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Bisphosphonate-associated atypical sub-trochanteric femur fractures: Paired bone biopsy quantitative histomorphometry before and after teriparatide administration

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ABSTRACT

Objectives: Bisphosphonate-associated atypical sub-trochanteric femur fractures (ASFF) may be seen with long-term bisphosphonate use, though these fractures are also seen in patients never exposed to bisphosphonates. One theory for the mechanism of action whereby bisphosphonates may induce these ASFF is over-suppression of bone turnover. Bisphosphonates suppress bone turnover, but in bisphosphonate clinical trials, over-suppression defined whether by maintaining the biochemical markers of bone turnover below the defined reference range or by quantitative bone histomorphometry, has not been observed.

Methods: We studied 15 clinic patients referred to The Colorado Center for Bone Research (CCBR) after they had a bisphosphonate-associated ASFF and performed quantitative bone histomorphometry both before and after 12 months of teriparatide (20 μg SQ/day). All patients had been on long-term alendronate (mean = 7 years, range: 6–11 years) and had already had intramedullary rods placed when first seen (6 weeks to 7 months after rod placement). Alendronate had been discontinued in all patients at the time of their first clinic visit to CCBR. All of the fractures fulfilled The American Society for Bone and Mineral Research major radiological criteria for ASFF.

Results: Three key dynamic histomorphometric features show that 7 of the 15 patients had unmeasurable bone formation, mineralizing surface, and mineral apposition, while the other 8 patients had measurable dynamic parameters; although for all 15 patients, the mean values for all 3 dynamic parameters was far below the average for the published normal population. Administration of teriparatide was associated with an increase in all 3 dynamic histomorphometric parameters. Baseline bone turnover markers did not correlate with the baseline histomorphometry. While there is heterogeneity in the bone turnover in patients with bisphosphonate ASFF, there is a large portion in this uncontrolled series that had absent bone turnover at the standard biopsy site (iliac crest). Discontinuation of the bisphosphonate and administration of the anabolic agent, teriparatide was associated with improvement in bone turnover.

Conclusions: While our study does not establish causality or address the ability of teriparatide to prevent progression of early stress fracture to displaced fractures, it does suggest that teriparatide may improve bone formation in these patients. Our study should stimulate other investigations using larger sample sizes and early stress fractures to see if anabolic agents can reverse these fractures from becoming displaced.

Introduction

Atypical sub-trochanteric femur fractures (ASFF) represent a small proportion of the total numbers of femur fractures that occur annually, though increasing numbers of epidemiological reports on these atypical fractures have been published [1–8]. The majority of femur fractures that occur in the osteoporotic population are "typical." That is, they are located above the lesser trochanter, either in the femoral neck or between the greater and lesser trochanter ("intertrochanteric"), and occur after falls. Atypical sub-trochanteric femur fractures derive their definition by 2 means: they occur with little to no trauma and are lower in the femoral

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shaft, below the lesser trochanter. Sub-trochanteric femur fractures were described before the United States marketing of the first bisphosphonate [9–11]. Thus, they may be seen in patients who have never received bisphosphonates [2–4]. The incidence of ASFF and/or their reporting rate has increased since the introduction of bisphosphonates for the treatment of post-menopausal osteoporosis and seems to be related to the duration of use. The Food and Drug Administration has suggested that their duration of use be limited to 3–5 years [12]. The American Society for Bone and Mineral Research (ASBMR) has published 2 papers on ASFF from a working group, which consisted of experts on femur fractures and bone biology, and they have suggested both major as well as minor criteria that should be present before the diagnosis is made of a bisphosphonate-associated ASFF vs a non-bisphosphonate-associated ASFF [13,14] (Tables 1 and 2).

The causality between bisphosphonate exposure and the development of ASFF has not been established. The association between bisphosphonate use, especially duration of use beyond 5 years, and the appearance of ASFF seems more plausible, and long-term bisphosphonate use is only one of the risk factors identified in association with ASFF [13,14]. The science underpinning the mechanism whereby bisphosphonates may mediate ASFF is not well clarified. One theory is over-suppression of bone remodeling by bisphosphonates, impairing the ability to repair stress fractures.

We have performed paired transiliac bone biopsies on 15 patients who presented with bisphosphonate-associated atypical sub-trochanteric femur fractures and performed double tetracycline-labeled quantitative bone histomorphometry both before and 12 months after institution of teriparatide therapy (20 μg SQ/day). Teriparatide has a different mechanism of action (anabolic) as opposed to bisphosphonates (anti-resorptive), and in published data comparing bone turnover marker changes between these 2 agents, teriparatide increased bone remodeling while alendronate decreased bone remodeling [15]. In addition, in a biopsy study of teriparatide administration following alendronate, teriparatide reduced microdamage accumulation in the iliac crest, suggesting that teriparatide might improve bone microarchitecture in previously alendronate-treated subjects [16]. In this study, bone remodeling was quantified by dynamic parameters of bone turnover. In this article, we report the findings of this intervention.

Methods

A total of 15 patients with bisphosphonate-associated atypical femur fractures were seen at The Colorado Center for Bone Research (CCBR) between the years 2004 and 2010 by one of the authors (P.D.M.). All patients had been on long-term alendronate (either 10 mg/day or when available 70 mg/week) for a mean duration of 7 years (duration range: 6–11 years). All of the fractures occurred without falls, were complete, and had been displaced. All subjects had already had intramedullary femur rods in place at the time they were seen (6 weeks to 7 months at the time of their first clinic visit). Radiological analysis (routine x-ray of the femurs) showed all of the features that fulfilled the ASBMR major criteria for bisphosphonate-associated atypical femur fractures (Table 1). All fractures were complete through both medial and lateral femoral shaft cortices, had a transverse appearance, and had a localized periosteal reaction and medial spike at the fracture site. Six of the 15 patients had bilateral femur fractures, and all patients had prodromal symptoms, described as a deep constant anterior thigh pain for weeks before the fracture. After a thorough history and physical examination, patients had blood drawn for the following: Fasting blood was obtained to measure the total serum calcium, albumin, creatinine concentrations and estimated glomerular filtration rate (eGFR), and total alkaline phosphatase. In addition, each patient at the time of their first office visit at CCBR had measurements done for serum parathyroid hormone (PTH), 25 hydroxyvitamin D^3, and bone-specific alkaline phosphatase (BSAP). Fasting second-voided urine was collected for the measurement of urinary collagen cross-link, N-telopeptide (NTX). All serum and urine measurements were performed by commercial laboratories. Bone mineral density of the hip and lumbar spine were performed using a Hologic, Inc (Waltham, MA, USA) dual-energy x-ray absorptiometry (DXA) instrument and T-scores were calculated from the manufacturer's reference population database (spine) or the National Health and Examination III (NHANES III) reference population database (hip). The bisphosphonate therapy was discontinued at the time of their first visit to CCBR. After informed consent, a double tetracycline-labeled transiliac bone biopsy was performed with a 9-mm Bordier–Meunier needle. The biopsy was taken 2 cm posterior and 2 cm inferior to the anterior-superior iliac crest. The tetracycline label timing utilized the standard labeling sequence and analysis as defined by The American Society for Bone and Mineral Research published standardization procedures [17,18]. In addition, our patients' quantitative histomorphometry results were compared to their own baseline pre-teriparatide control as well as to the normal published controls of the ASBMR standardized nomenclature committee for post-menopausal women [17,18]. Each patient had a single intact core with both cortices intact and placed in alcohol. Quantitative bone histomorphometry was performed defining both static as well as dynamic histomorphometric parameters. The histomorphometrist (E.M.) was blinded as to the treatment status of the patients. After fixation in 70% ethanol, the biopsy cores were dehydrated in graded alcohol and infiltrated with and embedded in methylmethacrylate without prior decalcification. Sections of 4-μm thickness were cut using a Reichert–Jung 2065 supercut rotary microtome (Leica, Nusslach, Germany) and these were stained with Goldner's trichrome. Bone histomorphometry was performed using the OsteoMeasure system (OsteoMetrics, Atlanta, GA) with 2 consecutive 7-μm thickness sections. If no

Table 1
The American Society for Bone and Mineral Research major criteria for the diagnosis of a bisphosphonate-associated atypical sub-trochanteric femur fracture

ASBMR Task Force 2013 revised case definition of bisphosphonate-associated atypical sub-trochanteric femur fractures
Major features
1. The fracture is associated with minimal or no trauma, as in a fall from a standing height or less
2. The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur
3. Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex
4. The fracture is non-comminuted or minimally comminuted
5. Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring")

Table 2
The American Society for Bone and Mineral Research minor criteria for the diagnosis of bisphosphonate-associated atypical sub-trochanteric femur fracture

ASBMR Task Force 2013 revised case definition of bisphosphonate-associated atypical sub-trochanteric femur fractures
Minor features
1. Generalized increase in cortical thickness of the femoral diaphysis
2. Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh.
3. Bilateral incomplete or complete femoral diaphysis fractures
4. Delayed fracture healing

Table 3
Baseline demographics of the study population

Baseline demographics
Age (average = 67 years, range: 57–87 years)
BMI: 28 kg/m^2 (range: 24–34 kg/m^2)
T-score femoral neck (average = −2.4, range: −1.8 to −4.1)
25 (OH) D^3 (average = 21 ng/ml, range: 16–44 ng/ml)
Urine NTX (38 nm BCE/nm creatinine, range: 12–78)
eGFR (average = 78 ml/min, range: 42–87 ml/min)
PTH (average = 29 pg/ml, range: 18–108 pg/ml)
BSAP (average = 18 IU/l, range: 12–28 IU/l)

tetracycline labels were seen in cortical surface or trabecular surfaces, 2 additional sections were examined. Quantitative histomorphometric static and dynamic parameters were measured and compared to published normal controls as well as to each patient's baseline biopsy. After the first bone biopsy, all patients were given teriparatide (20 μg SQ/day). At 12 months after teriparatide therapy, a second double tetracycline-labeled transiliac bone biopsy was performed from the opposite iliac crest and examined by the same reader (E.M.) who performed the first quantitative analysis. In addition, at the 12th month patients had repeat serum measurements of total serum calcium and BSAP.

Results

At baseline, the patient's demographics are shown in Table 3. Their average age was 67 years (range: 52–87 years) and all were female. The average T-score at the femoral neck was −2.4 (range: −1.8 to −4.1). Their average 25 hydroxyvitamin D^3 level was 21 ng/ml (range: 16–44 ng/ml) and serum PTH averaged 29 pg/ml (range: 18–108 pg/ml). The urine N-telopeptide (NTX) averaged 38 nm bone collagen equivalent (BCE)/nm creatinine (range: 12–78 nm BCE/nm creatinine) and BSAP averaged 18 IU/L (range: 12–28 IU/L).

The results of 3 dynamic parameters of quantitative bone histomorphometry at baseline and 12 months following teriparatide treatment are shown in Figures 1–3. These 3 dynamic parameters are presented since they represent the best dynamic methodology for assessing bone formation and mineralization.

Figure 1 shows the paired quantitative bone histomorphometry parameter: mineral apposition rate (MAR-micromoles/day), which is the distance between tetracycline labels divided by the time interval between label administration. The MAR provides an

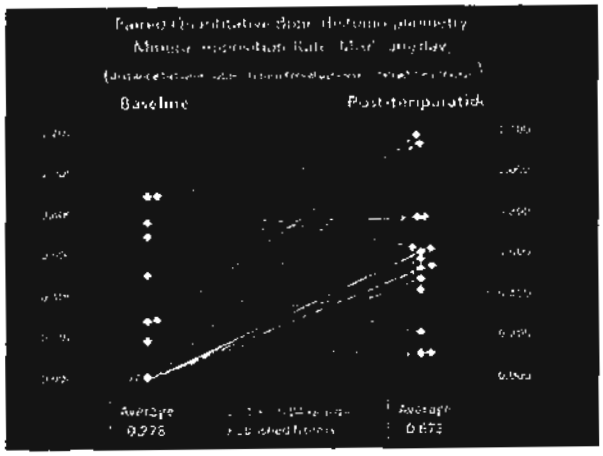

Fig. 1. Paired quantitative bone histomorphometry parameter: mineral apposition rate (MAR-micromoles/day) individual values pre- and post-teriparatide, the group mean values, and the average normal values from published normal controls.

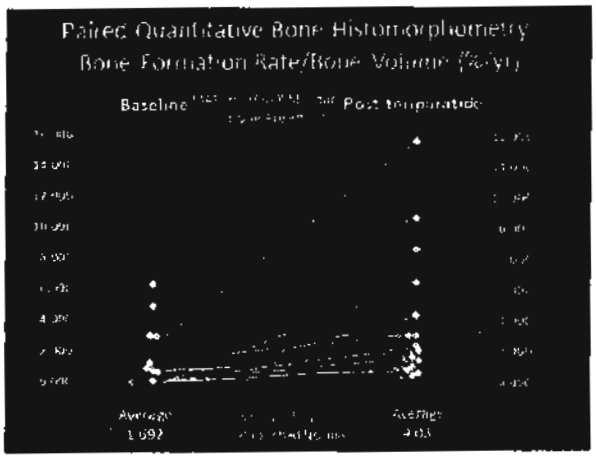

Fig. 2. Paired quantitative bone histomorphometry dynamic parameter: bone formation rate (BFR) individual values pre- and post-teriparatide, the group mean values, and the average normal values from published normal controls.

estimate of the mean rate of osteoid (or matrix) apposition, particularly in a steady state and in the absence of osteomalacia. In our patients there was heterogeneity in the MAR, though the mean MAR for the group at baseline (0.278 μm/day) but was far below the published average MAR from normal controls in the ASBMR's standardized nomenclature [17,18] (0.51 ± 0.04 μm/day). Seven of the patients had unmeasurable MAR. Following 12 months of teriparatide administration, the MAR increased. The increase in the group averaged 0.673 μm/day, though again for individual patients there was heterogeneity in the change with some patients showing a decline in their MAR.

Figure 2 shows the paired quantitative bone histomorphometry dynamic parameter, bone formation rate (BFR) expressed in its standard units: percentage/year. The BFR is calculated by using the MAR (in mm/year) multiplied by the mineralizing surface in mm of bone area. In a steady state, the BFR is identical to the mineral formation rate (MFR) and represents the volume of mineralized bone formed per unit time. The BFR per bone volume is equivalent to the bone turnover rate, which determines bone age and various age-dependent properties of bone. Again, in our patients there was heterogeneity of the baseline BFR, though all patients had a BFR below the average BFR for normal published controls (8.6–21.8%/year). The same 7 patients with unmeasurable MR had unmeasurable BFR. Our patients baseline average BFR was 1.69%/year. After

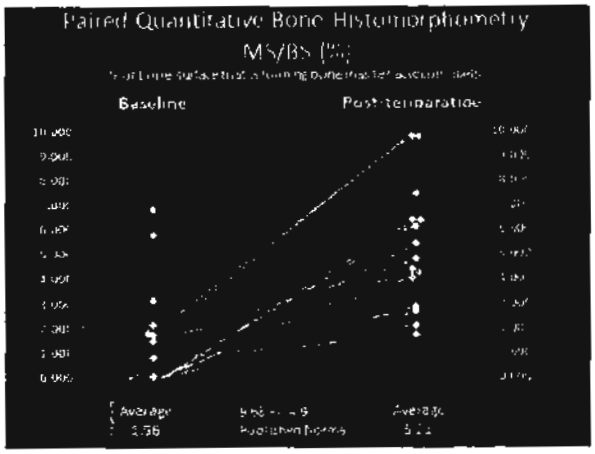

Fig. 3. Paired quantitative bone histomorphometry dynamic parameter, the mineralizing surface divided by the bone surface in percent (MS/BS). The individual values pre- and post-teriparatide are shown are, the group mean values, and the average normal values from published normal controls.

teriparatide the average BFR increased to 4.03%/year, though again there were patients who had little to no change in BFR.

Figure 3 shows the paired quantitative bone histomorphometry dynamic parameter, the mineralizing surface divided by the bone surface in percentage (MS/BS) for each individual patients and the mean MS/BS for this group on alendronate; and for each individual patients and the group mean the change in MS/BS after 12 months of teriparatide. This is calculated by calculating the percentage of the bone surface that is occupied by tetracycline labels and perhaps is a better indicator of osteoblast function and active mineralization than reporting the static parameter of the osteoblast number per se per millimeter of bone surface. In our patients, as in the previous figures showing dynamic parameters, there was heterogeneity in the MS/BS, though the average MS/BS (1.56%) was below the ASBMR's published normal average of 9.68 $\pm$ 4.95. For a third time those same 7 patients with unmeasurable MAR and BFR had unmeasurable MS/BS. After 12 months of teriparatide the MS/BS increased to 5.21% and, for this dynamic parameter, all patients had an increase in their mineralization.

Figures 4 and 5 represent photomicrographs from one of the patients analyzed before and after 12 months of teriparatide. Photomicrograph showing pre-Forteo treatment showing cancellous bone. In Figure 4, there is no evidence of osteoclastic or osteoblastic activity. No osteoid is present. The total osteoid surface in this case was not measurable. In Figure 5 several trabeculae are covered with osteoids. This indicates functional osteoblastic activity. The total osteoid surface in this case was 11%.

There was no apparent relationship between the baseline biochemical values and the baseline quantitative bone histomorphometry parameters. Four of the patients with the highest urinary NTX and highest BSAP had the lowest bone dynamic parameters. The only consistency was in the quantitative bone histomorphometry parameters. For individual patients at baseline, all 3 of the dynamic parameters were consistent patient to patient. Following teriparatide the BSAP on average did increase in the group of 15 to an average of 34 IU/L, though here again there was inconsistency between the change in BSAP and the change in any of the dynamic parameters for an individual patient.

Discussion

In this uncontrolled clinical study, the baseline quantitative bone histomorphometry parameters in patients with bisphosphonate-associated atypical sub-trochanteric femur fractures were below the average for published normal controls in both the ASBMR's standardized nomenclature committee report for post-menopausal women as well as normative data by Ott [19]. The ASBMR's normal values for MS/BS are slightly higher than the MS/BS-reported values from a summary of 5 published studies of post-menopausal women (weighted mean: 7.5% [18,19]. In our clinical report there was heterogeneity in the dynamic parameters of bone turnover at baseline, 7 of the 15 patients all had unmeasurable dynamic parameters of bone turnover. In published studies of bone histomorphometry in patients on alendronate, the MS/BS was reduced 90% as compared to placebo [20]. However, in 7 of our 15 patients, the reduction in MS/BS was 100% since it was undetectable. However, all 7 of these patients had an increase in all 3 dynamic parameters of bone turnover following teriparatide, including probably the most important measurement of osteoblast activity, the MS/BS. It is important to emphasize that while these changes in bone dynamic parameters may have been due to the osteoblast stimulation by the anabolic agent, teriparatide, these patients also had had their bisphosphonate discontinued as well). Bisphosphonates have a long residence time in bone, are recycled, and return to other resorptive surfaces even after discontinuation [21,22]. Data from bisphosphonate discontinuation clinical trials analyzing changes in bone turnover markers and/or bone mineral density are limited but do suggest continuation of the biological effect of bisphosphonates, especially alendronate and zoledronic acid, for a period of time after discontinuation [23–25]. This unique pharmacology of bisphosphonates makes the histomorphometric changes that we observed in our patients after teriparatide more likely to be due to the anabolic effect of this agent than the discontinuation of bisphosphonates. This observation is even more plausible since the biopsies were taken less than a year after bisphosphonate discontinuation, and, in the FLEX trial (Fosamax long-term extension) the bone mineral density and biochemical markers of bone turnover had not changed in that first year in the FLEX group taken off alendronate [23].

The mechanism whereby long-term bisphosphonate use is associated with the appearance of atypical sub-trochanteric femur fractures remains unknown [26–31]. A recent large systematic review and meta-analysis of bisphosphonate use and sub-trochanteric femur fractures does conclude that there is an increased risk with long-term exposure, though causality is not clear [5]. Discontinuing bisphosphonate may be associated with a reduction in fracture risk within the first year, despite the prolonged effect of retained bisphosphonate on reducing bone turnover [30–32]. Over-suppression of bone turnover that might impair healing of stress fractures is 1 theory but remains

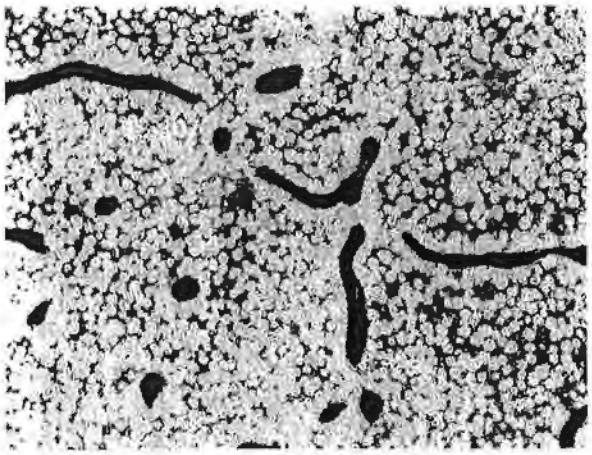

Fig. 4. Photomicrograph on pre-teriparatide treatment on cancellous bone. There is no evidence of osteoclastic or osteoblastic activity. No osteoid is present. This is consistent with frozen bones. The total osteoid surface in this case was not measurable.

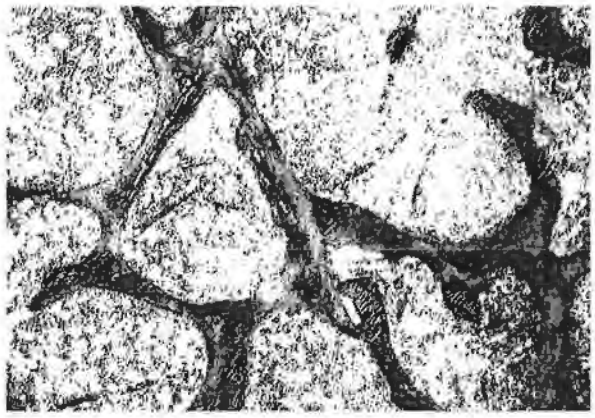

Fig. 5. Photomicrograph of post-teriparatide treatment on cancellous bone showing several trabeculae covered with osteoid. This indicates functional osteoblastic activity. The total osteoid surface in this case was 11%.

unproven. While the average bone dynamic parameters in our subjects were lower than published controls, there was also heterogeneity in these parameters. It is also possible that those patients with absent turnover at baseline had absent turnover even before bisphosphonates since the absence of tetracycline labels may be seen in a small proportion of healthy normal subjects, though not in 50% of the normal population [33,34].

While our observations do not establish that teriparatide might alter the course of early non-displaced femur fractures associated with long-term bisphosphonate use, the data is the only one published that has paired bone histomorphometry before and after any intervention in these patients. In addition, there does seem to be an effect of an anabolic agent, on fracture healing, a suggestion previously reported [35–37]. It would be unlikely that, especially the mineralizing surface, would increase even in those with unmeasurable MS/BS within 12 months of discontinuation of alendronate.

This study has many limitations. It was uncontrolled without a placebo group and studied patients after femur rods had been placed. Two simultaneous interventions were performed: discontinuation of the bisphosphonate and administration of teriparatide. Better and more preferred biochemical markers of bone turnover were not measured, especially the preferred markers of both the International Osteoporosis Foundation–International Federation of Clinical Chemistry and the National Bone Health Alliance–American Association for Clinical Chemistry: serum c-telopeptide (CTX) as the resorption marker and propeptide type 1 collagen (PINP) [38,39]. These biomarkers were not utilized in clinical practice when this study was started. In the future PINP will be the preferred marker for assessing a biological response to teriparatide since pooled data from the teriparatide clinical trials indicates that an increase in serum PINP from baseline $>10\ \mu g/L$ is strongly associated with either an increase in BMD and/or improvement in bone microarchitecture on bone biopsy [40]. In addition, our biopsies were taken from the iliac crest, the standard biopsy site from which all of the published normal static and dynamic parameters have been performed. Biopsies were not taken from the femur shaft where the clinical disease manifests itself. It is possible that the histomorphometry might differ at the site of the cortical shaft fracture seen with ASFF. In the only case published where bone histomorphometry was assessed close to the sub-trochanteric fracture site, bone turnover was normal, suggesting a different mechanism than "over-suppression" of bone turnover [41].

It would be most scientific to have paired bone biopsies in patients before and after long-term bisphosphonates as compared to untreated age-matched placebo controls performed in larger sample sizes and to have analyzed biopsy and biochemical changes in those who develop an ASFF as opposed to those who do not develop these atypical fractures. Such a study would be unethical in high-risk patients and would require an extraordinarily very large sample size to study since the calculated incident rate of these rare ASFF is approximately 100/100,000 patient years even with 8–10 years bisphosphonate exposure [42]. In addition, since the Food and Drug Administration suggests limiting the duration of use of bisphosphonates to 3–5 years and providing a bisphosphonate "drug-holiday" in only lower-risks patients; and, the appearance of these ASFF is even rarer before 5 years of bisphosphonate use (1.78/100,000 patient year exposure), it is unlikely that any such strong scientific study will be done [42].

Our data does suggest that there is heterogeneity in bone turnover in subjects with long-term alendronate exposure who have bisphosphonate-associated ASFF, but, that a large proportion has no bone turnover. However, our data certainly does not establish any causality or mechanism of action between bisphosphonate exposure and the induction of ASFF. The data does suggest that teriparatide might increase bone turnover in this study group, even in those with absent bone turnover at baseline. Our data does not provide any evidence that would indicate that teriparatide would heal an early cortical fracture detected by an early radiological examination, though fracture healing has been described in clinical reports and case series with teriparatide use [43–47]. Our data does call for larger studies of teriparatide or future bone anabolics in this population, especially in those with non-displaced fractures.

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