Effects of Pharmacologic Agents on Bone in Childhood: An Editorial Overview

Gordon L. Klein, MD, MPHa, Laura K. Bachrach, MDb, Ingrid A. Holm, MD, MPHc

aDepartment of Pediatrics, University of Texas Medical Branch, Galveston, Texas; bDepartment of Pediatrics, Stanford University School of Medicine, Stanford, California; cDivision of Endocrinology, Children’s Hospital of Boston, Boston, Massachusetts

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On April 14, 2005, a workshop on the skeletal effects of pharmacologic agents in children was held at the National Institutes of Health. Jointly sponsored by the American Society for Bone and Mineral Research (ASBMR) and the National Institute of Child Health and Human Development, the meeting was organized in response to suggestions from the Pediatric Bone Initiative of the ASBMR.1 Previous discussions at the 2003 ASBMR symposium on the state of pediatric bone research1 led to the conclusion that there was a lack of information on the effects of Food and Drug Administration–approved therapeutic agents on bone in children. Advances in pediatric medicine have produced a new population of children who are able to live into adulthood with chronic illnesses and were previously thought to have a poor prognosis for survival beyond their childhood years. Medications and direct effects of illness may compromise normal bone mineralization, leading to skeletal deformities and osteopenia at a relatively young age. Several topics discussed at the 2003 ASBMR symposium were further examined and developed in the recent National Institutes of Health workshop, such as the limitations of currently available pediatric bone density–reference data, the challenges of measuring bone mass and strength in children, clinical trial design, chronic drug effects on growing bone, and therapeutic agents for pediatric bone disorders. The following is a summary of all the presentations from the National Institutes of Health workshop on pediatric bone. Detailed summaries of selected talks are provided as well.

The first session provided basic background on normal bone accrual in children, the regulation of skeletal growth, and the effects of calcium, phosphorus, and vitamin D on growing bone.

Dr Jeffrey Baron and his co-workers2,3 reviewed the role of the growth plate in linear skeletal growth and work from his own laboratory to elucidate mechanisms of growth at the growth plate. Addressing specifically the role of the resting zone of the growth plate in longitudinal growth, he presented evidence that the resting zone contains chondrocyte stem-like cells that can regenerate the entire growth plate in the absence of the other 2 zones, the proliferative and hypertrophic. He then discussed growth-plate senescence and, with the use of rabbit and rat models, hypothesized that this phenomenon is a result of the finite capacity of chondrocytes to proliferate. Dr Baron proposed that “catch-up” growth, which occurs after recovery from a specific condition that inhibits growth, is explained by changes in the tempo of growth-plate senescence. In this model, inhibition of linear growth slows growth-plate senescence. When the inhibiting condition is resolved, the growth-plate chondrocytes have more of their proliferative capacity remaining and, thus, catch-up growth occurs. Conversely, estrogen accelerates growth-plate senescence, which leads to earlier “exhaustion” of
chondrocyte proliferative capacity and epiphysial fusion.

Dr Baron then went on to challenge the widely held belief that bone acquisition in childhood is like a “bank account” (ie, the belief that perturbations that lead to a transient decrease in bone acquisition during childhood will result in lower peak bone density). Instead, he hypothesized that periosteal new bone formation and endosteal bone resorption, which create a wider bone, would displace inadequately formed bone from a younger age. Moreover, Dr Baron then challenged the assumption that childhood and adolescent bone mass predicts adult bone mass. Evidence comes from work in his laboratory on a rabbit model in which dexamethasone-induced inhibition of bone accrual reversed when the dexamethasone treatment was stopped. At the metaphysis, this reversal was caused by the replacement of osteoporotic bone by healthy bone at the growth plate. At the periosteal surface, when the dexamethasone was stopped, the decrease in periosteal bone formation was halted and formation actually increased above normal. The mechanism for this catch-up growth at the periosteal surface is likely not the same as at the growth plate and may, instead, be a result of changes in mechanosensing. In humans, supportive evidence comes from the finding that the increase in bone density seen in children who received calcium supplements over 3 years disappears after treatment is stopped.

Dr Frank Rauch4 then spoke on the mechanisms behind the increase at the trabecular and periosteal surfaces that occur during childhood. At the trabecular surfaces, he provided evidence that changes in neither material density nor trabecular number account for the increase in trabecular bone mineral density (BMD) during puberty. Instead, studies performed in his laboratory have demonstrated that the increase in trabecular BMD during growth are caused by an increase in trabecular thickness and that this increase is caused by “remodeling with a positive balance,” which is a rather slow process (each remodeling cycle takes 9–10 months).

Next, Dr Rauch addressed the issue of bone growth in width, a poorly understood process that is just as crucial as bone growth in length. When the bone grows longer, the width must increase concomitantly to preserve bone strength. Periosteal bone formation in children differs from adults, not only because this process is more active in children but also because it is continuous (modeling), whereas in adults the process is cyclic (remodeling). Periosteal apposition is rapid early in life, slows with age, and is variable between bones, depending on the mechanical stimuli. Although systemic factors such as hormones are important in regulating periosteal bone growth, given that the growth is so site/bone specific, local factors such as mechanical load must play a predominant role.

In the last talk of this session, Dr Marie Demay5 addressed the effects of mineral homeostasis and vitamin D on growing bone and presented data from her laboratory on a vitamin D receptor (VDR)-knockout mouse model. This is the same defect seen in humans with hereditary vitamin D-resistant rickets. These mice developed rickets, osteomalacia, hypocalcemia, secondary hyperparathyroidism, and hypophosphatemia. However, when placed on a diet high in calcium, phosphorus, and lactose, all of the abnormalities were prevented, including the rickets and osteomalacia, which demonstrated that it is the secondary effects of the VDR on mineral metabolism, not the VDR itself, that are important for bone mineralization. Additional studies demonstrated that the abnormal mineral ion homeostasis led to expansion of the growth plate by impairing apoptosis of the late hypertrophic chondrocytes. Finally, Dr Demay demonstrated that phosphate mediates apoptosis of the hypertrophic chondrocytes via the mitochondrial apoptotic pathway. Overall, the studies presented by Dr Demay demonstrated that phosphate, not calcium, is crucial for apoptosis of the terminally differentiated chondrocytes and, thus, the mechanism by which VDR resistance leads to rickets.

The second session of the conference addressed the challenges of investigating bone health in the growing child. Dr Laura Bachrach outlined the barriers to recruitment and retention of subjects in clinical trials. An estimated 86% of US clinical trials in adults fail to complete cohort recruitment within the projected time frame, and attrition rates are typically 15% to 40%.6 Factors related to subjects, investigators, and protocols account for these failures. Potential subjects refuse to enroll or quit studies because of inconvenient or lengthy study visits, uncertainty about whether treatment will be provided, distrust of the research team, cultural or language barriers, or relocation. Minority group members and individuals with less education are less likely to participate; one review found that 70% of intervention studies had underenrollment of minority subjects.7 Most relevant to the meeting focus, parents are less likely to enroll young children. Factors that reduce investigator participation in clinical research include the competing roles of care provider and investigator, inadequate time, resources, or incentives for research, competing clinical trials, and unstable research support teams. Protocol-related variables that impede success include overly demanding visits, restrictive inclusion and exclusion criteria, and delays in the start of the trial. Negative input from the media and lengthy institutional review board processes also hamper successful recruitment.

Despite these barriers, Dr Bachrach identified examples of longitudinal observation studies of bone health in children and adolescents that had achieved notable success in recruitment and retention.8,9 Factors that contributed to these successful investigations included consistent and personable study staff, a robust source of
potential subjects, support from communities, schools, and relevant professional colleagues, convenient and efficient study visits, adequate incentives, and ongoing contact such as birthday or holiday greetings between study personnel and subjects between visits.

Dr Richard Henderson addressed the challenges of identifying appropriate enrollment criteria and therapeutic end points for pediatric trials. The most clinically relevant goal is the reduction of fractures. However, the annual fracture rate reaches 5% to 10% only in children with severe disabilities or osteogenesis imperfecta and is <3% for those with other chronic illnesses, which makes it hard to use fracture prevention as the standard for therapeutic success. Power calculations must take into account the frequency of fractures in untreated children, the anticipated effect size of active treatment, and the inevitable attrition during the study. Because control subjects will also likely benefit from receiving optimal standard-of-care treatment, such as vitamin D and calcium, this must also be factored into the model. In a sample “best-case” scenario, assuming a baseline annual fracture rate of 10%, an 80% reduction of fractures with active treatment, a 10% decrease in fractures in control subjects, and yearly attrition of 5%, a cohort of 92 subjects is needed. In a less favorable scenario with a 5% annual fracture rate, 40% treatment efficacy, 20% effect of control therapy, and 20% attrition, a cohort of 3422 subjects is needed. Recruiting a pediatric cohort of this size would be formidable. Dr Henderson also raised important ethical questions concerning the risk/benefit ratio when testing pharmacologic agents in children. Is it appropriate to enroll a child who has not yet had a fracture? Conversely, is it ethical to withhold a drug that has been proven efficacious for adult patients with osteoporosis from children who have already fractured a bone? Are proxy measures of bone fragility, such as BMD, sufficiently robust to use in select children at highest risk for enrollment in a study? Answers to these questions will influence the pool of potential subjects for recruitment, the heterogeneity of the cohort, and whether findings can be generalized to other patient groups.

Dr Vicente Gilsanz discussed the use of bone densitometry as an alternative end point for pediatric bone health research. In adults, the relationship between BMD and fracture rate is sufficiently robust that BMD can be used to diagnose osteoporosis, select patients for treatment, and monitor response to drug therapy. The value of bone densitometry for predicting fractures in children is more controversial.

Densitometry results are considerably more challenging to interpret in the growing child because of the changes in bone size and shape that were outlined in earlier talks. In addition, the correlation between BMD and fracture risk is not well established in children. Dual-energy x-ray absorptiometry (DXA), the most commonly used densitometry technique, provides a two-dimensional measurement of three-dimensional bones; therefore, bone size influences BMD results. For example, low BMD of a child may reflect his or her smaller body size, and longitudinal increases in BMD can reflect changes in bone size, bone density, or both. To distinguish between changes in bone size and mineral, bone mass can be evaluated by quantitative computed tomography (QCT). This technique measures volumetric BMD and is not influenced by bone size. As detailed in an article by Dr Gilsanz and his co-workers, QCT and DXA provide different information regarding the skeletal status of children. In a study with chronically ill and healthy youth, 19% were identified as having low spine bone mass for age (z score less than −2) using areal BMD measurements from DXA as compared with only 6% using volumetric BMD measurements from QCT. Smaller bone size accounted for the low bone mass in many of the children.

A critical question is whether DXA or QCT is a better surrogate measure of bone fragility in childhood. This issue remains unresolved because there are too few data linking QCT or DXA to fracture risk in children. The choice of an appropriate surrogate measure for fracture is a key area of controversy that must be resolved when planning bone-health–intervention studies in pediatric populations.

The third session focused on the use of bisphosphonates in children. Professor Graham Russell reviewed the current models of bisphosphonate action as antiresorptive agents. These drugs accumulate on the denuded surfaces of bone surrounding resorbing osteoclasts where they are taken up by the osteoclastic cells. Nitrogen-containing bisphosphonates interfere with biosynthesis of lipids attached to guanosine triphosphate–bound proteins, inactivating the proteins and inhibiting osteoclast motility and function. Non–nitrogen-containing bisphosphonates act by reversing reactions involved with protein synthesis, which results in accumulation of toxic products and leads to cell apoptosis. Bisphosphonates may also reduce bone resorption by interfering with glucocorticoid-induced apoptosis of bone cells; however, details of this activity require clarification. Different bisphosphonate compounds attach to bone surfaces with variable degrees of avidity. This strength of attachment of a given drug determines whether the compounds are longer or shorter acting. Bisphosphonates have been tested to only a limited extent in growing children. Many uncertainties persist regarding their use in pediatrics, including which bisphosphonate is preferred, in which dose it should be used, and for how long treatment should last. Little is known about the duration of the antiresorptive effect once bisphosphonates are discontinued in younger patients.

Addressing this latter issue, Dr Craig Langman (unpublished data, 2005) examined the duration of the
antiresorptive action of alendronate in a cohort of 46 children with fracturing osteoporosis. The cohort of 46 subjects had been treated for a median of 672 days (1.8 years) and was examined at a median of 410 days after cessation of bisphosphonate therapy. Only 1 of the 46 children studied had a decline in lumbar spine BMD \( z \) score between treatment termination and follow-up; 2 children had sustained an interval fracture. Urinary N-telopeptide of type I collagen, a marker of bone resorption activity, remained suppressed. These data suggest that alendronate therapy sustains antiresorptive activity for at least 1 year after termination.

Dr Francis Glorieux reviewed the experience that he and his co-workers\(^{13,14} \) have had with bisphosphonate therapy in osteogenesis imperfecta (OI). OI is associated with a high rate of bone turnover, which, when combined with the decreased ambulation, deformities, and pain, leads to bone loss. For these reasons, bisphosphonates were initially tried as a treatment for OI. Pamidronate therapy in children with OI results in significantly decreased skeletal pain, increased sense of well-being, and increased volumetric BMD and bone volume compared with untreated patients with OI. Dr Glorieux’s group has performed controlled trials using alendronate in patients with OI. The results showed a significantly higher vertebral spine BMD \( z \) score in the treated versus untreated patients. The vertebral shape was improved in the patients in the treated group, and the gain in height of the vertebral body, coupled with the increase in BMD with treatment, results in an increased amount of bone in the vertebrae. In the patients in the alendronate-treated group there was a nonsignificant trend toward a decreased fracture incidence, significant improvement in gross motor function, and no negative effects on growth. Bone-biopsy results showed a dramatic increase in cortical thickness and a more modest increase in trabecular bone volume. There was a decrease in bone turnover, but remodeling continued. The stiffness typical of bone in patients with OI did not deteriorate with treatment. The adverse effects of pamidronate treatment included an acute-phase reaction with treatment and a delay in the healing of osteotomies, neither of which are well understood.

Dr Glorieux ended with advice for clinicians treating children with OI. He concluded that his studies of pamidronate and alendronate in OI favor pamidronate. He stressed that children with mild OI should not be treated with bisphosphonates other than in the clinical research setting. Also, regarding the issue of when to discontinue treatment, he pointed out that when bisphosphonates are discontinued, the bone reverts back to its original untreated state, which leaves the untreated bone prone to fracture.

Dr Michael Whyte addressed the issue of bisphosphonate toxicity and began with his sobering prediction that there may be a higher prevalence of adverse effects from bisphosphonate therapy in the near future, likely because of increased use of these medications. Excess bisphosphonate can lead to an osteopetrosis-like state. In a case of “bisphosphate-induced osteopetrosis,” a boy presented to Dr Whyte and his co-workers after being treated with 4 times the dose of pamidronate recommended by Dr Glorieux’s group over a 3-year period.\(^{15} \) He had many of the signs, symptoms, and biochemical and bone-biopsy findings of genetic forms of osteopetrosis. Another patient, a 62-year-old woman with breast cancer who was treated for bone metastases with pamidronate and zoledronate for 7 years, had a very high BMD according to DXA and disturbances in bone remodeling. Other cases were presented that reiterated a disturbance in bone modeling and remodeling in children on bisphosphonates, which led to poor bone quality and an increased tendency to fracture. Bisphosphonate therapy has also been shown to lead to osteonecrosis of the jaw in adults, not children.

In an effort to deal with the complications of excessive bisphosphonate use, Dr Whyte’s group is proceeding with studies aimed at determining when someone may be at risk for excessive bisphosphonate effects by using tools such as bone biopsies, micro-computed tomography, and measurements of creatine kinase isoenzyme (CK-BB) and tartrate-resistant acid phosphatase. These studies may lead to a list of parameters that the clinician can follow when a patient receives bisphosphonates to determine when the patient should stop therapy because of risk of complication from excessive use.

Dr Joan Marini presented more data on trials of bisphosphonate therapy in children and mice with OI.\(^{16,17} \) In a placebo-controlled 2-year trial of olpadronate in the Netherlands, the treated group showed an increase in vertebral BMD and a decrease in the relative risk of long-bone fractures. No changes were seen in vertebral geometry, but the fact that approximately one third of the patients had type 1 OI may be explained by this negative finding. In the placebo-controlled alendronate trial discussed earlier by Dr Glorieux, the vertebral BMD increased, and there was a trend toward decreasing fracture rate in the treated group. Finally, the National Institute of Child Health and Human Development–sponsored trial of pamidronate in 18 children with types 3 and 4 OI showed increases in DXA \( z \) scores and improvement in vertebral geometry, midvertebral height, and vertebral area in the patients in the treated group during the first year but not the second year. There were no effects of treatment on fracture incidence, ambulation, muscle strength, or pain. Dr Marini concluded from these studies that bisphosphonates have a much more beneficial effect on the spine than on the long bones, and that the benefits in ambulation, pain, and endurance that were demonstrated in previous studies may have resulted from a placebo effect, because these studies were not placebo-controlled trials.
To further address the effects of bisphosphonates on bone, Dr Marini and her co-workers turned to a knock-in mouse model for type 4 OI, the brittle mouse. These mice were treated with subcutaneous alendronate from 2 to 14 weeks of age, killed, and compared with placebo-treated brittle mice and alendronate-treated wild-type normal mice. Alendronate had no effect on growth of either genotype. Treated brittle and wild-type mice showed an increase in BMD as measured by DXA. Bone volume per total volume more than doubled because of an increase in trabecular number, not thickness. Cortical thickness in the brittle mouse normalized. Mechanical properties were determined by assessing the 4-point bending to fracture. Stiffness significantly increased in the treated normal mice but not in the brittle mice. The “load to fracture” increased in both the wild-type and brittle mice because of the increased bone volume. However, the bone became more brittle in both mice. The material strength of the bone was less than that before treatment. Finally, the osteoblast surface decreased with treatment and the morphology of the osteoblast changed, which is consistent with a direct toxic effect on cells. Dr Marini concluded that the goal of bisphosphonates in OI should be to treat long enough to reap the benefits without paying the price of the negative effects.

The final session of the workshop dealt with hormones as pharmacologic agents. Dr Mary Leonard summarized recent studies of the effects of glucocorticoid therapy in children with chronic disorders by her and her co-workers. She emphasized the complex interactions between the effects of disease-related factors, such as inflammatory cytokines, immobility, and undernutrition, and the effects of glucocorticoids. Adverse effects on bone size and strength as well as body composition may be attributed to the underlying disease for which glucocorticoid therapy is prescribed as much as to the drug itself.

Dr Madhusmita Misra examined the key role of the sex steroids as other key hormonal influences on bone. Estrogen stimulates both linear growth and bone-mass accrual, indirectly through stimulation of growth hormone and insulin-like growth factor 1 production and directly by inhibition of osteoclastic bone resorption later in puberty. Androgens also affect bone, indirectly by aromatization to estrogen and directly via the osteoblast androgen receptor to increase periosteal bone apposition, which makes the male cortices thicker. In addition, androgens directly inhibit osteoclastic bone resorption later in puberty.

Next, Dr Robert Weinstein reviewed the skeletal effects of anticonvulsant drug therapy in children. He challenged the commonly cited model that bone loss associated with these agents is caused by osteomalacia. Instead, he attributed bone loss to a high-turnover state that results from drug-induced interference with calcium absorption as well as direct effects on osteoclasts and osteoblasts. The resultant hypocalcemia can exacerbate seizures that are treated with higher doses of anticonvulsants, which sets up a vicious cycle. The important issues to be addressed in this area include that of the mechanism of anticonvulsant effects on bone cells and whether some of the newer anticonvulsants will influence ionized calcium and parathyroid hormone levels in a manner similar to older agents.

Finally, Dr Gordon Klein summarized the recent work of his group on the anabolic effects of recombinant human growth hormone (rhGH) in the treatment of bone loss after burn injury. He observed that children who received 12 months of rhGH had significantly greater increases in bone mineral content and bone area of the total body than did placebo-treated control patients. This raised the question of whether bone size or bone calcium accretion is more important in the reduction of fracture risk in this population. The other issue raised by the study was that of whether effects of growth hormone on bone are primary or secondary to the increase in lean body mass, which preceded gains in bone mineral content in the rhGH-treated group.

Collectively, these presentations reinforced the need to develop meaningful clinical end points for evaluation, to modify the available diagnostic tools to more precisely evaluate the skeleton of the growing child, and to use our knowledge of bone biology and pharmacology to more effectively intervene to prevent or reverse processes that adversely affect bone.

What follows are articles selected by the organizing committee as among the most instructive for the understanding of the interaction of chronic disease and chronic drug treatment on pediatric bone.

REFERENCES
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