

NEWS

Atypical Femoral Fractures: Perspective, Not Panic

Recent IBMS BoneKEy webinar examined clinical and radiological characteristics, epidemiology, pathogenetic mechanisms, risk factors, and clinical management

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For a condition that experts agree is a relatively rare phenomenon, atypical femoral fractures (AFFs) of the subtrochanteric and diaphyseal regions have captured an impressive amount of attention from both bone experts and non-experts alike. Physicians who have seen patients with AFFs firsthand; readers who have followed a steady stream of cases appearing in medical journals; task forces and working groups aiming to delineate knowns and unknowns, to devise recommendations for clinical practice, and to identify the most pressing research needs; investigators debating the causes of AFFs at major conferences in the bone field; and layreaders drawn to headlines in the *New York Times* and other popular press publications – all have evinced great interest in these fractures that were first described in the published medical literature in the *Journal of Clinical Endocrinology & Metabolism* in 2005.

Despite their infrequent nature, AFFs have attracted all of this activity because of concerns over their potential link to bisphosphonates (BPs), the anti-resorptive drugs used by millions of osteoporosis sufferers worldwide. However, the precise connection, if any, between these agents and AFFs has been unclear, as have the potential pathophysiological mechanisms underlying them and the risk factors that might predispose particular individuals to sustaining them. Recently, these uncertainties, along with the clinical management of the small number of patients who have sustained AFFs, as well as the potential clinical implications for the large population of BP users who have not, were

the focus of “Bisphosphonates and Atypical Femoral Fractures: What Should Clinicians Know and Do,” the sixth IBMS BoneKEy webinar (listen to a recording of the entire webinar [here](#)). Featuring a presentation by Juliet Compston, Professor of Bone Medicine at the University of Cambridge School of Clinical Medicine in the UK and a panel discussion by experts with deep understanding of AFFs, this April 18th, 2011 webinar concluded that a proper sense of perspective, rather than panic, is appropriate when considering these fractures, particularly with regard to the widespread use of BPs in the bone field. Indeed, while AFFs are serious fractures and clinicians should be alert to their appearance, and while fundamental ideas about their causes, risk factors and other issues remain at a relatively young stage, the webinar discussion emphasized that the number of fractures that BPs prevent is orders of magnitude greater than the number of AFFs to which they may potentially contribute.

Distinct Fractures with a Low Incidence and a Possible Association with BP Use

With more than 300 cases now having been reported in the published literature (and more submitted as unpublished abstracts to meetings), a relatively clear picture of the clinical and radiological features of AFFs has emerged. The x-ray of an AFF will reveal a fracture occurring in the lateral cortex of the femur (anywhere from just distal to the lesser trochanter to just proximal to the supracondylar flare); this fracture can be a complete fracture running the length of both the lateral and medial

cortices, in which case a medial spike is often observed, or can be an incomplete fracture of just the lateral cortex. Furthermore, the fractures exhibit a transverse or short oblique configuration and are noncomminuted in nature, resembling a piece of chalk that has been broken in half, and occur with minimal or no trauma. In addition to these major features, AFFs also often exhibit cortical thickening and can occur bilaterally in the contralateral femur. Patients also often report experiencing thigh or groin pain for weeks or months before sustaining these fractures, which can also exhibit delayed healing.

In addition to these now well-recognized clinical and radiological features, AFFs, experts agree, are quite rare, though it has been difficult to pinpoint the precise incidence of these fractures because relevant studies have usually lacked access to x-rays that could confirm whether fractures identified as subtrochanteric or femoral shaft fractures actually had atypical features. Indeed, despite this uncertainty, Dr. Compston cited a variety of epidemiological data to support the view that AFFs are relatively uncommon. "The data suggest that subtrochanteric or femoral shaft fractures, in all, comprise between 5-10% of all hip and femoral fractures in the elderly. Studies have suggested that of these subtrochanteric and femoral shaft fractures, about 15-30% may have atypical features, and the atypical fractures probably constitute only about 1% of all hip and femoral fractures," according to Dr. Compston, who also reminded the webinar audience that AFFs still need to be taken very seriously, especially when patients present with bilateral fractures or with fractures that heal poorly.

Though they are rare, AFFs raise concern because most patients who suffer these fractures report use of BPs, the mainstay of treatment for osteoporosis and other conditions such as cancer-induced bone disease, and thus much of Dr. Compston's presentation focused on the conflicting data regarding the potential association between AFFs and BP use. Arguing against a role for BPs in the development of AFFs, noted Dr.

Compston, is the observation that these fractures do in fact occur in individuals who have never taken a BP. Meanwhile, the clinical trials that proved the efficacy of BPs in treating osteoporosis do not suggest an increased risk of these fractures. Indeed, a *post hoc* analysis of data from the FIT and FLEX trials of alendronate and the HORIZON Pivotal Fracture Trial of zoledronic acid, published last year in the *New England Journal of Medicine* by Dennis Black and colleagues, found no significant increase in risk of subtrochanteric or diaphyseal femoral fractures in BP users compared to those taking a placebo, although most patients in these trials were on BPs for only a short period of time (for less than 5 years) and in addition, the investigators lacked access to x-rays. Furthermore, some early epidemiological studies were unable to document a relationship between AFFs and BP use, though these studies too have been limited by the unavailability of x-rays. For instance, in a widely cited age- and gender-matched cohort study by Bo Abrahamsen and colleagues published in *JCEM* in December of last year, the authors, using data from Denmark's National Hospital Discharge Register, and National Prescription Database, found that the increase in subtrochanteric and diaphyseal fractures, in treated vs. untreated subjects, that they observed in their study was greater relative to the increase in classical hip fractures in treated vs. untreated subjects that they also found. However, when the investigators compared the risk of subtrochanteric and diaphyseal fractures in those in the highest quartile of alendronate use (an average of 9 years of treatment) to that of those in the lowest quartile of use (3 months of treatment), they found no difference. Consequently, while subtrochanteric and diaphyseal fractures were more common in patients taking alendronate than in control subjects, the authors concluded that underlying this association were patient factors, rather than use of a BP.

In contrast, other recent epidemiological studies do suggest an association between subtrochanteric and diaphyseal fractures and BP use. For instance, Dr. Compston

pointed to a study published in March of this year in the *Journal of Bone and Mineral Research* suggesting that an increase in BP use documented using data from the US Medical Expenditure Panel Survey paralleled or even preceded an increase in the rate of subtrochanteric fractures the authors found using data from another database, the US National Inpatient Sample. Likewise, in yet another epidemiological study published in the *Journal of the American Medical Association* in February, of more than 200,000 women 68 years and older from an Ontario, Canada database that was the authors' purview, Park-Wyllie and colleagues were able to document a statistically significant increase in the risk of subtrochanteric and femoral shaft fractures in women who had taken BPs for more than 5 years compared to women taking these drugs for transient (<100 days) periods; such a statistically significant relationship could not be found for women taking BPs for short-term (up to 3 years) or intermediate (up to 5 years) periods of time.

Like other epidemiological investigations, the above study was hampered by a lack of access to x-rays. However, an unpublished epidemiological study from Richard Dell and colleagues making use of the California health insurer Kaiser Permanente's database of hip fractures, a study in which the investigators did have access to x-rays to prove that the femoral fractures were in fact atypical, found that the incidence of AFFs was 2 out of 100,000 patients per year for 2 years of BP use, but this increased to 78 out of 100,000 patients per year for 8 years of BP use, again suggesting an association between BP use and AFFs. Finally, case-control studies that had x-ray access also provide evidence of an association between AFFs and BP use. For instance, Dr. Compston pointed to data from Joseph Lane and colleagues published in *Osteoporosis International* in 2009. Though limited by small numbers (a total of just 41 subtrochanteric/femoral shaft fractures were identified), the study showed that while the number of patients with femoral neck and intertrochanteric fractures decreased with increasing duration of BP use, the number of

patients with AFFs increased with increasing duration of use.

In sum, considering such data, and considering the more recent epidemiological evidence described above, the data do suggest that while classical hip fracture rates have been declining, the rate of AFFs has been rising (though the absolute numbers of these fractures are very small), and furthermore, there does appear to be an association with BP use. Interestingly, though, studies of patients who have received high doses of BPs, as in the case of cancer-induced bone disease, for instance, have not reported large numbers of AFFs. "At the moment I think it's a little bit premature to be thinking that it's purely a bisphosphonate-mediated or bisphosphonate-associated effect," noted panelist Larry Suva, Professor of Orthopaedics and Physiology and Biophysics at the University of Arkansas for Medical Sciences in Little Rock. Dr. Suva, also Director of the Center for Orthopaedic Research at UAMS, pointed to data from the AZURE trial looking at the role of BPs in breast cancer bone metastases, where subjects received very high levels of BPs over a short time period but did not exhibit any increase in atypical femoral fractures. Consequently, Dr. Compston and the panelists were careful to emphasize that the most recent epidemiological studies indicate that the association between BPs and AFFs appears to be one of *duration* of BP use, rather than dose.

Pathogenetic Mechanisms: No Firm Answers, but Intriguing Clues

While some progress, then, has been made regarding the epidemiology of AFFs and their association with BPs, a deep understanding of the pathogenetic mechanisms underlying them is not yet at hand, though clues do allow for some reasonable speculation. One hint is that AFFs resemble another type of fracture with which the bone/orthopedics field is quite familiar. "Atypical femoral fractures have many of the characteristics of stress fractures," according to panelist David Burr, Professor of Anatomy and Cell Biology at

Indiana University School of Medicine in Indianapolis. "They have a radiolucent line, there's a periosteal stress reaction or callus, and there's often pre-fracture groin pain," according to Dr. Burr, also a co-chairperson of the American Society for Bone and Mineral Research Task Force that released its report on AFFs last year. However, Dr. Burr also noted that, unlike typical femoral stress fractures that usually occur medially, atypical fractures occur laterally, suggesting that a biomechanical alteration, such as excessive foot pronation, may be involved in the pathogenesis of AFFs. Interestingly, Dr. Burr also added that if AFFs are in fact stress fracture-like, then another potential pathogenetic mechanism – a deficiency in the bone remodeling process – could also be a part of this biomechanical account of AFFs. "Normally stress fractures that begin to develop will be repaired if the remodeling system is working effectively, but if in fact these [AFFs] are stress fracture-like, and remodeling is reduced for whatever reason, and these fractures can't be repaired, then they will tend to grow and eventually can result in full fractures," Dr. Burr said. In short, the combination of altered lower limb biomechanics in a person with reduced remodeling and thus an impaired ability to repair the microdamage characteristic of a stress fracture or a fracture akin to one may be enough to do the trick.

An inability to effectively repair microdamage could be one of several potential adverse consequences of a long-term suppression of bone turnover by BPs, and whether the latter is, in fact, at play in producing AFFs has received more attention than any other potential pathophysiological mechanism. In this regard, Dr. Compston referred to a study published last year by Socrates Papapoulos and colleagues in *Bone* that analyzed bone biopsy data, when it was available, from patients with AFFs. Their investigation found that while a suppression of bone turnover was often observed, about 1/3 of the biopsies did show double tetracycline labeling, and, furthermore, the authors were able to document normal or increased resorption in about 1/4 of biopsies in which resorption was evaluated, and they also found

increased resorption at the fracture site in one patient. "The findings have been quite heterogeneous, and, importantly, there are no studies that show that bone turnover in patients with atypical fractures is more suppressed than in patients taking bisphosphonates who do not develop atypical fractures, and the more potent bisphosphonates like alendronate and zoledronate suppress bone turnover somewhere in the region of 80-90%," Dr. Compston noted. Indeed, because BPs work by suppressing bone turnover, it is difficult to ascertain whether suppressed bone turnover, when found in AFF cases, is a causal factor, or rather simply evidence that BPs are acting like they are supposed to act.

A clue that yet another possible AFF mechanism may be important comes from a consideration of the configuration of these fractures: unlike typical femoral fractures that are spiral in nature, AFFs have a transverse or short oblique configuration, and they also occur with minimal or no trauma. "This is very typical of a brittle fracture, so it suggests that whatever the biomechanics may be, there may also have been changes to the properties of bone tissue itself," Dr. Burr said. Indeed, he noted that it is clear from animal models that BPs increase non-enzymatic collagen cross-linking; this cross-linking helps to stabilize the bone matrix and contributes to the mechanical properties of bone. However, it is accompanied by the accumulation of advanced glycation end products, which have been shown to increase bone brittleness.

Any discussion of pathogenetic mechanisms of AFFs must also address the issue of cortical thickening, a phenomenon that has been observed in many, though not all, AFF cases. One key question is whether this cortical thickening existed prior to BP use, or rather developed in response to long-term BP use. However, according to Dr. Compston, the latter possibility seems unlikely based on the current understanding of how BPs work. "Cortical thickening requires either periosteal and/or endosteal apposition, and apposition can only occur by bone formation, and we have no evidence

that bisphosphonates increase bone formation,” Dr. Compston said. Consequently, it is possible that AFF patients had thicker cortices to begin with, or perhaps that the cortical thickening represents bone’s attempt to repair microdamage.

While only further studies will be able to clarify such issues, the panel agreed that a looming obstacle to a better understanding is that one particular research tool – an animal model of AFFs – will likely not be forthcoming anytime soon. Indeed, if it is in fact duration of BP administration that is important in AFFs, any animal model of AFFs would need to replicate such long-term use, an achievement that will be very difficult to manage in a timely and inexpensive fashion.

Patient Care

Of more immediate concern, however, are clinical issues, key topics to which the panel devoted much of its discussion. First, how can patients at risk for AFFs be identified? Unfortunately, while a number of potential risk factors, such as use of glucocorticoids, use of proton pump inhibitors, or the presence of co-morbidities, have been postulated, none of them have truly compelling data in their support, though the evidence for glucocorticoids is probably the strongest of all the contenders. Bone turnover markers appear of little use to predict who may sustain an AFF. Indeed, not only have these markers not been thoroughly studied, but the reports that do exist are inconsistent, with low, normal and high levels all having been found in AFF patients. In addition, the measurement itself of bone turnover markers is problematic; for instance, if a patient has experienced a fracture, bone turnover markers may be higher simply because of that fact, rather than being an indication of an underlying problem. “Bone turnover markers haven’t been terribly helpful up to now, and I certainly don’t think there is any evidence they can be used prognostically to predict who will or won’t develop these atypical fractures,” Dr. Compston concluded.

While the potential risk factors for AFFs are unclear, it is also impractical to screen all patients taking BPs to identify those who might be at risk, considering that these fractures are so uncommon. However, since patients who are on BPs, and many individuals who aren’t taking these drugs, already have bone density tests performed, one measure that could be taken, according to panelist Fergus McKiernan, is to simply open up the scanning window of a DXA scan such that a greater length of the femur is visualized. “We have within the last year found 2 cases of atypical fractures, which had otherwise been unrecognized, by this method,” according to Dr. McKiernan, Director of the Center for Bone Diseases at Marshfield Clinic in Wisconsin. “It’s a labor-intensive search, but the information is there and it’s free, and now I think we have data that says it’s reasonable to open up the scan field and look at the long femur on a DXA,” according to Dr. McKiernan, who noted studies he has conducted showing that modifying a DXA scan in this way does not appear to interfere with BMD measurements of the proximal femur.

Another measure that could be taken to prevent AFFs is simply to recognize that patients concerned about their general skeletal health but who are unlikely to benefit from BPs – such as individuals with osteopenia and low fracture risk – should not be treated unnecessarily with these drugs. In fact, panelist Elizabeth Shane noted that for her patients who have been on BPs for several years, her current clinical practice is to reassess the original rationale for starting BPs in such patients and to determine whether continued treatment is necessary. “Many patients who are sent to me have been started on bisphosphonates years before, and I think it’s worthwhile to go back and re-visit why the patient was started on a bisphosphonate and to make sure that such a patient would be started today with our more recent focus on treating people who are at higher risk,” according to Dr. Shane, Professor of Medicine at Columbia University’s College of Physicians and Surgeons in New York City who also co-chaired the ASBMR Task Force on AFFs.

When patients for whom BPs had always been appropriate reach, say, the 5-year mark for duration of therapy, whether discontinuing BPs for a period of time referred to as a “drug holiday” becomes an important question in light of the apparent association between duration of BP use and AFFs. The panelists agreed that, unfortunately, there is little published long-term data to guide treatment decisions along these lines. Indeed, the only data the bone field has in this regard comes from the FLEX trial of alendronate, which followed patients up to 10 years. Data from this trial showed that subjects who stopped taking alendronate after 5 years of treatment did not have a higher risk of fracture, except for clinical vertebral fractures. In addition, a *post-hoc* analysis of the FLEX trial found that in subjects without a prevalent vertebral fracture who continued to take alendronate for an additional 5 years, a further reduction in non-vertebral fractures was only seen in those with a T-score of -2.5 or less. However, not only do these data derive from small sample sizes, but also from studies that differ from what a real-world drug holiday might look like; the FLEX trial evaluated what happened after 5 years without treatment, but in actual clinical practice the physician might stop treatment for a year or two with continued monitoring of the patient. In terms of preventing AFFs, then, the evidence whether or not to embark on a drug holiday is very limited, however, the panelists agreed that it is nonetheless a reasonable option to consider.

Also with regard to AFF prevention, another interesting question concerns the role of physical activity in patients who take BPs. “Considering the similarity we see between the occurrence of atypical femoral fractures in bisphosphonate-treated patients and stress fractures that we see in other circumstances, is there a relationship between atypical femoral fractures in bisphosphonate-treated patients and the level or type of physical activity they do?” asked Serge Ferrari, BoneKEy editor-in-chief and moderator of the webinar. “For clinicians, should we perhaps not recommend that our elderly patients on bisphosphonates jog or go on vibrating

platforms?” The panelists noted that while there are no compelling data available now to answer this question, anecdotal evidence suggests that AFF patients often appear to suffer these fractures after a period of above-normal physical activity. In addition, from a demographic perspective, AFF patients tend to be younger than the typical postmenopausal osteoporosis patient, and of course younger patients tend to be more active.

In short, considering all the uncertainties around what the bone field knows and does not know about risk factors, caution, and perhaps most of all, the physician's clinical experience and judgment, are the most important factors. “I don't think it's possible to predict who is going to develop atypical femoral fractures,” Dr. Compston said. “I think the best we can do at the moment is, first, not treat unnecessarily, second, always consider whether a finite duration [of BP treatment] might be adequate or not and not just automatically continue for life, and third, have that index of clinical suspicion, so when a patient has unexplained groin or thigh pain we do imaging as quickly as possible.”

The panel also discussed the appropriate measures to take when the signs and symptoms of AFFs are already present, such as the patient whose x-ray reveals a lucent line suggesting the beginning of a fracture akin to a stress fracture, and periosteal reaction and cortical thickening of the lateral cortex. “The first thing I would do is x-ray the other femur, because there is a good chance you will find 2 fractures,” Dr. McKiernan said, in reference to the bilaterality of AFFs that has been documented in many cases. Dr. McKiernan also advised referring AFFs to physicians with experience with these types of fractures. For patients with complete fractures, prompt surgical intervention, in the form of intramedullary rodding is advised, and prophylactic nail fixation is recommended for patients with incomplete fractures who are also experiencing pain; such patients should also use crutches or walkers to eliminate loading.

The panel also noted that teriparatide could be considered particularly in patients who show evidence of poor healing (as there is some anecdotal clinical evidence that it can help with healing in AFF cases, and there is also evidence from animals and a bit of data from human studies that teriparatide can help with fracture non-union). Finally, while there are no data yet to suggest that vitamin D deficiency is playing a causal role in producing AFFs, deficiency of this vitamin that is key to bone health has been found in AFF patients so any deficiency should be corrected, as in all patients.

Conclusion

Undoubtedly the concern over AFFs is warranted, considering how debilitating these fractures are, and because of the potential link with BPs, prescribed by doctors to improve the bone health of millions of patients worldwide. However, because the absolute number of people sustaining these fractures is low, and since osteoporosis is a serious disease for which BPs have proven benefits, keeping the very favorable risk/benefit ratio of BPs in clear sight is important. Indeed, when considering AFFs, the take-home message of the seventh IBMS BoneKEy webinar was that a proper sense of perspective, rather than panic, is the most reasonable outlook.