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Severely Suppressed Bone Turnover: A Potential Complication of Alendronate Therapy

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Alendronate, an inhibitor of bone resorption, is widely used in osteoporosis treatment. However, concerns have been raised about potential oversuppression of bone turnover during long-term use. We report on nine patients who sustained spontaneous nonspinal fractures while on alendronate therapy, six of whom displayed either delayed or absent fracture healing for 3 months to 2 yr during therapy.

Histomorphometric analysis of the cancellous bone showed markedly suppressed bone formation, with reduced or absent osteoblastic surface in most patients. Osteoclastic surface was low or low-normal in eight patients, and eroded surface was decreased in four. Matrix synthesis was markedly diminished, with absence of double-tetracycline label and absent or reduced single-tetracycline label in all patients. The same trend was seen in the intracortical and endocortical surfaces.

Our findings raise the possibility that severe suppression of bone turnover may develop during long-term alendronate therapy, resulting in increased susceptibility to, and delayed healing of, nonspinal fractures. Although coadministration of estrogen or glucocorticoids appears to be a predisposing factor, this apparent complication can also occur with monotherapy. Our observations emphasize the need for increased awareness and monitoring for the potential development of excessive suppression of bone turnover during long-term alendronate therapy. (*J Clin Endocrinol Metab* 90: 1294–1301, 2005)

ALENDRONATE, A POTENT inhibitor of bone resorption, is now widely used in the treatment of osteoporosis. A number of randomized clinical trials have shown that it significantly increases bone density of spine and hip and reduces the incidence of fractures in osteoporotic patients (1–4).

Although alendronate is generally safe and effective, it carries the potential risk of oversuppressing bone turnover that can potentially impair some of the biomechanical properties of bone. In experimental animals, alendronate has been shown to inhibit normal repair of microdamage arising from marked suppression of bone turnover, which, in turn, results in accumulation of microdamage (5–7). A 2- to 7-fold increase in microdamage accumulation after pharmaceutical suppression of bone remodeling was associated with a 20% reduction in bone toughness (the ability to sustain deformation without breaking), without reduction in bone strength (6–8). However, the clinical significance of these changes in biomechanical measurements has not yet been well defined.

In addition to microdamage accumulation, chronic oversuppression of bone turnover by alendronate may allow secondary mineralization to continue (9), producing hypermineralized bone that may be more brittle (10, 11). The degree of mineralization has been shown to affect the material properties of bone, with low mineralization levels (as seen in osteomalacia) causing reduced stiffness and strength, and hypermineralization likely contributing to reduced fracture toughness (10, 11).

Ott (12) speculated that chronic alendronate therapy in humans might impair mechanical strength of bone. This suggestion was based on the apparent increase in fracture rate with prolonged therapy (2), though challenged by the authors of that report (13). Recently, Whyte *et al.* (14) described a 12-yr-old boy who, after 3 yr of treatment with iv bisphosphonate (pamidronate), presented with findings consistent with osteopetrosis, *i.e.* increased bone density and impaired remodeling. The authors, however, acknowledged that the dose of pamidronate given to the patient was more than four times the amount typically given to children with osteogenesis imperfecta.

In this report, we describe bone biopsy data from nine patients with osteoporosis or osteopenia treated with alendronate for 3–8 yr alone or in combination with estrogen. All patients had spontaneous nonspinal fractures that developed after 1–8 yr of alendronate treatment. Histomorphometric analysis of bone biopsy samples revealed a marked suppression of bone turnover.

Subjects and Methods

Patients

Nine patients (eight postmenopausal women and one man) on long-term alendronate treatment were included in this report. Four patients (patients 1–4) were from the Henry Ford Hospital in Detroit, and five (patients 5–9) were from the University of Texas Southwestern Medical Center in Dallas. Alendronate was given at a dose of 10 mg/d or 70 mg/wk for 3–8 yr along with supplemental calcium. Eight patients were

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Abbreviations: BFR, Bone formation rate; BMD, bone mineral density; BsAP, bone-specific alkaline phosphatase; GIO, glucocorticoid-induced osteoporosis; NTx, N-telopeptide; SSBT, severe suppression of bone turnover.

also given vitamin D, 400–800 IU/d, whereas one patient was maintained on a pharmacological dose of vitamin D. Relevant clinical data are summarized in Table 1.

In patients 1–4, alendronate was given alone, without estrogen or glucocorticoid (group A, Table 1). Patients 1–3 were postmenopausal women without prevalent fractures, in whom alendronate treatment was started elsewhere because of either osteoporosis or osteopenia by bone density. Patient 4 was started on alendronate when he presented with metatarsal stress fractures and was found to have osteopenia by bone density.

In patients 5–7 (group B, Table 1), alendronate was administered with estrogen. Patients 5 and 7 took estrogen continuously for 12 and 15 yr, respectively, whereas patient 6 received it intermittently for 3 yr. Although none had prevalent fractures, alendronate was started elsewhere for postmenopausal osteoporosis (patients 5 and 6) or osteopenia (patient 7) of spine or hip by bone density.

Patients 8 and 9 were given alendronate for glucocorticoid-induced osteoporosis (GIO; group C, Table 1). Patient 8 has been taking glucocorticoid for asthma for 20 yr, and patient 9 for fibromyalgia for 8 yr, before alendronate was begun. Glucocorticoid was continued during and after alendronate was stopped in patient 9 and was tapered and eventually discontinued in patient 8. Patient 9 was on vitamin D, 50,000 IU thrice a week, for postsurgical hypoparathyroidism. Both women had fractures of the femoral shaft and metatarsal bones after minimal trauma before alendronate treatment.

Nonspinal fractures during alendronate therapy

All nine patients developed atraumatic nonspinal fractures while on alendronate treatment (Table 1) and while performing normal daily activities such as walking, standing, or turning around. Among the seven patients who were not on glucocorticoid (patients 1–7), atraumatic nonspinal fractures (sacrum, rib, ischium, pubic rami, femoral shaft) developed after 3–8 yr of alendronate treatment. One patient (patient 2) also had a lumbar vertebral fracture. Among those with GIO, patient 8 developed a separation of previously formed callus of the fractured femoral shaft 1 yr after starting alendronate. Patient 9 fractured the right femoral shaft, at the site of a previous fracture, while walking, after 2 yr of alendronate treatment.

Because the patients continued taking alendronate after the fracture(s), we had the opportunity to radiographically assess fracture healing while still on treatment (Table 1). In six patients (patients 3 and 5–7 without glucocorticoid, and patients 8 and 9 on glucocorticoid), evidence of delayed fracture healing (lack of adequate callus formation and filling in of fracture gap) was observed 3 months to 2 yr after fracture occurrence in the ischium, pubic rami, and femoral shaft. In one (patient 8), delayed healing of the femoral fracture persisted for 2 yr despite internal fixation and bone graft. In the remaining patients (patients 1, 2, and 4), fracture healing could not be assessed because bone biopsy was obtained shortly after the incident fractures.

Bone biopsy

The decision to perform bone biopsy was based on the unusual clinical presentation of these patients. First, the fracture sites (*e.g.* bilateral femoral shaft, pubic bone, ischium) were not the typical sites for osteoporotic fractures. Second, a majority of these patients (patients 1–7) were fracture-free in the intervening years before the presentation. Last, six of nine patients (patients 3 and 5–9) presented with delayed fracture healing. After obtaining an informed consent, bone biopsies were performed while patients were still on alendronate therapy (3–8 yr) and about 1 month to 2 yr after incident fractures (Table 1).

A transiliac bone biopsy was obtained using a 7.5-mm diameter trocar under local anesthesia, following *in vivo* double-tetracycline labeling as previously described (15). A 2-10-4-4 labeling regimen with declomycin was used in Dallas, and a 3-11-3-4 regimen with oxytetracycline was used for the patients at the Henry Ford Hospital. Specimens were prestained for 72 h in Villanueva, Osteochrome (Polysciences, Inc., Warrington, PA). After dehydration in increasing concentrations of alcohol, the specimens were embedded in methylmethacrylate and kept at 37 C until fully polymerized. The embedded biopsy samples were then sectioned on a Reichert-Jung model E microtome (Cambridge Instruments, Heidelberg, Germany) at a thickness of 10 μm. A total of six sequential sections were cut from each specimen. Sections 1, 3, and 5 were mounted directly to slides and were examined under UV light for tetracycline uptake. Sections 2, 4, and 6 were mounted to slides, deplasticized in xylene, stained with toluidine blue, and examined for static measurements. Histomorphometric measurements were made with an Aus Lena microscope video camera, and an image capture program (Bioquant Bone Morphometry Program; R & M Biometrics, Nashville, TN). Histomorphometric measurements and calculations were based on modifications of previously published methods (16–18). The bone formation rate (BFR) was calculated as half of the single-labeled surfaces plus all the double-labeled surfaces multiplied by mineral apposition rate in $\mu m^3/\mu m^2/d$ (19). When no double-labeled surfaces were observed, BFR was calculated as half of the single-labeled surfaces multiplied by 0.3 μm/d as previously described (19). The nomenclature of the measured and calculated variables is according to the criteria established by the Committee on Bone Histomorphometry of the American Society for Bone and Mineral Research (20). Slides, both for fluorochrome assessment and toluidine blue stained for static measurements, were analyzed by a single investigator (J.E.Z.) at the University of Texas Southwestern

TABLE 1. Clinical data

Patient	Age (yr)/ sex	Diagnosis	Duration of alendronate treatment (yr)	Other medications	Incident fractures (yr on alendronate)	Delayed/absent healing on alendronate (fracture site)	Fracture healing yes/no (months off alendronate)
Group A							
1	55/F	PO	6	Ca, D	Sacrum (6)	NA	No (12)
2	76/F	PO	7	Ca, D	Vertebra, rib (7)	NA	Yes (6)
3	52/F	POpen	8	Ca, D	Femoral shaft (8)	4 months (femoral shaft)	No (9)
4	68/M	IO	8	Ca, D	Bilateral femoral shaft (8)	NA	No (8)
Group B							
5	68/F	PO	3	E2, Ca, D	Sacrum, ischium (3)	3 months (ischium)	Yes (8)
6	70/F	PO	5	E2, Ca, D	Pubic rami (3)	2 yr (pubic rami)	Yes (4)
7	67/F	POpen	5	E2, Ca, D	Bilateral femoral shaft (5)	9 months (left femoral shaft)	Yes (5)
Group C							
8	49/F	GIO (asthma)	3	Prednisone, Ca, D	Proximal femur (1)	2 yr (femur)	No (8)
9	64/F	GIO (fibromyalgia)	4	Prednisone, Ca, D	Metatarsal, proximal femur (3)	8 months (proximal femur)	Yes (3)

PO, Postmenopausal osteoporosis; POpen, postmenopausal osteopenia; IO, idiopathic osteoporosis; E2, estrogen; Ca, calcium; D, vitamin D; NA, not available or not applicable; F, female; M, male.

TABLE 2. Histomorphometric findings in cancellous bone

	Patient									Control (mean ± SD)
	1	2	3	4	5	6	7	8	9	
BV/TV (%)	14.3	15.2	14.7	9.7	9.4	12.2	17.2	10.9	8.9	21.2 ± 4.9
OV/BV (%)	0.42	0.66	0.17	0.07	0	0	2.5	0.89	0.05	1.85 ± 1.07
O.Th (μm)	4.3	8.0	4.6	4.5	0	0	10.2	4.0	3.9	9.3 ± 2.1
Ob.S/BS (%)	1.7	0	0.14	0	0	0	0.7	3.6	0.2	4.4 ± 2.0
ES/BS (%)	3.5	9.3	9.2	5.6	0.9	2.1	4.3	1.3	1.7	4.0 ± 2.0
Oc.S/BS (%)	1.0	0.3	0.35	0.12	0	0.2	0.35	0.3	0.1	0.7 ± 0.7
dLS/BS (%)	0	0	0	0	0	0	0	0	0	4.3 ± 2.9
sLS/BS (%)	0.6	0	0.42	0.44	0	0	0.5	0	0.3	6.0 ± 4.1
BFR ($\mu m^3/\mu m^2/yr$)	1.0	0	0.7	0.2	0	0	0.6	0	0.4	15 ± 0.8

BV, Bone volume; TV, total volume; OV, osteoid volume; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S/BS, osteoclastic surface/bone surface; dLS, double-label tetracycline label; sLS, single tetracycline label. BFR, Bone formation rate calculated as ½ × sLS/BS × MAR (micrometers per day) obtained from cortical doubled-labeled surfaces as previously described (19). BFR for four patients was calculated as ½ × sLS/BS × 0.3 μm/d as previously described (19).

Medical Center, who was blinded to the patients' identity. For patients in whom no tetracycline double labels were observed, all three cut sections were examined for the presence of any tetracycline labeling.

Biochemical measurements and bone densitometry

Laboratory studies were done either on the day of, or shortly before, bone biopsy. In some patients, not all tests could be obtained. Serum samples were assayed for calcium, phosphorous, creatinine, PTH (ELISA kit; Alpco Diagnostics, Windham, NH), 25-hydroxyvitamin D (ELISA, Alpco Diagnostics), bone-specific alkaline phosphatase (BsAP-Alkphase-B; Quidel, Mountain View, CA), and osteocalcin (Oc, ELISA; Diagnostic Systems Laboratories, Webster, TX). Urine was collected in 24-h pools for calcium, creatinine, N-telopeptide (NTx, Osteomark; Ostex International, Seattle, WA), and hydroxyproline (OH-pro, Hypronosticon; Organon Teknika Corp., Durham, NC). Spot fasting urine samples were used for the analysis of NTx and creatinine in patients 1–4. Except for serum calcium, phosphorous, and creatinine, the remaining serum and urine analyses from all patients were performed at the Mineral Metabolism laboratory in Dallas.

Bone mineral density (BMD) of L2–L4 vertebrae, femoral neck, and distal third of the radius was measured by dual-energy x-ray absorptiometry (Hologic QDR, Waltham, MA). Selected x-rays and bone scans were obtained to confirm the presence of fractures and to determine the status of fracture healing (callus formation and filling in of fracture gap).

Results

Bone histomorphometry

Quantitative bone histomorphometric findings of the cancellous bone are summarized in Table 2. Bone volume was reduced in all patients, but the most striking finding was severe depression of bone formation with absence of double-tetracycline labeling in all nine patients (Fig. 1, A and B). Five of the nine biopsy specimens revealed occasional single tetracycline labels (patients 1, 3, 4, 7, and 9). The mean calculated BFR was almost 100-fold lower than in healthy postmenopausal women (Ref. 16; see Table 4). In seven patients (patients 2–7 and 9), cancellous bone surfaces were quiescent with minimal, or no, identifiable osteoblasts (Fig. 2, A and B). Osteoid thickness and volume were either normal or reduced, excluding the possibility of osteomalacia. In addition, there was a trend toward low bone resorption; osteoclastic surface was low or low-normal, except in patient 1, who received alendronate without estrogen, and eroded surface was also reduced in four patients (patients 5, 6, 8, and 9).

All patients had decreased intracortical osteoid surface (Table 3A). Osteoblast surface was also reduced except in patient 1. Five patients (patients 2, 3, 5, 6, and 8) displayed low osteoclast and eroded surfaces. The same trend was observed for endocortical surface, with reduced osteoid and osteoblast surfaces in all patients. Osteoclast surface was low, except in three (patients 2, 4, and 7), and eroded surface was reduced except in four (patients 1–4). Dynamic parameters were also markedly reduced for both intracortical and endocortical bone surfaces, although a greater reduction was seen at the endocortical bone surfaces (Table 3B).

Table 4 summarizes the mean values for the different histomorphometric measurement at the three bone compartments (cancellous, endocortical, and intracortical bone surfaces) compared with control subjects. Except for the intracortical osteoclast surface, all the surface and dynamic parameters were significantly lower in the patients with severe suppression of bone turnover (SSBT) compared with the published controls. The mean BFR at the three bone surfaces

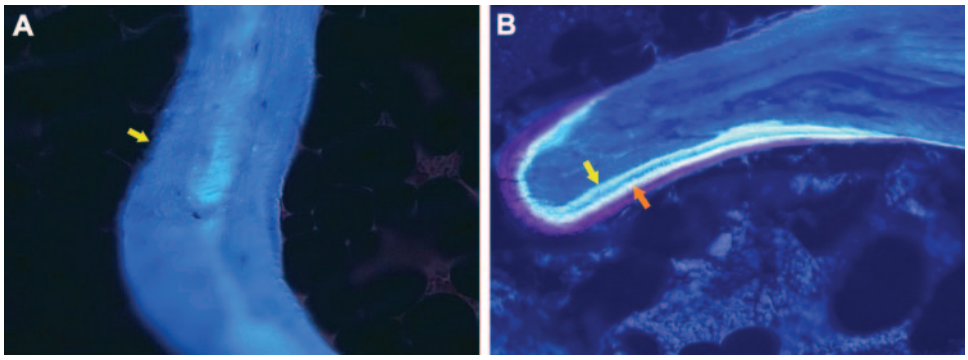

FIG. 1. A, Photomicrograph under UV light from patient 5, showing absence of double label (*yellow arrow*). B, Photomicrograph under UV light from a normal subject, showing two distinct areas of double label with tetracycline. The faint inner label is from the first course of tetracycline (*yellow arrow*), and the more prominent outer label is from the course of tetracycline given 10 d later (*orange arrow*).

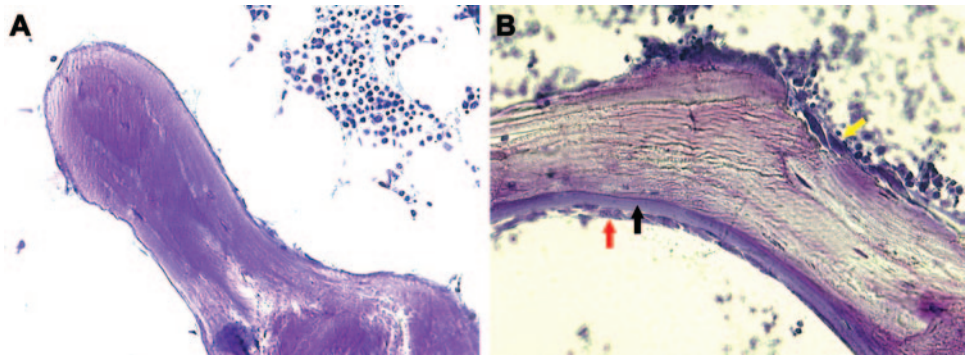

FIG. 2. A, Trabecular bone from patient 5, showing absence of surface osteoid, osteoclasts, and osteoblasts (×160). B, Trabecular bone from a normal subject, showing abundant osteoid (*black arrow*), surface osteoclasts (*yellow arrow*), and osteoblasts (*red arrow*) (×160).

was 30- to 100-fold lower than the corresponding values in healthy controls (15).

Laboratory findings at the time of bone biopsy

Serum calcium, phosphorus, creatinine, 25-hydroxyvitamin D, and PTH were within the reference range (Table 5). Although serum BsAP ranged widely, serum Oc was either low or at the lower limit of the reference range. Urinary NTx was low to midnormal in seven and high-normal in two. Urinary OH-pro was low or low-normal in all five patients in whom it was measured.

BMD before and after alendronate therapy

BMD results before the initiation of alendronate therapy, obtained from outside institutional records, were limited. Among the six postmenopausal women not on glucocorticoids, four had osteoporosis and two had osteopenia when alendronate treatment was begun. Among four patients with osteoporosis, the T-score of at least one site was still in the osteoporotic range (below −2.5 SD) in two patients (patients 2 and 6) but was in the osteopenic range (−1.0 to more than −2.5 SD) in two patients (patients 1 and 5) after alendronate treatment (Table 5). Among two with osteopenia, patient 7 was no longer osteopenic, whereas data for patient 3 were unavailable. In patient 4, T-scores were reported to be in the osteopenic range before alendronate treatment and remained in the osteopenic range after treatment. Baseline BMD data were reportedly in the osteopenic range in the two patients on glucocorticoids, and both had normal BMD after 3–4 yr of alendronate treatment.

Fracture healing after stopping alendronate

Therapy was stopped after obtaining a bone biopsy in all patients. Assessment of fracture healing after discontinuation of treatment was available in all patients (Table 1). Four patients had delayed healing. Patients 1, 3, and 4, who were on alendronate alone, continued to have evidence of nonhealing fractures 12, 8, and 9 months off treatment, respectively, and patient 8 (GIO) continued to have poor fracture healing 8 months after discontinuation of alendronate. The remaining four patients had satisfactory fracture healing. In patient 2, fracture healing was noted at 6 months. In patient 5, callus formation was noted at 3 months, and a significant reduction in pain and improvement in mobility occurred after being off of treatment for 8 months. Patient 6 showed robust callus formation in the nonhealing pelvic fracture 4

TABLE 3. Resorption and formation parameters on the intracortical and endocortical surfaces

	Patient									Control (mean ± SD)[a]
	1	2	3	4	5	6	7	8	9	
A. Intracortical surface										
OS/BS (%)	5.3	0.3	1.6	1.4	0	3.2	5.9	3.8	0.27	18.7 ± 7.9
Ob.S/BS (%)	11.8	0	0	0	0	2.2	0	1.4	0	5.86 ± 3.36
ES/BS (%)	4	0.22	2.8	7.5	0	0	7.5	0.9	2.9	6.30 ± 4.83
Oc.S/BS (%)	1.04	0.03	0.6	1.2	0	0	0.9	0.15	1	1.01 ± 0.79
dLS/BS (%)	3.2	0.2	0.6	0	0	1.1	0.14	1.4	0.2	
sLS/BS (%)	7.1	0.8	1.1	0	0	0	0.7	1.1	0.3	9.2 ± 4.9
MAR (μm/d)	1.0	0.5	1.0	0	0	0.8	0.6	0.7	0.8	0.65 ± 0.18
BFR/BS ($\mu m^3/\mu m^2$/yr)	24.0	1.0	4.0	0	0	3.0	1.0	6.0	0.5	23.0 ± 15
B. Endocortical surface										
OS/BS (%)	12.1	0.86	1.5	1.4	0	0	3.9	2.2	0.74	24.4 ± 14.4
Ob.S/BS (%)	0.94	0	0	0	0	0	0	0	0	6.86 ± 7.05
ES/BS (%)	10.5	10.9	4.2	7.3	0.63	3.8	4	3.1	2.7	9.56 ± 5.21
Oc.S/BS (%)	0	1.7	0.5	1.0	0	0.33	1.27	0.58	0	1.41 ± 1.68
dLS/BS (%)	0	0	0	0	0	0	0	0	0	
sLS/BS (%)	0.6	0	0	0.2	0	0	0.5	0	0	12.5 ± 9.8
MAR (μm/d)	0	0	0	0	0	0	0	0	0	0.53 ± 0.14
BFR/BS ($\mu m^3/\mu m^2$/yr)	0.3	0	0	0.1	0	0	0.3	0	0	25 ± 23

OS, Osteoid surface; BS, bone surface; Ob.S, osteoblastic surface; ES, eroded surface; Oc.S, osteoclastic surface; dLS/BS, double-labeled surface; sLS/BS, single-labeled surface; MAR, mineral apposition rate. Intracortical BFR was calculated as (dLS/BS + ½ sLS/BS) × MAR; endocortical BFR was calculated as ½ × sLS/BS × 0.3 μm/d (19).

[a] Refs. 15 and 16.

TABLE 4. Comparison of the mean values for selected histomorphometric measurements between patients and controls

	Cancellous bone		Endocortical surface		Intracortical surface	
	Patients	Control	Patients	Control	Patients	Control
OS/BS (%)	3.70 ± 5.09[c]	14.30 ± 6.30	2.52 ± 3.79[c]	24.40 ± 14.40	2.42 ± 2.22[c]	18.70 ± 7.90
Ob.S/BS (%)	0.70 ± 1.22[c]	4.40 ± 2.00	0.10 ± 0.31[c]	6.86 ± 7.05	1.71 ± 3.87[c]	5.86 ± 3.36
Oc.S/BS (%)	0.30 ± 0.29[a]	0.70 ± 0.70	0.60 ± 0.61[b]	1.41 ± 1.68	0.55 ± 0.50	1.01 ± 0.79
BFR ($\mu m^3/\mu m^2$/yr)	0.32 ± 0.37[c]	15.0 ± 0.80	0.08 ± 0.13[c]	25.0 ± 23.0	4.39 ± 7.63[c]	23.0 ± 15.0

Data are presented as mean ± SD. OS, Osteoid surface; BS, bone surface; Ob.S, osteoblastic surface; Oc.S, osteoclastic surface. Statistical significance *vs.* control group depicted as [a] $P < 0.05$; [b] $P < 0.01$; and [c] $P < 0.001$.

months after stopping alendronate, with associated improvement in pain. Patient 7 had evidence of fracture healing at 5 months associated with resolution of pain. In patient 9 (GIO), femoral shaft fracture showed complete healing at 3 months. None of the patients developed new fractures after alendronate was discontinued.

Discussion

We describe our clinical observations in nine unselected patients maintained on long-term alendronate therapy for osteoporosis/osteopenia who developed biopsy-proven SSBT. The universal presentation of these patients was spontaneous or atraumatic nonvertebral fracture(s), with delayed or nonhealing of fractures exhibited by six patients while still on alendronate, and by four patients after discontinuation of therapy.

All nine patients displayed histomorphometric evidence of SSBT, similar to the so-called adynamic bone or low turnover described in patients on chronic maintenance hemodialysis (21). The bone surfaces were virtually devoid of cellular elements, BFR was reduced, and matrix formation was severely impaired. In addition, bone resorption was reduced in most patients. Reduced rates of bone formation and resorption were also found on both intracortical and endocortical bone surfaces, indicative of a generalized involvement. To distinguish from adynamic bone, we refer to the condition described in this report as SSBT, defined histologically by reduced osteoblastic and osteoclastic surfaces with decreased or absent tetracycline labeling.

Clinically, SSBT was characterized by incident nontraumatic fractures involving the skeletal areas that are rich in cortical bone, with fractures usually occurring at atypical sites such as femoral shafts, pubic bone, and ischium. In addition, fracture healing appeared to be impaired in most patients with SSBT. Fracture healing was absent or incomplete in six patients, who continued alendronate therapy for 3 months to 2 yr after the onset of incident nonspinal fractures. When alendronate was stopped, fracture healing was still incomplete at 8–12 months in four patients.

There is some evidence that alendronate may have contributed to the histological and clinical picture of SSBT described above. Suppression of bone turnover, to the degree we encountered here, by bone histomorphometry is uncommon in untreated postmenopausal osteoporosis. Coadministration of estrogen has been shown to exaggerate suppression of bone turnover (22, 23), as was seen in three of our patients. However, fractures occurred at sites not typically seen in osteoporosis. Moreover, in some patients, the nonspinal fractures healed poorly while on alendronate, but healed satisfactorily after stopping treatment in most patients. Glucocorticoids alone could suppress osteoblastic bone formation, but sometimes increase osteoclastic resorp-

TABLE 5. Biochemical and BMD findings at the time of bone biopsy

	Patient									Reference range
	1	2	3	4	5	6	7	8	9	
Serum										
Calcium (mg/dl)	9.4	9.6	10.0	9.9	9.3	10.1	9.1	9.5	9.5	8.5–10.5
Phosphorous (mg/dl)	NA	NA	4.0	NA	3.8	4.4	4.3	3.2	3.5	2.5–5.0
Cr (mg/dl)	1.0	0.9	1.4	1.5	0.6	0.7	0.8	0.9	1.1	0.7–1.4
PTH (pg/ml)	31	31	42	29	40	34	28	39	12	10–65
25-OH-vit D (ng/ml)	35	36	28	37	47	47	39	31	180	8–55
BsAP (U/liter)	79	19	37	58	17	13	23	24	56	12–30
Oc (ng/ml)	7.8	9.0	6.9	6.1	3.6	3.4	7.4	3.0	2.8	5–25
Urinary										
Calcium (mg/d)	NA	NA	NA	316	200	193	204	279	121	F: 100–250 M: up to 300
NTx (nmol BCE/mmol Cr)	53.3	8.8	49.1	24.8	24	31	31	26	28	5–65
OH-Pro (mg/d)	NA	NA	NA	NA	13	13	17	26	28	20–40
BMD, T-scores										
L2–L4	−2.4	−3.3	NA	+1.2	−1.2	−2.0	+1.3	−0.7	−0.5	>−2.5
Femoral neck	−1.4	−3.0	NA	−1.1	−2.1	−3.1	NA	−0.8	−0.6	>−2.5
Radial shaft	−0.8	−4.1	NA	NA	−1.3	−2.2	+0.4	−1.0	−0.7	>−2.5

25-OH-vit D, 25-Hydroxyvitamin D; Oc, osteocalcin; Cr, creatinine; OH-Pro, hydroxyproline; NA, not available. To convert values for serum calcium to millimoles per liter, multiply by 0.20. Multiply by 0.323 to convert values for phosphorus to millimoles per liter and by 88.4 to convert values for creatinine to micromoles per liter. To convert values for PTH to picomoles per liter, multiply by 0.102 and multiply by 0.025 to convert values for urinary calcium to millimoles per day. Multiply by 7.6 to convert values for OH-Pro to micromoles per day, and multiply by 0.17 to convert values for osteocalcin to nanomoles per milliliter.

tion, a feature not seen in our two patients with GIO. Chronic steroid treatment in a patient with hypoparathyroidism (as in patient 9) may suppress both bone formation and resorption, but we are unaware of any report showing histomorphometric abnormality with nonspinal fractures.

Prior reports support the view that SSBT may be pathogenetically related to chronic bisphosphonate treatment. In experimental animals, alendronate can impair microdamage repair and compromise some of the biomechanical properties of bone (5–8). In humans, a clinical picture resembling so-called marble bone disease was described after intermittent iv pamidronate treatment (14). Based on an apparent increase in fracture rate after long-term alendronate treatment, a concern has previously been raised that alendronate might impair bone strength (12). More recently, osteonecrosis of the jaw requiring surgical removal of affected tissue was reported in 59 patients who had received iv bisphosphonate for malignancy and in seven patients who took oral bisphosphonate for osteoporosis (24). Although the mechanism was not clearly defined, low bone remodeling was cited as a possible cause of this condition. A recent article reported that alendronate given over a period of 10 yr was safe and effective (25). However, the nonvertebral fracture rate appeared to be numerically the same or higher (three and four women with nonvertebral facture/100 subject-year for the 10- and 5-mg groups, respectively) during the late period of alendronate treatment, compared with the early period (three women with fracture/100 subject-year), despite a higher bone density. Although this trial was not designed to test fracture efficacy, apparently no attempt was made to ascertain whether patients who sustained nonspinal fractures displayed evidence of impaired fracture healing. Overall, the above reports suggest that excessive suppression of bone turnover by bisphosphonate may affect biomechanical competence of bone (26).

Several factors may have contributed to the development of SSBT. One factor is concurrent diseases: GIO in two patients and postsurgical hypoparathyroidism in one patient. Both chronic glucocorticoid treatment (27) and parathyroid insufficiency (28) are known to reduce bone turnover and could have exaggerated the effect of alendronate. Thus, the nonspinal fractures appeared to develop sooner compared with the patients on alendronate alone (1–3 yr *vs.* 6–8 yr, respectively).

Another factor may have been concurrent estrogen therapy. Among six postmenopausal women with osteoporosis/osteopenia, three were on both estrogen and alendronate, whereas three received alendronate alone. The onset of spontaneous fractures was earlier among patients on combination therapy, compared with those on monotherapy (3–5 yr *vs.* 6–8 yr), and the indices of bone resorption on bone biopsy tended to be lower in those taking estrogen. Thus, combination therapy with another antiresorptive agent, such as estrogen, might cause a more severe suppression of bone turnover (21, 22) and might have increased the potential for developing SSBT.

The third factor may be the duration of alendronate therapy. The skeletal half-life of alendronate is long (29), which could explain the residual effect on bone density 3 yr after withdrawal of the drug (30). It is therefore possible that the suppressive effect of this drug on bone resorption might be cumulative over time. Four patients in this report were treated with alendronate without estrogen or glucocorticoid; they developed spontaneous nonspinal fractures 6–8 yr after alendronate therapy, compared with 3–5 yr for those taking alendronate with estrogen and 1–3 yr for patients who also received glucocorticoids.

We acknowledge that this report has some limitations and unanswered questions. First, the biochemical markers did not reveal as prominent a suppression of bone turnover as the histomorphometric indices. Most patients displayed low or low-normal urinary NTx, OH-proline, and serum Oc, but serum BsAP was inconsistent. The results are compatible with previous reports showing that alendronate may exert a more marked suppression (90–95%) of bone turnover at the tissue level (31) compared with only a 50% reduction from baseline in biochemical markers (32, 33). The discordance between the histomorphometric and biochemical markers of bone turnover could be related to the variable degree of suppression at different skeletal sites. Although bone histomorphometry reflects local bone turnover, the changes in biochemical markers are more reflective of changes in the whole skeleton. Another possible explanation is the effect of fractures on bone turnover. Development of fractures has been shown to significantly increase bone turnover markers (34). Last, the less impressive or inconsistent changes in biochemical markers of bone turnover may have been due to inherent analytical and biological variability of the assays. The key issue to consider is that the quantitative histomorphometric analysis, upon which we based the bone turnover state in the diagnosis of SSBT, is generally regarded as the gold standard for the assessment of bone turnover.

Second, the presentation of patient 1 appears to be somewhat different than in others. Serum BsAP and urinary NTx were higher than in others, and osteoclastic and osteoblastic surfaces did not differ from the control group on the cancellous and intracortical bone surfaces. However, the patient shared many of the features of the other eight patients, both clinically and objectively, with BFR being markedly decreased on the cancellous and endocortical bone surfaces. It is possible that this case represents one end of the spectrum of varying degrees of bone turnover suppression manifested by SSBT.

Third, three of seven patients without GIO had the unusual occurrence of femoral shaft fractures. We offer no explanation for this finding except to note that the reduction in elastic modulus reported to occur during bisphosphonate treatment was more marked in cortical than in trabecular bone (35).

An important limitation of this report is the lack of a control group. Published randomized trials with alendronate showed that some patients developed nontraumatic appendicular fractures while receiving either alendronate or placebo (1–3). Thus, although arguments were presented earlier linking SSBT to bisphosphonate therapy, a definitive causal relationship cannot be made. It is also possible that the development of SSBT in the cases described in this report represents an atypical response to alendronate therapy. However, most of our patients demonstrated the expected treatment outcomes, at least in the first few years of therapy,

such as a satisfactory rise in BMD. The absence of SSBT despite a substantial suppression of bone turnover in a previous bone histomorphometric study (31) might be a reflection of a relatively short duration of alendronate therapy of 2–3 yr. In our patients, nonspinal fractures did not develop during the first 3–6 yr of treatment among those maintained on alendronate alone or with estrogen. Except for the two patients with GIO, we do not believe that there was an underlying condition that predisposed to the development of SSBT. Seven patients on alendronate alone or with estrogen did not have prevalent fractures. Vitamin D deficiency and osteomalacia were excluded as potential reasons for poor fracture healing.

Finally, we cannot infer from our observations whether SSBT is unique to alendronate or can also develop with other bisphosphonates. That all nine patients with SSBT described here took alendronate may simply reflect the longer availability and wider usage of this bisphosphonate.

In conclusion, our clinical experience suggests that alendronate can potentially cause SSBT, resulting in increased susceptibility to nonspinal fractures that heal poorly. This complication appears to occur earlier when alendronate is coadministered with either glucocorticoids or estrogen. However, it can also develop after treatment with alendronate alone if the treatment is prolonged. Our observation does not diminish the important role of alendronate in the management of osteoporosis. Rather, it emphasizes the need for awareness of this potential complication during therapy. Although biochemical markers of bone turnover appear to be of limited value, the onset of spontaneous nonspinal fractures, particularly of femoral shaft on alendronate treatment, should raise the level of suspicion for this complication. Additional studies are needed to determine how long bisphosphonates can safely be given.

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