

## **NEWS**

### **A Fracture Is a Fracture Is a Fracture**

*Using levels of trauma to define osteoporotic fractures may be a thing of the past*

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When an elderly person breaks a bone "accidentally", physicians try to determine the circumstances of the mishap, particularly the nature and size of the forces that acted on the bone. Were only small forces involved – did the patient simply trip and fall to the ground in an act of clumsiness, or slip on the ice on a cold winter day? Or did large forces impact the bone – did the patient fall from a tall ladder used to clean out a roof's gutter, or become the unfortunate victim in an assault or high-speed car crash? According to current definitions employed by the bone field, however, only the first type of broken bone, known as a low-trauma fracture, would be considered related to low bone mineral density (BMD) and therefore as an osteoporotic fracture, since healthy bones, the conventional thinking has been, should be able to withstand the presumably small forces generated in low-trauma situations. In contrast, the second type of fracture, of the high-trauma variety, has traditionally been seen as unrelated to low BMD and therefore not as an osteoporotic fracture; surely anyone's bones would break when large forces, of the sort thought to be experienced in automobile wrecks, come into play.

New analyses of data coming from the Study of Osteoporotic Fractures (SOF) and the Osteoporotic Fractures in Men Study (MrOS) are now providing the strongest evidence to date to overturn this line of thinking. In fact, when viewed along with related studies, a picture already envisioned by top experts in the bone field, but less appreciated by the general medical profession and by many patients, is coming into even clearer focus: *all* fractures, regardless of the level of trauma that precipitates them, in elderly individuals

should be considered as potentially indicative of underlying bone fragility and therefore worthy of assessment and treatment considerations. "The word 'fracture' – not just 'fragility fracture' or 'low-trauma fracture' – but the word 'fracture' itself in a man or woman over the age of 50 should lead to the performance of a bone density test, and if the bone density is low, you have an indication for treatment," says Ethel Siris, an osteoporosis expert and professor of clinical medicine at Columbia University.

While the new research suggests that the distinction between low- and high-trauma is not an adequate standard by which to distinguish healthy from weak bones in elderly people, earlier research suggests that it is an inappropriate criterion in children as well, as past studies have demonstrated that childhood fractures, often sustained in high-trauma circumstances, are also associated with bone weakness. All of this begs the question: why would a high-trauma fracture, whether in a youngster or in an elderly individual, be associated with bone fragility?

That these fractures have not traditionally been perceived as related to low BMD largely reflects faulty assumptions about, and a generally poor understanding of, the forces that impact the skeleton during accidents. In fact, according to many of the experts who spoke to *BoneKEy*, the new findings demonstrate not only a blind side to the bone field's knowledge of skeletal biomechanics, but also to a dearth of information about a host of issues related to fractures, including both their treatment and the determinants of future fracture risk. In short, the findings bring current gaps in

understanding into much sharper relief and highlight some of the obstacles the bone field faces in its efforts to manage osteoporosis.

### The Study

The genesis of the new study (1), published late last year by Steven Cummings and colleagues in *JAMA*, was that the conventional thinking about high-trauma fractures had in fact never been rigorously tested. "It's been assumed for a long time that fractures that occur under so-called 'high-trauma' conditions are occurring because the forces involved are so great and are therefore unrelated to underlying low bone density," says Dawn Mackey, lead author of the study. "We felt this was something that needed to be tested, because the assumption that we've been making had such important consequences for research and clinical practice," according to Mackey, a research associate at the California Pacific Medical Center Research Institute in San Francisco.

Consequently – and building upon earlier evidence from the 1998 Geelong Osteoporosis Study, the first to demonstrate a link between high-trauma fractures and low BMD – Mackey and colleagues evaluated women who took part in SOF, and men who took part in MrOS, both well-designed prospective cohort studies that have provided the bone field with a great deal of information about osteoporosis. They found that low BMD was associated with both low- and high-trauma fracture risk: in multivariate-adjusted models, a 1-SD reduction in total hip BMD was associated with an increased risk of high-trauma fracture of 45% in women and 54% in men, similar to the increased risk of low-trauma fracture that was observed. The researchers also found that in women, both high- and low-trauma fractures were associated with a similarly increased risk for future nonspine fracture, with an increased risk of 34% in those with high-trauma fractures compared to those with no high-trauma fractures, and of 31% in those with low-trauma fractures compared to those with no low-trauma fractures. While there were not enough

fracture events to achieve adequate statistical power in men, similar trends regarding future fracture risk were also seen in that group.

None of these findings surprise osteoporosis experts. In fact, top clinicians say that they had already integrated the conclusions supported by the *JAMA* study into their understanding of fractures and into their assessment and treatment of patients. Nonetheless, while the message had already been received by the osteoporosis cognoscenti, the larger medical world has been less aware. "For the general practicing physician, the idea that any kind of non-spine fracture may be trying to tell us something meaningful not just about low bone density, but also about subsequent fracture risk, is a very important observation that has not been much appreciated in clinical practice," says Steven Harris, an osteoporosis expert and clinical professor of medicine at the University of California, San Francisco. The new findings may also surprise patients; clinicians note that many elderly individuals with low bone mass who break a bone will attribute their fractures solely to the circumstances – "it was just a really bad fall," patients might say – and not to underlying bone fragility. No longer is this a tenable view.

### A Continuum of Bone Fragility

While the *JAMA* study shows that the distinction between low- and high-trauma is not useful in identifying bone fragility and future fracture risk in older adults, that distinction also doesn't appear useful in identifying bone fragility in children, according to Serge Ferrari, an associate professor of osteoporosis genetics at Geneva University Hospital in Switzerland and also *BoneKEy* Editor-in-Chief. In a paper published in *The Journal of Bone and Mineral Research* in 2006 with René Rizzoli, Jean-Philippe Bonjour and Thierry Chevalley, Dr. Ferrari and his colleagues followed a cohort of girls through childhood and adolescence, measuring their BMD through time. "What we found was that bone mass gain throughout puberty and, as these young women reached peak bone mass,

their bone density at several sites, was significantly lower in those who had a history of fracture in childhood compared to those who didn't, not just at the sites of fracture, but at different sites throughout the skeleton," Dr. Ferrari says.

This was a puzzling observation at the time, Dr. Ferrari notes, since fractures in childhood and adolescence were not generally thought to be associated with weak bones, but rather to the large forces that youngsters are likely to experience in high-trauma situations such as bicycle or skiing accidents. "Consequently, we hypothesized that a fracture might be the hallmark of bone fragility, irrespective of the circumstances of the trauma," Dr. Ferrari says, adding that the *JAMA* study reinforces this view, since it also found that in the elderly population it examined, all fractures, regardless of whether they were classified as low- or as high-trauma, were associated with low BMD.

Dr. Ferrari stresses that when the study he conducted with his colleagues is viewed alongside the *JAMA* research and related work, a picture of a continuum of bone fragility, throughout the life of an individual, emerges. For instance, he notes that it is often said that only fractures that occur after a specific point in time – 45 or 50 years of age, for example – are predictors of future fracture risk because fractures before that age are more likely to be due to high-trauma, traditionally thought to be unrelated to bone fragility. The new research, to Dr. Ferrari, confirms his belief that this age-threshold, at which point fractures are to be viewed as risk factors for future fractures, is arbitrary, since all fractures, regardless of when they occur and regardless of the level of trauma that precipitates them, may be based upon bone fragility. Put another way, there is no one specific point in time when bone fragility suddenly comes into play as an explanation of fractures; rather, it may be an ever-present factor.

### **Wouldn't Anyone Fracture in a Car Accident?**

Results from children and adults, then, show that high-trauma fractures can be associated with low BMD. Why is this the case – why would a fracture experienced in a horrible car wreck, for instance, be associated with bone fragility? On the one hand, experts say this makes perfect sense: fragile bones are more likely to break than healthy bones in low-trauma affairs, so why wouldn't the same principle hold true for high-trauma circumstances – why wouldn't a person with fragile bones experience a fracture in a car accident, while a person with stronger bones would be spared?

Resistance to the idea that a high-trauma fracture might be associated with bone fragility stems at least in part from erroneous assumptions about the forces involved in high-trauma situations. "What's interesting about the new research is that it suggests that the forces that develop in so-called 'high-trauma' events are not so dramatically large that they would overwhelm the strength of anybody's bones," says Tony Keaveny, a bone biomechanics expert and professor of mechanical engineering and bioengineering at the University of California, Berkeley. In fact, to both the *JAMA* study authors, and to most experts familiar with the findings, the assumption that high-trauma must involve incredibly great forces that would overpower even those with the strongest of bones, and conversely that low-trauma must involve only small forces that would overwhelm only those with the weakest of bones, seems arbitrary and unappreciative of the complexity involved in estimating the nature and magnitude of forces in situations that may be quite different and therefore difficult to compare.

For instance, Dr. Keaveny notes that in a low-trauma accident such as falling from a standing height or less and breaking a hip, the force exerted on the bone is determined by characteristics like the height of the individual, since taller people will hit the ground at a greater speed since they have further to fall, and thus will generate larger forces than shorter people, all other things being equal. Meanwhile, when two automobiles collide and a driver or

passenger fractures a rib, characteristics of the individuals such as height may be less important than the traits of the external objects – the cars themselves – including how fast they are moving and their size. In addition, the angle at which the force is applied to the bone may also differ. During the hip fracture, the force may be applied in a direction for which the greater trochanter is especially vulnerable to breaking. In the car wreck, the forces may be larger, but if they aren't applied in a direction for which the bone is particularly vulnerable, the driver may walk away unharmed. Alternatively, the car accident may involve relatively small forces, but if the force is imparted at an unusual angle at which the bone is especially susceptible, the individual may fracture anyway. "Biomechanically," Dr. Keaveny stresses, "the way the force develops in low-trauma and high-trauma fractures can be quite different."

This fact may also explain why the skeletal locations of the fractures in the *JAMA* study differed between low- and high-trauma affairs – why, for instance, on a percentage basis, there were more rib fractures than hip fractures in high- than in low-trauma circumstances. In fact, Dr. Keaveny notes that very little information exists regarding the biomechanics of forces that develop on the ribs and other skeletal locations where many of the fractures were observed. Developing a better understanding of these forces is not enough; knowing how the bone will respond when subjected to them is also necessary. The effort currently underway in the osteoporosis field to use 3-D models such as finite element analysis, to understand the factors underlying bone strength that may allow for better fracture risk prediction than that currently allowed by 2-D bone density scans, may help in this regard.

### **Mind the Gap(s)**

While a better understanding afforded by these new techniques of the variables that determine bone strength will be important, John Eisman, director of the bone and mineral research program at the Garvan Institute of Medical Research in Sydney,

Australia, wonders whether this will be the most fruitful area of endeavor. "Going beyond BMD to look at bone microstructure and other aspects of bones – I'm not sure that will be the place that gives us the greatest bang for our buck. Part of the increase in fracture risk you see in the high-trauma fracture patients may be related to their bones, however, lifestyle, behavioral and other factors that we don't capture very well may also be important," he stresses.

In fact, many experts emphasize that the *JAMA* research reveals additional gaps in other important areas and highlights the obstacles osteoporosis experts face in their efforts to assess and treat the disease. For instance, the new research does not shed any light on which particular kinds of fractures are predictors of future fracture risk, according to Michael McClung, director of the Oregon Osteoporosis Center in Portland. "We're well aware that having a previous hip fracture or spine fracture is a very important predictor of future fracture risk, and we use that in our risk assessment algorithms," Dr. McClung explains. "This research addresses the question of whether high-trauma fractures are also predictors of future fracture risk, but the more important and more difficult question is not whether a fracture is high- or low-trauma, but rather which specific kinds of fractures are predictors or determinants of future fracture risk. Do other fractures, such as ankle or rib fractures, also predict future fracture risk? This paper highlights the point that we aren't very proficient in our understanding of what fractures mean in a clinical or risk-predictive setting."

According to Dr. McClung, the *JAMA* study also underscores a gap in the field's understanding of how to treat particular patient populations. Specifically, while experts agree that high-trauma fracture patients merit treatment if their bone density levels are found to be osteoporotic, what about high-trauma fracture patients who have bone density values in the osteopenic range, or in the normal range? "With the exception of the Women's Health Initiative estrogen study, no study has demonstrated that osteoporosis drugs reduce fracture risk

in patients who don't have osteoporosis. Consequently, taking someone who doesn't have osteoporosis, who presents with a high- or low-trauma fracture, and deciding to treat on that basis is not yet supported by evidence, " according to Dr. McClung, who also stresses that because this is the case, treating on the basis of a prior fracture alone is not enough; other clinical risk factors are very important to consider.

Regarding treatment, another key unanswered question is whether the drugs currently used for low-trauma fractures will help for the high-trauma variety. "We really need to get a better sense of whether the small changes in bone mass and improvements in bone quality associated with anti-resorptive or anabolic agents are able to minimize the fracture outcomes in the setting of high-trauma fractures," Dr. Siris notes. Furthermore, experts hope that the *JAMA* study's focus on high-trauma fractures will not cause physicians to lose sight of what they see as an even bigger problem: getting those with the traditional low-trauma fractures into treatment. "One of the great tragedies of osteoporosis over the years has been that many older patients who have even classic osteoporotic fractures, such as spinal compression fractures, Colles' fractures, and hip fractures, have not been diagnosed as osteoporotic and started on some form of subsequent therapy, so we're having enough trouble with conventional osteoporotic fractures, much less these high-trauma fractures," Dr. Harris emphasizes.

Meanwhile, for Paul Miller, medical director of the Colorado Center for Bone Research in Lakewood, Colorado, the *JAMA* study raises other concerns that including more patients in the osteoporosis category may not do the osteoporosis field any favors with those responsible for reimbursing the costs of treatment. "What I fear is that as we in the osteoporosis world have a difficult enough time getting payors to pay for therapies with evidence from clinical trials, we push the envelope for treatment recommendations to the point where payors state we are overstating the disease, which they are

already claiming," says Dr. Miller, also a clinical professor of medicine at the University of Colorado Health Sciences Center. While bone experts acknowledge the difficult healthcare environment in which they practice, many of them note that since the proportion of high- to low-trauma fractures in the *JAMA* study is relatively low, including high-trauma fractures will not add an unduly large amount of costs to the system.

Perhaps most of all, the *JAMA* research illustrates another hurdle the field has faced, and may always continue to face: devising a definition, which will serve as a paragon for everyone, everywhere, specifying what should count as an osteoporotic fracture. "This paper can be viewed as a commentary on the difficulty of defining a fracture that is associated with osteoporosis. High-energy and low-energy trauma don't provide a gold standard," says John Kanis, an emeritus professor and director of the WHO Collaborating Centre for Metabolic Bone Diseases at the University of Sheffield in the UK. Dr. Kanis is quick to add that other methods don't fare much better. "Defining an osteoporotic fracture as one that results from a fall from standing height or less doesn't provide a gold standard, nor does having an expert committee define what one is," he stresses. While Dr. Kanis and his colleagues have worked to develop their own criteria, he notes that these criteria, which define an osteoporotic fracture as one that is associated with low BMD and whose incidence increases with age, are not perfect either; there is simply no gold standard that will make a universally applicable, international definition a reality. Levels of trauma don't serve as a gold standard, but in this regard, they are in very good company.

## References

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