Bone Health in Children with Physical Disabilities
AACPDM 2014: BRK 10

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Disclosure Information
AACPDM 68th Annual Meeting Sept 10-13, 2014

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Disclosure of Relevant Financial Relationships
We have no financial relationships to disclose.

Disclosure of Off-Label and/or investigative uses:
We will be discussing “off-label” use of pamidronate, which is not approved by the FDA for children.

Agenda
- Introduction and background: Why is it important to talk about bone health?
- The evidence: Health promotion and surveillance of bone health.
- Take a look at a clinical practice guideline.
- The use of DXA in pediatric patients.
- The evidence: Treatment of osteoporosis and fragility fractures.
- Group discussion: Gaps in the evidence, challenges in clinical practice.
Learning Objectives

- To identify key components of the prevention and evaluation of low bone mineral density in children with disabilities.
- To develop skill in implementing nutrition based interventions for preventing and treating low bone mineral density in children with disabilities.
- To understand how bone density is measured in patients with disabilities and what the measurements mean.
- To understand the evidence for treatment modalities of osteoporosis of children with physical disabilities, specifically bisphosphonates.

Why is this important?

- Children with CP have low bone mineral density (BMD), putting them at increased risk of osteoporosis.
- Osteoporosis: presence of low BMD + fracture history.
- Risk Factors: decreased weight bearing & exposure to sunlight, medication, poor nutrition, pubertal irregularities.
- Approximately 20% of children and young adults with CP who cannot walk independently develop fragility fractures.

Why is this important?

Fractures can or may cause
- Significant pain and impairment
- Hospitalization and surgery
- Missed school for the child and work for the parents
- Loss of mobility and thus worsening of bone density
- Accusations of abuse
- Litigation
It is important for parents and health care providers to know how to improve bone mineral density and prevent fragility fractures.

The Evidence: Health Promotion & Surveillance

**Systematic Reviews:**
Fehlings et al. (2011); Houghs et al. (2010); Novak et al. (2013)

1. Weight bearing / physical activity
2. Calcium & Vitamin D supplementation
3. Bisphosphonates

Levels of Evidence: Fehlings et al. (2011)

<table>
<thead>
<tr>
<th>Colour Legend for Treatment Effectiveness on BMD (Evidence):</th>
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<tbody>
<tr>
<td>Effective (A)</td>
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<td>Probably Effective (B)</td>
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<tr>
<td>Possibly Effective (C)</td>
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<td>Data Inadequate (U)</td>
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Levels:
- **Level B**: Possibly Effective
- **Level C**: Possibly Effective
- **Level U**: Inadequate
Weight bearing / physical activity

- Therapy sessions focusing on weight bearing, stander, vibrating platform, gait trainer, combination
- Inadequate data (BMD & fragility #)
- No significant adverse events

Fehlings et al. (2011); Chad et al. (1999); Caulton et al. (2004); Eisenberg et al. (2009); Ruck et al. (2010); Pin et al. (2006); Starck et al. (2010); Wren et al. (2010); Hough et al. (2010); Novak et al. (2013)

Many of you might disagree...

Vibration platform strengthened bones, improved walking in moderate cerebral palsy
Dr. S. Gusso et al, 2013, New Zealand

ClinicalTrials.gov
Effect of Botox and Vibration on Bone in Children With Cerebral Palsy
Drs. Hodges & Miller, Delaware


- Wren et al (2010): 31 children with CP GMFCS I-IV, ages 6-12yrs, stood on a vibrating platform (30 Hz, 0.3g peak acceleration) at home for 1.5 minutes a day, for 6 months. They stood on the floor without the platform for another 6 months.
  - Greater increase in cortical bone. No difference seen in density of cancellous bone
- Ruck et al (2010): 20 children with CP GMFCS I-IV, ages 5-12yrs, assigned routine school PT of school PT+ 3min per session of side alternating WBVT for 6months.
  - Average walking speed was improved. No positive effect on BMD.
- Afzal et al (2014): 14 girls with Rett Syndrome received LMMS 20min/day x 5 days/week for 6months. Crossover pilot study.
  - Those with adherence of >65% showed an increase in spine BMD. Other benefits reported by parents: improved mobility, more regular BMs, greater participation in ADLs.
Calcium and Vit D supplementation

- Activated version of Vit D, Elemental Calcium 500mg
- Significant increase in BMD
- Possibly effective (BMD)
- Inadequate data (fragility #)
- No significant adverse events

Fehlings et al. (2011); Jekovec-Vrhovsek et al. (2000); Iwasaki et al. (2008); Hough et al. (2000); Novak et al. (2013)

More on Vit D...

- There has been an explosion of clinical studies being done related to Vit D - not all related to bone health.
- Evidence supports Health Canada and Institute of Medicine DRIs: 400-600IU daily depending on age.
- Supplemental Vit D above these recommendations is not associated with improved calcium absorption in children.
- Still many questions and controversy... testing, how much Vit D, how to titrate.

Abrams & Tosiello, 2014; Health Canada & IOM, 2010; Singh & Bonham, 2014

Bisphosphonates

- Probably effective (BMD)
- Possibly effective (fragility #)
- Short-term adverse events: fever, flu-like symptoms, and hypocalcaemia.

Henderson et al. (2001); Clyce et al. (2003); Pollock et al. (2006); Swales et al. (2006); Bachrach et al. (2006); Seeman et al. (2013); Seeman et al. (2013); Hough et al. (2013)
Assessment of Bone Density in Children and Adolescents

- DXA is the preferred method for assessing bone mineral content (BMC) and areal bone mineral density (aBMD) throughout the world, because of its speed, precision, safety, low cost, and widespread availability.
- The posterior-anterior spine and total body less head (TBLH) are the preferred skeletal sites for performing BMC and aBMD measurements in most pediatric subjects. Both sites are highly reproducible.
- Other sites may be useful depending on clinical need.
- The hip is not a preferred site in growing children because of variability in skeletal development.

Other Skeletal Sites: Proximal Femur and Total Hip

- The proximal femur region, commonly assessed by DXA in adults, is more challenging to evaluate in children.
- Skeletal landmarks, which guide proper positioning, may not be well developed in young children. This can lead to errors in positioning and placement of the region of interest (ROI) using standard software.
- The skeletal landmarks are fully formed by late adolescence. Many clinical centers begin to include measures of the hip region during middle to late adolescence (e.g., age 13 and older) as teenagers who possess threats to bone health are approaching the transition to adult providers.

Other Skeletal Sites: Lateral Distal Femur (LDF)

- In children with physical disabilities, the total-body and spine DXA scans are often rendered useless by the presence of metallic hardware and/or contractures.
- The lateral distal femoral (LDF) DXA scan was developed as a scan mode for just such children.
- Accessible in most patients with physical disabilities, and less susceptible to motion.
- The distal femur is a common site for fracture.
- At this time, reference data for LDF are only available for Hologic scanners.

Limitations of DXA

- Both BMC and aBMD are highly influenced by skeletal dimensions, with short stature and small bone size making bone density appear lower than if measured by pQCT.
- Adjustments based on bone size, height, bone age or pubertal maturity have all been suggested.
- The ISCD recommends that in children with short stature or growth delay, spine and TBLH BMC and areal BMD results should be adjusted. For the spine, adjust using either BMAD* or the height z-score. For TBLH, adjust using the height z-score.
- However, obtaining a reliable height measurement for children with contractures can be difficult or impossible.

BMAD (Bone mineral apparent density) = BMC (L1-L4)/ Ap
The diagnosis of osteoporosis in children and adolescents should NOT be made on the basis of densitometry criteria alone.

The diagnosis of osteoporosis requires the presence of both low bone density (Z-score < -2.0) AND a clinically significant fracture history.

A clinically significant fracture history means one or more of the following:

- Vertebral compression fracture
- Two or more long bone fractures by age 10 years
- Three or more long bone fractures at any age up to age 19 years

Which Patients Should Get A DXA?

- Patient who has had a previous fragility fracture
  - Wait till cast is off
  - Expect that callus formation will raise the apparent bone density temporarily. Can use the contralateral femur as a baseline if DXA is done soon after
- Patient who has "low bone mass" or "osteopenia" identified by x-ray
- Patient being considered for bisphosphonate treatment
- Patient where the DXA will change or influence treatment decision

Treatment With Bisphosphonates

- Bone biopsies have shown that children with cerebral palsy and low bone density have accelerated bone resorption. Bisphosphonates act at the bone tissue level by inhibiting bone resorption.
- Bisphosphonates have been extensively studied for treating osteoporosis in the elderly, and have been approved by the FDA for this purpose
- In the pediatric population, studies have been published on the use of pamidronate to treat Osteogenesis Imperfecta (OI), as well as CP, DMD and Spina Bifida, among others
Which Patients Should Get Treated with Bisphosphonates?

- Patient with at least one fragility fracture, low BMD and “everything else” that can be done has already been done (i.e. standing when possible, adequate calcium and phosphorus intake, sufficient vitamin D level)
- Patient with low BMD who is a surgical candidate for bony procedure, where hardware may not hold because of poor bone quality
- Get a dental exam before starting to be sure no extractions or extensive dental work will be needed

The Use of Bisphosphonates in Children

- In children, the best studied drug is Pamidronate, which is administered intravenously, for 3 consecutive days, every 3-4 months
- The IV form is given to assure more complete and uniform drug dosing
- The side effects can include fever, chills, neutropenia, hypocalcemia, hypophosphatemia, bone pain, nausea and vomiting
- ONJ has been described in adults who received BPs, but not in children (so far)

The Use of Bisphosphonates in Children With Cerebral Palsy

- Randomized, placebo-controlled, double-blind study looked at 6 pairs of matched patients. One patient of each pair received saline, the other Pamidronate in a dose of 1 mg/kg/dose, for 3 consecutive days every 3 months, for a total of 15 doses, over one year
- BMD was dramatically increased in the children who received pamidronate. Greatest increase in BMD was seen in region 1 of the distal femur: range of 38% to 185% (average 89% ± 21%) over 18 months
- Z-score improvement was also greatest in region 1 of the femur, increasing from -4.0 ± 0.6 to -1.8 ± 1.0

We retrospectively examined the records of 25 children with spastic quadriplegic CP (GMFCS Level 4 or 5) who had suffered at least one non-traumatic fracture (range 1 to 11) and who were treated with pamidronate.

Treatment followed a standardized protocol of 1mg/kg/dose to a maximum of 35 mg, for 3 consecutive days every 3-4 months.

All patients received a total of 15 doses of pamidronate over an average of 13.6 months.

These 25 children had sustained a total of 86 fractures before treatment, over a cumulative 280.6 person-years, for a fracture rate of 30.6% per year.

Following treatment with five 3-day courses of pamidronate, patients were followed for an average of 4.1 years (107.5 person-years in total).

8 children experienced 14 fractures from the time the first dose of pamidronate was given, for a fracture rate of 13.0% per year. This was a significant decrease in fracture rate (p=0.02).

Of the 17 children without fracture, the longest follow-up is 10.5 years.

In the majority of patients (57%) site of fracture after treatment corresponded with location of pamidronate bands.

An additional 14% of fractures occurred at the site of osteotomy – a recognized location of stress risers.

We did not see sub-trochanteric fractures, of the type being described after prolonged use of bisphosphonates in adults, and in children with OI.
The Use of Bisphosphonates in Children

Alternative Treatments:
- IV Zoledronic acid (Zometa), every 6 months
  - Inadequate evidence in children
  - Much more convenient (1/2 hour infusion)
- Oral meds:
  - RCT of Risedronate in children ages 4-15 years with OI showed improved BMD and decreased fracture rate
  - Bishop, N, Lancet. 2013 Aug
- IV Pamidronate, at different intervals (such as one day every month)

Low Magnitude Mechanical Stimuli (LMMS) are Anabolic to Bone
Effect of Strain on Bones

- Strain signals, which arise in bone tissue during loading, enhance bone density.
- The absence of such signals is considered the key factor in the bone fragility of children who are non-ambulatory.
- Experiments in animals have demonstrated that high frequency (10-90 Hz), extremely low magnitude (<100 microstrain) stimuli are anabolic to trabecular bone.
- Brief exposures to these low-level signals can inhibit disuse osteoporosis.


Hindlimb Unloading

Questions for Discussion

- Who should be treated with bisphosphonates? Which drug?
- What is the end point of treatment?
- At what age can we treat with oral bisphosphonates?
- Long-term risks and benefits? Will we see ONJ in children?
- Defining a pediatric fracture risk threshold.
- What to do when the child has kidney stones or nephrocalcinosis?
- Can vibration therapy be used for children with GMFCS IV and V? How?
- Knowledge translation strategies? Have you implemented a bone health clinical practice guideline in your organization?
Thank you!

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