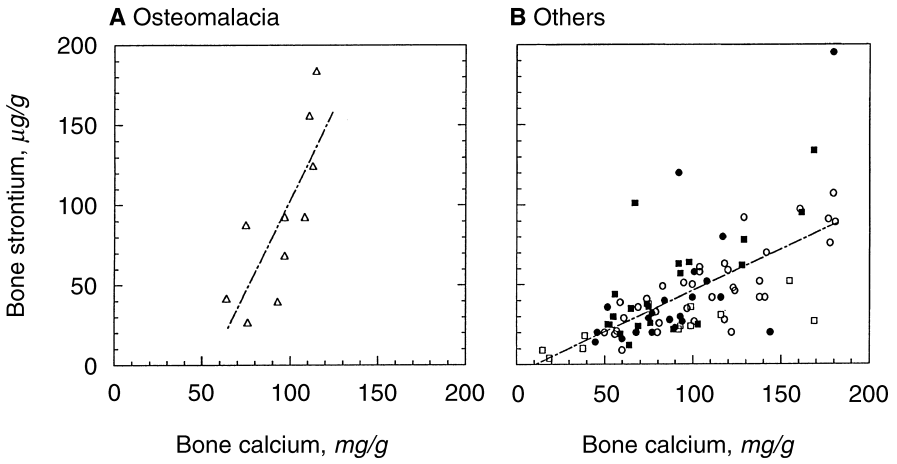

Fig. 4. Relationships between the bone calcium and bone strontium concentration in patients with osteomalacia (*A*) and those presenting the other types of renal osteodystrophy (*B*). A striking difference was noted between the slopes of both regression curves. Symbols are: (○) adynamic bone disease; (●) mixed disease; (□) normal histology; (■) osteitis fibrosa; (△) osteomalacia. In panel A, $r = 0.775$; $P = 0.008$; $Y = 2.22x - 120$. In panel B, $r = 0.677$; $P = 0.0001$; $Y = 0.52x - 5.7$.

In the present study, to our knowledge for the first time, strontium levels were assessed in duplicates of bone biopsies with known histologic and histomorphometric characteristics that were obtained from ESRF patients treated by hemodialysis. Considering the bone strontium/calcium ratio, a significantly increased overall value was noted in ESRF patients as compared with that of subjects with normal renal function. A more interesting observation was made within the dialysis population itself. Here, by classifying the patients according to the five different types of renal osteodystrophy, a distinct increase in the bone strontium concentration as well as the strontium/calcium ratio was observed in those individuals presenting the histologic features of osteomalacia. This type of renal bone disease is characterized by an increased amount of osteoid resulting from a deficient mineralization, as evidenced by an increased mineralization lag time, reduced double-labeled surface, mineral apposition rate, and BFR. To our knowledge, no such relationship has previously been demonstrated in ESRF patients enrolled in a chronic hemodialysis program. Interestingly, in a recent epidemiological study in children with normal renal function, a link between a high soil strontium and increased prevalence of "rickets," diagnosed on the basis of a series of clinical symptoms such as bone deformities, craniotabes, rachitic rosary, delayed closure of fontanels, and conspicuous bulging at the wrists, has been suggested [31]. Experimentally, it has been shown that the administration of the element to animals with normal renal function may result in a bone lesion with a histologic resemblance to that seen in "vitamin D-deficient rickets" [32]. The particular form of rickets produced by strontium, the so-called strontium-induced rickets [33, 34], however, differs from calcium- or phosphorus-deficiency rickets in that vitamin D supplements do not correct the lesion [34, 35]. As a possible explanation for this observation, an inhibitory effect of strontium on the $1\alpha,25\text{-}(OH)_2D_3$ biosynthesis has been formulated [11, 35]. This physiopathological mechanism, however, cannot be taken into account to explain our observations in ESRF. Indeed, in the presence of a dramatically reduced renal mass, 1α-hydroxylase activity is clearly reduced. Aside from its effect on bone mineralization, it has to be mentioned that strontium, as demonstrated in rats with normal renal function, may also affect osteoblast function, osteoid deposition, and bone resorption in a complex, dose-dependent way [13, 15]. Because of their ability to uncouple bone resorption from bone formation, the potential use of strontium compounds in the treatment of osteoporosis has been considered [36].

As early as 1973, Rudolf, Alfrey, and Smythe used x-ray fluorescence and found distinctly increased (fivefold to eightfold) strontium concentrations in skeletal muscle of dialyzed uremics, as compared with those of nondialyzed individuals and controls [37]. They suggested that increased strontium levels originate from the use of untreated high strontium tap water used to prepare the dialysis fluids, and promoted the idea that strontium might play some role in renal osteodystrophy.

The present bone biopsy study is limited in its ability to demonstrate a causal relationship between increased bone strontium levels and the development of osteomalacia. Support for such an association is provided by the results of a worldwide epidemiological study recently published by our group, where we noted large country-to-country and center-to-center variations in the serum strontium levels of dialysis patients. In these patients, high serum strontium levels appeared to originate from the use of high strontium dialysis fluids, resulting from the addition of contaminated concentrates [38]. It should be noted that diet (for example, drinking water, cereals, grains, seafood), medication, environment, among other factors, to a certain extent may also be responsible for the accumulation of the element in the ESRF patient.

In the present study, no significant correlation could be found between bone strontium levels and vitamin D intake. The percentage of patients taking vitamin D analogues, however, was significantly higher in the osteomalacia group as compared with all other types of renal osteodystrophy. Although such a finding is difficult to interpret, it is well known that pathways of gastrointestinal absorption of strontium and calcium are identical [27]. In this context, our recent findings of a multicenter study demonstrating serum calcium levels to be significantly lower in patients with high serum strontium (>100 μg/L) are worth being mentioned [38].

Evidence for a causal role of strontium in the development of osteomalacia has recently been presented from an experimental study in which the dietary administration of strontium in a chronic renal failure rat model resulted in the development of osteomalacic lesions in all of the animals, as judged by established histologic criteria [39]. An additional interesting finding was that rats loaded solely with aluminum developed adynamic bone disease, whereas those receiving both strontium and aluminum developed either adynamic bone or a more severe form of osteomalacia. Here, the observation of a severe mineralization defect in rats receiving both elements points toward a possible synergy between strontium and aluminum in the development of osteomalacia. In this context, the striking correlation noted in the present study between the bone strontium and aluminum content in dialysis patients with osteomalacia, as opposed to those presenting the other types of renal osteodystrophy, is of particular interest. Studies are being performed to check whether or not osteomalacic lesions in the remnant kidney model may also be induced at more physiologically relevant dosages. Here, it should be noted that comparing the effects of strontium on bone at a given dose in animals versus dialysis patients is complex in view of the substantial differences that exist between both species in terms of bone and metabolic turnover, residual renal function, gastrointestinal absorption, parenteral uptake, and so forth.

Based on the present observations, it is not possible to unravel the mechanism by which strontium interferes with the bone metabolism in the development of this particular renal bone disease. In searching for such a mechanism, it is interesting to note that in the present bone biopsy study, increased bone strontium levels were only associated with osteomalacia and not with adynamic bone, another type of low turnover bone disease that is frequently found in ESRF [40]. This indirectly indicates that strontium accumulation in the osteomalacic patients did not occur secondary to the low turnover state of the patients' bone. Moreover, the absence of increased bone strontium levels in patients with adynamic bone in contrast to those having osteomalacia suggests that strontium adversely affects the formation of bone without interfering with the synthesis of collagen, that is, osteoblastic activity. Hence, strontium most probably directly affects bone mineralization by interference with the process of calcification. The possibility that an increased deposition of strontium occurred secondary to the presence of osteomalacia or the patients' uremic state can be further weakened by our data on bone zinc, as no variation in concentration was noted for any type of renal osteodystrophy and the levels found in subjects with normal renal function.

In the present study, we have not been able to ultrastructurally localize strontium in bone at the concentration in which the element is present in dialysis patients with osteomalacia. In strontium-loaded rats, however, both histochemical and EPXMA analysis revealed the element to be present in calcified bone, mainly in close proximity to the osteoid calcification front, suggesting a potential interference with bone mineralization [39]. In previous studies, the element has been attributed an inhibitory role in nucleation and hydroxyapatite growth, the latter being due to the element's ability to easily enter the hydroxyapatite lattice where it competes with calcium and slows down crystal growth because of its larger size [41]. The interaction of strontium with the calcium incorporation in bone might also, to a certain extent, be reflected by the differences in the slopes of the linear regression curves correlating bone calcium with bone strontium levels in the osteomalacic patients versus those presenting the other types of renal osteodystrophy. Note, however, that based on these figures, the opposite, that is, a preferential accumulation of strontium in osteomalacic bone, cannot be excluded.

In conclusion, data of the present study indicate that strontium may accumulate in ESRF patients treated by hemodialysis. The deposition of the element in bone of these subjects is associated with the presence of osteomalacia. The extent to which strontium plays either a causal, contributive, or secondary role in the development of this particular type of renal osteodystrophy is not yet clear and is under current investigation.

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