

## **NEWS**

### **From Video Games to Bisphosphonates?**

#### ***Pediatric bone health specialists expressed concern for the current and future skeletal health of children during recent IBMS BoneKEy webinar***

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Adults who say that youth is wasted on the young probably don't think of bone health when they make this assertion. But considering the behavior of the current generation of children and teenagers, skeletal health should very much be a concern for those who believe that today's young people are mis-spending their early years. In fact, kids who choose sedentary indoor activities like playing video games and surfing the internet with junk food at-the-ready, at the expense of more active, outdoor pursuits like bike riding, do so at just the time when sufficient physical activity, proper nutrition, and adequate sunlight exposure are most important for proper skeletal growth and development, since the ultimate health of the adult skeleton depends so strongly on what occurs skeletally during a youngster's formative years.

"Adolescence is a crucial period for bone health. What happens during this time will determine one's peak bone mass as well as one's skeletal strength," stressed Dr. Catherine Gordon, Director of the Bone Health Program at Children's Hospital Boston, during the introduction to her presentation for The Management of Bone Fragility/Low Bone Mass in Children and Adolescents, the eighth IBMS BoneKEy webinar, which took place in June (click [here](#) to listen to the webinar in its entirety). Following her presentation of the risk factors for bone fragility and low bone mineral density (BMD) in the pediatric population, the measurement tools available to clinicians to assess pediatric bone health, and the management of children diagnosed

with bone disease, a truly international panel of experts, with representation from Canada, the United Kingdom, Europe and Australia, focused on diagnostic and therapeutic dilemmas facing physicians who work with youngsters. This lively discussion, created and moderated by Dr. Craig Langman, the Isaac A Abt, MD Professor of Kidney Diseases at Northwestern University's Feinberg School of Medicine, and Head of Kidney Diseases at Children's Memorial Hospital in Chicago, Illinois, focused not only on the penchant for video games and other lifestyle factors that are so worrisome to physicians concerned with pediatric skeletal health, but also on topics like how to handle children who have suffered multiple fractures before adolescence, the role of clinical history and BMD scans during diagnosis, the impact of steroids on bone health, as well as the risks and benefits of treatment.

#### **Diagnostic Issues in Pediatric Patients: Multiple Fractures, the Importance of Clinical History, and the Place of BMD Scans**

The first diagnostic matter the panel debated was how to assess children who have experienced recurrent fractures before adolescence. "As an orthopedic surgeon, the first thing I think about is where the fracture occurs, and what the energy of the fracture is," said panelist Dr. Jay Janicki, who treats pediatric fracture cases at Children's Memorial Hospital in Chicago. Indeed, fractures of the hand and foot, which are not customarily linked to skeletal fragility, will be less concerning than

fractures of the radius, for instance, or metaphyseal fractures of the tibia, which do have a more compelling association with weak bones. Meanwhile, high-energy fractures that any child, healthy or not, would be expected to sustain raise less cause for concern than fractures resulting from low-energy circumstances that only skeletally fragile children would experience.

This recognition that not all fractures are the same is particularly important, noted panelist Dr. Nick Bishop, because it is not at all unusual for children to have experienced several fractures by an early age. "Approximately 20% of children by the age of 16 will have had 2 or more fractures, so it's not an uncommon event to have a second fracture. We know that children who are very active are at higher risk for fracture, irrespective of what their bone density is, and so the energy of the fracture, the kind of trauma that led to it, and our consideration of whether this is a fracture we would expect in any child are very relevant," according to Dr. Bishop, Professor of Paediatric Bone Disease at the University of Sheffield in the UK.

Understanding the type of fracture, and the circumstances under which the fracture has occurred, are elements of what the panelists agreed is the most important aspect of discerning diagnostically whether skeletal fragility is present in children: the clinical history of the patient. Important aspects of the clinical history include quality of life assessments, as well as an understanding of what risk factors the pediatric patient is likely to have in the future. "Is this a child who will continue to receive steroids, for example, and will thereby be at continued risk, or is this a child who will cease steroids and thereby have the potential to spontaneously reconstitute bone mass and reshape vertebral bodies?" asked panelist Dr. Leanne Ward, from Children's Hospital of Eastern Ontario and the University of Ottawa in Canada, also noting that younger children will have more opportunity to achieve the latter than older children.

Of all the risk factors that put the skeletons of children and adolescents in jeopardy – a

long list of diseases including osteogenesis imperfecta, childhood malignancies, inflammatory bowel disease, cerebral palsy and cystic fibrosis, to name just a handful, as well as a number of medications with bone side effects – the panel focused on the use of glucocorticoids in children, agreeing that such children need particular attention with regard to their skeletal health, for a number of reasons. Many children must take these drugs, for a variety of chronic conditions, and not only are these medications known to have adverse skeletal consequences by affecting bone strength and the rate of bone growth, but even relatively low levels of exposure to steroids can have a serious skeletal impact. Furthermore, children who take glucocorticoids are already at risk for bone problems before they even start taking their medication. "Risk factors for a low bone mass are additive," Dr. Gordon noted. "Children on glucocorticoids have an underlying disease that puts them at risk, and steroids are one more step. I watch these children like a hawk, and I particularly watch their growth." In addition, children on glucocorticoids are at particular risk for vertebral fractures, which are often asymptomatic.

Speaking of vertebral fractures, the presence of back pain is another vital component of the clinical history to which clinicians should be alert. "The key element in the history that general practitioners and pediatricians can always pick up on is that back pain in children is abnormal and merits further assessment and investigation," Dr. Bishop said. Panelist Dr. Craig Munns, Senior Staff Specialist at The Children's Hospital at Westmead in New South Wales, Australia stressed the lateral spine x-ray as an integral part of his own clinical practice. "The importance of doing the lateral spine x-ray in children can't be overemphasized for picking up both symptomatic fractures but also asymptomatic vertebral fractures in children, especially those on steroids," he emphasized.

The pediatric patient's clinical history is particularly important since, as in adults, skeletal fragility can be present even when

BMD is normal. For instance, Dr. Ward noted a recent case in her clinical practice, reported earlier this year in *Pediatric Nephrology*, of a 10-year-old boy with steroid-sensitive nephrotic syndrome who presented with back pain as a result of moderate vertebral fractures sustained 5 years after diagnosis and who had received glucocorticoids over that time frame. However, this patient's BMD Z-score was within the normal range. "This case nicely highlights that BMD isn't everything," Dr. Ward said.

Nevertheless, while the panelists emphasized the vital importance of clinical history, they agreed that the BMD scan is still a useful screening tool in pediatric patients. When these tests are performed, which sites are the most useful ones to study in children? "We generally use lumbar spine and total body scans, apart from some very specific conditions like cerebral palsy when we also use other sites," explained panelist Dr. Maria Luisa Bianchi of her and her colleagues' clinical practice. "In general, lumbar spine and total body measurements are very useful, the latter because they are able to give you information about body composition, which is especially important in kids," according to Dr. Bianchi, from the Istituto Auxologico Italiano in Milan, Italy. Lumbar spine and total body measurements are particularly important sites since the hip is considered an unreliable site for bone densitometry in the pediatric population because of confounding factors such as variation between children in skeletal development.

The final diagnostic issue under discussion was the importance of lifestyle aspects in increasing skeletal fragility and the risk for fractures. "I don't think lifestyle factors can be underestimated," according to Dr. Munns, expressing a sentiment with which the panel wholeheartedly agreed. Dr. Munns drew particular attention to the importance of physical activity, which develops muscle, the latter known to have an importance influence on bone development. Overall, it is mechanical challenges that push bones to develop, stimuli that will be absent in kids who prefer sitting to exercising. A lack of

physical activity can also lead to obesity, another lifestyle factor of particular concern, and Dr. Bishop pointed to research he and colleagues have performed in this area. "Children who are obese and who have had a previous fracture have substantially lower bone mass for their body size than children who are obese and haven't had a previous fracture," he said, noting that unlike in adults where fat is thought to have a protective effect on bone, fat in children may be skeletally detrimental. Of course, one factor leading to obesity is poor nutrition, the latter yet another hugely important lifestyle issue of concern to pediatric bone specialists. In this regard, not only is adequate intake of calcium and achievement of sufficient vitamin D levels important (the latter increasingly difficult to achieve with young people who either stay indoors or who use sunscreen, when they do venture outside, that blocks the synthesis of vitamin D in the skin), but children with diseases like cystic fibrosis are already malnourished because of their primary disease, in which case adequate protein intake should also be a focus. Considering these several lifestyle factors, many of which may be present in a single individual, the panel's discussion of diagnostic issues concluded on a somber note. "Is our society now creating an environment in which lower bone mineral density will be the norm, where osteoporotic hip fractures will begin to occur not in the '60s or the '70s as they do now, but in younger people in their '40s and '50s? This is a big concern," Dr. Janicki said.

#### **Therapeutic Concerns in the Pediatric Population: Bisphosphonates, and the Risks and Benefits of Treatment**

Turning next to treatment matters, the panel tackled the question of which children and adolescents should receive therapy, such as a bisphosphonate, to improve their skeletal health. Dr. Ward noted 5 criteria that she uses in her clinical practice, standards that the panel agreed would make youngsters suitable candidates for treatment. First, patients should exhibit evidence of bone fragility, and not just reductions in BMD, since there is insufficient evidence to treat with a bisphosphonate in the latter case.

Examples of such patients include children with spontaneous vertebral fractures or with recurrent low-trauma fractures of the extremities, particularly of the lower extremities. Vertebral fractures are particularly important to treat before puberty, when the vertebrae can still be re-shaped effectively and a child can grow to his or her expected height. Second, an unfavorable BMD trajectory, where a child is not gaining bone mass as one would normally expect or is perhaps even losing bone mass, would make that child a good candidate for treatment. In this circumstance, the most salient factor is not the BMD value in and of itself, but the direction in which it is heading. However, if the unfavorable direction of BMD is the result of a slow progression through puberty, that is, if it is due to poor growth, then that underlying cause should be the clinician's primary focus, rather than necessarily rushing to prescribe a bisphosphonate. Third, just as an understanding of anticipated risk factors is an important part of the clinical history for the physician attempting to make a diagnosis of skeletal fragility, it is also important in determining whether to treat or not. For instance, Dr. Ward noted the example of a child with a minimally symptomatic vertebral compression fracture who is being weaned off of steroids; in this case, because the risk factor is going to disappear and thus the child will have the opportunity to rebuild his or her bone mass, watching the patient may be a better decision than recommending a bisphosphonate. A fourth criterion to sway the treatment decision is also another key aspect of the diagnostic process, namely, a consideration of the patient's age. Indeed, a bisphosphonate may be more appropriate in an older child with less potential to rebuild bone than a younger child. The final factor is an obvious one, and perhaps the most important of all: is the child in pain? "Symptomatology has the potential to trump the other criteria," Dr. Ward said, offering the example of back/vertebral fracture pain so severe that it prevents a crying youngster from attending school.

For children meeting one or more of these criteria for an important fracture, a

bisphosphonate may be warranted, but clinicians must ensure that such children are vitamin D-replete. They must also be certain that these patients can properly metabolize and eliminate bisphosphonates from their systems. "It is important to ensure that children have sufficient kidney function, since these drugs are all excreted by the kidney, and in very young children you need good estimating equations or actual measurements of kidney function," Dr. Langman stressed.

For children who are deemed appropriate candidates for bisphosphonates or other drugs, what are the benefits of treating? First and foremost, the panel agreed that the child should be the primary beneficiary of treatment – "you are treating the patient, not the bone density," Dr. Munns emphasized – and the main benefit of treatment is an improvement in the child's overall well-being and function. Gains in this regard include stabilizing fractures, interrupting the fracture/re-fracture cycle, alleviating pain, and restoring mobility. With these benefits in hand, clinicians can then focus on indices like BMD and a timely advancement through growth and puberty; again, with pediatric patients, it is often the trajectory of progress that is crucial, rather than just a single snapshot moment in time.

Of course, treatment always comes with associated risks, particularly with regard to long-term bisphosphonate treatment. While many pediatric patients have now received a decade's worth of bisphosphonates without any ill effects, recent reports of worrisome complications of long-term use, such as atypical subtrochanteric/diaphyseal fractures in adult patients, suggest that long-term exposure of children to these agents could also potentially cause problems. "My orthopedic colleagues complain bitterly that, particularly in children with osteogenesis imperfecta, we are creating children with bones made of concrete, where they find it very difficult to place intramedullary rods, and then there are also concerns about bones that shatter, rather than break in a normal way, when put under load," Dr. Bishop said. Dr. Janicki noted that while he does see some differences in the bones of

patients upon whom he operates, such as those with osteogenesis imperfecta, who have taken long-term bisphosphonates, because these agents have clear benefits in reducing the risk of fragility fractures, they are worth the risks. Potentially these risks could be mitigated by short drug holidays. In addition, it may just be that long-term use of bisphosphonates, particularly in cases where the threat to bone health is transient, such as in a patient taking steroids for a limited time, is not necessary, or perhaps the amount of medication could be reduced to a maintenance dose.

### **Conclusion**

The health of the skeleton is undoubtedly an issue with which physicians who treat pediatric patients should be concerned. In particular, many children will have an underlying condition that will put their skeletons at risk, and these youngsters merit special consideration. In such cases, heightened attention to bone health will pay dividends decades down the line because of the importance of the health of the young skeleton to the health of the mature skeleton. For this same reason, The Management of Bone Fragility/Low Bone Mass in Children and Adolescents stressed that clinicians must focus on healthy children too, particularly because the lifestyle that the current generation of young people has adopted is antithetical to good bone health. In this instance, encouraging exercise, a better diet, and more sunlight is the most fruitful approach. Otherwise, when today's video gamers and computer addicts, now sitting in darkened rooms eating food high in calories but low in nutritious content, turn into elderly adults reminiscing about their childhood, they may lament not only that they wasted their youth on frivolous pursuits, but that by doing so, it turned out they needed bisphosphonates too.