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NEWS

Atypical Subtrochanteric and Femoral Shaft Fractures in Bisphosphonate Users: Five Years and Counting, Yet Still Too Many Unanswered Questions

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In March of 2005, an article appeared in *The Journal of Clinical Endocrinology & Metabolism* describing 9 patients with osteoporosis or osteopenia who had suffered nonspinal fractures, in the absence of trauma, during a course of alendronate therapy ranging from 3-8 years. Iliac crest bone biopsies revealed severely suppressed bone turnover in all 9 patients, including a handful of patients who had suffered specifically from femoral shaft fractures. The study's authors speculated quite cautiously, given the uncontrolled nature of their investigation, that alendronate might play a causal role in producing these atraumatic fractures through their suppression of bone turnover.

Since this first case series, the bone field has witnessed the publication of approximately 3 dozen additional case reports/case series describing atypical subtrochanteric and femoral shaft (ST/FS) fractures both in patients taking bisphosphonates and in those not taking these drugs. Yet, though it has been more than 5 years since the initial *JCEM* findings, most of the essential questions about these fractures remain unanswered. Indeed, experts say the true incidence of atypical ST/FS fractures is unknown, and a firm understanding of the risk factors potentially predisposing bisphosphonate users to them is also currently out of reach. In fact, whether a true causal link exists, at all, between the potential risk factor that most often receives the blame – bisphosphonate use itself – and the development of these fractures remains an open question, and many experts suspect that bisphosphonate use alone is unlikely to be sufficient in causing them. In addition, the pathogenetic mechanisms responsible for atypical ST/FS fractures remain similarly elusive.

Impeding efforts to understand such issues is the lack of a clear definition of these fractures as well as a specific fracture code to diagnose them. In addition, many studies of these fractures have lacked access to x-rays, a truly limiting factor since many of the unique characteristics of atypical ST/FS fractures are observable only upon radiographs. Furthermore, limitations inherent to epidemiological studies, and to *post hoc* analyses, which have been undertaken in an effort to understand the nature and extent of the problem, have circumscribed the value of those investigations. Finally, despite its long experience with bisphosphonate use, the bone field is still missing some crucial data about the use of these drugs in the more general population of bisphosphonate users – such as how long it is safe to treat patients with bisphosphonates, and whether drug holidays are warranted – information that would be of direct relevance both to understanding the biology of atypical ST/FS fractures and to guiding patient care.

One conclusion that bone experts do feel can be stated quite firmly – that, despite all the above unknowns, atypical ST/FS fractures are rare, and should not discourage the majority of patients for whom bisphosphonates are indicated from taking them – should be reassuring both to physicians and to patients worried about this potential complication. Yet the rarity of their occurrence is yet another obstacle to a more firm understanding; currently, engaging in educated speculation is often the best that investigators can do as they attempt to study a phenomenon for which there is a notable dearth of instances. Clearly, then, researchers face quite a challenge in gaining more profound insight into these

fractures, and experts hope there is a better way forward.

Atypical Fractures with an Uncertain Causal Link to Bisphosphonate Use

The idea that a bisphosphonate, which remains in the skeleton for a long period of time, could potentially lead to adverse skeletal outcomes did not spring originally from publication of the first case series of atypical ST/FS fractures; in fact, potential complications of bisphosphonate use had been a theoretical worry for quite some time. “Ever since bisphosphonates were approved in 1995, people have expressed concern about a possible downside to suppressing bone turnover,” says Fergus McKiernan, who along with colleagues presented one of the early case series of atypical fractures in an article published in *JCEM* in 2008 describing 3 patients with FS fractures. “Those concerns have been addressed with various pre-clinical investigations in animal models, and in all the major clinical trials – you read those trials and a point is made that no adynamic bone is seen on biopsies when they were performed – so it's been an ongoing concern,” according to Dr. McKiernan, director of the Center for Bone Diseases at Marshfield Clinic in Wisconsin.

What attracted the attention of the bone field when the first case series was published, and when subsequent cases appeared in the literature – what made these fractures “atypical” – was that they were occurring spontaneously, without the trauma of a fall; while not as common as femoral neck or intertrochanteric fractures, ST/FS fractures do occur (around 5-10% of all osteoporotic fractures are of this type), yet they are usually associated with high trauma. A second clue pointing to the atypical nature of these fractures came from an assessment of how the bone was fracturing. Indeed, in contrast to a spiral or comminuted fracture pattern usually seen with ST/FS fractures, patients described in the case series/reports have presented with transverse or short oblique fractures, with the fractured bone resembling a piece of chalk that has broken into two pieces. Other distinguishing characteristics of these fractures include their occurrence in the femur's lateral cortex often in areas of cortical thickening and beaking. Also striking to fracture experts is that many patients with fractures in one femur often experience fractures with identical characteristics in the contralateral femur, and sometimes concomitantly with the initial fracture (Fig. 1).

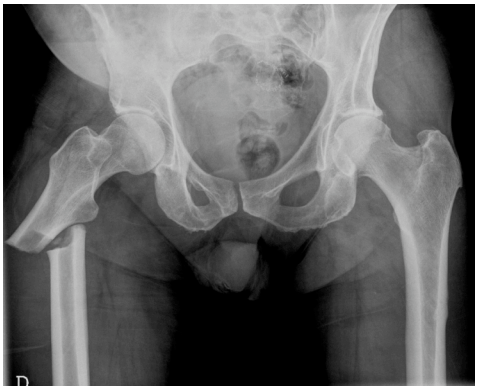

Fig. 1. An atypical femoral fracture. Image provided courtesy of R. Peter and B. Uebelhart (Geneva University Hospital, Switzerland).

While the atypical ST/FS fractures have distinct features that osteoporosis experts and orthopedists now recognize, less clear is whether bisphosphonates have a causal role in producing them. One of the most widely cited studies addressing this issue, an epidemiological investigation by Bo Abrahamsen and colleagues published in *The Journal of Bone and Mineral Research* in 2008, relied on national hospital discharge register data, and prescription database data, from Denmark and failed to document such a link. This study compared 5,000 patients who had been exposed to alendronate to a matched cohort of over 10,000 untreated controls; all subjects had experienced a prior non-hip fracture. Dr. Abrahamsen and his co-authors found that the risk of ST/FS fractures in alendronate users compared to the untreated matched controls [hazard ratio (HR) of 1.46 (95% CI, 0.91-2.35, $p = 0.12$)] was similar to the risk of classical hip fractures in alendronate users compared to the controls (HR = 1.45, 95% CI, 1.21-1.74, $p < 0.001$). They also found that high adherence to treatment reduced the risk of both hip fractures and ST/FS fractures, and that the ratio between classical hip fractures and ST/FS fractures remained the same in the treated and untreated cohorts even with long-term (> 6

years) exposure to alendronate. Based on this and other data, the authors concluded that the ST/FS fractures were more likely to be the result of osteoporosis than of treatment with alendronate. In March of 2010, the FDA cited Dr. Abrahamsen's study in a *Drug Safety Communication*, which concluded that "the data that FDA has reviewed have not shown a clear connection between bisphosphonate use and a risk of atypical subtrochanteric femur fractures."

This epidemiological study, though, along with others that rely on health register data, is viewed with skepticism for a number of reasons that investigators with these studies fully acknowledge. One of the most glaring is that currently there is no single, widely-accepted definition of these fractures, nor is there a specific code to diagnose them as atypical. "Usually these fractures would be coded simply by anatomy, but what we really want to know is whether the fractures are low trauma or spontaneous, what the radiology looks like, and other atypical features. Even if these characteristics were recognized at the time, there is no way for the physician who treats patients to actually flag results in health registers as an unusual type of fracture," says Dr. Abrahamsen, a consultant physician in endocrinology at Copenhagen University Hospital Gentofte and a professor at the University of Southern Denmark. This makes it difficult to determine precise rates of atypical ST/FS fractures because epidemiological studies like Dr. Abrahamsen's are thus forced to consider one global grouping of all ST/FS fractures rather than a more focused subgrouping of only those ST/FS fractures that actually have atypical features. For this reason, it is possible that the estimates of the number of atypical ST/FS fractures have actually been overstated. Conversely, some physicians say that atypical ST/FS fractures are often miscoded as typical fractures, so epidemiological investigators who rely on codes for their studies may actually be missing many atypical ST/FS fractures, again making it hard to determine the true incidence of these fractures. Epidemiological studies have also lacked access to x-rays, making it impossible to confirm whether the fractures under consideration are in fact atypical. Considering all of these drawbacks, along with the more customary limitations of epidemiological studies, such as confounding by indication – in the case of atypical ST/FS fractures, people taking bisphosphonates are already at higher risk for all types of fractures – experts say the epidemiological evidence causally linking bisphosphonate use to atypical ST/FS fractures is weak.

Like past epidemiological studies, a recent *post hoc* analysis of 3 of the bone field's randomized clinical trials of bisphosphonates also faced obstacles such as a lack of access to x-rays and the absence of a precise definition of atypical ST/FS fractures, but new ones as well. Indeed, this study, published in the May 13, 2010 issue of *The New England Journal of Medicine*, analyzed data from the FIT and FLEX trials of alendronate, and the HORIZON Pivotal Fracture Trial of zoledronic acid. Of the more than 14,000 women participating in these three trials, the *NEJM* investigators documented 12 ST/FS fractures in 10 patients, and did not find any significant increase in risk of these fractures in bisphosphonate-treated patients compared to placebo. While the overall rate of these fractures, estimated by the *NEJM* authors at 2.3/10,000 patient years, is reassuring, experts nonetheless point to characteristics of the clinical trials themselves that make those trials ill-suited to addressing many of the open questions about atypical ST/FS fractures. For example, long-term exposure to bisphosphonates (*i.e.*, greater than 5 years) may be important for the development of atypical ST/FS fractures, but the FIT and HORIZON trials each followed patients for less than 5 years, and while the FLEX trial followed patients out to 10 years, the number of patients enrolled in FLEX (N = 1099) was not very high. As another example, many of the people whom experts suspect might be at risk of atypical ST/FS fractures were excluded from the clinical trials. For instance, while the clinical trials included primarily patients with a significant degree of bone loss, a recent meta-analysis of all the published case reports/case series of atypical ST/FS fractures by Socrates Papapoulos and colleagues found that 18% of patients had normal BMD. Similarly, while

the clinical trials tend to exclude patients who take steroids or who have many co-morbid conditions, both of these factors may predispose patients to atypical ST/FS fractures. In addition, some of the women in the clinical trials of alendronate received a dose of alendronate that was lower than the dose typically prescribed by doctors. Finally, some experts say the biggest limitation of all is that, because of the rarity of atypical ST/FS fractures, the *NEJM* study was statistically underpowered and thus unable to provide definitive answers. “All of the studies that have been presented up until now do have clear deficiencies,” according to Dr. Papapoulos, expressing a sentiment voiced repeatedly by the experts interviewed by *BoneKEy* for this article.

Speculation About Biological Mechanisms

In the absence of conclusive studies, the existence of a plausible biological mechanism through which bisphosphonates could result in atypical ST/FS fractures would bolster the case for a causal role for these agents. Yet, while experts say there are several plausible mechanisms, they stress that because evidence for each one that has been proposed is either contradictory or lacking, all they can really do is speculate.

For instance, a severe suppression of bone turnover caused by bisphosphonates is a commonly cited explanation to account for the contribution of these drugs to atypical ST/FS fractures, but experts point to several holes in this theory. The most obvious is that this suppression is not always evident. “When we analyzed all the data that had been published, it was very clear to us that this was not a common denominator of all cases. There were reports in which, indeed, there was suppression of bone turnover, but there were also instances in which this was not the case,” according to Dr. Papapoulos, who analyzed the biopsy data as part of his meta-analysis published in *Bone* in August. Dr. Papapoulos and his colleagues concluded therefore that severe suppression of bone turnover cannot be the only explanation for atypical ST/FS fractures. A second deficiency of the theory is that suppression of bone turnover is in fact what one would expect to see in bisphosphonate-treated patients, since that is how these drugs function. Thus, the presence of suppressed bone turnover in the bone biopsies may simply be due to the bisphosphonate, and have no relation to the atypical ST/FS fractures. Of note, biochemical markers of bone turnover are normal in most cases, according to the recent meta-analysis, and do not differ from what one would expect to see in bisphosphonate-treated patients. Third, considering that relatively few (about two dozen) biopsies have been studied, and considering that most of the biopsies have been taken from the iliac crest, a site far away from the fracture, experts agree that the biopsy data shed only limited light on whether a severe suppression of bone turnover is the actual culprit.

Still, as most of the biopsies do show suppression of bone turnover, it remains a viable, if not the sole mechanism. What is the path, though, by which such suppression might lead to atypical ST/FS fractures? One hypothesis is that patients with this feature have an inability to repair bone microdamage; eventually these individuals accumulate enough microdamage such that a fracture akin to a stress fracture occurs; and finally the stress fracture progresses to a complete fracture. While experts note that, radiographically, the atypical ST/FS fractures do in fact look like stress fractures, there is as yet no histological evidence to support the microdamage hypothesis in these individuals.

Interestingly, according to Robert Recker, while bisphosphonates have received the lion's share of the blame for causing atypical ST/FS fractures, he thinks that patients who sustain these fractures have a pre-existing (*i.e.*, before bisphosphonates were even started) defect in the type of bone remodeling that is targeted to repair microdamage at specific sites in the skeleton. While a bisphosphonate may exacerbate this problem, it is also possible that the bisphosphonate simply doesn't help such patients who might have fractured anyway once enough time had passed for enough microdamage to accumulate. “I think

these atypical fractures are due to suppression of the bone remodeling that is targeted to repair microdamage. Ordinarily, targeted remodeling seems robust to the non-targeted remodeling suppression observed with bisphosphonates. However, when patients' targeted remodeling is less robust than usual, and they are put on bisphosphonate therapy, they are either not improved, or they could be made worse," according to Dr. Recker, a professor of medicine and director of the Osteoporosis Research Center at Creighton University in Nebraska.

An alternative to the microdamage hypothesis is the theory that, for some reason, patients with atypical ST/FS fractures may have brittle bone. “If you look at the radiographs, the bones appear to fracture transversely and you tend to end up with a medial spike, which is very typical of a more brittle-type fracture. This suggests that something besides the accumulation of microdamage may be happening, since a bone can accumulate microdamage yet still fracture in a way that does not resemble a brittle fracture,” according to David Burr, co-chairperson of the American Society for Bone and Mineral Research (ASBMR) Task Force studying atypical ST/FS fractures and a professor at Indiana University School of Medicine in Indianapolis. Along these lines, one possibility that experts increasingly mention – one that they concede is entirely speculative at this point since there is no clinical data available – is that with long-term bisphosphonate use, older bone that would ordinarily be replaced remains present for longer, and the collagen in this older bone becomes more highly crosslinked through non-enzymatic glycation, resulting in bone that is less able to absorb energy.

Support of a brittle bone hypothesis also comes from a recognition that the impact of bisphosphonates to increase bone stiffness can be beneficial or harmful depending upon the particular bone compartment that is affected, according to David Little, BoneKEy associate editor. “Bisphosphonates increase stiffness, and while this is good in trabecular bone, cortical bone is different. Regions like subtrochanteric bone absorb stress by bending of the entire macrostructure. This is why all long bones have a gentle bow. If the bone is too stiff, it can't bend and a stress fracture forms transversely. This happens in other brittle conditions," according to Dr. Little, head of the orthopedic research and biotechnology unit at The Children's Hospital at Westmead in Australia. In support of this view, Dr. Little notes that anti-resorptives like zoledronic acid and denosumab are much more effective for reducing vertebral fractures than for non-vertebral, long bone fractures.

Risk Factors

While speculation will continue regarding pathogenetic mechanisms, many of the experts who spoke to *BoneKEy* believe there is more to the story than bisphosphonates. “My feeling is that bisphosphonates are probably insufficient in and of themselves to cause these fractures. There likely will also be either a genetic predisposition, or a co-morbid condition, or other factors, drugs, toxins or behaviors that result in the phenotype of these fractures, though I don't think we know what they all are yet,” Dr. McKiernan says.

Yet, identifying what these other predisposing factors might be that put particular individuals at risk has been extremely challenging. Indeed, none of the risk factors that have been suggested thus far are convincing to experts, primarily because data on them come from the uncontrolled case reports/case series, as well as from the epidemiological studies, with all of their limitations. Thus, whether use of glucocorticoids – about 25% of patients with atypical fractures take oral glucocorticoids – or use of proton pump inhibitors – used in nearly 40% of patients – are true risk factors remains uncertain, though experts appear much more confident in the former than in the latter. The case of glucocorticoids is another example of how existing clinical trials in the bone field are often not that helpful in providing insight into potential risk factors, since the trials of bisphosphonate treatment in glucocorticoid-induced osteoporosis are primarily short-term studies that do not extend beyond a few years, when knowledge of long-term effects is desired.

Perhaps the potential risk factor that best illustrates the challenges and complexities facing researchers concerns the thickening of femur cortices that has been noted in some patients with these fractures; several competing theories have been proposed. First, Dr. Recker believes that the cortical thickening is not the cause of the atypical fractures but rather reflects the attempt of the bone to repair microdamage; he notes that he sees the same phenomenon in distance runners whose bones attempt to repair stress fractures in the tibia. A second theory agrees that the thickened cortices are not the cause of atypical fractures, but for a different reason: they are the result of long-term treatment with bisphosphonates. However, several experts say the evidence that bisphosphonate treatment causes cortical thickening is weak. “More and more I believe that the cortical thickening is not the result of treatment with a bisphosphonate,” says Dr. Papapoulos, who argued in his meta-analysis that bisphosphonate treatment is unlikely to cause cortical thickening in the femur, a site characterized by relatively low bone remodeling rates, because bisphosphonates are taken up by the skeleton mainly in areas with high bone remodeling rates, such as the spine and femoral neck.

Agreeing with this line of thinking is Joseph Lane, an orthopedic trauma surgeon at Hospital for Special Surgery in New York City. In 2009, Dr. Lane published a retrospective case-control study of atypical ST/FS fractures in *Osteoporosis International*, which found that more patients with atypical fractures were taking long-term bisphosphonates than patients with intertrochanteric/femoral neck fractures, and that the use of bisphosphonates was associated with the x-ray pattern observed in patients with the atypical fractures. Based on another study he did at his institution, not of patients with atypical ST/FS fractures, but of patients who had been treated with long-term bisphosphonates, Dr. Lane believes that the thickened cortices are unlikely to be the result of bisphosphonate treatment. “We looked at patients who had been on bisphosphonates for up to 10 years, and we were unable to note any increase in the thickness of the cortex, so I suspect that patients with atypical fractures probably started with thick bones to begin with,” according to Dr. Lane. Thus a third theory is that the cortical thickening is indeed a preexisting, predisposing factor for atypical ST/FS fractures. While it is unclear exactly how thickened cortices might cause problems, it is a plausible hypothesis because bones with this characteristic are not always stronger, as there are diseases like hypophosphatasia where bones have thickened cortices but nonetheless break easily.

In the end, it may well be that bisphosphonates push an already vulnerable person over the edge to developing atypical ST/FS fractures. Yet whether it is thickened cortices, or low targeted remodeling, or a genetic predisposition to brittle bone, or concomitant use of other drugs, or the presence of co-morbid conditions, or a combination of some or all of these potential predisposing risk factors, can only be answered by further research.

The Shape of Future Investigations

With answers to so many fundamental questions about atypical ST/FS fractures still beyond its reach, the bone field is at the stage where scientific societies have been devising recommendations for research necessary to provide more clarity (click here for the ASBMR Task Force report). From a clinical perspective, a standard definition of atypical ST/FS fractures, as well as a specific fracture code to diagnose them, is the most obvious need. In addition, Dr. McKiernan says that a web-based, international, secure, validated registry for cases of these fractures would be extremely helpful, since the low number of these fractures makes prospective trials unlikely. Considering the rarity of cases, experts agree that cooperation amongst researchers, including sharing of data, will be vital. Investigators also stress that additional information from the more general population of bisphosphonate users is crucial to help patients. “Although we have a great deal of experience in the use of bisphosphonates, we still know too little about issues such as dosing, cycling, and

drug holidays. If we found that we could use less bisphosphonate and still get the same beneficial effect on lowering the risk of common osteoporotic fractures, then this might ultimately end up helping patients, particularly if bisphosphonates do turn out to have a causal relationship with these relatively rare atypical fractures. It must be stressed, however, that a causal relationship between bisphosphonates and atypical femur fractures has not been established," according to Elizabeth Shane, co-chairperson of the ASBMR Task Force and a professor of medicine at Columbia University's College of Physicians and Surgeons in New York City.

While new tools to identify atypical ST/FS fractures once they have already occurred are necessary, also crucial will be new preventive approaches for identifying patients likely to, but who have still not yet fractured. Because of the impracticality, both in terms of expenses and exposure to radiation, of taking x-rays of all patients on bisphosphonates, Dr. McKiernan notes the bone field may already have a ready-made solution. "Everyone who is on bisphosphonates, and many people who are not, have bone density tests, and DXA machines capture an image of the proximal femur. If we open the DXA imaging window up a bit and capture more of the femur, which we can do, this could be a reasonable point of service mechanism, with no additional radiation or cost, by which we could potentially identify these fractures before patients are aware of them, and then monitor them over time," according to Dr. McKiernan.

Also necessary will be translational research related to specific pathogenetic mechanisms that have been proposed. "We need research that allows us to distinguish targeted from non-targeted remodeling, and if we could find a way to tell when a patient's targeted remodeling is too low, that would be great to know because then we would stop the bisphosphonate and go on to something else," Dr. Recker says.

From a basic science perspective, experts agree that the development of an animal model to study atypical ST/FS fractures would be highly useful, particularly to understand pathogenetic mechanisms. An equally important and partially unanswered question for future research is to determine whether suppression of bone remodeling by potent anti-resorptives impairs the adaptative (modeling) response of the skeleton to loading.

More People Should Be Put on Bisphosphonates, Not Less!

Though the bone field has much work to do, fortunately, experts stress firmly that the overall incidence of atypical ST/FS fractures is low and that a risk/benefit ratio still favors the use of bisphosphonates, and so panic is certainly not warranted. As noted above, the *NEJM* analysis concluded that the rate of atypical ST/FS fractures was 2.3/10,000 patient years, which is similar to estimates from another recent epidemiological study published in *Osteoporosis International*. Because of this, physicians stress the importance of keeping the value of bisphosphonates in proper perspective. "If a person is at high risk for fracture – if, for example, an individual has already experienced a fracture or has very low bone density or other common risk factors – bisphosphonates are still safe and effective drugs to use, and people shouldn't be afraid of these medications if they're used correctly and in the right patient populations," Dr. Shane emphasizes.

Unpublished work that did have access to x-ray data is also reassuring. Indeed, Richard Dell, an orthopedic surgeon with Kaiser Permanente, says he has looked at thousands of x-rays as the physician in charge of the health insurer's hip fracture database. Over a three-year period from January 2007 to December of 2009, he identified approximately 100 cases of atypical ST/FS fractures in the Northern and Southern California patients comprising the Kaiser database, but during that same time period, saw a reduction in hip fractures of about 5,000. "Roughly 50 hip fractures are prevented for every 1 of these atypical fractures that you might cause. In fact, the conclusion of our study is to put more people on bisphosphonates, because the benefit far outweighs the risk, and we still

don't have full penetration of those who need to be put on an oral bisphosphonate," according to Dr. Dell.

That one outcome of an investigation into atypical ST/FS fractures is the assertion that bisphosphonates should be used more often, not less, may be surprising, particularly to patients alarmed about these fractures. A further outcome experts hope will come from its grappling with atypical ST/FS fractures is a better understanding of bone biology and how to alter bone and fracture risk through pharmacological means. It is too early to tell whether this outcome will come to fruition, and if it does, whether the lessons learned will be unexpected ones; the story of atypical ST/FS fractures continues to unfold...